SUBSTITUTION OF HETEROCYCLIC NUCLEI

by

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UNIVERSITY OF TASMANIA
HOBART

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Except as stated therein this thesis contains no material which has been accepted for the award of any other degree or diploma in any university, and, to the best of my knowledge and belief, this thesis contains no copy or paraphrase of material previously published or written by another person, except when due reference is made in the text of this thesis.

Misbahul Ain Khan
INTRODUCTION

Most of the aryl-substituted five membered heteroaromatic compounds are synthesised by condensations of the parent rings. In a number of cases aryl and other substituents have been introduced into an existing heteroaromatic ring. However, difficulties are met in the syntheses of some compounds: for example, 1,aryl substituted pyrazoles and 1-aryl substituted 1,2,4-triazoles can be synthesised from the corresponding arylhydrazines, but in cases such as \( \mathbf{g}-(\text{pyrazol-1-yl})\text{benzonitrile} \) and \( \mathbf{g}-(1,2,4-\text{triazol-1-yl})\text{-benzonitrile} \) one would require \( \mathbf{g}\)-cyanophenylhydrazine. This hydrazine had earlier been claimed to have been obtained by the reduction of diazotized \( \mathbf{g}\)-aminobenzonitrile (Ber., 36, 805 (1903)) or \( \mathbf{g}\)-phentriazon-oxime with zinc chloride and hydrochloric acid (Ber., 22, 626 (1896)), but recently it has been suggested that the compound obtained in the two reductions was \( \mathbf{3}\)-aminoindazole (Chem. and Ind., 1234 (1958)).

Difficulties are also met in synthesising the 1-substituted arylindoles, though the 2-substituted arylindoles have easily been prepared by the Fischer-indole synthesis. Also, C-aryl substituted imidazoles can be prepared relatively easily but again N-aryl
substituted imidazoles are not easy to synthesise by routine methods. A survey of literature revealed that most of the N-aryl-substituted five membered heteroaromatics with different functional groups in the phenyl ring have not been described. Only in the case of nitrophenyl compounds, some of the nitrophenylazoles had earlier been obtained by direct nitration of corresponding phenylazoles. As nitration or other substitution reactions of phenylazoles can lead to a number of isomers, some of which could be difficult to isolate, such an approach could be inconvenient, and thus methods were sought to prepare N- and C-substituted five membered heteroaromatics.

The Ullmann condensation (using different copper preparations) was earlier used in the N-arylation of carbazole and more recently in the N-arylation of imidazole, indazole, benzimidazole etc. This condensation was extended to other azoles and aryl halides carrying different substituents were employed for N-arylation of a number of azoles.

For the preparation of C-aryl heteroaromatics two arylation reactions employing amino compounds (Gomberg and Meerwein) have been found to give satisfactory results and were employed in a few exploratory experiments. Accordingly, this thesis has been divided
into three chapters: the Ullmann condensation, Meerwein arylations and Gomberg arylations. A review of literature has been included for the Ullmann condensation, while in the case of the other two chapters references have been made to existing reviews and more recent literature. Prevalent views as to the mechanism of these reactions have also been presented.

The practice of Chemical Abstracts has been followed for the abbreviation of journals.
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SUMMARY

ACKNOWLEDGEMENTS
CHAPTER I

THE ULLMANN CONDENSATION
In the well-known Ullmann syntheses of biaryls two aromatic halides are condensed in the presence of a metallic agent. Copper is the most effective catalyst in these condensations:

\[ RX + R'X + M \rightarrow RR' + MX_2 \]

This synthesis has been well reviewed by Fantas (1). Another review by Bacon and Hill (2) covers a much broader area of copper catalysed reactions.

Another discovery due to Ullmann (3) is the catalysis by small amounts of copper of the condensation of aniline with o-chlorobenzoic acid. This method of arylation of amines has been used as a general method in the preparation of substituted amines (4, 5) and also in the preparation of aryl ethers (5 - 9) and aryl thiocarbonates (8, 10). It is often employed in the syntheses of natural products (11), and is a standard route to derivatives of acridine (12). The process is carried out in the presence of a base, usually potassium carbonate.
In the present work the Ullmann condensation is applied to the condensation of haloaryls with five-membered heteroaromatics which have a free NH and undergo substitution at the N atom in the presence of a copper catalyst. The heteroaromatic may be the parent one (e.g. pyrazole) or the part of a condensed ring system (e.g. benzimidazole). A review of such reactions is presented here in a tabular survey (Table I). The probable mechanism of the condensation will be discussed in the light of this survey and the present work in a later section.

Only those reactions which involve the use of a copper catalyst for the condensation have been included in the survey and thus those condensations yielding N-arylheteroaromatics but not employing the Ullmann conditions (13, 14, 105) have been excluded.

Table I: N-ARYLHETEROCYCLES PREPARED BY THE ULLMANN CONDENSATION

\[
\text{ArH} + \text{Ar'}X \rightarrow \text{ArAr'}
\]

<table>
<thead>
<tr>
<th>Product Ar-Ar'</th>
<th>Ar'X</th>
<th>Experimental Conditions (^{a,b})</th>
<th>Yield</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrrole</td>
<td>N-pyrrolyferrocene</td>
<td>A, 120</td>
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<td>15</td>
</tr>
<tr>
<td>Indole</td>
<td>N-indoleyferrocene</td>
<td>&quot;</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>N-phenyl indole</td>
<td>A, I</td>
<td>50</td>
<td>16</td>
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</tbody>
</table>
Table I (contd.)

<table>
<thead>
<tr>
<th>Carbazole</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>9-phenylcarbazole</td>
<td>bromobenzene</td>
<td>B, 180-220</td>
<td>–</td>
</tr>
<tr>
<td>&quot;</td>
<td>iodobenzene</td>
<td>C, 190-200</td>
<td>66</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>C, J</td>
<td>88</td>
</tr>
<tr>
<td>&quot;</td>
<td>bromobenzene</td>
<td>C, 50-60</td>
<td>20</td>
</tr>
<tr>
<td>9-(o-nitrophenyl)-carbazole</td>
<td>o-chloronitrobenzene</td>
<td>C, 240-250</td>
<td>50-60</td>
</tr>
<tr>
<td>9-(4'-methyl-2'-nitrophenyl)-carbazole</td>
<td>2-chloro-5-methyl-nitrobenzene</td>
<td>C, 220-230</td>
<td>35</td>
</tr>
<tr>
<td>9-(4'-cyano-2'-nitrophenyl)-carbazole</td>
<td>2-chloro-5-cyanonitrobenzene</td>
<td>C, 180-190</td>
<td>15</td>
</tr>
<tr>
<td>9-(4'-acetyl-2'-nitrophenyl)-carbazole</td>
<td>3-nitro-4-(X)-acetophenone</td>
<td>C</td>
<td>0</td>
</tr>
<tr>
<td>&quot;</td>
<td>X = Cl, Br or I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-(4'-chloro-2'-nitrophenyl)-carbazole</td>
<td>2,5-dichloronitrobenzene</td>
<td>C, 220-230</td>
<td>35</td>
</tr>
<tr>
<td>9-(2',4'-dinitrophenyl)carbazole</td>
<td>2,4-dinitrochlorenzene</td>
<td>C, 170-180</td>
<td>50</td>
</tr>
<tr>
<td>9-(p-chlorophenyl)-carbazole</td>
<td>p-chloroiodobenzene</td>
<td>C, 200</td>
<td>70</td>
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<tr>
<td>9-(p-carboxethoxyphenyl)carbazole</td>
<td>ethyl, p-iodobenzoate</td>
<td>C, 220-230</td>
<td>80</td>
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<tr>
<td>9-(p-carboxyphenyl)-carbazole</td>
<td>p-iodobenzoic acid</td>
<td>C</td>
<td>–</td>
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<tr>
<td>9-(p-biphenylyl)-carbazole</td>
<td>4-bromobiphenyl</td>
<td>C, J</td>
<td>10</td>
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<tr>
<td>9-(4'-carbazol-9''-yl-phenyl)-carbazole</td>
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<td>C, J</td>
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<td>9-(4''-N-carbazolyl-biphenyl)-carbazole</td>
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<td>D,I</td>
<td>13</td>
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<td>2-(carbazol-9'yl)-pyridine</td>
<td>2-bromopyridine</td>
<td>D, J</td>
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</tr>
<tr>
<td>2-(carbazol-9'yl)-quinoline</td>
<td>2-chloroquinoline</td>
<td>D</td>
<td>10</td>
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<td>Formula</td>
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<tr>
<td>2-nitro-4-methyl-2'-bromobenzene</td>
<td>C, 244</td>
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<td>23</td>
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<td>C, 244</td>
<td>50</td>
<td>23</td>
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<tr>
<td>9-(4'-bromo-2-carbazol-9'-yl-phenyl)-carbazole</td>
<td>C, 244</td>
<td>78</td>
<td>23</td>
</tr>
<tr>
<td>p-bromiodobenzene</td>
<td>C, 244</td>
<td>-</td>
<td>23</td>
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<tr>
<td>9-(4'-nitrophenyl)-carbazole</td>
<td>C, I</td>
<td>60-65</td>
<td>24</td>
</tr>
<tr>
<td>p-iodo,N,N-dimethylaminophenyl)-carbazole</td>
<td>E,K</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>2,4-dicarboxymethoxy-iodobenzene</td>
<td>C, I</td>
<td>48</td>
<td>26</td>
</tr>
<tr>
<td>1-iodoanthraquinone</td>
<td>F, I</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td><strong>3-Carboxethoxy carbazole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-carboxethoxy-9-(9-nitrophenyl)carbazole</td>
<td>C</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td><strong>2,6-Dicarboxethoxycarbazole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,6-dicarboxethoxy-9-(9-nitrophenyl)carbazole</td>
<td>C</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td><strong>1-Carboxethoxycarbazole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2'-dicarboxylcarbazole</td>
<td>C, I</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>2-Carboxethoxycarbazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,2'-dicarboxylcarbazole</td>
<td>C, I</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td>3-Carboxethoxycarbazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,2'-dicarboxylcarbazole</td>
<td>C, I</td>
<td>34</td>
<td>26</td>
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<table>
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<tr>
<td>1-Nitrocarbazole</td>
</tr>
<tr>
<td>1-nitro-9-(p-tolyl)-carbazole</td>
</tr>
<tr>
<td>1-nitro-9-(p-carbamethoxyphenyl)-carbazole</td>
</tr>
<tr>
<td>1-nitro-9-phenyl-carbazole</td>
</tr>
<tr>
<td>3-Nitrocarbazole</td>
</tr>
<tr>
<td>3-nitro-9-phenyl-carbazole</td>
</tr>
</tbody>
</table>

Pyrazolanthrone

<table>
<thead>
<tr>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-chloro-5,8-dioxo-naphtho[1,2,3-cd] quin[3,2,1,hi] indazole</td>
</tr>
<tr>
<td>N-benzanthryl-pyrazolanthrone</td>
</tr>
<tr>
<td>N,N'-dibenzanthryl-pyrazolanthracenylpyrazole</td>
</tr>
<tr>
<td>2-N-pyrazolanthryl-benzanthrone</td>
</tr>
<tr>
<td>3-R,5,10-dioxobenz[6,7] indazolo[2,3,4-fgh] byrido[3',2',6,7]-naphth[2,1,8-mna]-acridine</td>
</tr>
<tr>
<td>R=N-α-aminoanthraquinonyl or N-α-aminoopyrimidinoanthrone</td>
</tr>
<tr>
<td>5,10-dioxobenz[6,7] indazolo[4,3,2-hij] naphth[1',2',3',1,8]-isoquino[4,5,6-c]-quinoline</td>
</tr>
<tr>
<td>2,10-dipyrazolanthryl-naphthanthrone</td>
</tr>
<tr>
<td>Compound</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>5,4,18-trioxo-pyrazolo[3,4,5-klm]-anthrazone</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>9,18-dioxo-dipyrazolo[5,4,3,2-fgh, 5',4',3',2'-uvw]-anthrazone</td>
</tr>
<tr>
<td><strong>Indazoles</strong></td>
</tr>
<tr>
<td>1-phenylindazole</td>
</tr>
<tr>
<td>1-(p-tolyl)indazole</td>
</tr>
<tr>
<td>1-(p-dimethylaminophenyl)indazole</td>
</tr>
<tr>
<td>1-(a-naphthyl)-indazole</td>
</tr>
<tr>
<td>1-(m-nitrophenyl)-indazole</td>
</tr>
<tr>
<td><strong>6-Nitroindazoles</strong></td>
</tr>
<tr>
<td>1-phenyl, 6-nitroindazole</td>
</tr>
<tr>
<td><strong>Imidazoles</strong></td>
</tr>
<tr>
<td>1-phenylimidazole</td>
</tr>
<tr>
<td>1-(o-methoxyphenyl)-imidazole</td>
</tr>
<tr>
<td>1-(m-methoxyphenyl)-imidazole</td>
</tr>
<tr>
<td>1-(p-methoxyphenyl)-imidazole</td>
</tr>
<tr>
<td>1-(p-bromophenyl)-imidazole</td>
</tr>
<tr>
<td>1-(p-dimethylamino-phenyl)imidazole</td>
</tr>
<tr>
<td>p-(imidazol-1-yl)benzaldehyde</td>
</tr>
<tr>
<td>p-(imidazol-1-yl)acetophenone</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Benzimidazole</th>
<th>Aryl Halide</th>
<th>Catalysts and Solvents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-phenylbenzimidazole bromobenzene</td>
<td>G, I</td>
<td>25, 16</td>
</tr>
<tr>
<td>&quot;</td>
<td>G, I</td>
<td>73, 37</td>
</tr>
<tr>
<td>m-(benzimidazol-1-yl)-m-bromotoluene</td>
<td>G, I</td>
<td>70, 37</td>
</tr>
<tr>
<td>&quot;</td>
<td>p-(benzimidazol-1-yl)-p-bromotoluene</td>
<td>G, I</td>
</tr>
<tr>
<td>1-(p-dimethylamino-phenyl)benzimidazole</td>
<td>p-bromo,N,N-dimethyl aniline</td>
<td>G, I</td>
</tr>
<tr>
<td>&quot;</td>
<td>α-bromonaphthalene</td>
<td>G, I</td>
</tr>
<tr>
<td>1,2-diphenylbenzimidazole</td>
<td>G, I</td>
<td>7, 37</td>
</tr>
</tbody>
</table>

The catalyst and the solvent used: A, cupric bromide; B, copper powder; C, copper bronze; D, copper bronze plus iodine; E, phenyl lithium and cuprous iodide; F, copper acetate; G, cuprous bromide; H, pyridine; I, nitrobenzene; J, light petroleum b.p. 190-210°C; K, isomylether; L, "dichlorobenzene"; M, naphthalene.

The temperature at which the reaction was conducted is given in °C.

The effects of different variables on the Ullmann condensation are discussed below.

THE ARYL HALIDE. It is commonly observed that aryl halides under Ullmann conditions react according to the usual order of reactivity of
the halogens i.e. I > Br > Cl, but no systematic study appears to have been carried out. The literature refers to all three halides, aryl bromides and aryl chlorides being more in common use. While chlorobenzene has seldom been employed for the Ullmann condensations, chloride activated by other groups such as nitro and carboxyl, unsubstituted iodobenzene (18, 19, 28) and bromobenzene (16, 17, 20, 37) gave good yields of the desired products. Where a mixed aryl dihalide is used, the more reactive halogen is substituted. For example, in the arylation of carbazole by p-iodobromobenzene, the product formed was 9-(p-bromophenyl)carbazole and not the corresponding iodophenyl compound (23). Montmollin and Montmollin (14) had earlier obtained 9-(p-chlorophenyl) carbazole by heating a mixture of potassium salt of carbazole and an excess of p-bromochlorobenzene at 210° in a closed vessel; thus the bromo-group was replaced in preference to the chloro-group.

The aryl halides used quite often carry other substituents such as nitro, methyl, nitrile, acetyl, halo, carboxy, phenyl, carbomethoxy, dimethylamino, methoxy or formyl groups. Some of these groups make the chloro-group reactive enough to be substituted by the heterocycle moiety, while in the case of bromo- or iodo-groups these substituents will enhance the reactivity of the already reactive halo-group. However, Dunlop and Tucker (18) found that 3-nitro 4(X)-acetophenones (where X = chloro, bromo or iodo) did not give substituted products when reacted with carbazole under Ullmann conditions.
2-Bromopyridine, 2-chloroquinoline (22), iodoanthraquinone (27) and α-bromonaphthalene (37) have also been employed for the arylations of some five-membered N-heteroaromatics. In most of the cases reported in the literature both activated as well as unactivated haloaryls have been used, and thus the Ullmann condensation affords a good route for the preparation of N-aryl-heteroaromatics.

THE CATALYST. In all the Ullmann condensations carried out so far, copper, in one form or the other, has been applied as the catalyst. Although a number of N-aryl heteroaromatics have been prepared by the condensation of the heterocyclic compound with the aryl halide in the presence of alkalis at elevated temperatures or high pressures in the sealed tubes or in ethanolic solutions with more reactive halides (e.g. 2,4-dinitrohalobenzenes) (13, 14), the majority of heterocyclic compounds arylate under Ullmann conditions and in almost all the cases studied give better yields than the uncatalysed condensations.

Dunlop and Tucker (18) have studied the arylations of carbazole by 4-substituted 2-chloronitrobenzene and by other halobenzenes. These workers found that arylations performed under identical conditions always gave better yields when a copper catalyst was employed. The reaction between carbazole and ethyl, p-iodobenzoate in the presence of a copper catalyst gave 80% yield of the desired product while no condensation was observed in the absence of a catalyst.
Similarly, 9-(2'-nitro,4-chlorophenyl)carbazole was obtained in 35% yield in the condensation of 2,5-dichloronitrobenzene and carbazole in the presence of the catalyst, while the reaction failed when no catalyst was used. The condensation between carbazole and p-chloroiodobenzene gave 17% yield of 9-p-chlorophenylcarbazole without a catalyst and 70% when copper bronze was used.

Most of the early reactions were conducted using copper bronze or copper powder as the catalyst. Gilman and Honeycutt (22) employed copper bronze in the presence of a trace of iodine in the arylations of carbazole. Other catalysts employed are cuprous iodide (25), copper acetate (17, 36) and cuprous bromide (15, 16, 37, 38). Simonov et al. (16, 37, 38) have successfully used cuprous bromide in the N-arylation of a host of heteroaromatics.

THE SOLVENT. Most of the early Ullmann condensations were brought about without the use of a solvent. The reacting components were either heated at elevated temperatures between 170-250° in open vessels (18, 21, 23, 28) or in an autoclave at 180-220° (17). Since it is easier to control the reaction temperature by using a high boiling solvent, solvents like nitrobenzene found their way in these condensations (19, 22, 24, 26, 27, 29, 30, 35, 36) and even at present it is a favourite solvent for these Ullmann condensations (16, 37, 38). The high boiling point, relative inertness under the
experimental conditions, high solubility of the heterocyclic and arylhalide and the easy removal by steam distillation seem to be the factors in favour of this solvent. The side reaction of nitrobenzene with the copper catalyst giving triphenylamine by reduction and arylation as observed in the Ullmann biaryl synthesis (39) has not been reported in the Ullmann condensations of heterocyclics.

Relatively few other solvents have been used in these condensations. These include light petroleum b.p. 190-210°C (20, 22), isocyclic ether (25), dichlorobenzene (30) and naphthalene (35). Martsochka, Pozharskii and Simonov (37) have found nitrobenzene to be a better solvent than other solvents they employed for condensations. In the N-phenylation of benimidazole by bromobenzene in various solvents the highest yield (73%) of N-phenylbenimidazole was obtained in nitrobenzene. The yields of N-phenylbenimidazole using other solvents were found to be: N,N-diethylaniline, 57%; tetralin, 48% and bromobenzene, 21%.

These authors ascribe the high efficiency of nitrobenzene to its relatively high boiling point and considerable polarity.

The aryl halide used in the condensation, if present in excess, could also act as a solvent and perhaps most of the earlier reactions using iodobenzene (28), p-iodotoluene (23), 2-chloroquinoline (22), p-chloroiodobenzene (18) and p-chloronitrobenzene (13), were conducted
under these conditions. The yield of the product, however, is reduced as in the phenylation of benzimidazole by bromobenzene using bromobenzene as the solvent (37). There is only one mention of the use of pyridine as the solvent in the condensation (15).

Dimethylformamide has been found to be an excellent solvent in the Ullmann biaryl synthesis (1b) but so far there is no mention in the literature of the use of this solvent for the Ullmann condensation of heteroaromatics. Also, dimethyl sulphoxide, which is quite an effective solvent for the nucleophilic substitution of activated aromatic halides (40), has not yet found application in the Ullmann condensation.

THE BASE. The most common and effective base in the Ullmann condensations is anhydrous potassium carbonate, but a variety of other bases have also been used. Phenyllithium was employed in the N-arylation of carbazole by p-iodo, N,N-dimethylaniline (25). In the condensation of carbazole with 1-iodoanthraquinone copper acetate performed the dual function of a catalyst and the base (27). In preparations of some benzanthrones potassium or sodium acetate (29, 36) or potassium hydroxide has also been employed (32, 33).
RESULTS AND DISCUSSION

The Ullmann condensations between various five membered N-heteroaromatics and aryl halides were carried out. The heteroaromatics used were all unsubstituted, either the parent or with fused benzene rings, having a free NH. The aryl halides had a function in the ring which helped activate the halogen of the aryl halide and thus facilitated the condensation. A number of new N-substituted heteroaromatics were thus obtained and these are listed in the table (II) below. The individual condensations will be described separately following the table.

Table II: NEW N-ARYLHETEROCAROMATICS OBTAINED IN ULLMANN CONDENSATIONS.

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<td>N</td>
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![Chemical Structure](image)

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<sup>c</sup> m.p. values are approximate.
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<td>5.6</td>
<td>6.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>p-Acetylphenyl</td>
<td>92.8</td>
<td></td>
<td>81.6</td>
<td>5.5</td>
<td>5.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table II (contd.)

<table>
<thead>
<tr>
<th>Compound</th>
<th>mp</th>
<th>Formula</th>
<th>C (Found)</th>
<th>H (Found)</th>
<th>N (Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Pyridyl</td>
<td>59-60</td>
<td>C_{12}H_{10}N_{3}</td>
<td>73.8 (73.8)</td>
<td>4.6 (4.6)</td>
<td>21.5 (21.5)</td>
</tr>
<tr>
<td>β-Pyridyl</td>
<td>107-108</td>
<td>C_{14}H_{10}N_{3}</td>
<td>76.4 (76.7)</td>
<td>4.2 (4.1)</td>
<td>19.2 (19.2)</td>
</tr>
<tr>
<td>γ-Pyridyl</td>
<td>67-68</td>
<td>C_{16}H_{12}N_{2}O</td>
<td>76.7 (76.3)</td>
<td>5.4 (5.1)</td>
<td>10.7 (11.9)</td>
</tr>
<tr>
<td>p-Guanophenyl</td>
<td>134-135</td>
<td>C_{15}H_{12}N_{2}O</td>
<td>75.5 (75.3)</td>
<td>5.2 (5.1)</td>
<td>11.7 (11.9)</td>
</tr>
<tr>
<td>m-Guanophenyl</td>
<td>77-78</td>
<td>C_{15}H_{12}N_{2}O</td>
<td>74.9 (74.3)</td>
<td>5.4 (5.1)</td>
<td>11.8 (11.9)</td>
</tr>
<tr>
<td>p-Acetylphenyl</td>
<td>164-166</td>
<td>C_{18}H_{13}N_{3}</td>
<td>78.8 (79.7)</td>
<td>5.5 (4.8)</td>
<td>15.6 (15.5)</td>
</tr>
</tbody>
</table>
Table II (contd.)

61. γ-Pyridyl $^c, i$  
60.2

151-152  $C_{17}H_{12}N_4$  75.0  4.7  20.6

62. m-Nitrophenyl $^c$  
53.7

132-133  $C_{18}H_{12}N_2O_2$  74.7  4.4  9.2

---

a. b.p. for liquids are underlined.
b. The figures in parentheses refer to the calculated values.
c. Crystallised from chloroform/light petroleum (b.p. 40-60°C).
d. Crystallised from benzene.
e. Crystallised from ethanol.
f. Crystallised from aqueous ethanol.
g. Liquid gives the corresponding acid on hydrolysis.
h. Due to very small amounts elemental analyses were not obtained. The probable structure was assigned on the basis of spectra; see p.40 & 41.
i. Prepared as a reference compound.
j. Liquid gives the picrate m.p. 185-186°C (from ethanol).
k. Small amount of liquid, gave picrate m.p. 212-213°C (from ethanol).
l. This compound was earlier prepared by R. Robinson and S. Thornley (J.Chem.Soc., 2169 (1924)), but no elemental analyses were reported.
Table II (contd.)

m. Liquid.
n. Hydrochloride m.p. 252-254°.

In some cases, such as compounds No. 21 and 57 in Table II, the elemental analyses were not satisfactory due to impure samples. The two compounds mentioned were liquids and were obtained in small quantities and were difficult to purify. The picrates of these liquids, however, gave satisfactory analyses (see experimental section).

ARYLATION BY HALONITROBENZENES.

In addition to the new nitrophenylazoles listed in Table II the following nitrophenylazoles were also obtained from the Ullmann condensation. These nitrophenylazoles were previously prepared by different routes.

TABLE III: N-NITROPHENYLAZOLES.

<table>
<thead>
<tr>
<th>No.</th>
<th>Nitrophenylazole</th>
<th>Yield</th>
<th>m.p.</th>
<th>Lit.m.p.</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(g)</td>
<td>°C</td>
<td>°C</td>
<td></td>
</tr>
<tr>
<td>63.</td>
<td>1-((p-Nitrophenyl)pyrrole</td>
<td>1</td>
<td>185-186</td>
<td>181</td>
<td>41</td>
</tr>
<tr>
<td>64.</td>
<td>1-((o-Nitrophenyl)pyrazole</td>
<td>65.5</td>
<td>85-87</td>
<td>88-89</td>
<td>42</td>
</tr>
</tbody>
</table>
Table III (contd.)

<table>
<thead>
<tr>
<th>Number</th>
<th>Compound</th>
<th>Number</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>1-(m-Nitrophenyl)pyrazole</td>
<td>31.2</td>
<td>74-75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>94-95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>42,43</td>
</tr>
<tr>
<td>66</td>
<td>1-(p-Nitrophenyl)pyrazole</td>
<td>24.3</td>
<td>171-173</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>42</td>
</tr>
<tr>
<td>67</td>
<td>1-(p-Nitrophenyl)imidazole</td>
<td>53.9</td>
<td>210-211</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>68</td>
<td>1-(p-Nitrophenyl)-1,2,4-triazole</td>
<td>68.2</td>
<td>113-114</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>69</td>
<td>1-(m-Nitrophenyl)-1,2,4-triazole</td>
<td>6</td>
<td>146-148</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>70</td>
<td>1-(p-Nitrophenyl)-1,2,4-triazole</td>
<td>33.9</td>
<td>194-196</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>71</td>
<td>1-(p-Nitrophenyl)-benzimidazole</td>
<td>45.3</td>
<td>80-82</td>
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<td></td>
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<td></td>
<td>47</td>
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<tr>
<td>72</td>
<td>1-(m-Nitrophenyl)-benzimidazole</td>
<td>8.1</td>
<td>151-152</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47</td>
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<tr>
<td>73</td>
<td>1-(p-Nitrophenyl)-benzimidazole</td>
<td>27.5</td>
<td>181-183</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>74</td>
<td>9-(p-Nitrophenyl)carbazole</td>
<td>89.7</td>
<td>156-158</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>75</td>
<td>9-(p-Nitrophenyl)carbazole</td>
<td>0.2</td>
<td>211-213</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13</td>
</tr>
</tbody>
</table>

Gilman and Honeycutt (22) have earlier reported failure in the arylation of carbazole by 2-bromopyridine in pyridine as the solvent. Simonov et al. (16, 37) have effected N-phenylation of imidazole,
benzimidazoles and indazoles using cuprous bromide as the catalyst and nitrobenzene as the solvent. In the present investigations no phenyl-1,2,4-triazole was obtained when an attempt was made to phenylate 1,2,4-triazole by bromobenzene with cuprous bromide as the catalyst and nitrobenzene as the solvent. Recently Tomita and his workers have obtained diaryl ethers in good yields when they employed pyridine as the solvent and cupric oxide as the catalyst (9). These conditions were not adequate for the phenylation of 1,2,4-triazole, but good yields were obtained when these reaction conditions were employed for the O-, and p-nitrophenylation of 1,2,4-triazole and then extended for the N-nitrophenylation of other five-membered N-heteroaromatics. Dimethylformamide was also used in the N-(m-nitrophenylation) of some of the azoles.

The attempted N-arylation of pyrrole by o-chloronitrobenzene in two experiments resulted in the formation of tar and most of the o-chloronitrobenzene was recovered unchanged. The N-(p-nitrophenylation) by p-chloronitrobenzene resulted in only 1% yield of 1-(p-nitrophenyl)pyrrole. No attempt was made for the N-(m-nitrophenylation).

When pyrazole was condensed with o-, and p-chloronitrobenzene in pyridine corresponding 1-nitrophenylpyrazoles were obtained.
Two condensations of pyrazole with o-chloronitrobenzene under identical conditions gave 65.5 and 61.9% yield of 1-(o-nitrophenyl)pyrazole. 1-(m-Nitrophenyl)pyrazole was obtained in 31.2% yield in the condensation of m-chloronitrobenzene with pyrazole in dimethylformamide.

1-o- and (p-nitrophenyl)imidazoles were obtained in the condensations of the o- and p-chloronitrobenzene with imidazole in pyridine. However, 1-(m-nitrophenyl)imidazole was obtained on condensing m-chloronitrobenzene with imidazole in dimethylformamide. All three isomeric 1-(nitrophenyl)imidazoles were degraded to the corresponding nitroanilines when treated with dimethyl sulphate and sodium hydroxide (44).

Similarly in the N-nitrophenylation of 1,2,4-triazole o- and p-chloronitrobenzene in pyridine smoothly gave 1-o- and (p-nitrophenyl)-1,2,4-triazole respectively. No 1-(m-nitrophenyl)-1,2,4-triazole could be obtained on attempted condensation of m-chloronitrobenzene and 1,2,4-triazole in pyridine or quinoline as a solvent with cupric oxide or cupric chloride as the catalyst. In these attempted m-nitrophenylation bright coloured products were observed to be formed which were perhaps copper complexes of 1,2,4-triazole. However, 1-(m-nitrophenyl)-1,2,4-triazole was obtained when the condensation was effected in dimethylformamide. No 4-(nitrophenyl)-1,2,4-triazoles were obtained in these nitrophenylation.
Indole was easily arylated by \( \text{p-chloronitrobenzene} \) giving 1-\( \text{e} \)- and 1-(\( \text{p-nitrophenyl} \))indole respectively. The 1-\( \text{e} \)-nitrophenylation by \( \text{m-chloronitrobenzene} \) in either pyridine or dimethylformamide failed, but when \( \text{m-bromonitrobenzene} \) was replaced for \( \text{m-chloronitrobenzene} \) a high yield (79.6\%) of 1-(\( \text{m-nitrophenyl} \))-indole resulted on conducting the experiment in pyridine with cupric oxide catalyst.

1-\( \text{e} \)- and 1-(\( \text{p-nitrophenyl} \))benzimidazoles were similarly obtained in the condensation of benzimidazole with \( \text{e} \)- and \( \text{p-chloronitrobenzene} \). The condensation of benzimidazole with \( \text{m-chloronitrobenzene} \) in either pyridine or dimethylformamide were unsuccessful, while \( \text{m-bromonitrobenzene} \) condensation with benzimidazole in pyridine gave 8.1\% yield of 1-(\( \text{m-nitrophenyl} \))-benzimidazole.

Carbazole behaved similarly to the indole and benzimidazole and gave 9-\( \text{e} \)- and (\( \text{p-nitrophenyl} \))carbazole in the usual condensation reaction, though 9-\( \text{p-nitrophenylation} \) gave only 0.2\% yield. 9-\( \text{m-Nitrophenylation} \) using \( \text{m-chloronitrobenzene} \) in dimethylformamide failed, but when \( \text{m-bromonitrobenzene} \) condensation with carbazole was carried out in pyridine 9-(\( \text{m-nitrophenyl} \))carbazole resulted in 53.7\% yield.
ARYLATION BY HALOPYRIDINES.

In these condensations 2- and 3-bromopyridines and 4-chloropyridine hydrochloride were employed to effect N-arylations. Almost all the N-pyridylazoles obtained in these condensations were new compounds and are listed in Table II above.

When Ullmann condensations between pyrazole and 2- and 3-bromopyridine and 4-chloropyridine hydrochloride were effected, the corresponding N-α-, β-, and γ-pyridy1pyrazoles were obtained. The three isomeric pyridylpyrazoles were identical with those prepared by the condensation of 1:1:3:3-tetramethoxypropane and hydrazino-pyridines. The yields of the three isomeric N-pyridylpyrazoles by these condensations were: 2-(pyrazol-1'-yl)pyridine, 44.9; 3-(pyrazol-1'-yl)pyridine, 36.4 and 4-(pyrazol-1'-yl)pyridine 30.5%.

Imidazole gave the three N-pyridylimidazoles under the usual Ullmann condensations in the yields between 30-50%.

The arylation of 1,2,4-triazole by the halopyridines gave both 1- and the 4-(pyridyl)-1,2,4-triazoles and are listed in Table IV below. The two pyridyltriazoles 2-(1',2',4'-triazol-4'-yl)pyridine and 3-(1',2',4'-triazol-4'-yl)pyridine were earlier prepared by Wiley and Hart (48) by a different method.
Table IV: ARYLATION OF 1,2,4-TRIAZOLE BY HALOPYRIDINES.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Bromopyridine</td>
<td>23</td>
<td></td>
<td></td>
<td>28.5</td>
<td>92-93</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>76</td>
<td></td>
<td></td>
<td>2.7</td>
<td>167-168</td>
<td>169</td>
<td>48</td>
</tr>
<tr>
<td>3-Bromopyridine</td>
<td>24</td>
<td></td>
<td></td>
<td>11.1</td>
<td>82-83</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td></td>
<td></td>
<td>0.4</td>
<td>162</td>
<td>162</td>
<td>48</td>
</tr>
<tr>
<td>4-Chloropyridine Hydrochloride</td>
<td>25</td>
<td></td>
<td></td>
<td>5.7</td>
<td>120-120.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td></td>
<td></td>
<td>2.1</td>
<td>108-110</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
4-(1',2',4'-Triazol-4'-yl)pyridine (compound No. 35) was also prepared in 5.6% yield by the condensation of 4-aminopyridine and N,N'-diformylhydrazine using Wiley and Hart's method (48). Although 2- and 3-(indol-1'-yl)pyridines were obtained in 79.1 and 57.4% yields respectively in these arylations under usual Ullmann condensations, the arylation of indole by 4-chloropyridine hydrochloride proved to be difficult. The following reaction conditions gave either unreacted indole or intractable tars: (a) normal Ullmann condensation conditions with a reflux period of 20.5 hrs.; (b) usual conditions with a reflux period of 4 hrs.; and (c) liberation of 4-chloropyridine prior to condensation and carrying the condensation under reduced pressure (aspirator vacuum) on a water bath for 20 hrs. A very small amount (2.6%) of 4-(indol-1'-yl)pyridine (compound No. 41) was obtained when condensation was performed in dimethylformamide.

Benzimidazole gave the three isomeric N-(benzimidazol-1'-yl)-pyridines in good yields. 4-(Benzimidazol-1'-yl)pyridine (compound No. 53) was also prepared in 63.8% yield using Robinson and Thornley's method (49).

Gilman and Honeycutt (22) had earlier obtained 2-(carbazol-9'-yl)pyridine when they performed the condensation in
light petroleum (b.p. 190-210°) using copper bronze as the catalyst plus iodine. In the present investigations this 2-(carbazol-9'-yl)-pyridine has been obtained in 59.3% yield.

ARYLATION BY HALOBENZONITRILES.

The N-cyanophenylations of various azoles were performed using 2-chloro, 3- and 4-bromobenzonitriles. All the N-azolylbenzonitriles obtained from the Ullmann condensations are new compounds and are listed in Table II.

The Ullmann condensation of pyrazole and 2-chlorobenzonitrile gave 6.2% yield of 2-(pyrazol-1'-yl)benzonitrile, a liquid which was characterised by hydrolysis in polyphosphoric acid to the corresponding acid: o-(pyrazol-1-yl)benzoic acid. From the same condensation 3.3% yield of o-(pyrazol-1-yl)benzoic acid was also obtained. Condensations with 3-, and 4-bromobenzonitriles gave the corresponding pyrazolylbenzonitriles in good yields.

Imidazole gave 2-(imidazol-1'-yl)benzonitrile on condensation with 2-chlorobenzonitrile. 3-Bromobenzonitrile on condensation with imidazole afforded the corresponding 3-(imidazol-1'-yl)benzonitrile together with a small amount of p-(imidazol-1-yl)benzoic acid. 4-Bromobenzonitrile and imidazole gave 4-(imidazol-1'-yl)benzonitrile in
A yield of 73\% in addition to a small amount of the corresponding p-(imidazol-1-yl)benzoic acid.

1,2,4-Triazole on condensation with 2-chlorobenzonitrile gave 2-(1',2',4'-triazol-1'-yl)benzonitrile and with 3-chlorobenzonitrile 3-(1',2',4'-triazol-1'-yl)benzonitrile and a small amount of m-(1,2,4-triazol-1-yl)benzoic acid were obtained. The Ullmann condensation of 1,2,4-triazole with 4-bromobenzonitrile gave 4-(1',2',4'-triazol-1'-yl)benzonitrile in 11.5\% yield together with p-(1,2,4-triazol-1-yl)benzamide (3.8\%) and a small amount of p-(1,2,4-triazol-1-yl)benzoic acid (50). 2-(Indol-1'-yl)benzonitrile was obtained in the Ullmann condensation in a very small yield (3.6\%), while 3-(indol-1'-yl)benzonitrile was obtained in 55.9\% yield, together with 6.6\% yield of m-(indol-1-yl)benzamide. The Ullmann condensation of 4-bromo-benzonitrile gave 4-(indol-1'-yl)benzonitrile in 77\% yield and a very small amount of impure p-(indol-1-yl)benzoic acid.

The N-cyanophenylation of benzimidazoles by halobenzonitriles gave the expected (benzimidazol-1'-yl)benzonitriles in yields ranging from 12.2\% (2-(benzimidazol-1'-yl)benzonitrile) to 41.6\% (4-(benzimidazol-1'-yl)benzonitrile).
ARYLATION BY BROMOACETOPHENONES.

N-Acetylphenylazoles were obtained in the condensations of various N-heteroaromatics by \( \sigma \), \( \pi \), and \( \rho \)-bromoacetophenones and these are listed in Table II. Some of the derivatives of these acetophenones were prepared and are described in the experimental section.

When pyrazole was condensed with the three isomeric \( \sigma \), \( \pi \), and \( \rho \)-bromoacetophenones, corresponding \( \sigma \), \( \pi \) and \( \rho \)-(pyrazol-1-yl)-acetophenones were obtained in yields of \( > 50 \% \).

From the condensation of imidazole with \( \sigma \)-bromoacetophenone, after refluxing for 48 hrs., a compound \( C_{11}H_{10}N_{2}O \) m.p. 182-189\(^0\) in 65\% yield was obtained which gave a negative iodoform test and lacked a \( \gamma_{C=O} \) in its infrared spectrum. When the experiment was repeated at a reflux period of 7 hrs. \( \sigma \)-(imidazol-1-yl)acetophenone was obtained in 33.4\% yield together with the compound m.p. 182-183\(^0\) in 47.7\% yield. The \( \pi \) and \( \rho \)-(imidazol-1-yl)acetophenones were obtained in the condensation of imidazole and \( \pi \) and \( \rho \)-bromoacetophenones in 68.2 and 32.1\% yield respectively. Sitkina and Simonov (38) had earlier obtained \( \rho \)-(imidazol-1-yl)acetophenone in 65\% yield by effecting the condensation in nitrobenzene with cuprous bromide catalyst.

All the three isomeric imidazolylacetophenones were degraded to the corresponding aminoaetophenones, when treated with dimethylsulphate and sodium hydroxide.

In the condensation of \( \sigma \)-bromoacetophenone and 1,2,4-triazole, \( \sigma \)-(1,2,4-triazol-1-yl)acetophenone was obtained in 36.9\% yield together with
a compound, \( \text{C}_{10}\text{H}_9\text{N}_2\text{O} \), m.p. 158-159\(^\circ\) in 23.3% yield. This compound lacked \( \text{C}=\text{O} \) in infrared spectrum and gave a negative iodoform test. The condensation of \( \text{m-} \) and \( \text{p-} \) bromoacetophenones gave \( \text{m-} \) and \( \text{p-} \)(1,2,4-triazol-1-yl)acetophenones in 10.6 and 5.1% yield respectively and considerable amounts of \( \text{m-} \) and \( \text{p-} \) bromoacetophenones were recovered unchanged from these experiments.

The Ullmann condensations of indole with \( \text{o-} \), \( \text{m-} \) and \( \text{p-} \) bromoacetophenones gave \( \text{o-} \), \( \text{m-} \) and \( \text{p-} \)(indol-1-yl)acetophenones in yields of 74.0, 60.2 and 92.8% respectively.

Benzimidazole was condensed with \( \text{o-} \) bromoacetophenone giving a compound, \( \text{C}_{15}\text{H}_{12}\text{N}_2\text{O} \), m.p. 223-224\(^\circ\) in 83.1% yield when the reflux time was 46 hrs. Performing the condensation at a reflux period of 3 hrs. gave \( \text{o-} \)(benzimidazol-1-yl)acetophenone in 46.0% yield accompanied by a very small amount of compound m.p. 223-224\(^\circ\); some \( \text{o-} \) bromoacetophenone (37.3%) was also recovered unchanged. The condensation of benzimidazole with \( \text{m-} \) and \( \text{p-} \) bromoacetophenone afforded the expected \( \text{m-} \) and \( \text{p-} \)(benzimidazol-1-yl)-acetophenones.

The analytical results for most of the azolylacetophenone semi-carbazones were satisfactory. However, some of the semi-carbazones of azolylacetophenones (e.g. compounds \( \text{7,8,9,33,48} \) and \( \text{49} \)) gave low values for nitrogen. Compounds \( \text{6} \) and \( \text{48} \) had carbon and hydrogen analyses within the range of 0.1-0.4%. The discrepancies in analytical figures suggest the loss of one nitrogen from most of these compounds. Low figures for nitrogen analyses could also be attributed to either impure analytical samples or
the inaccuracies of analyses. Unfortunately it was not possible to repurify or repeat analyses performed on these samples. Other possibilities of loss of nitrogen by hydrolysis or by some rearrangement taking place during semicarbazone formation cannot be ruled out at this stage.

ARYLATION BY HALOALCOHOLS.

In two exploratory experiments condensation of pyrazole with γ-chlorobenzoic acid and indole with γ-iodobenzoic acid was effected. Pyrazole gave 26.9% yield of γ-(pyrazol-1-yl)benzoic acid accompanied by 20.1% yield of 1-phenylpyrazole. γ-(Indol-1-yl)benzoic acid was obtained from the condensation of indole and γ-iodobenzoic acid in 30% yield.

INFRARED SPECTRA.

The characterisation of various N-arylanilines was based on comparison with the known compounds where these have already been reported in the literature. The three isomeric N-nitrophenyl-imidazoles were degraded to the corresponding nitroanilines and the N-acetylphenyl-imidazoles to the corresponding aminoacetophenones. All the new compounds listed in Table II gave satisfactory elemental analyses. The infrared spectra of all the compounds were recorded and the characteristic N-H peak of the starting azoles was found to be absent and the various peaks characteristic of the groups introduced by N-arylation appeared in the spectra. The position of infrared absorption bands due to various groups in the compounds obtained from the Ullmann condensation have been grouped in the various tables below.
The aromatic nitro group has two identical N-O bonds which vibrate asymmetrically causing strong absorption at 1500-1560 cm\(^{-1}\) and symmetrically causing somewhat weaker absorption at 1300-1400 cm\(^{-1}\). All the nitrophenylazoles, isolated during the present work displayed strong bands at these N-O stretching frequencies. Strong bands in the region 650-1000 cm\(^{-1}\) attributable to the C-H deformation modes of the substituted phenyl groups (51) were also observed. A strong band near 740 cm\(^{-1}\) observed in the infrared spectra of most of the nitrophenylazoles could be attributed to C-N stretching of the nitroaromatics (82f).

Table V lists the strong infrared absorption bands of the various nitrophenylazoles obtained in the Ullmann condensation.

**Table V: INFRARED ABSORPTION BANDS OF NITROPHENYLAZOLES.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Infrared absorption regions (cm(^{-1}))</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(\gamma)N-O asym.</td>
</tr>
<tr>
<td></td>
<td>(1500-1560)</td>
</tr>
<tr>
<td>1-((o-Nitrophenyl)pyrazole(^a))</td>
<td>1545</td>
</tr>
<tr>
<td>1-((m-Nitrophenyl)pyrazole(^a))</td>
<td>1535</td>
</tr>
<tr>
<td>1-((p-Nitrophenyl)pyrazole(^a))</td>
<td>1527</td>
</tr>
<tr>
<td>1-((o-Nitrophenyl)imidazole)</td>
<td>1508</td>
</tr>
</tbody>
</table>
Table V (contd.)

<table>
<thead>
<tr>
<th>Compound</th>
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<th>Shoulder</th>
<th>Shoulder</th>
<th>Shoulder</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(m-Nitrophenyl)imidazole</td>
<td>1525</td>
<td>1324, 1376</td>
<td>650, 734, 816</td>
<td></td>
</tr>
<tr>
<td>1-(p-Nitrophenyl)imidazole</td>
<td>1501, 1525</td>
<td>1358</td>
<td>720, 750, 855</td>
<td></td>
</tr>
<tr>
<td>1-(o-Nitrophenyl)-1,2,4-triazole</td>
<td>1510</td>
<td>1361</td>
<td>749, 784, 852, 953, 989</td>
<td></td>
</tr>
<tr>
<td>1-(m-Nitrophenyl)-1,2,4-triazole</td>
<td>1510</td>
<td>1360</td>
<td>662, 730, 804, 872, 882, 955, 988</td>
<td></td>
</tr>
<tr>
<td>1-(p-Nitrophenyl)-1,2,4-triazole</td>
<td>1506</td>
<td>1336</td>
<td>748, 855, 975</td>
<td></td>
</tr>
<tr>
<td>4-(o-Nitrophenyl)-1,2,4-triazole</td>
<td>1518</td>
<td>1348</td>
<td>735, 782, 842, 992</td>
<td></td>
</tr>
<tr>
<td>4-(m-Nitrophenyl)-1,2,4-triazole</td>
<td>1515</td>
<td>1318, 1345</td>
<td>748, 850</td>
<td></td>
</tr>
<tr>
<td>4-(p-Nitrophenyl)-1,2,4-triazole</td>
<td>1515</td>
<td>1345</td>
<td>750, 855</td>
<td></td>
</tr>
<tr>
<td>1-(o-Nitrophenyl)indole</td>
<td>1524</td>
<td>1363</td>
<td>744, 774, 853</td>
<td></td>
</tr>
<tr>
<td>1-(m-Nitrophenyl)indole</td>
<td>1520</td>
<td>1345</td>
<td>670, 720, 738, 760, 770, 860, 880</td>
<td></td>
</tr>
<tr>
<td>1-(o-Nitrophenyl)indole</td>
<td>1503</td>
<td>1333</td>
<td>736, 856</td>
<td></td>
</tr>
<tr>
<td>1-(o-Nitrophenyl)benzimidazole</td>
<td>1527</td>
<td>1353</td>
<td>746, 767, 793, 857, 892</td>
<td></td>
</tr>
<tr>
<td>1-(m-Nitrophenyl)benzimidazole</td>
<td>1525</td>
<td>1350</td>
<td>740, 750, 762</td>
<td></td>
</tr>
<tr>
<td>1-(p-Nitrophenyl)benzimidazole</td>
<td>1501</td>
<td>1350</td>
<td>730, 856, 869</td>
<td></td>
</tr>
<tr>
<td>9-(o-Nitrophenyl)carbazole</td>
<td>1520</td>
<td>1357</td>
<td>726, 752, 782, 850</td>
<td></td>
</tr>
<tr>
<td>9-(m-Nitrophenyl)carbazole</td>
<td>1520</td>
<td>1345</td>
<td>678, 718, 740</td>
<td></td>
</tr>
<tr>
<td>9-(p-Nitrophenyl)carbazole</td>
<td>1500, 1516</td>
<td>1333, 1351</td>
<td>690, 720, 743, 845, 857, 919</td>
<td></td>
</tr>
<tr>
<td>9-(p-Nitrophenyl)pyrrole</td>
<td>1500</td>
<td>1312</td>
<td>745, 850, 921</td>
<td></td>
</tr>
<tr>
<td>3-Methyl-1-(p-nitrophenyl)-indazole</td>
<td>1492, 1505</td>
<td>1320, 1335</td>
<td>744, 848</td>
<td></td>
</tr>
<tr>
<td>3-Methyl-1-(p-nitrophenyl)-indazole</td>
<td>1530 (sh.)</td>
<td>(sh.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pyridines and substituted pyridines display strong bands in the general region of 1415-1610 cm\(^{-1}\) due to pyridine ring C=C and C=N stretching vibrations. In the region of C-H out of plane bending vibration bands typical of the number of adjacent hydrogen atoms, occur in substituted pyridines (82g).

The position of high intensity bands, occurring in the various pyridylazoles in the regions 1450-1600 cm\(^{-1}\) and 650-1000 cm\(^{-1}\) are listed in Table VI below.

Table VI: INFRARED ABSORPTION BANDS OF PYRIDYLAZOLES.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Infrared absorption regions (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C=C and C=N stretching</td>
</tr>
<tr>
<td></td>
<td>(1450-1600)</td>
</tr>
<tr>
<td>2-(Pyrazol-1'-yl)pyridine(^a)</td>
<td>1458, 1472, 1521, 1580, 1594</td>
</tr>
<tr>
<td>3-(Pyrazol-1'-yl)pyridine(^a)</td>
<td>1458, 1480, 1492, 1520, 1588</td>
</tr>
<tr>
<td>4-(Pyrazol-1'-yl)pyridine</td>
<td>1575, 1596</td>
</tr>
</tbody>
</table>
Table VI (contd.)

<table>
<thead>
<tr>
<th>Compound Description</th>
<th>ν (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(Imidazol-1'-yl)pyridine</td>
<td>1430, 1595</td>
</tr>
<tr>
<td>3-(Imidazol-1'-yl)pyridine</td>
<td>1490, 1578</td>
</tr>
<tr>
<td>4-(Imidazol-1'-yl)pyridine</td>
<td>1505, 1570, 1588</td>
</tr>
<tr>
<td>2-(1',2',4'-Triazol-1'-yl)-pyridine</td>
<td>1452, 1470, 1500, 1595</td>
</tr>
<tr>
<td>3-(1',2',4'-Triazol-1'-yl)-pyridine</td>
<td>1510, 1578, 1582</td>
</tr>
<tr>
<td>4-(1',2',4'-Triazol-1'-yl)-pyridine</td>
<td>1510, 1590</td>
</tr>
<tr>
<td>2-(1',2',4'-Triazol-4'-yl)-pyridine</td>
<td>1462, 1480, 1500, 1510</td>
</tr>
<tr>
<td>3-(1',2',4'-Triazol-4'-yl)-pyridine</td>
<td>1500, 1522, 1580</td>
</tr>
<tr>
<td>4-(1',2',4'-Triazol-4'-yl)-pyridine</td>
<td>1512, 1590</td>
</tr>
<tr>
<td>2-(Indol-1'-yl)pyridine</td>
<td>1460-70, 1520, 1584</td>
</tr>
<tr>
<td>3-(Indol-1'-yl)pyridine</td>
<td>1450, 1480, 1510, 1580</td>
</tr>
<tr>
<td>4-(Indol-1'-yl)pyridine</td>
<td>1468, 1500, 1514, 1558, 1590</td>
</tr>
<tr>
<td>2-(Benzimidazol-1'-yl)-pyridine</td>
<td>1462, 1470 (sh.), 1482 (sh.), 1578, 1588</td>
</tr>
<tr>
<td>3-(Benzimidazol-1'-yl)-pyridine</td>
<td>1450, 1490, 1580</td>
</tr>
<tr>
<td>4-(Benzimidazol-1'-yl)-pyridine</td>
<td>1490, 1500 (sh.), 1582</td>
</tr>
<tr>
<td>4-(2'-Phenyl, benzimidazol-1'-yl)pyridine</td>
<td>1575</td>
</tr>
</tbody>
</table>
Benzonitriles are characterised by the C=N stretching frequency which occurs at 2220-2240 cm\(^{-1}\) (82h). All the azolylbenzonitriles listed in Table VII displayed bands in this region together with the bands, in the region 650-1000 cm\(^{-1}\), characteristic of substitution pattern on the benzene ring.

Table VII: INFRARED ABSORPTION BANDS OF AZOLYLBENZONITRILES.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Infrared absorption regions (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C=N stretching (2220-2240)</td>
</tr>
<tr>
<td>2-(Pyrazol-1'-yl)benzonitrile(^a)</td>
<td>2228</td>
</tr>
<tr>
<td>3-(Pyrazol-1'-yl)benzonitrile</td>
<td>2225</td>
</tr>
<tr>
<td>4-(Pyrazol-1'-yl)benzonitrile</td>
<td>2225</td>
</tr>
</tbody>
</table>

\(^a\) Liquid film.
Table VII (contd.)

<table>
<thead>
<tr>
<th>Compound</th>
<th>λ (cm⁻¹)</th>
<th>ν (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(Imidazol-1'-yl)benzonitrile</td>
<td>2230</td>
<td>728, 732, 772, 820</td>
</tr>
<tr>
<td>3-(Imidazol-1'-yl)benzonitrile</td>
<td>2232</td>
<td>670, 754, 790, 884</td>
</tr>
<tr>
<td>4-(Imidazol-1'-yl)benzonitrile</td>
<td>2225</td>
<td>722, 810 (sh.), 828</td>
</tr>
<tr>
<td>2-(1',2',4'-Triazol-1'-yl)-benzonitrile</td>
<td>2235</td>
<td>668, 762, 868, 884, 958, 980</td>
</tr>
<tr>
<td>3-(1',2',4'-Triazol-1'-yl)-benzonitrile</td>
<td>2235</td>
<td>670, 802, 872, 958</td>
</tr>
<tr>
<td>4-(1',2',4'-Triazol-1'-yl)-benzonitrile</td>
<td>2234</td>
<td>660, 835 &amp; 844 (doublet), 872, 952, 978</td>
</tr>
<tr>
<td>2-(Indol-1'-yl)benzonitrile</td>
<td>2232</td>
<td>720, 735, 760, 770</td>
</tr>
<tr>
<td>3-(Indol-1'-yl)benzonitrile</td>
<td>2232</td>
<td>680, 718, 736, 758, 794, 890</td>
</tr>
<tr>
<td>4-(Indol-1'-yl)benzonitrile</td>
<td>224 &amp; 2235</td>
<td>728, 748, 770, 838</td>
</tr>
<tr>
<td>2-(Benzimidazol-1'-yl)-benzonitrile</td>
<td>2222</td>
<td>735, 758, 785</td>
</tr>
<tr>
<td>3-(Benzimidazol-1'-yl)-benzonitrile</td>
<td>2232</td>
<td>678, 735, 758, 762, 792, 882</td>
</tr>
<tr>
<td>4-(Benzimidazol-1'-yl)-benzonitrile</td>
<td>2232</td>
<td>740, 760, 855</td>
</tr>
</tbody>
</table>

* Liquid film.

The azolylacetophenones obtained from the Ullmann condensations had strong bands in the region of 1670-1700 cm⁻¹ which could be ascribed
to the C=O stretching of an aralkyl ketone. These bands in conjunction with strong bands in the region 650-1000 cm\(^{-1}\) for various azolylacetophenones are listed in the following table (VIII).

Table VIII: INFRARED ABSORPTION BANDS OF AZOLYLACETOPHENONES.

<table>
<thead>
<tr>
<th>Compound</th>
<th>C=O stretching (1670-1700)</th>
<th>C-H out of plane bending (650-1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(Pyrazol-1'-yl)-acetophenone</td>
<td>1695</td>
<td>760,938</td>
</tr>
<tr>
<td>3-(Pyrazol-1'-yl)-acetophenone</td>
<td>1672</td>
<td>680,765,790,915,940</td>
</tr>
<tr>
<td>4-(Pyrazol-1'-yl)-acetophenone</td>
<td>1672</td>
<td>760,828,838,934</td>
</tr>
<tr>
<td>2-(Imidazol-1'-yl)-acetophenone</td>
<td>1690</td>
<td>652,764</td>
</tr>
<tr>
<td>3-(Imidazol-1'-yl)-acetophenone</td>
<td>1674</td>
<td>650,680,758,790,908 &amp; 914 (doublet),990</td>
</tr>
<tr>
<td>4-(Imidazol-1'-yl)-acetophenone</td>
<td>1670</td>
<td>650,740,820,900,955</td>
</tr>
<tr>
<td>2-(1',2',4'-Triazol-1'-yl)-acetophenone</td>
<td>1689</td>
<td>672,765,879,950,982</td>
</tr>
<tr>
<td>3-(1',2',4'-Triazol-1'-yl)-acetophenone</td>
<td>1686</td>
<td>662,952,988</td>
</tr>
<tr>
<td>4-(1',2',4'-Triazol-1'-yl)-acetophenone</td>
<td>1670</td>
<td>664,832,955,980</td>
</tr>
</tbody>
</table>
Table VIII (contd.)

<table>
<thead>
<tr>
<th>Compound</th>
<th>ν (cm⁻¹)</th>
<th>738,756,775</th>
<th>685,712,735,758,790</th>
<th>728,740,760,840</th>
<th>740,760,782</th>
<th>675,742,762,790</th>
<th>748,752,830</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(Indol-1'-yl)acetophenone a</td>
<td>1682</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-(Indol-1'-yl)acetophenone a</td>
<td>1682</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-(Indol-1'-yl)acetophenone</td>
<td>1670</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2-(Benzimidazol-1'-yl)-</td>
<td>1695</td>
<td></td>
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<tr>
<td>acetophenone</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3-(Benzimidazol-1'-yl)-</td>
<td>1675</td>
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<tr>
<td>acetophenone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-(Benzimidazol-1'-yl)-</td>
<td>1680</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>acetophenone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ a \text{ liquid film.} \]

The azolybenzamides and benzoic acids obtained from some of the Ullmann condensations possessed strong bands characteristic of these functional groups and are listed in Tables IX and X below.

Table IX: AZOYL BENZAMIDES

<table>
<thead>
<tr>
<th>Compound</th>
<th>Infrared absorption regions (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N-H stretching) Amide I Amide II C-H out of</td>
</tr>
<tr>
<td></td>
<td>(C=O (N-H) plane bending) bending)</td>
</tr>
<tr>
<td>2-(Pyrazol-1-yl)-benzamide</td>
<td>3400,3180(br.) 1648 1595,1615 748 &amp; 752</td>
</tr>
<tr>
<td></td>
<td>(doublet), 932</td>
</tr>
</tbody>
</table>
Table IX (contd.)

<table>
<thead>
<tr>
<th>Compound</th>
<th>ν(O-H)</th>
<th>ν(C=O)</th>
<th>ν(C-H out of plane)</th>
<th>ν(C=O) (broad)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2,4-Triazol-1-yl-&lt;br&gt;bzamide</td>
<td>3360 (br.), 3170</td>
<td>1664</td>
<td>1605</td>
<td>778, 850, 952, 980</td>
</tr>
<tr>
<td>m-Indol-1-yl-&lt;br&gt;bzamide</td>
<td>3395, 3180</td>
<td>1648</td>
<td>1600, 1610</td>
<td>715, 726, 742, 892 (m)</td>
</tr>
</tbody>
</table>

Table X: AZOLYLBENZOIC ACIDS.

<table>
<thead>
<tr>
<th>Compound</th>
<th>ν(O-H)</th>
<th>ν(C=O)</th>
<th>ν(C=O) (broad)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazol-1-yl-&lt;br&gt;bzonic acid</td>
<td>2440-2632 (w)</td>
<td>1700</td>
<td>689, 750, 950 (broad band)</td>
</tr>
<tr>
<td>Imidazol-1-yl-&lt;br&gt;bzonic acid</td>
<td>2558, 2670 (w)</td>
<td>1685</td>
<td>662, 698, 748, 940 (broad)</td>
</tr>
<tr>
<td>Imidazol-1-yl-&lt;br&gt;bzonic acid</td>
<td>2670, 2725 (w)</td>
<td>1670 (br.)</td>
<td>752, 850, 928 (broad)</td>
</tr>
<tr>
<td>1,2,4-Triazol-1-yl-&lt;br&gt;bzonic acid</td>
<td>2620, 2675 (w)</td>
<td>1695</td>
<td>662, 698, 750, 975 (broad)</td>
</tr>
<tr>
<td>1,2,4-Triazol-1-yl-&lt;br&gt;bzonic acid</td>
<td>2620, 2730 (w)</td>
<td>1670 (br.)</td>
<td>664, 768, 850, 958, 970 (broad)</td>
</tr>
<tr>
<td>Indol-1-yl-&lt;br&gt;bzonic acid</td>
<td>2530, 2570, 2650 (w)</td>
<td>1680</td>
<td>700, 712, 740, 750, 774, 795, 930 (broad)</td>
</tr>
<tr>
<td>Indol-1-yl-&lt;br&gt;bzonic acid</td>
<td>2550, 2670, 2730 (w)</td>
<td>1675</td>
<td>718, 752, 850, 930 (m) (m) (broad)</td>
</tr>
</tbody>
</table>

Infrared absorption regions (cm⁻¹)
As can be seen from the results presented in Tables II, III and IV, the Ullmann condensation is a satisfactory reaction for the preparation of most of the five-membered N-aryl heteroaromatics. Except in the case of condensation of o-bromoacetophenone with imidazole, 1,2,4-triazole and with benzimidazole no abnormal substitutions, such as the von Richter reaction (52), has taken place in these condensations. The orientation of the substituted azoles are compatible with the infrared spectra. In some cases the compounds obtained from the present condensation were found to be identical in m.p., mixed m.p. and the spectra with the compounds already described in the literature (for example 1-nitrophenyl-pyrazoles and 1-nitrophenyl-1,2,4-triazoles). A few compounds were also prepared using unambiguous routes (such as 1-pyridylpyrazoles from pyridylhydrazines and 1,1,3,3-tetramethoxypropane) and compared with the products isolated from the Ullmann condensation, and found to be identical in all respects. Bacon et al. (55) report the formation of biaryls in the reaction of aryl halides with cuprous oxide catalyst in pyridine. In the present work no biaryls were isolated from any of the reactions studied.

**MECHANISM**

The Ullmann condensation of the five-membered N-heteroaromatics, being a copper catalysed reaction, falls in the same class as the Ullmann biaryl and diarylethers synthesis. This condensation
of the heteroaromatics with haloarenes in the presence of a catalyst is essentially a nucleophilic substitution at an aromatic carbon atom by the nitrogen of the heteroaromatic ring and as such can be regarded as an extension of nucleophilic substitution of haloaryls by amines. The aromatic nucleophilic substitutions have been described in a review by Bunnett and Zahler (53). The clear mechanism for these copper catalysed nucleophilic substitutions is obscure. However, it has been proposed that the catalysis involves the joint association of the aryl halide and the nucleophile with the surface of cuprous oxide (or cupric oxide) or other species employed (54). Bunnett and Zahler propose the following scheme for Ullmann condensations:

$$\text{C}u\text{Cu}^+$$

Representation of the copper compound as $\text{Cu}^+$ and of the nucleophilic reagent ($Y$) as an anion are for the purpose of convenience only. This mechanism assigns to the copper catalyst the role of
increasing the replaceability of the halogen atom by converting it to an onium-compound. This is similar to increasing the replaceability of an amino group by quaternisation.

The results of the present work are in agreement with the nucleophilic substitution mechanism. The unactivated haloaryls (e.g. bromobenzene, iodobenzene and \( p \)-bromoanisole) failed to arylate 1,2,4-triazole under the Ullmann conditions. Similar difficulty was met in the arylation of the azoles by \( m \)-nitrochlorobenzene in pyridine solvent. In all the cases \( o \) and \( p \)-nitrochlorobenzenes gave good yields of the products, \( o \)-nitrochlorobenzene giving higher yield than the \( p \)-isomer. The copper assisted reactions are frequently very variable in rate, and are sometimes completely inhibited, depending e.g. upon what anion, reagent, or solvent molecules, or specific complexing agents are present in the system to compete as ligands for the metal. This fact could well explain the failure of some of the reactions of azoles (e.g. \( m \)-nitrophenylation) under Ullmann conditions. Some of the azoles (e.g. benzimidazole, imidazole and 1,2,4-triazoles) are known to form complexes with copper salts (56). This may be a source of competition in the reaction of a relatively inactive haloaryl and some of the azoles. In those cases where an arylated product could not be isolated in the arylation of 1,2,4-triazole, bright coloured solids were noticed
in the reaction mixtures pointing to the possibility of formation of some sort of copper complexes. The higher yields obtained in the arylation by $\alpha$- and $\beta$-haloaryls also suggest the possibility that some kind of nucleophilic substitution is taking place in these Ullmann condensations. For instance, in the arylation of azoles by $\alpha$- and $\beta$-nitrochlorobenzene, the negative charge in the hypothetical intermediate can easily be accommodated by oxygen of the nitro group by resonance (53) and thus will help stabilise this intermediate. Thus in a simple case the following intermediates will facilitate the substitution:

\[
\begin{align*}
\text{Y} & \begin{array}{c}
\text{X} \\
\text{N}^+ \\
\text{O}^-
\end{array}
\end{align*}
\quad \text{etc. and}
\]

\[
\begin{align*}
\text{Y} & \begin{array}{c}
\text{X} \\
\text{N}^+ \\
\text{O}^-
\end{array}
\end{align*}
\quad \text{etc.}
\]

The better yields of the arylated products in the $\alpha$-nitro-phenylation of most of the azoles seem to be due to some special effect of the $\alpha$-substituent. An $\alpha$-nitro group seems to facilitate the substitution of the halogen more than the $\beta$-nitro group. If steric and mesomeric effects were more important the $\beta$-nitro group would have been more reactive in these substitutions. However, the
present results indicate that in these substitutions the inductive effect of the nitro group seems to be playing a major role in the ortho position and also the o-nitro group seems to have some favourable effect on the substitution. Bunnett and Morath (57) studied the reaction of piperidine with o- and p-nitrochlorobenzene and found o-nitrochlorobenzene to be more reactive than the p-isomer. The transition states postulated were I and II for the two isomers. Small change in rate, energy of activation and entropy of activation indicated that the transition state II, in spite of its zwitterionic character, is less extensively solvated than the transition state I.

In the transition state II the sites of positive and negative charge in the zwitterion, the piperidine nitrogen atom and a nitro oxygen atom, are ideally located for direct electrostatic interaction. This mutual interaction amounts to a "built-in" solvation and largely satisfies the tendency of the charged atoms to gather solvent molecules.
about them. It is stated that three factors play important roles in the substitution of halides by amines. First, the inherent preferentially ortho-activating effect of the nitro group; second, steric interference with coplanarity in the ortho transition state, tending to retard ortho-substitution; and finally, "built-in solvations" in the ortho-transition state which restores the predominance of ortho substitution. The ortho-carboxylate group (-COO⁻) has also been found to be ortho-activating in a similar nucleophilic substitution reaction and this was found to fit in well with this "built-in solvation" concept (58). Other explanations like hydrogen bonding have also been forwarded to explain the acceleration by ortho groups (59).

The most recent mechanism of the Ullmann biaryl synthesis is suggested by Fanta (1(b)). It is suggested that the particular role of an ortho-electronegative group in promoting the reaction may be due to the possibility of chelation as well as electron withdrawal from the aromatic nucleus, which will facilitate nucleophilic attack of copper as shown below in (a) for the hypothetical complex formed by the reaction of copper and o-bromonitrobenzene.

\[
\text{(a) \quad \text{Br} \quad \text{Cu} \quad \text{NO}_2}
\]

\[
\text{(b) \quad \text{I} \quad \text{Br}^- \quad \text{Cu} \quad \text{NO}_2}
\]

\[
\text{(c) \quad \text{Cu}^+ \quad \text{Cu}^+}
\]
In the second stage (b) nucleophilic attack of the complex takes place on a second molecule of aryl halide. It would appear necessary for the complex (a) to first release the bromide ion while remaining attached to the copper surface. The nucleophilic attack of the residue can be maintained by a further flow of electrons from the copper. In the final step (c) of the reaction, the covalent biaryl bond is formed with release of the iodide ion.

A similar mechanism has been put forward by Weingarten (7) for the related copper salt promoted Ullmann diareether synthesis. It is proposed that cuprous bromide and not the cupric bromide is the reactive catalyst species responsible for the diareether formation. The following scheme gives the mechanism. (Potassium phenoxide is denoted by KO\(\phi\).)
Weingarten suggests that the catalytic influence of the copper arises through the interaction of the catalytic species with the π electrons of the aromatic system rather than with those of the leaving halogen atom.

No mechanism, as yet, has been proposed for the Ullmann condensations of N-heteroaromatics and arylhalides, but it is not unlikely that it may be proceeding by a mechanism very similar to that of biaryl or diarylether syntheses. From the observed facts arising from the synthetic experiments of the present work and the findings of the other investigators only a tentative mechanism could be proposed at this stage. However, an elaborate and more conclusive mechanism could only be postulated from the kinetic and other data which is beyond the scope of the present work. The investigations reported in this thesis mainly deal with the synthetic applications and scope of these condensations.

Though a majority of the Ullmann condensations have been carried out on the N-heteroaromatics with a free NH, in the presence of a base such as anhydrous potassium carbonate, a few condensations have been effected by using the metallic salts such as N-potassium carbazole (17) and N-sodiopyrrole (15), and good yields of N-aryl substituted products have been obtained from these reactions. Thus it is quite likely that metallic salts which could be formed
in situ in these condensations be of the reactive species. All the N-heteroaromatics employed in the present work - pyrazole, imidazole, 1,2,4-triazole, indole, benzimidazole and carbazole - have been found to give the metallic derivatives (60). These potassium derivatives of various heteroaromatics can then take part in the condensation via conversion into the corresponding copper salt and this copper heteroaromatic can possibly react according to a scheme similar to that proposed by Weingarten (see p. 48). The copper salt of 1,2,4-triazole had earlier been prepared by Strain (56c) by the action of 1,2,4-triazole on cuprous amide. This copper salt has also been prepared by other workers (56b, 61). Copper salts of pyrazole (56b), imidazole (56b, 62) and benzimidazole (56b, d, 63) have also been reported.

Intermediates such as copper phenoxide (and a π-complex with copper phenoxide) and aryl copper have been postulated to take part in the Ullmann diarylether (7) and biaryl synthesis (64) respectively, and as mentioned in the preceding paragraph that various azoles form copper salts, it is more likely that in the Ullmann condensations of heteroaromatics such an intermediate can also be responsible for the arylations. However, another mechanism, where the potassium salt of a heteroaromatic is reacting via its anion in a copper catalysed nucleophilic substitution on the
halocaryl, can also explain the formation of N-arylazoles. The latter mechanism would be similar to that for the formation of N-alkyl heteroaromatics via their alkali salts such as the alkylation of 1,2,4-triazole by alkyl halides (65).

It has been observed that solvents containing heterocarbons, such as pyridine, dissolve copper salts to form complexes which are catalytic in the Ullmann diarelether synthesis, thus allowing use of lower temperatures (66). Gilman and Straley have earlier reported the solubility of phenyl copper in pyridine (67). Furthermore, copper salts are also known to form stable complexes with nitrogen heterocycles (68).

These observations could explain the high efficiency of pyridine as the solvent in our investigations and perhaps its additional catalytic effect somewhat similar to that exhibited by pyridine in the nucleophilic substitution of cyanuric chloride by aryl amines (69). There is only one reported instance of the use of pyridine as solvent in the Ullmann condensation of carbazole with 2-bromopyrididine and it was found to be ineffective in the preparation of 9-(α-pyridyl)carbazole (22). There is virtually no mention of the use of dimethylformamide in the Ullmann condensations though it has been successfully employed for Ullmann
biaryl synthesis and other reactions (70). Dimethylformamide is reported to act through its complexing action towards copper salts — thus promoting various reactions (71). Another advantage of the use of pyridine and dimethylformamide in our investigations was the high solubility of the two reactants — heteroaromatic and aryl halide — in these solvents.

The copper catalysts used in the condensations are either Cu (I) or Cu (II) salts and are effective in these arylations. Williams, Kinney and Bridger (66) have found that in the Ullmann diarylether syntheses oxidation-reduction of copper ions takes place in the system, and both cupric and cuprous salts can be used. These workers investigated the reduction of complexed cupric ions to cuprous ions by copper powder which indicates that the active catalyst contains cuprous copper. Evidence that the catalyst acts through the aromatic ring was also obtained by them.

The results of present investigations are in agreement with the tentative mechanism suggested and could be explained in the light of the properties of different heteroaromatics. Our failure in attempts to arylate pyrrole was probably due to the decomposition and polymerisation of pyrrole giving intractable tars. These decompositions and tar formations could take place in the presence of small amounts of acids (72).
Methylation of the sodium salt of indole by methyl iodide gives N-methylindole as the principal product, together with some 2-methyl-indole and skatole (73). In our experiments the only isomer formed in the various arylations was the N-substituted indole. There was no evidence of the formation of any of the 2-, or 3- aryl indoles in these condensations. All the N-aryl indoles except N-(α-pyridyl)indole, formed in our experiments, were new compounds. N-(α-pyridyl)indole had earlier been prepared in a very small quantity (74) but our procedure affords this compound in 79% yield.

In the attempted arylation of indole by 4-chloropyridine hydrochloride difficulties were met and only a small amount of the product could be obtained. This could be due to the two well known observations: (a) that 4-chloropyridine as a free base is subject to dimerization giving N-(4'-pyridyl)-4-chloropyridinium chloride (75), and (b) the polymerisation of indole under acidic conditions (73).
As the arylation of indole was conducted using 4-chloropyridine hydrochloride the presence of acid in the salt would help polymerisation of indole and prevent arylation.

The N-arylation of indole by 3-bromobenzonitrile and of 1,2,4-triazole by 4-bromobenzonitrile gave the corresponding azolylbenzamides together with the expected benzonitriles. These amides probably are produced by the metal catalysed hydration (76) of the nitriles formed in the arylation. Also in the arylations of various heteroaromatics by halobenzonitriles small amounts of azolylbenzoic acids were formed. These acids are perhaps the products of hydrolysis of the nitriles by a small amount of water liberated during the reaction.

Only a few experiments were conducted using carbazole and good yields of 9-(α-nitrophenyl)carbazole and 9-(α-pyridyl)carbazole were obtained. Martsokha, Posharskii and Simonov (37) reported failure in the arylation of carbazole under Ullmann conditions and ascribed this to the strong steric hindrance effect; our own experiments with carbazole are in disagreement with this explanation. In our experience condensations with α-chloronitrobenzene and 2-bromopyridine with carbazole gave products in yields of 89.7 and 59.3% respectively. Here acceleration, due to the ortho-nitro group rather than steric hindrance was observed. This is incompatible
with the explanation of Simonov et al. (37) but in agreement with the concept of "built in solvation" (p. 46).

In the arylation of pyrazole, imidazole and benzimidazole only one N-arylazole was obtained since for N-arylations the two N-positions were identical in the unsubstituted compounds. In the case of benzimidazole and imidazole the two nitrogens are equivalent and the same product is produced irrespective of the nitrogen attacked, while in 1,2,4-triazole the molecule is capable of giving two isomers, 1- and 4-aryl triazole (R = aryl).

The alkylation of 1,2,4-triazole under basic conditions was found to give exclusive 1-alkyl-1,2,4-triazoles (65). Rikerblom (77) in a recent study of the methylation of 3-amino-5-(2'-furyl)-1,2,4-triazole has demonstrated that methylation in alkaline solution gave a mixture of 1- and 2-methyl-3-amino-5-(2'-furyl)-1,2,4-triazole. Methylation in neutral solution gave 3-amino-5-(2'-furyl)-4-methyl 1,2,4-triazole as shown in the following scheme.
Other products of di- and trimethylation and methylation on amino groups were also formed in small amounts. These observations by Åkerblom were in agreement with the calculated values of $\pi$-electron densities at the nitrogen centres of the neutral molecule and of the anionic form of 1,2,4-triazole. The calculations had earlier predicted the highest electron density at 4-position in the neutral molecule while in the anionic form 1- and 2- positions had higher electron density than the 4-position (78).

Although Jacquier, Roumestant and Viallefond (105) have obtained both 1- and 4-$p$-nitrophenyl-1,2,4-triazole and 1- and 4-$p$-nitrophenyl-3-methyl-1,2,4-triazole in the nucleophilic substitution of $p$-fluoronitrobenzene with 1,2,4-triazole and 3-methyl-1,2,4-triazole respectively, in our experiments of N-arylation of
1,2,4-triazole by nitrohalobenzenes, halobenzonitriles and haloacetophenones only 1-substituted N-aryl 1,2,4-triazoles were formed. However, in the N-arylation with halopyridines both 1- and 4-pyridyl-1,2,4-triazoles were formed, e.g. in the arylation by 2- and 3-bromopyridines both the 1- and 4-N-substituted triazoles

A = 2-Bromopyridine
B = 3-Bromopyridine
C = 4-Chloropyridine hydrochloride
were formed, although the 4-isomer was formed in a very small yield. In the arylation by 4-chloropyridine hydrochloride the main product formed was 4-N-substituted triazole. All the 4-substituted pyridyl-triazoles were prepared by unambiguous routes using Wiley and Hart's diformylhydrazine method (48) and were found to be identical with the compounds isolated from the reaction. The 4-(α-, β- and γ-pyridyl)triazoles formation perhaps takes place in a similar manner as the electrophilic attack in azoles at a multiple bonded (pyridine type) nitrogen atom which is then followed by a loss of proton from the NH group (79a).

\[ \text{Pyx} = \text{Halopyridine} \]

The analogy can be drawn between the above-mentioned reaction and the reaction between benzimidazoles or N-substituted benzimidazole with 2,4-dinitrochlorobenzene (30). When benzimidazole and N-substituted benzimidazoles were treated with 2,4-dinitrochlorobenzene
in the presence of sodium acetate and ethanol or just fused together, onium salts of the following type were formed.

"Abnormal" products of arylation by o-bromoacetophenone.

In the reaction of bromoacetophenone with different heterocaromatics "normal" substitution products i.e. various N-azolylacetophenones were obtained. While in the condensation between o-bromoacetophenones and imidazole and benzimidazole prolonged heatings gave products which did not give the iodoform test and lacked the characteristic $\nu_C=O$ bands of aralkyl ketones in their infrared spectra in the region 1670-1700 cm$^{-1}$, these products, however, analysed for the same empirical formula as the corresponding acetophenone of the azole. 1,2,4-Triazole on the other hand gave a mixture of products analysing for triazolylacetophenone. The lower melting compound had a $\nu_C=O$ band at 1689 cm$^{-1}$, while the higher melting compound lacked the $\nu_C=O$ band and gave a negative iodoform test. The condensations of imidazole and benzimidazole with
g-bromoacetophenone at a lower reflux period gave the expected acetophenone together with the "abnormal" product. The following table gives the reaction time for these condensations and the yield of the two products obtained together with infrared spectra bands in the region 3000-3500 cm\(^{-1}\).

Table XI: CONDENSATION OF G-BROMOACETOPHENONE WITH IMIDAZOLE, BENZIMIDAZOLE AND 1,2,4-TRIAZOLE.

<table>
<thead>
<tr>
<th>Azole</th>
<th>Time hrs</th>
<th>azoyl- acetophenone</th>
<th>&quot;abnormal&quot; product</th>
<th>Infrared bands in the region 3000-3500 cm(^{-1}) for &quot;abnormal&quot; product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imidazole</td>
<td>48</td>
<td>-</td>
<td>65</td>
<td>3070-3090(br); 3125</td>
</tr>
<tr>
<td>&quot;</td>
<td>7</td>
<td>33.4</td>
<td>47.7</td>
<td></td>
</tr>
<tr>
<td>1,2,4-Triazole</td>
<td>48</td>
<td>36.9</td>
<td>23.3</td>
<td>3160(br)</td>
</tr>
<tr>
<td>Benzimidazole</td>
<td>46</td>
<td>-</td>
<td>83.1</td>
<td>3225, 3340(sh); 3385(br) strong bands</td>
</tr>
<tr>
<td>&quot;</td>
<td>3</td>
<td>46 (^b)</td>
<td>a</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) A small quantity admixed with benzimidazole was obtained; 37.3\% of g-bromoacetophenone was also recovered unchanged from the reaction mixture.

\(^b\) 73.4\% on the basis of recovered g-bromoacetophenone.
\(\text{o-(Imidazol-1-yl)acetophenone}\) on heating under reflux was found to change into the higher melting product.

Table XI shows the effect of reflux time on the formation of "normal" azolylacetophenones. The shorter reflux periods favour the formation of "normal" azolylacetophenones while carrying out the condensations over a long period results in the unexpected compounds. The failure to isolate the expected acetophenones from the condensations of imidazole and benzimidazole with \(\text{o-bromo-acetophenone}\) at reflux times of 48 and 46 hrs. respectively, and formation of these acetophenones together with the "abnormal" products at shorter reflux period indicates the possible initial formation of the "normal" expected acetophenone followed by its conversion into the "abnormal" products. It is also not unlikely that these "abnormal" products are formed simultaneously with the expected acetophenones though in a small quantity. The conversion of the normal acetophenones to these products under the reaction condition provides evidence for the possible initial formation of the "normal" reaction product which is converted into the "abnormal" products.

Since the "abnormal" products were formed only in the case of imidazole, 1,2,4-triazole and benzimidazole, and not in the condensation of pyrazole and indole, it is believed that these reactions
take place with the compounds containing structure of the kind, e.g.,

\[ \text{structure} \]

and

In the case of imidazole the product obtained in the condensation with o-bromoacetophenone can be tentatively assigned the structure as below (I) where the H of OH can also take place in hydrogen bonding as shown in II.

\[ \text{structure I} \]

\[ \text{structure II} \]

In this case the O-H stretching vibration is shifting to lower frequencies (see Table XI). This could probably be due to the formation of a strong intermolecular hydrogen bond. The higher
melting point of I can also be due to such a hydrogen bonding. At
this stage the possibility of hydrogen bondings of the type \( \text{O} - \text{H} \cdots \text{N} \)
cannot be ruled out, but the bands at lower frequencies perhaps
arise from very strong intermolecular hydrogen bonding. Recently
the infrared spectra of compounds III and IV have been reported
(81) and as can be seen that the \( \text{O} - \text{H} \) in IV appears at lower
frequencies than in III, this could be due to intensive hydrogen
bonding in IV. The broad band at 3333-3320 cm\(^{-1}\) in IV has been
ascribed as characteristic of a polymeric alcohol (51b). Structures
like II can perhaps give rise to intramolecular bonds.

![Chemical Structures](image)

III. \( R=\text{H} \quad \text{Ar}=\text{Ph} \)

IV

IR. 3333-3320 cm\(^{-1}\) (broad band)

IR. 3356 & 3570 cm\(^{-1}\) (KBr)
3448 & 3600 cm\(^{-1}\) (CHCl\(_3\))

The infrared spectrum of I also displayed strong bands centred
at 745 cm\(^{-1}\) with shoulders at 725 and 758 cm\(^{-1}\), which could be
attributed to an \( \alpha \)-disubstituted benzene ring.
The abnormal products from imidazole, 1,2,4-triazole and benzimidazole have been tentatively assigned the structures I, V and VI respectively. Since in the condensations of o-, m- and p-bromoacetophenones with pyrazole and indole and in the condensation of m- and p-bromoacetophenones with imidazole, 1,2,4-triazole and benzimidazole, only normal products were obtained, structures such as VII can be ruled out. It is believed that if a simple reduction has taken place during the condensation giving rise to compound VII, such products could also be formed in other condensations. This is not compatible with the experimental observations and points to a reaction specific of position 2- of imidazole and benzimidazole and position 5- of 1,2,4-triazole. The presence of a hydroxyl group in
the product I was also established by its esterification with benzoyl chloride. The benzoate ester which was obtained as a low melting solid lacked O-H absorption in the infrared spectrum. A strong absorption band at 1720 cm\(^{-1}\) appeared and this could be assigned to the carbonyl stretching frequency of a benzoate ester (82). In addition to the \(\nu_{\text{C=O}}\) strong bands at 702 and 750 cm\(^{-1}\) with shoulders at 684 and 730 cm\(^{-1}\) were also observed; these bands could be attributed to an o-disubstituted benzene ring of I together with the mono substituted benzene ring introduced during esterification. 

Badger and Moritz (83) have reported a diffused band appearing at 3300-3100 cm\(^{-1}\) in the spectrum of 8-hydroxyquinoline at higher concentration which they ascribe to intermolecular hydrogen bonding of structure VIII, while intermolecular hydrogen bonding due to IX was found to give rise to a band at 3416 cm\(^{-1}\).

![Diagram](https://via.placeholder.com/150)

**VIII**

**IX**

Imidazole undergoes electrophilic substitutions at 2-, and 4- positions. The nitration of imidazole takes place at 4-position and
the diazo-coupling occurs at 2-position; benzimidazole also is
iodinated at 2-position (84), though the reactive species taking
part in these substitutions could be different. Earlier it was
found that N-vinylimidazole and N-vinylbenzimidazole hydroxylate at
2-position when heated with formaldehyde or paraformaldehyde (85).

N-substituted imidazoles also undergo thermal condensation
with aldehydes to give N-imidazol-2-yl-carbinols (86).
2-Lithioimidazoles carrying substituents at N atom were obtained by
the treatment of N-substituted imidazoles with N-butyl lithium.
These lithioimidazoles, when treated with benzophenone gave the
2-substituted carbinol (X) in over 75% yield (87).

\[
\begin{align*}
\text{imidazole} & \xrightarrow{\text{n-butyl lithium}} \text{imidazole-Li} & \text{imidazole-Li} & \xrightarrow{\text{benzophenone}} \text{carbinol X} \\
& & & R = \text{CH}_3 \text{ or } \text{C}_6\text{H}_5
\end{align*}
\]

In view of the foregoing facts it is assumed that product I
can arise in a similar fashion by the electrophilic thermal
condensation at 2-position of the imidazole ring, possibly by some
kind of intramolecular catalyst assisted reaction. The reaction
giving rise to I could possibly be envisaged as follows:
This is reminiscent of the electrophilic substitution of thiophene (79b).
No further attempts, at this stage, have been made to synthesise or investigate further these "abnormal" reaction products.

The infrared spectra of various N-aryl heteroaromatics have been recorded in the tables V-XI. Only strong bands have been listed in the region 650-1000 cm\(^{-1}\) characteristic of C-H deformation modes and other regions characteristic of the various substituents present in the N-aryl group, introduced into these N-heteroaromatics through various arylations. The infrared spectra are quite compatible with the structures assigned to these compounds. All the compounds prepared lacked the absorption attributable to an \(\equiv\text{N-H}\) (bonded or non-bonded) in the spectrum which rules out any possibility of substitution at the carbon atoms of the heteroaromatics either as the main reaction or by thermal rearrangement from nitrogen to carbon as has been observed in the case of N-substituted pyrroles (79c) and N-methylimidazole (34).

It has previously been observed (38) that a strong band in the region 925-960 cm\(^{-1}\) is associated with the C-H vibration of the pyrazole carbons, and that its position in substituted 1-phenyl-pyrazoles is diagnostic of substitution in the pyrazole ring; absorption in the range 925-942 cm\(^{-1}\) is noted for compounds without
substituents in the pyrazole ring, while absorption in the region 950-960 cm\(^{-1}\) is observed with compounds carrying substituents.

All the N-arylpyrazoles prepared in our present work show strong absorption bands in the region 925-942 cm\(^{-1}\) attributable to a free C-H vibration of a pyrazole ring while no bands in the region 950-960 cm\(^{-1}\) were observed. This is in agreement with the previous suggestion. A tentative assignment for the different substituted N-arylazoles infrared absorption bands could be made as 

\(\omega\)-disubstituted 735-770 cm\(^{-1}\); \(\pi\)-disubstituted 770-795 cm\(^{-1}\) and 

\(\mu\)-disubstituted 795-850 cm\(^{-1}\) (all strong bands) (82b). The characteristic strong bands at ca. 740 cm\(^{-1}\) due to 1,2-disubstituted benzene in indole and benzimidazole were also observed in addition to the bands attributable to other substitution patterns mentioned earlier.

The strong infrared bands of various N-nitrophenylazoles are tabulated above (Table V) for the \(\nu\)\(_{N-O}\) \(\text{asym.}\) and \(\nu\)\(_{N-O}\) \(\text{sym.}\). It was observed that \(\text{N-O}\) asymmetric stretching frequencies of the para-substituted nitrophenylazoles were lower than the corresponding meta-isomers due to the conjugation between the heterocaromatic and the aryl ring. The \(\text{N-O}\) asymmetric stretching frequencies of the ortho-isomer do not differ very much from the meta-isomers perhaps due to the lack of coplanarity between the two rings caused by the ortho-
nitro-group. As can be seen from Table V the frequency for the absorption due to \( \text{N-O\ sym.} \) is also affected.

The pyridylazoles show strong bands in the region 1450-1600 cm\(^{-1}\) characteristic of C=C and C=N stretching frequencies of pyridines. The different substituted pyridines can be characterised by observing the out of plane vibrations in the region 690-830 cm\(^{-1}\) (82c).

The benzonitriles absorb in the region 2220-2240 cm\(^{-1}\) and can easily be characterised. In heteroaromatic substituted benzonitriles the bands attributable to C=N stretching in the region 2222-2235 cm\(^{-1}\) were observed and could be attributed to this stretching mode.

All the heteroaromatic substituted acetophenones displayed a strong band in the carbonyl stretching frequency region (1670-1700 cm\(^{-1}\)) of aralkyl ketones; strong to medium bands due to symmetric CH\(_3\) deformation were also observed in the region 1350-1370 cm\(^{-1}\).

In the case of amides two bands in the region near 3350 and 3180 cm\(^{-1}\); strong bands at 1620-1670 cm\(^{-1}\) attributed to asymmetric and symmetric NH\(_2\) stretching frequencies, and C=O stretch and NH deformation respectively are observed (82d). Azolylbenzamides were found to have bands attributable to N-H stretching frequencies at
3170-3180 and 3260-3400 cm\(^{-1}\); C=O stretching 1648-1664 cm\(^{-1}\) and N-H deformation (Amide II) 1595-1615 cm\(^{-1}\).

The azolylbenzoic acids displayed broad bands in the O-H stretching region due to strong hydrogen bonding. These bands were accompanied by the usual C=O stretching bands in the region 1670-1700 cm\(^{-1}\).

\(\alpha\)-(Pyrazol-1-yl)benzoyl chloride.

In an attempt to prepare \(\alpha\)-(pyrazol-1-yl)acetophenone from \(\alpha\)-(pyrazol-1-yl)benzoic acid following the general method of Klein and Bergmann (89) for the preparation of substituted acetophenones, the acid chloride of \(\alpha\)-(pyrazol-1-yl)benzoic acid was needed. When thionyl chloride was added to the acid a brisk reaction set in with the evolution of heat and the reaction mixture solidified. This was kept at room temperature for 12 hours and then heated under reflux for two hours on a steam bath. The solid initially formed on the addition of thionyl chloride to the acid did not seem to react further. When the reaction mixture was freed of thionyl chloride a solid m.p. 238-242° (decomp.) was obtained. This solid was subjected to distillation under reduced pressure but failed to distil and intensive decomposition was noticed to be taking place. The distillation was abandoned and the solid in the crude form was used for further reaction giving the desired acetophenone.
This acid chloride has not been described in the literature. On treatment of this acid chloride with ammonia the corresponding amide was obtained. When dissolved in cold water this acid chloride immediately gave 2-(pyrazol-1-yl)benzoic acid, identical in m.p., mixed m.p. and infrared spectra with the authentic sample. The infrared spectrum of this acid chloride showed two strong bands of equal intensity at 1705 and 1738 cm\(^{-1}\) with shoulder at 1808 cm\(^{-1}\). Aromatic acid chlorides are known to absorb strongly at 1765-1785 cm\(^{-1}\) and a second weaker band at 1735-1750 cm\(^{-1}\) (82e). The unusual properties of this acid chloride can be explained if the charged structure XI is assumed to represent the acid chloride. The chloride could easily be precipitated by silver nitrate. The easy hydrolysis

![Diagram of structures XI and XII](image)

of the acid chloride possibly takes place as follows:
The amide is probably formed in a similar manner. The somewhat unusual infrared absorption due to the C=O stretching frequency could also be attributed as due to the effect of +ve nitrogen atom next to carbonyl C=O reducing the tendency for oxygen to draw electrons and thus resulting in absorptions at higher wave numbers. Structure XII arising from the protonation of pyrazole nitrogen by HCl liberated in the reaction can also be put forward. The elemental analysis, however, is compatible with structure XI and not XII. (See p.90 for analysis.)
It has previously been observed that the reaction of an acid chloride or anhydride with pyridine yields an N-acyl-(or aryl)-pyridinium salt (XIII, \( R = \) alkyl or aryl) which can be stabilised by resonance (107).

\[
\begin{align*}
\text{Pyridine} & \xrightarrow{\text{RCOX}} \quad \text{Pyridinium salt (XIII, } R = \text{ alkyl or aryl)} \\
\end{align*}
\]
The compound (XI) most likely arises from a similar facile intramolecular attack on the pyridine type nitrogen of the pyrazole ring. This compound can also be resonance stabilised through the contribution of structures such as XIV and XV.

The condensation of pyrazole with \( \sigma \)-chlorobenzoic acid resulted in the formation of \( \sigma \)-(pyrazol-1-yl)benzoic acid together with 20.1% yield of 1-phenylpyrazole. 1-Phenylpyrazole undoubtedly is produced by the copper catalysed decarboxylation of \( \sigma \)-(pyrazol-1-yl)benzoic acid. The decarboxylation of \( \sigma \)-(pyrazol-1-yl)benzoic acid under the Ullmann condensation conditions is very similar to the decarboxylation of aromatic acids with copper catalysts (106).
Alley and Shirley (96) had earlier obtained 4-oxopyrazolo-[1,5-a]indoline (XVII) by an intramolecular cyclisation of 1-phenylpyrazole-5-carboxylic acid (XVI) using polyphosphoric acid as the condensing agent.

Attempts to prepare XVII by intramolecular condensation of o-(pyrazol-1-yl)benzoic acid (XVIII) in either polyphosphoric acid or concentrated sulphuric acid failed. This failure is understandable in the light of the facts that all such intramolecular cyclisation could be carried out by typical Friedel-Crafts catalysts (108) and are essentially electrophilic aromatic substitutions.
The electrophilic substitution reactions occur only at the 4-position of pyrazole (109) and 4-, 2'- and 4'-position of 1-phenylpyrazole as demonstrated by the nitration of 1-phenylpyrazole.

\[
\begin{array}{c}
\text{Pyrazole} \\
\text{1-Phenylpyrazole}
\end{array}
\]

with mixed acids at 100° (42). While in the cyclisation XVI \(\rightarrow\) XVII the attack of acylium ion would take place on the 2'-position of the phenyl ring, which is reactive towards electrophilic reagents, the substitution XVIII \(\rightarrow\) XVII would involve position 5- which is not reactive towards electrophilic substitution and so the failure observed in cyclisation XVIII \(\rightarrow\) XVII.

**ULTRAVIOLET SPECTRA.**

The following Table XIII lists the ultraviolet spectra of various arylazoles obtained during the Ullmann condensation.
Table XIII: ULTRAVIOLET SPECTRA OF ARYLazoLES IN METHANOL.

<table>
<thead>
<tr>
<th>R</th>
<th>$\lambda_{\text{max}}$ (m$\mu$ (log $\varepsilon$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Nitrophenyl</td>
<td>225 (3.55); 328 (3.66)</td>
</tr>
<tr>
<td>o-Nitrophenyl$^a$</td>
<td>238 (4.18); 300 (3.27)</td>
</tr>
<tr>
<td>m-Nitrophenyl$^a$</td>
<td>250 (3.88)</td>
</tr>
<tr>
<td>p-Nitrophenyl$^a,b$</td>
<td>318 (4.29)</td>
</tr>
<tr>
<td>o-Cyanophenyl</td>
<td>222 (4.37); 254 (3.99); 292 (3.48)</td>
</tr>
<tr>
<td>m-Cyanophenyl</td>
<td>226 (5.44); 260 (4.28); 294 infl. (3.28)</td>
</tr>
<tr>
<td>p-Cyanophenyl</td>
<td>214 (4.42); 278 (4.72)</td>
</tr>
<tr>
<td>o-Acetylphenyl</td>
<td>215 infl. (4.09); 226 (4.17); 248 (3.94); 284 infl. (3.25)</td>
</tr>
<tr>
<td>m-Acetylphenyl</td>
<td>240 (4.01); 300 (3.18)</td>
</tr>
</tbody>
</table>
Table XIII (contd.)

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Wavenumber (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Acetylphenyl</td>
<td>215 inf. (3.79); 288 (4.17)</td>
</tr>
<tr>
<td>2-Pyridyl</td>
<td>250 (4.03); 280 (4.01)</td>
</tr>
<tr>
<td>3-Pyridyl</td>
<td>212 (3.64); 256 (4.03)</td>
</tr>
<tr>
<td>4-Pyridyl</td>
<td>214 (3.79); 265 (4.21)</td>
</tr>
<tr>
<td>o-Carboxyphenyl</td>
<td>217 (3.65); 246 (3.52)</td>
</tr>
<tr>
<td>p-Carbamoylphenyl</td>
<td>214 (3.97); 246 (3.75)</td>
</tr>
<tr>
<td>o-Nitrophenyl</td>
<td>215 (4.3); 254 sh. (4.07)</td>
</tr>
<tr>
<td>m-Nitrophenyl</td>
<td>237 br. (4.19)</td>
</tr>
<tr>
<td>p-Nitrophenyl</td>
<td>217 (4.41); 293 (4.46)</td>
</tr>
<tr>
<td>o-Cyanophenyl</td>
<td>211 (4.14); 233 inf. (3.75); 284 (2.99)</td>
</tr>
<tr>
<td>m-Cyanophenyl</td>
<td>215 (4.31); 246 inf. (3.85); 284 (2.96)</td>
</tr>
<tr>
<td>p-Cyanophenyl</td>
<td>209 (3.38); 260 (3.97)</td>
</tr>
<tr>
<td>o-Acetylphenyl</td>
<td>213 (4.20); 280 (3.04)</td>
</tr>
<tr>
<td>m-Acetylphenyl</td>
<td>215 inf. (4.21); 228 (4.28); 291 (3.10)</td>
</tr>
<tr>
<td>p-Acetylphenyl</td>
<td>212 (4.06); 270 (4.21)</td>
</tr>
<tr>
<td>2-Pyridyl</td>
<td>225 br. (3.71); 272 (3.58)</td>
</tr>
</tbody>
</table>
Table XIII (contd.)

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Wavenumbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Pyridyl</td>
<td>225 br. (3.76); 270 (3.37)</td>
</tr>
<tr>
<td>4-Pyridyl</td>
<td>250 very br. (4.21)</td>
</tr>
<tr>
<td>m-Carboxyphenyl</td>
<td>214 (3.65); 225 br. (3.62)</td>
</tr>
<tr>
<td>p-Carboxyphenyl</td>
<td>239 (4.02)</td>
</tr>
<tr>
<td>o-Nitrophenyl</td>
<td>218 (4.85); 284 infl. (4.26)</td>
</tr>
<tr>
<td>m-Nitrophenyl</td>
<td>237 (4.26)</td>
</tr>
<tr>
<td>p-Nitrophenyl</td>
<td>217 (4.50); 285 (4.59)</td>
</tr>
<tr>
<td>o-Cyanophenyl</td>
<td>214 (4.34); 235 (3.91); 282 (3.24)</td>
</tr>
<tr>
<td>m-Cyanophenyl</td>
<td>219 (3.74); 245 (3.35)</td>
</tr>
<tr>
<td>p-Cyanophenyl</td>
<td>212 (3.83); 258 (4.14)</td>
</tr>
<tr>
<td>2-Pyridyl</td>
<td>237 (3.99); 272 (3.79)</td>
</tr>
<tr>
<td>3-Pyridyl</td>
<td>237 (3.93); 270 sh. (3.49)</td>
</tr>
<tr>
<td>4-Pyridyl</td>
<td>242 (4.02)</td>
</tr>
<tr>
<td>o-Acetylphenyl</td>
<td>218 (3.96); 237 sh. (3.31); 278 (2.98)</td>
</tr>
<tr>
<td>m-Acetylphenyl</td>
<td>229 (4.16); 292 (2.82)</td>
</tr>
<tr>
<td>p-Acetylphenyl</td>
<td>211 (3.96); 267 (4.21)</td>
</tr>
<tr>
<td>m-Carboxyphenyl</td>
<td>219 (3.86); 242 infl. (3.66)</td>
</tr>
</tbody>
</table>
Table XIII (contd.)

\[ \begin{align*}
\text{p-Carboxyphenyl} & \quad 210 (3.50); 256 (3.70) \\
\text{p-Carbamoylphenyl} & \quad 213 (3.78); 257 (4.07)
\end{align*} \]

\[ \text{\includegraphics[width=0.2\textwidth]{diagram1.png}} \]

\[ \begin{align*}
\text{o-Nitrophenyl} & \quad 209 (4.17); 253 (3.61) \\
\text{m-Nitrophenyl} & \quad 222 (3.94); 256 \text{ infl.} (3.50) \\
\text{p-Nitrophenyl} & \quad 219 (3.68); 276 (3.89) \\
\text{2-Pyridyl} & \quad 226 (3.92); 267 (3.63) \\
\text{3-Pyridyl} & \quad 223 (3.81); 264 (3.34) \\
\text{4-Pyridyl} & \quad 244 (4.00)
\end{align*} \]

\[ \text{\includegraphics[width=0.2\textwidth]{diagram2.png}} \]

\[ \begin{align*}
\text{o-Nitrophenyl} & \quad 215 (4.95); 256 (4.74); 347 (3.65) \\
\text{m-Nitrophenyl} & \quad 218 (3.99); 259 (4.16); 290 \text{ sh.} (3.78); 298 \text{ sh.} (3.78) \\
\text{p-Nitrophenyl} & \quad 211 (4.94); 233 (4.80); 263 (4.68); 355 (4.70) \\
\text{o-Cyanophenyl} & \quad 223 (3.92); 230.5 \text{ infl.} (3.85); 262 (3.82); 290 (3.40); 318 (3.34)
\end{align*} \]
Table XIII (contd.)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Wavenumbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>m-Cyanophenyl</td>
<td>218.5 (4.40); 229 inf. (4.06); 262 (4.00); 298 (3.75)</td>
</tr>
<tr>
<td>p-Cyanophenyl</td>
<td>216 (4.22); 270 (3.88); 316 (3.95)</td>
</tr>
<tr>
<td>2-Pyridyl</td>
<td>212.8 (4.35); 255 (4.32); 308 (4.12)</td>
</tr>
<tr>
<td>3-Pyridyl</td>
<td>215 (4.40); 260 (4.15); 300 (3.84)</td>
</tr>
<tr>
<td>4-Pyridyl</td>
<td>213 (4.16); 263 (3.99); 308 (3.87)</td>
</tr>
<tr>
<td>o-Acetylphenyl</td>
<td>215 (5.33); 262 (4.09); 284 inf. (3.83); 291 inf. (3.72)</td>
</tr>
<tr>
<td>m-Acetylphenyl</td>
<td>217 (5.12); 242 (4.96); 260 inf. (4.86); 288 (4.52)</td>
</tr>
<tr>
<td>p-Acetylphenyl</td>
<td>220 (4.20); 271 (3.85); 325 (3.96)</td>
</tr>
<tr>
<td>m-Carboxamylphenyl</td>
<td>218.5 (4.36); 260 (4.00); 294 (3.67)</td>
</tr>
<tr>
<td>o-Carboxyphenyl</td>
<td>217 (4.54); 262 (4.14); 286 sh. (3.88)</td>
</tr>
<tr>
<td>p-Carboxyphenyl</td>
<td>217 (3.92); 240 (3.79); 270 sh. (3.50); 310 (3.44)</td>
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<tr>
<td>o-Nitrophenyl</td>
<td>211 (4.59); 244 (4.50); 273 inf. (4.27); 281 sh. (4.20); 330 (3.72)</td>
</tr>
<tr>
<td>m-Nitrophenyl</td>
<td>249 (4.3)</td>
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<tr>
<td>p-Nitrophenyl</td>
<td>210 (4.23); 250 (4.00); 273 (3.89); 313 (3.99)</td>
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</tbody>
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Table XIII (contd.)

<table>
<thead>
<tr>
<th>Phenyl</th>
<th>211 (4.28); 267 (3.95); 290 (3.93)</th>
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<tbody>
<tr>
<td>4-Pyridyl</td>
<td>212 (4.33); 245 infl. (3.99); 270 sh. (4.08); 296 (4.17)</td>
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- 83 -
Table XIII (contd.)

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<tbody>
<tr>
<td><strong>α-Nitrophenyl</strong></td>
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<td><strong>m-Nitrophenyl</strong></td>
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<tr>
<td><strong>p-Nitrophenyl</strong></td>
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<td><strong>2-Pyridyl</strong></td>
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<td><strong>p-Nitrophenyl</strong></td>
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\[ R \quad \text{CH}_3 \]

- b In chloroform solution.
- c J.C. Powers (J. Org. Chem. 29, 2534 (1965)) reports 210 (4.0); 255 (3.95); 309 (3.67) in ethanol.
- e See also Ref. 111.
EXPERIMENTAL

GENERAL

Analyses are by the Australian Microanalytical Service, Division of Organic Chemistry, G.S.I.R.O., and the University of Melbourne, Parkville, Victoria.

Melting points (m.p.) were observed using a Gallenkamp melting point apparatus and are uncorrected. Boiling points (b.p.) are also uncorrected. The abbreviation "lit." refers to values reported in the literature.

Infrared spectra were recorded for the 600-3500 cm\(^{-1}\) region using a Perkin-Elmer double beam spectrophotometer No. 221. Solid samples were examined as mulls; Nujol and hexachlorobutadiene were used as mulling agents. Liquid samples were examined as thin films between plates.

Ultraviolet spectra were recorded in methanol (A.R.) using a Perkin-Elmer 4000 \(\AA\) spectracord.

Organic extracts were dried with anhydrous magnesium sulphate.
Unless otherwise stated, light petroleum refers to fractions of b.p. 40–60°C.

Alumina (type H; Light and Co. Ltd.) was used for adsorption chromatography.

Analyses for all the new compounds have been listed in Table II.

The following starting materials were obtained commercially and used without further purification: pyrrole (Hopkins and Williams); pyrazole, imidazole, indole and 4-chloropyridine hydrochloride (Fluka); 1,2,4-triazole, o-chloronitrobenzene, m-chloronitrobenzene, and p-chloronitrobenzene (Dr. Th. Schuchardt, Munich); carbazole (B.D.H.); o-chlorobenzonitrile, m-bromobenzonitrile, p-bromobenzonitrile, m-bromoacetophenone and p-bromoacetophenone (Aldrich & Co.); and 2- and 3-bromopyridine (Halewood Chemicals). Anhydrous potassium carbonate used was from Hopkins and Williams. The A.R. cupric oxide used was from General Chemical and Pharmaceutical Co. Sudbury, Middlesex. A.R. pyridine was dried over potassium hydroxide.

Benzimidazole m.p. 174–176°C was prepared by the method of Wagner and Millet (90). m-Bromonitrobenzene m.p. 55–56°C was prepared from m-bromoaniline via a Sandmeyer reaction (91a) and purified by
chromatography on alumina with benzene. \(\alpha\)-Bromoacetophenone b.p. 113-115° (aspirator vacuum); semicarbazone m.p. 160-164°, was prepared in 88.7% yield by the method of Klein and Bergmann (89).

\(N, N'\)-diformalhydrazine m.p. 156-160° was prepared following the method of Ainsworth and Jones (92) using hydrazine hydrate and formamide. 4-(\(\alpha\)-Pyridyl)-1,2,4-triazole m.p. 169° and 4-(\(\beta\)-pyridyl)-1,2,4-triazole m.p. 154-158° were prepared by Wiley and Hart's method (48) and 2,2'-dinitrobiphenyl m.p. 125-126° according to Vogel (91b).

\(\alpha\)-Tolylhydrazine m.p. 190° (decomp.) was prepared in 79% yield by the method of Bullock and Hand (93).

1-(\(\alpha\)-Tolyl)pyrazole. This was prepared by the general method of preparation of 1-substituted pyrazoles (42). 1,1,3,3-Tetramethoxypropane (100 g) and \(\alpha\)-tolylhydrazine hydrochloride (94 g) in 95% ethanol (500 ml) were heated under reflux for 3.5 hrs., ethanol was evaporated under reduced pressure. The residue was dissolved in water and treated with solid sodium carbonate, and filtered. The filtrate was extracted with ether and the residue was washed several times with ether. The combined ether extracts were dried, filtered and the ether was removed from the filtrate. The residue was distilled giving 1-(\(\alpha\)-toly1)pyrazole b.p. 238-246°, yield 59.5 g; 63.3%. lit. b.p. 246.5/754.1 mm (94).
c-(Pyrazol-1-yl)benzoic acid was prepared in 66.3% yield by the oxidation of (o-tolyl)pyrazole by alkaline potassium permanganate. m.p. 140-142°, lit. m.p. 138-139° (95); 140-142° (96).

1-Phenylpyrazole b.p. 245-246°, lit. b.p. 246.5°/765.4 mm (94) was prepared in 69.8% yield using the method employed for 1-(o-tolyl)-pyrazole.

4-(o-Nitrophenyl)-1,2,4-triazole. This was prepared following Wiley and Hart's method (48). A mixture of o-nitroaniline (13.8 g) and N,N'-diformyl hydrazine (8.8 g) was heated at a temperature of 120° for 18 hrs. and then the temperature was slowly raised to 180° and maintained at 180° for 7 hrs. The reaction mixture after cooling at room temperature was dissolved in benzene and chromatographed on alumina. Using benzene as eluting solvent, 6.8 g of unchanged o-nitroaniline m.p. 71-72° was recovered from the column. The solvent was then changed to chloroform when from the eluents 4-(o-nitrophenyl)-1,2,4-triazole m.p. 127-129° was obtained after removing the solvent. This was recrystallised from chloroform/light petroleum giving crystals m.p. 131-132°. Yield: 4.38 g; 23.1%.
4-(o-Aminophenyl)-1,2,4-triazole. 4-(o-Nitrophenyl)-1,2,4-triazole (4.38 g) was reduced with tin (5 g) and hydrochloric acid (15 ml) taking usual precautions. The mixture was heated for 12 hrs. on a water bath, cooled, made strongly alkaline with 33% sodium hydroxide solution and then extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried and then filtered. The solvent was evaporated from the filtrate leaving 4-(o-aminophenyl)-1,2,4-triazole m.p. 131-132°. Yield: 3.54 g; 96%. A small portion was crystallised from ethyl acetate, m.p. 135-6°. Anal. calcd. for C_{8}H_{8}N_{4}: C, 60.0; H, 5.0; N, 35.0%. Found: C, 60.8; H, 5.3; N, 34.7%. Ultraviolet absorption: \( \lambda_{\text{max}} \) 215, 239, 296 \( \text{m} \mu \), \( \log \varepsilon \) 3.84, 3.85, 3.35. The infrared spectrum: \( \nu \text{NH}_{2} \), 3400, 3340 cm\(^{-1}\) asym. and sym.; 3230 cm\(^{-1}\) bonded NH; \( \text{NH}_{2} \) bending 1630 cm\(^{-1}\); 1:2-disubstituted benzene 1602, 1490, 1508, 1522 and 760 cm\(^{-1}\).

o-(Pyrazol-1-yl)acetophenone. The general method of Walker and Hauser (97) as modified by Klein and Bergmann (89) was used for this compound.

Thionyl chloride (60 ml) was added to o-(pyrazol-1-yl)benzoic acid (20 g), an exothermic reaction set in, the reaction mixture was cooled and then kept at room temperature for 12 hrs. and heated under reflux for 2 hrs. on a water bath. The excess thionyl chloride
was removed and the solid was subjected to distillation under reduced pressure when slight decomposition of the solid was observed and the attempt to purify the product was abandoned. The crude material m. 238-242° (decomp.) was used in the next step. The infrared spectrum: strong bands 1705 and 1788 cm\(^{-1}\), 1803 cm\(^{-1}\) (sh.) in the carbonyl region and 770 cm\(^{-1}\) for 1:2-disubstituted benzene. Anal. calcd. for C\(_{10}\)H\(_7\)Cl\(_2\)O\(_2\): C, 53.5; H, 4.0; N, 12.5; Cl, 15.9%. Found: C, 53.8; H, 4.3; N, 12.3; Cl, 15.9%. (See discussion p. 71.)

In a 500 ml flask "super dry" ethanol (2.5 ml) and carbon tetrachloride (0.3 ml) was added to magnesium turnings (3.9 g). As soon as the reaction started chlorobenzene (25 ml) was added and then, dropwise, a mixture of diethyl malonate (25 g) and ethanol (10 ml) was added. The temperature was not allowed to rise above 70° during this period. At its end the mass was heated at 75° for 4 hrs., cooled to room temperature and chlorobenzene (42 ml) was added. To this mixture, at a temperature not exceeding 35°, crude "acid chloride" m.p. 238-242° (decomp.) was added in small portions. After 12 hrs. at room temperature 25% sulphuric acid (33 ml) was added. The mixture was heated on a water bath for 1.5 hrs., cooled and the organic layer separated. The latter was concentrated under reduced pressure (aspirator vacuum) at 100° and the residue heated under reflux for 10 hrs. with a mixture of glacial acetic acid (33 ml) and
20% sulphuric acid (33 ml). The reaction mixture was chilled in an
ice bath, made alkaline with 33% sodium hydroxide solution, and
extracted with several portions of ether. The combined ethereal
extract was washed with water, dried, filtered and the solvent was
distilled off. The residue was distilled in vacuo and fraction
b.p. 126-128°/1.7 mm was collected. Yield: 6.67 g; 33.7% (based on
the starting acid). Semicarbazone m.p. 174-175° (from aqueous
ethanol). Anal. calcd. for C_{12}H_{13}N_5O: C, 59.3; H, 5.4; N, 28.8%.
Found: C, 60.9; H, 5.7; N, 23.9%. (C_{12}H_{13}N_4O.H_2O requires: C, 60.5;
H, 5.9; N, 23.5% (see p. 31).

2-Hydrazinopyridine m.p. 42-44° was prepared in 58.1% yield by the
method of Gregory and Wiggins (98).

3-Hydrazinopyridine. This hydrazine was prepared by the diazotization
of 3-aminopyridine and subsequent reduction of the diazonium chloride
by stannous chloride. The yield of 3-hydrazinopyridine was 21.9%.
m.p. 50-52°. lit. m.p. 53-55° (99).

4-Hydrazinopyridine hydrochloride. 4-Chloropyridine hydrochloride
(10 g) and hydrazine hydrate (50 ml) were heated together for 17 hrs.,
cooled, and the reaction mixture extracted with ether, the ether
extract was dried and filtered. The solvent was evaporated from the
extract giving residue which was redissolved in ether and dry HCl gas was passed through the ethereal solution to give a small amount of 4-hydrazinopyridine hydrochloride m.p. 228-234° (decomp.). The reaction mixture left after ether extraction was concentrated in vacuo on a water bath and the solid obtained was chilled in an ice bath and treated with 50 ml of 33% sodium hydroxide solution. This basic solution was extracted with ether. Through this ethereal solution dry HCl gas was passed and the precipitated 4-hydrazinopyridine hydrochloride filtered off. Yield: 2.4 g; 24.4% m.p. 236-240° (decomp.) lit. m.p. 238° (decomp.) (100).

The hydrazinopyridines thus obtained were condensed with 1,1,3,3-tetramethoxypropane in a similar way as used for 1-(o-tolyl)-pyrazole and the following 1-pyridylpyrazoles were obtained after treating the crude pyridylpyrazole with charcoal and chromatography on alumina using benzene as eluting solvent.

Table XIV: 1-PYRIDYL PYRAZoles.

<table>
<thead>
<tr>
<th>R</th>
<th>Yield %</th>
<th>m.p. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Pyridyl</td>
<td>44.9</td>
<td>36-40</td>
</tr>
<tr>
<td>3-Pyridyl</td>
<td>36.4</td>
<td>30-31</td>
</tr>
<tr>
<td>4-Pyridyl</td>
<td>30.5</td>
<td>84-85</td>
</tr>
</tbody>
</table>
All the pyridylpyrazoles thus obtained were identical in m.p., mixed m.p. and infrared spectra, with the pyrazoles obtained from the Ullmann condensation of halopyridines with pyrazole.

\[4-(1',2',4'-\text{Triazol-4'-yl})\text{pyridine}\]. Wiley and Hart's method (48) was used with slight modification in the product isolation procedure for this preparation. A mixture of 4-aminopyridine (2.2 g) and diformylhydrazine (2 g) was heated slowly to 130° and kept at this temperature for 9 hrs. and then the temperature was slowly raised to 175° and kept at this temperature for 6 hrs. The reaction mixture was cooled to room temperature, dissolved in 20 ml of ethanol and the ethanolic solution was treated with charcoal and filtered. Ether (75 ml) was added to the filtrate and kept overnight at 0° but no product could be isolated. The solvent was then removed and the residue thus obtained was subjected to chromatography over alumina. The column was eluted with a mixture of 50% chloroform/benzene and the various fractions eluted were collected. These fractions were combined and the solvent was evaporated from the combined fractions giving solid m.p. 105-112°. This was crystallised from chloroform/light petroleum and thus needles of \[4-(1',2',4'-\text{triazol-4'-yl})\text{pyridine}\] m.p. 110-111° were obtained. Yield: 0.2 g; 5.6%.
Further elution of the column with 50% chloroform/benzene
gave unreacted 4-aminopyridine.

\[ N-(4\text{-pyridyl})-o\text{-phenylenediamine}. \] The amine was prepared by the
following modification of Robinson and Thornley's method (49).

4-Chloropyridine hydrochloride (10.8 g) was neutralised with a 5% sodium carbonate solution and immediately extracted with chloroform.
The chloroform extract was dried and filtered. To this filtered
solution o-phenylenediamine (6 g) was added and the mixture heated
under reduced pressure (aspirator) at 98°C on an oil bath for 1.5
hrs.; chloroform was allowed to escape during the reaction. The
temperature was then slowly raised to 140°C and the reaction mixture
was kept at this temperature for an additional 1.5 hrs. The reaction
mixture was dissolved in hot dilute HCl, filtered and the filtrate
was made alkaline with sodium hydroxide solution. The brown
precipitate obtained was filtered off and crystallised from boiling
water after treating with animal charcoal. \[ N-(4\text{-pyridyl})-o\text{-phenylenediamine} \]
(elongated prisms) m.p. 175-178°C was obtained.

lit. m.p. 173.5°C (49). Yield: 1.96 g; 19%.

\[ 4\text{-}([\text{Benzimidazol-1-y1}])\text{pyridine}. \] A mixture of \[ N-(4\text{-pyridyl})-o\text{-phenylenediamine} \]
(0.88 g) and formic acid (1 ml) was heated on a
water bath for 15 hrs. The reaction mixture was made alkaline with sodium hydroxide solution (5%) and extracted with chloroform. The chloroform extract was dried, filtered and the solvent was evaporated giving residue m.p. 109-112°, recrystallisation from chloroform/light petroleum giving 4-(benzimidazol-1'-yl)pyridine m.p. 121-123°. lit. m.p. 123° (49). Yield: 0.6 g; 63.8%.

4-(2'-Phenyl-benzimidazol-1'-yl)pyridine. This compound was prepared by the method of Hein et al. (101). N-(4-pyridyl)-α-phenylene-diamine (0.3 g) and benzoic acid (0.3 g) was mixed with poly-phosphoric acid (5 ml) to a paste and heated at a temperature of 250 ± 5° with stirring for 25 mins. The reaction mixture was added to 200 ml of cold stirring water and let stand for 1 hr. This mixture was cooled in an ice bath and treated with 33% sodium hydroxide solution. The basic solution was extracted with chloroform. The extract was dried, filtered and chloroform evaporated leaving a solid which was crystallised from chloroform/light petroleum giving the product m.p. 164-166°. Yield: 0.3 g; 73.5%.

1,2-Di(γ-pyridyl)benzimidazole was prepared following the method of Bower, Stephens and Wibberley for the preparation of 2-substituted benzimidazoles from aldehydes (102). A mixture of N-(4-pyridyl)-
o-phenylenediamine (0.3 g) and isonicotinoylaldehyde (0.17 g) in glacial acetic acid (5 ml) was heated under reflux for 5 min., cooled, poured into water and basified with ammonia. The ammoniacal solution was extracted with chloroform. The chloroform extract was dried, filtered and the solvent evaporated from the filtrate. The residue was dissolved in benzene and the benzene solution was treated with charcoal and filtered. The filtrate was freed of the solvent giving the product. Yield: 0.2 g; 50.2%.

A portion of this product was chromatographed over alumina; benzene was used as the eluting solvent. The first few fractions gave a solid m.p. 151-152° which on recrystallisation from chloroform/light petroleum gave 1,2-di(γ-pyridyl)benzimidazole m.p. 151-152°.

c-(Pyrazol-1-yl)benzamide. A mixture of the acid chloride (1.8 g) from c-(pyrazol-1-yl)benzoic acid (see p. 89) and 0.88 ammonia (15 ml) was stirred for 0.5 hr. The reaction mixture was extracted with ether. The ether extract was dried and filtered. The solvent was removed from the filtrate leaving a very small amount of solid m.p. 146-147° which displayed strong bands in the infrared spectrum attributed to an aryl amide (see p. 40).
THE ULLMANN CONDENSATIONS.

The Ullmann condensations between azoles and different halocarlyls in pyridine with cupric oxide as the catalyst were carried out. In a typical experiment a mixture of 0.05 mole of the azole, 0.05 mole of the halocarlyl, anhydrous potassium carbonate (7 g) and cupric oxide (0.25 g) in pyridine (10 ml) was heated under reflux for 16 hrs. After cooling, the reaction mixture was filtered. The residue was extracted either with benzene or chloroform. The solvents were removed from the combined filtrates and the residue obtained was chromatographed over alumina giving the desired products. The individual reactions are described below.

Ullmann Condensation of Pyrrole.

The Ullmann condensations of pyrrole were carried out with the following chloronitrobenzenes (underlined).

(i) o-Chloronitrobenzene. A mixture of pyrrole (3.5 g), o-chloronitrobenzene (7.85 g), anhydrous potassium carbonate (7 g) and cupric oxide (0.25 g) in pyridine (10 ml) was heated under reflux for 7 hrs. The reaction mixture was extracted with benzene and the
residue obtained on removal of the solvents was chromatographed over alumina. Only \( p \)-chloronitrobenzene could be obtained. There was no evidence of the presence of \( 1-(p \)-nitrophenyl)pyrrole.

(ii) \( p \)-Chloronitrobenzene. Pyrrole (3.5 g) was condensed with \( p \)-chloronitrobenzene (11.9 g) in the manner described above for \( o \)-chloronitrobenzene. The total reaction time was 11 hrs. The reaction mixture was extracted with benzene and the benzene solution was chromatographed over alumina when only the starting \( p \)-chloronitrobenzene could be obtained. This \( p \)-chloronitrobenzene obtained from the chromatography was redissolved in benzene and chromatographed when \( p \)-chloronitrobenzene (9 g) was recovered on elution with benzene followed by \( 1-(p \)-nitrophenyl)pyrrole m.p. 185-186\(^\circ\). lit. m.p. 181\(^\circ\) (41). Yield: 0.1 g; 1%.

**Ullmann Condensation of Pyrazole.**

The Ullmann condensations of pyrazole were carried out using the following halobenzenes (underlined).
(i) o-Chloronitrobenzene. A mixture of pyrazole (3.4 g), o-chloronitrobenzene (11.9 g) and anhydrous potassium carbonate in pyridine (10 ml) was heated under reflux and to this refluxing solution cupric oxide (0.25 g) was added and the mixture allowed to reflux for 12 hrs. and cooled. The reaction mixture was filtered and the residue extracted with benzene (300 ml). The solvent was evaporated from the combined filtrate and extract. The residue obtained was dissolved in benzene. The benzene solution was treated with charcoal and filtered. The solvent was evaporated from the filtrate leaving behind the crude product. This crude material was chromatographed over alumina using benzene as the eluting solvent. The first few fractions on evaporation of benzene gave unreacted o-chloronitrobenzene (4.2 g). Further elution with benzene gave 1-(o-nitrophenyl)pyrazole m.p. 85-87°. lit. 83-89° (42). Yield: 6.2 g; 65.5 %.

(ii) m-Chloronitrobenzene. A mixture of pyrazole (3.4 g), m-chloronitrobenzene (7.85 g) and anhydrous potassium carbonate (7 g) in dimethylformamide (15 ml) was heated under reflux and to this refluxing mixture cupric oxide (0.25 g) was added and then let reflux for 46 hrs. The reaction mixture was cooled, filtered and the residue was extracted with benzene. The combined filtrate and the extract was freed of the solvents. The residue thus obtained
was chromatographed over alumina using benzene as the eluting solvent. The first few fractions afforded unchanged \( m \)-chloronitrobenzene (1.6 g) m.p. mixed m.p. 43-44\(^\circ\), followed by 1-(\( m \)-nitrophenyl)-pyrazole m.p. 74-75\(^\circ\) (mixed m.p. with pyrazole 45-52\(^\circ\)). Yield: 2.95 g; 31.2%.

(iii) \( p \)-Chloronitrobenzene. The reaction between pyrazole (3.4 g) and \( p \)-chloronitrobenzene (7.85 g) was carried out as in the case of \( o \)-chloronitrobenzene. Chromatography over alumina using benzene as eluting solvent gave unchanged \( p \)-chloronitrobenzene (4.02 g) followed by 1-(\( p \)-nitrophenyl)pyrazole. m.p. 171-173\(^\circ\). Yield: 1.2 g; 24.3% (based on the recovery of \( p \)-chloronitrobenzene).

(iv) 2-Bromopyridine. The reaction between pyrazole and 2-bromopyridine (7.9 g) was carried out over a reaction period of 16 hrs. The reaction mixture was worked up as described for the reaction (ii) above. Chromatography over alumina using benzene gave 1-(\( \alpha \)-pyridyl)pyrazole m.p. 38-40\(^\circ\). This was identical in all respects (m.p., mixed m.p. and infrared spectrum) with a sample synthesised through an unambiguous route (described on p. 92). Yield: 3.1 g; 42.5%.
(v) 2-Bromopyridine. The reaction was carried out as usual between pyrazole and 3-bromopyridine over a reaction period of 60 hrs. The reaction mixture was worked up as described previously giving 1-(β-pyridyl)pyrazole m.p. 30-31°. This was identical (m.p., mixed m.p., infrared spectrum) with the sample synthesised from 3-hydrizinopyridine (described on p. 92). Yield: 3 g; 41.2%.

(vi) 4-Chloropyridine hydrochloride. A mixture of pyrazole (3.4 g), 4-chloropyridine hydrochloride (7.5 g) and anhydrous potassium carbonate (14 g) in pyridine (25 ml) was heated under reflux. Cupric oxide (0.25 g) was added to this refluxing mixture and heating continued for 16 hrs. The reaction mixture was cooled and filtered. The residue was extracted from the filtrate with benzene. The solvents were removed from the combined filtrate and the extract and the residue thus obtained was chromatographed over alumina with benzene. The benzene eluents did not afford any product and the eluting solvent was changed to 10% chloroform/benzene when 4-(pyrazol-1'-yl)pyridine, m.p. 84-86° was obtained. This was identical in all respects (m.p., mixed m.p., infrared spectra) with a synthetic sample (see p. 92). Yield: 0.45 g; 6.2%.

(vii) 2-Chlorobenzonitrile. A mixture of pyrazole (3.4 g), 2-chlorobenzonitrile (6.85 g), anhydrous potassium carbonate (7 g)
in pyridine (10 ml) was heated under reflux and to this refluxing solution cupric oxide (0.25 g) was added. The heating was continued for 24 hrs. The reaction mixture was cooled and then extracted with chloroform. The combined filtrate and extract was freed of the solvent. The residue thus obtained was chromatographed over alumina. With benzene as eluting solvent unchanged 2-chloro-benzonitrile (4.6 g) was recovered followed by a liquid. This liquid was identified as 2-(pyrazol-1'-yl)benzonitrile. Yield: 0.52 g; 6.2%. On washing the column with chloroform 2-(pyrazol-1-yl)benzoic acid was obtained. Yield: 0.37 g; 3.8%. This was found to be identical (m.p., mixed m.p. and infrared spectra) with an authentic sample.

The method of Snyder and Elston (103) for the hydrolysis of nitriles to the corresponding amides by polyphosphoric acid was used. The product obtained on hydrolysis was the acid and not the expected amide. The hydrolysis was carried out as follows: A small amount of the liquid (2-(pyrazol-1'-yl)benzonitrile) obtained from the preceding experiment was mixed with 10 ml of the polyphosphoric acid and stirred at 110-120° for 15 minutes, cooled and poured into 50 ml of stirring water. This mixture was allowed to stand for a few minutes before extracting the mixture with three 100 ml portions of ether. The combined ethereal extracts
were dried, filtered and the ether was removed, leaving a solid m.p. 134-136°. (Mixed m.p. with \( \alpha \)-(pyrazol-1-yl)benzoic acid m.p. 134-138°). The infrared spectrum was also identical with that of \( \alpha \)-(pyrazol-1-yl)benzoic acid. No amide was isolated from this hydrolysis.

(viii) 3-Bromobenzonitrile. A mixture of pyrazole (1.7 g), 3-bromobenzonitrile (4.55 g) and anhydrous potassium carbonate (3.5 g) was heated under reflux with the addition of 0.25 g of cupric oxide, for 25.75 hrs. The reaction mixture was filtered and the residue extracted with chloroform. The solvent was removed from the combined filtrate and extracts. The residue thus obtained was chromatographed over alumina. Benzene was used as the eluting solvent giving unchanged 3-bromobenzonitrile (1.5 g) from the first few fractions followed by 3-(pyrazol-1'-yl)benzonitrile m.p. 63-64°. Yield: 1.75 g; 41.5%. Recrystallisation from chloroform/light petroleum raised the m.p. of 3-(pyrazol-1'-yl)benzonitrile to 65-66°.

(ix) 4-Bromobenzonitrile. The reaction of pyrazole (1.7 g) and 4-bromobenzonitrile (4.55 g) was carried out as in the case of 3-bromobenzonitrile over a reflux period of 90 hrs. The reaction mixture was worked up as in the preceding experiment and from
chromatography with benzene as eluting solvent 4-(pyrazol-1-yl)benzonitrile m.p. 89-91° was obtained (from chloroform/light petroleum). Yield: 1.98 g; 46.9%.

(x) o-Bromoacetophenone. A mixture of pyrazole (1.7 g) o-bromoacetophenone (5 g) and anhydrous potassium carbonate (3.5 g) in pyridine (10 ml) was heated under reflux, with the addition of cupric oxide (0.25 g), for 18 hrs. The reaction was extracted with benzene and the benzene extract was treated with charcoal. The residus obtained after removal of the solvent was subjected to chromatography over alumina using benzene as eluting solvent. An oil was obtained on evaporation of benzene from the eluents. This was identical (infrared spectrum, semicarbazone) with a synthetic sample of o-(pyrazol-1-yl)acetophenone. Yield: 2.65 g; 56.6%.

(xi) m-Bromoacetophenone. The reaction between pyrazole (1.7 g) and m-bromoacetophenone was carried out as in experiment (x) over a period of 48 hrs. The reaction mixture was extracted with chloroform and worked up as usual. Chromatography over alumina with benzene gave a small amount of unchanged m-bromoacetophenone followed by m-(pyrazol-1-yl)acetophenone m.p. 64-65° (chloroform/light petroleum). Yield: 2.88 g; 61.9%. Semicarbazones, m.p. 197-198° (aqueous ethanol). Calcd. for C₁₂H₁₃N₂O: C, 59.3; H, 5.4; N, 28.8%. Found: C, 59.7; H, 5.5; N, 27.5%. (See p.31.)

(xii) p-Bromoacetophenone. The reaction of pyrazole (1.7 g) with p-bromoacetophenone (5 g) was carried out over a reflux period of 48 hrs. as in the case of m-bromoacetophenone. After this period the reaction mixture was
extracted with chloroform. The solvents were removed leaving a solid which was crystallised from benzene and thus \( \text{p-}(\text{pyrazol-1-yl})\text{acetophenone m.p. 105-107}^\circ \) was obtained. This was twice recrystallised from chloroform/light petroleum when shining plates m.p. 109-110\(^\circ\) of \( \text{p-}(\text{pyrazol-1-yl})\text{acetophenone were obtained. Yield: 3.5 g; 74.6\%. Semi-} \)
carbazone m.p. 199-200\(^\circ\) (from aqueous ethanol). Anal. calcd. for
\( \text{C}_{12}\text{H}_{13}\text{N}_5\text{O}: \text{C, 59.3; H, 5.4; N, 28.8\%. Found: C, 60.9; H, 5.3; N, 25.2\% (p.31) }\)

(xiii) \( \text{a-Chlorobenzoic acid.} \) Cupric oxide (0.25 g) was added to a refluxing mixture of pyrazole (3.4 g), \( \text{a-Chlorobenzoic acid (7.83 g)} \) and anhydrous potassium carbonate (14 g) in pyridine (30 ml) and heated under reflux for 24 hrs. The reaction mixture was cooled and filtered (the pyridine solution). The residue from the filtration of the reaction mixture was extracted several times with water and this aqueous extract was acidified with hydrochloric acid. The acidified solution on keeping for two days deposited crystals m.p. 135-137\(^\circ\) which depressed the m.p. of \( \text{a-Chlorobenzoic acid (mixed m.p. 82-96}^\circ\) but not the m.p. of \( \text{a-}(\text{pyrazol-1-yl})\text{benzoic acid. This product m.p. 135-137}^\circ\) was identical with \( \text{a-}(\text{pyrazol-1-yl})\text{benzoic acid. Yield: 2.53 g; 26.9\%. Unreacted a-Chlorobenzoic acid (0.458 g) was also obtained from the acidified aqueous extract. }\)

The pyridine extract after removal of the solvent left residue which on distillation gave \( \text{1-phenylpyrazole, identical (infrared} \)
spectra) with an authentic sample prepared from phenylhydrazine
and 1,1,3,3-tetramethoxypropane. Yield: 1.45 g; 20.1%.

An attempt to prepare 4-oxopyrazolo-[1,4,a]indoline m.p.
107-110° (96) by the cyclisation of \( o \)-(pyrazol-1-yl)benzoic acid
either by concentrated sulphuric acid or by polyphosphoric acid
failed.

**Ullmann Condensation of Imidazoles.**

Various condensations of imidazoles were carried out with the
following halobenzenes (underlined):

(i) \( o \)-Chloronitrobenzene. The reaction between imidazole
(3.4 g) and \( o \)-chloronitrobenzene (11.9 g) was carried out in a
similar manner to that for pyrazole (p. 99). The total reflux period
was 11 hrs. The chromatography over alumina with benzene as
eluting solvent afforded some unchanged \( o \)-chloronitrobenzene followed
by 1-(\( o \)-nitrophenyl)imidazole m.p. 97-98°. Recrystallisation from
chloroform/light petroleum gave crystals with the same m.p. Yield:
6.1 g; 64%. 

1-(o-Nitrophenyl)imidazole obtained from the Ullmann condensation was subjected to degradation by the method of Forsyth and Pyman (44). 1-(o-Nitrophenyl)imidazole (0.3 g) and dimethylsulphate (0.3 ml) was heated at 100° for 30 mins., then boiled with a solution of 5% sodium hydroxide (15 ml) for a few minutes. On cooling needle shaped crystals were deposited. These crystals were identical in m.p. and mixed m.p. 68-70° with an authentic sample of o-nitroaniline. The infrared spectra were also identical. The product was recrystallised from water. An additional quantity of o-nitroaniline was obtained on ether extraction of the basified filtrate. Yield: 0.07 g; 31.1%.

(ii) m-Chloronitrobenzene. To a refluxing mixture of imidazole (3.4 g), m-chloronitrobenzene (7.85 g) and anhydrous potassium carbonate (7 g) in dimethylformamide (15 ml), cupric oxide (0.25 g) was added and allowed to heat under reflux for 19.5 hrs. The reaction mixture was cooled and filtered. The residue from the filtration was extracted with benzene. The combined filtrate and extracts were freed of solvents leaving a residue. This residue was chromatographed over alumina with benzene as eluting solvent. Unchanged m-chloronitrobenzene (1.64 g) was recovered from the eluting fractions. The solvent was changed to 50% chloroform/benzene and from the different fractions collected 1-(m-nitrophenyl)imidazole.
m.p. 109-111° was obtained on removal of the solvent. A sample was crystallised from chloroform/light petroleum m.p. 112-112.5°. Yield: 2.83 g; 29.9%.

A small sample (0.3 g) on degradation with dimethylsulphate and sodium hydroxide gave \( m \)-nitroaniline m.p. 110-111°, mixed m.p. 113-114° with an authentic sample of \( m \)-nitroaniline (identical infrared spectra). Yield: 0.32 g; 14.6%.

(iii) \( p \)-Chloronitrobenzene. The procedure employed was the same as for the condensation with \( p \)-chloronitrobenzene (experiment (ii)). Total reflux period 10 hrs. The reaction mixture was worked up as usual. The chromatography of the crude material over alumina using benzene as the eluting solvent afforded unchanged \( p \)-chloronitrobenzene (6.1 g). The solvent was changed to chloroform when the different chromatographic fractions were obtained. On removal of the solvent from these fractions 1-(\( p \)-nitrophenyl)-imidazole m.p. 210-211° was obtained. lit. m.p. 204-205° (44). Yield: 5.1 g; 53.9%.

A small amount of 1-(\( p \)-nitrophenyl)imidazole was treated with dimethylsulphate and sodium hydroxide solution (as for the degradation of 1-(\( p \)-nitrophenyl)imidazole. \( p \)-Nitroaniline (identical m.p., mixed m.p. 150-152° and infrared spectra) was obtained.
(iv) 2-Bromopyridine. The reaction between imidazole (3.4 g) and 2-bromopyridine (7.9 g) was carried out in the usual manner over a total reflux period of 19 hrs. The combined filtrate and benzene extract was treated with charcoal, filtered and the solvents removed from the filtrate. The residue thus obtained on chromatography over alumina with benzene as eluting solvent gave 2-(imidazol-1′-yl)pyridine m.p. 38-40°. Yield: 2.7 g; 37%

(v) 3-Bromopyridine. The reaction between imidazole (3.4 g) and 3-bromopyridine (7.9 g) was carried out over a reflux period of 24 hrs. The residue from the combined filtrate and extract was chromatographed over alumina. Elution with a mixture of 50% chloroform/benzene gave 3-(imidazol-1′-yl)pyridine m.p. 51-53°. A small portion of the imidazolylypyridine was distilled at 125°/5 mm and from the distillate crystals m.p. 56-58° (chloroform/light petroleum) were obtained. Yield: 3.7 g; 50.6%

(vi) 4-Chloropyridine hydrochloride. The reaction between imidazole (3.4 g) and 4-chloropyridine hydrochloride (7.5 g) was carried out in the same way as for pyrazole and 4-chloropyridine hydrochloride (p.101) described earlier. Total reaction time was 12 hrs. The reaction mixture was cooled, filtered and the residue thus obtained was extracted with benzene and then chloroform
(extract A). The combined filtrate and benzene extracts were treated with charcoal and filtered. The residue obtained after removal of the solvent was chromatographed over alumina using benzene as eluting solvent. 4-(Imidazol-1'-yl)pyridine (1.7 g) m.p. 113-116° was obtained after removal of the solvents from the eluents.

The extract A was treated with charcoal, filtered and the solvent removed from the filtrate giving an additional crop of 4-(imidazol-1'-yl)pyridine m.p. 110-112°. A small portion on crystallisation from chloroform/light petroleum gave colourless crystals m.p. 115-116°. Yield: 2.2 g; 30.1%.

(vii) 2-Chlorobenzonitrile. Imidazole (3.4 g) and 2-chlorobenzonitrile (6.85 g) was condensed in the usual manner over a reaction time of 50 hrs. The reaction mixture was filtered after cooling and the residue was extracted with chloroform. The solvent was removed from the combined filtrate and the residue thus obtained was dissolved in benzene. The benzene solution was treated with charcoal and filtered. The filtrate was concentrated giving 2-(imidazol-1'-yl)benzonitrile, clusters of needles, m.p. 147-148° (1.35 g). An additional amount (2.25 g) was obtained from the mother liquor. Yield: 3.6 g; 42.7%.
(viii) 3-Bromobenzonitrile. Imidazole (1.7 g) and 3-bromo-
benzonitrile (4.55 g) was reacted over a period of 50.5 hrs. The
reaction mixture was extracted with chloroform. The solvent was
removed from the extract and the residue thus obtained was dissolved
in hot benzene and treated with charcoal and filtered. The solvent
was removed from the filtrate and the residue was chromatographed
over alumina. On elution with benzene unchanged 3-bromobenzonitrile
(1.85 g) m.p., mixed m.p. 38-40° was obtained. The solvent was
then changed to 50% chloroform/benzene when from the different
fractions 3-(imidazol-1'-yl)benzonitrile m.p. 152-156° was obtained.
A small portion was crystallised from chloroform/light petroleum
raising the m.p. to 156-157°. Yield: 0.56 g; 13.2%.

The residue left after filtering the reaction mixture of the
benzonitrile and imidazole was extracted with water and the aqueous
extract was acidified with hydrochloric acid and extracted with
ether. The ether extract on removal of the solvent left m-(imidazol-
1-yl)benzoic acid m.p. 144-146°. Yield: 0.03 g; 0.6%.

(ix) 4-Bromobenzonitrile. The reaction was carried out over
a period of 50 hrs. as with 3-bromobenzonitrile. The chloroform
extract on removal of the solvent left a solid m.p. 143-147°. This
solid was first washed with a little benzene to remove unreacted
4-bromobenzonitrile and was then crystallised from benzene (charcoal) giving crystals of 4-(imidazol-1-yl)benzonitrile m.p. 154-155°. Recrystallisation from chloroform/light petroleum gave m.p. 154-155°. Yield: 3.1 g; 73%.

The aqueous extract of the residue from the reaction mixture on acidification and extraction with ether gave 4-(imidazol-1-yl)-benzoic acid, m.p. 235-236°. Yield: 0.03 g; 0.6%.

(x) o-Bromostyrenone. The reaction between imidazole (1.7 g) and o-bromostyrenone (5 g) was carried out over a reflux period of 48 hrs. The reaction mixture was cooled, filtered and the residue extracted with chloroform. The solvent was removed from the combined filtrate and extract and the residue thus obtained was dissolved in ethanol and treated twice with charcoal and ethanol removed giving product m.p. 171-173°. A small portion of this product was dissolved in ethanol and treated with charcoal, filtered and the filtrate concentrated. A small amount of water added and left to crystallise and filtered. Crystals m.p. 182-183° were obtained. This compound lacked bands in the region of carbonyl absorption in the infrared spectra (see p. 59). Yield: 3.2 g; 65%. This product did not give the isodiform test. Anal. calcd. for C₁₁H₁₀O₂: C, 71.0; H, 5.4; N, 15.1; O, 8.6%. Found: C, 70.4; H, 5.5; N, 14.8; O, 9.0%. Ultraviolet absorption: λₘₐₓ 217 and 262 mµ. logε 4.31 and 3.68.
A small sample of this product was dissolved in 5 ml of pyridine and treated with 0.5 ml of benzoyl chloride, heated on a hot plate for a few minutes and then added to water with stirring and left for 2 hrs., then 20 ml of 5% sodium carbonate solution was added and left for 0.5 hrs. The oily layer was extracted with chloroform. The extract was dried and filtered. The solvent was evaporated leaving an oil which was chromatographed over alumina with a mixture of 25% chloroform/benzene, giving the ester. This ester solidified on cooling.

The reaction between imidazole and α-bromoacetophenone was repeated and the heating time was reduced from 48 hrs. to 7 hrs. The residue from the chloroform extract of the reaction mixture was chromatographed over alumina. With benzene as the eluting solvent a small amount of unchanged α-bromoacetophenone was recovered. The solvent was then changed to 50% chloroform/benzene. Removal of the solvent from the various fractions left a syrupy liquid, α-(imidazol-1-yl)acetophenone. This was rechromatographed and was found to analyse for an imidazolylacetophenone. Yield: 1.6 g; 33.4%.

This syrupy liquid gave a picrate m.p. 185-186° (ethanol).

α-(Imidazol-1-yl)acetophenone picrate Anal. calcd. for C_{17}H_{13}N_{5}O_8: C, 49.2; H, 3.1; N, 16.9%. Found: C, 49.1; H, 3.3; N, 16.6%.
In the chromatography of the reaction mixture the column was eluted with chloroform. The eluents obtained left product m.p. 180-183°. This was identical with the product (m.p., mixed m.p. and infrared spectra) obtained in the reaction of imidazole and o-bromoacetophenone at a higher reaction period. Yield: 2.2 g; 47%.

A small amount of o-(imidazol-1-yl)acetophenone was heated for 24 hrs. in the presence of anhydrous potassium carbonate and cupric oxide in pyridine. The reaction mixture was cooled and filtered and the residue extracted with chloroform. The solvents were removed from the combined filtrates and the residue thus obtained was passed through a column of alumina. On elution with benzene a very small amount of o-imidazolylacetophenone was recovered. Changing the eluting solvent to chloroform afforded product m.p. 160-172° (recrystallised, chloroform/light petroleum m.p. 181-182°). This was identical with the product m.p. 182-183° obtained in the arylation of imidazole with o-bromoacetophenone over a reaction period of 48 hrs.

(xi) m-Bromoacetophenone. The reaction was carried out as usual over a period of 48 hrs. and extracted with chloroform. The residue from this extract was chromatographed over alumina. A small amount of unchanged m-bromoacetophenone was recovered when the column
was eluted with benzene. The solvent was then changed to 25% chloroform/benzene and \( m \)-(imidazol-1-yl)acetophenone m.p. 68-70° was obtained after removing the solvent from the various fractions collected. On twice recrystallisation from chloroform/light petroleum a purer product m.p. 72-73° was obtained. Yield: 3.2 g; 68.2%. Semicarbazone m.p. 201-202° (aqueous ethanol). Anal. calc. for \( C_{12}H_{13}N_5O \): C, 59.3; H, 5.4; N, 28.8%. Found: C, 59.3; H, 5.4; N, 28.1%.

(xii) \( \beta \)-Bromoacetophenone. The reaction between imidazole (1.7 g) and \( \beta \)-bromoacetophenone (5 g) was performed over a period of 48 hrs. The reaction mixture was cooled and then extracted with chloroform. The solvent was evaporated and the residue subjected to chromatography over alumina. With benzene as eluting solvent a small amount of unchanged \( \beta \)-bromoacetophenone was obtained. Changing the solvent to 50% chloroform/benzene gave \( \beta \)-(imidazol-1-yl)-acetophenone m.p. 119-120°. Yield: 3.3 g; 82.1%. Semicarbazone m.p. 237-238° (aqueous ethanol). lit. m.p. 118-119°, semicarbazone m.p. 232° (38).

Ullmann Condensation of 1,2,4-Triazole.

1,2,4-Triazole was allowed to condense with the following
haloaryls (underlined):

(i) \( \alpha \)-Chloronitrobenzene. A mixture of 1,2,4-triazole (3.45 g) \( \alpha \)-chloronitrobenzene (11.9 g) and anhydrous potassium carbonate (7 g) in pyridine (10 ml) was heated under reflux for 16 hrs., cooled and filtered. The residue was extracted with chloroform and the solvent was removed from the combined extract. The residue thus obtained was chromatographed over alumina. On eluting with benzene the first few fractions gave unchanged \( \alpha \)-chloronitrobenzene. Further elution with benzene gave a product \( m.p. 113-114^\circ \) which depressed the \( m.p. \) of 2,2'-dinitrobiphenyl (mixed \( m.p. 90-92^\circ \)). This product was found to be identical in all respects (\( m.p. \), mixed \( m.p. \) and infrared spectra) with an authentic sample of 1-(\( \alpha \)-nitrophenyl)-1,2,4-triazole \( m.p. 113-114^\circ \) (45). Yield: 6.48 g; 68.2%.

(ii) \( m \)-Chloronitrobenzene. The reaction using \( m \)-chloronitrobenzene was performed as for \( \alpha \)-chloronitrobenzene in the preceding experiment. The heating time was prolonged to 21 hrs. The working up of the reaction mixture gave only unchanged \( m \)-chloronitrobenzene. In another experiment the heating time was extended to 36 hrs. but again unchanged \( m \)-chloronitrobenzene was recovered. Another experiment was performed with quinoline instead of pyridine as the solvent; no arylation
product could be isolated. Similarly using cupric chloride instead of cupric oxide as the catalyst failed to arylate 1,2,4-triazole. In all these experiments bright coloured residue, insoluble in benzene, were observed to be formed in the reaction mixtures.

To a refluxing mixture of 1,2,4-triazole (3.45 g), m-chloronitrobenzene (7.85 g) and anhydrous potassium carbonate (7 g) in dimethylformamide (20 ml) cupric oxide (0.25 g) was added and the mixture was allowed to reflux for a period of 14 hrs. The solvent was removed from the reaction mixture by distillation. The residue from the distillation was extracted with benzene and this extract was treated with charcoal and filtered. The solvent was removed from the filtrate. The residue thus obtained was dissolved in ether and dry HCl gas passed through the ethereal solution. The precipitate formed was filtered off and made alkaline with 5% sodium hydroxide solution. This sodium hydroxide extract was exhaustively extracted with ether. The ether extract was dried and filtered. The solvent was evaporated from the extract and thus 1-(m-nitrophenyl)-1,2,4-triazole m.p. 146-148° (from chloroform/light petroleum) was obtained. Yield: 0.53 g; 6%. This was identical (m.p., mixed m.p., infrared spectra) with an authentic sample (45). m-Chloronitrobenzene (2.65 g) was also recovered unchanged from the reaction.
(iii) p-Chloronitrobenzene. The reaction between 1,2,4-triazole (3.45 g) and p-chloronitrobenzene (11.9 g) was carried out over a period of 16 hrs. The reaction mixture was worked up in a manner similar to that of p-chloronitrobenzene reaction (experiment (i)). The chromatography on alumina with benzene as eluting solvent afforded unchanged p-chloronitrobenzene (8.8 g). Elution with 25% chloroform/benzene gave unchanged 1-(p-nitrophenyl)-1,2,4-triazole, m.p. 194-196° (ethanol) lit. m.p. 190° (46). This was identical with an authentic sample obtained from p-nitrophenylhydrazine by the aza-salt method (110). Yield: 1.27 g; 13.4% (33.9% on the basis of recovered p-chloronitrobenzene).

(iv) 2-Bromopyridine. The reaction between 1,2,4-triazole (3.45 g) and 2-bromopyridine (7.9 g) was carried out over a period of 16 hrs. The combined filtrate and chloroform extract was treated with charcoal and filtered. The solvents were removed from the filtrate. The residue thus obtained was chromatographed over alumina. On using benzene as eluting solvent 2-(1',2',4'-triazol-1'-yl)pyridine m.p. 91-92° was obtained. Recrystallisation from chloroform/light petroleum gave crystals m.p. 92-93°. Yield: 2.1 g; 28.5%.

The eluting solvent was changed to 50% chloroform/benzene and 2-(1',2',4'-triazol-4'-yl)pyridine m.p. 167-168° was obtained. This
was identical in all respects (m.p., mixed m.p., infrared spectra) with an authentic sample. Yield: 0.17 g; 2.7%.

(v) 2-Bromopyridine. The reaction between 1,2,4-triazole (3.45 g) and 3-bromopyridine (7.9 g) was carried out as for 2-bromopyridine (: the preceding experiment) over a reflux period of 17 hrs. The combined filtrate and chloroform extract was freed of solvents and the residue obtained was chromatographed over alumina. Eluting with benzene gave 1 g of unchanged 3-bromopyridine. On changing the solvent to 50% chloroform/benzene residue m.p. 81-83° was obtained which was recrystallised from chloroform/light petroleum giving 3-(1',2',4'-triazol-1'-yl)pyridine m.p. 82-83°. Yield: 0.81 g; 11.1%.

Further elution of the chromatography column with 50% chloroform/benzene gave 3-(1',2',4'-triazol-4'-yl)pyridine m.p., mixed m.p. 154-158° identical with an authentic sample. The infrared spectra of the two compounds were also identical. Yield: 0.03 g; 0.42%.

(vi) 4-Chloropyridine hydrochloride. A mixture of 1,2,4-triazole (3.45 g) 4-chloropyridine hydrochloride (7.5 g) and anhydrous potassium carbonate (14 g) in pyridine (25 ml) was heated
under reflux and to this refluxing mixture cupric oxide (0.25 g) was added. The reaction mixture was allowed to reflux for 22 hrs., cooled and filtered. The residue extracted with chloroform and the combined filtrate and extract treated with charcoal, filtered and the solvent was evaporated from the filtrate. The residue (dark brown) was chromatographed over alumina. The eluting solvent used was 25% chloroform/benzene and 50% chloroform/benzene. Various fractions were collected and on removal of the solvent yielded 0.41 g of a compound m.p. 118-120°. This was crystallised from chloroform/light petroleum giving 4-(1',2',4'-triazol-1'-yl)pyridine m.p. 120-120.5°. Yield: 0.41 g; 5.7%.

On continuing elution with 50% chloroform/benzene a small amount of material was obtained. This was rechromatographed over alumina with 50% chloroform/benzene and 4-(1',2',4'-triazol-4'-yl)- pyridine was obtained. This was identical with a synthetic sample prepared from diformyl hydrazine and 4-amino pyridine (see p. 93). Yield: 0.16 g; 2.1%.

(vii) 2-Chlorobenzonitrile. The reaction between 1,2,4-triazole (1.725 g) and 2-chlorobenzonitrile (3.44 g) was carried out as usual over a period of 165 hrs. The reaction mixture was cooled, filtered and the residue was extracted with hot benzene. The...
solvents were removed from the combined filtrate and extracts. The residue thus obtained was chromatographed over alumina. On elution with benzene 2-chlorobenzonitrile (0.8 g) was recovered unchanged.

The solvent was changed to 50% chloroform/benzene giving solid m.p. 114-115° (mixed m.p. with 1,2,4-triazole 90-98°). This was recrystallised from chloroform/light petroleum giving 2-(1',2',4'-triazol-1'-yl)benzonitrile m.p. 120-121°. Yield: 0.42 g; 9.8%.

(viii) 3-Bromobenzonitrile. The reaction between 1,2,4-triazole (1.725 g) and 3-bromobenzonitrile (4.55 g) was carried out over a reflux period of 64 hrs. as with 2-chlorobenzonitrile above. The residue obtained after removal of the solvents from the combined filtrate and chloroform extracts was chromatographed over alumina. On elution with benzene unchanged 3-bromobenzonitrile (1.42 g) was recovered. Changing the solvent to 50% chloroform/benzene afforded a solid m.p. 146-149°. This, on further crystallisation with chloroform/light petroleum gave 3-(1',2',4'-triazol-1'-yl)benzonitrile m.p. 154-154.5°. Yield: 0.36 g; 8.4%.

The residue (left after the reaction mixture was extracted with chloroform and the filtrate) was extracted with water. The aqueous extract was acidified with hydrochloric acid and extracted with chloroform. On removal of chloroform a very small amount of
solid m.p. 248–250°C was obtained which is believed to be m-(1,2,4-triazol-1-yl)benzoic acid.

(ix) 4-Bromobenzonitrile. The reaction between 1,2,4-triazole (1.725 g) and 4-bromobenzonitrile (4.55 g) was carried out as with 3-bromobenzonitrile. The reaction time was 50 hrs. The reaction mixture was cooled and filtered. The residue was extracted with several portions of hot chloroform. The combined filtrate and extracts were freed of the solvent leaving behind a solid residue. This solid residue was dissolved in chloroform when a small portion was found to be insoluble in cold chloroform and was filtered off (A). The chloroform solution was chromatographed over alumina. When the eluting solvent was benzene unchanged 4-bromobenzonitrile (2.8 g) was obtained. The solvent was changed to 50% chloroform/benzene giving 4-(1',2',4'-triazol-1'-yl)benzonitrile m.p. 166-167°C and was recrystallised from chloroform/light petroleum, m.p. 166-167°C. Yield: 0.5 g; 11.5%.

A small portion of the residue (A) m.p. 280–286°C was dissolved in ethanol and treated with charcoal, filtered and the filtrate concentrated giving crystals m.p. 289–290°C (decomp.). A tentative structure β-(1,2,4-triazol-1-yl)benzamide is assigned on the basis of elemental analysis and infrared spectrum. Yield: 0.18 g; 3.8%.
The aqueous extract of the residue from the reaction mixture gave a very small amount of material on acidification of the aqueous extract with hydrochloric acid and extraction of this acidified solution with chloroform. This compound m.p. 273-282° is presumed to be p-(1,2,4-triazol-1-yl)benzoic acid. lit. m.p. > 270°(50).

An earlier reaction between 1,2,4-triazole and 4-chlorobenzonitrile failed to give any arylation product. Unchanged 4-chlorobenzonitrile was recovered.

(x) o-Bromoacetoephone. The reaction between 1,2,4-triazole (1.725 g) and o-bromoacetoephone (5 g) was carried out over a reflux period of 48 hrs. in a manner similar to that described for imidazole and o-bromoacetoephone. The reaction mixture was cooled and filtered. The residue was extracted with chloroform. The solvents were removed from the combined filtrate and extract and the residue thus obtained was chromatographed over alumina. Elution of the column with benzene afforded a very small amount of unchanged o-bromoacetoephone. Elution was continued with benzene followed by 25% chloroform/benzene when from these two solvents o-(1,2,4-triazol-1-yl)acetophenone m.p. 84-86° was obtained on removal of the solvents from the eluents. Yield: 1.69 g; 36.9%. o-(1,2,4-Triazol-1-yl)acetophenone picrate m.p. 121-122° (ethanol), depressed the m.p.
of picric acid (mixed m.p. 82-95°). Anal. calcd. for C_{16}H_{12}N_{6}O_{3}: C, 46.2; H, 2.9; N, 20.2%. Found: C, 46.5; H, 3.2; N, 19.9%.

On eluting the chromatography column with 50% chloroform/benzene a solid m.p. 143-151° was obtained on removal of the solvent from the eluents. This was recrystallised from chloroform/light petroleum giving crystals m.p. 158-159°. This material lacked infrared absorption in the carbonyl region and gave a negative iodoform test. Yield: 1.07 g; 23.3%. Anal. calcd. for C_{10}H_{9}N_{3}O: C, 64.2; H, 4.8; N, 22.5; O, 8.6%. Found: C, 63.8; H, 4.9; N, 22.7; O, 9.2%. Ultraviolet absorption: \( \lambda_{\text{max}} \) 214, 260 and 282 nm (log ε 4.20, 3.7, 3.25).

(xi) \( m \)-Bromoacetophenone. The reaction was carried out as usual between 1,2,4-triazole (1.725 g) and \( m \)-bromoacetophenone (5 g) over a reflux period of 50 hrs. Chromatography over alumina with benzene gave unchanged \( m \)-bromoacetophenone (3.63 g). Elution with 25% chloroform/benzene gave residue m.p. 109-111° on removal of the solvent. On crystallisation with chloroform/light petroleum \( m \)-(1,2,4-triazol-1-yl)acetophenone m.p. 113-114° was obtained. Yield: 0.49 g; 10.6%.

(xii) \( p \)-Bromoacetophenone. Total reflux period of this reaction between 1,2,4-triazole (1.725 g) and \( p \)-bromoacetophenone (5 g) was
23 hrs. The reaction mixture was worked up in the usual manner and subjected to chromatography over alumina, unchanged p-bromoacetophenone (3.7 g) was eluted with benzene. Elution with 50% chloroform/benzene afforded a residue m.p. 145-147° on removal of the solvent. This residue was crystallised from chloroform/light petroleum giving p-(1,2,4-triazol-1-yl)acetophenone m.p. 153-154°. Yield: 0.24 g; 5.1%. Semicarbazone m.p. 249-250° (from aqueous ethanol). Calcd. for C₁₁H₁₂N₂O: C, 54.1; H, 4.9; N, 34.4%. Found: C, 51.4; H, 5.4; N, 27.1%. (C₁₁H₁₂N₂O.1.5H₂O requires: C, 51.4; H, 5.8; N, 27.2%, see p.31).

**Ullmann Condensation of Indole.**

Ullmann condensations of indole were performed with the following haloaryl (underlined):

(1) p-Chloronitrobenzene. A mixture of indole (5.85 g), p-chloronitrobenzene (7.85 g), anhydrous potassium carbonate (7 g) in pyridine (10 ml) was heated under reflux and to this cupric oxide (0.25 g) was added. The reaction mixture was allowed to reflux for 18.25 hrs., cooled and filtered. The residue was extracted with benzene. The combined filtrate and extract was treated with charcoal and filtered. The solvents were evaporated from the filtrate leaving a residue which was dissolved in benzene and chromatographed over
alumina. The first few fractions from benzene gave a small mixture of unchanged $o$-chloronitrobenzene and indole followed by a product m.p. 81-82$^\circ$. This product m.p. 81-82$^\circ$ was crystallised from chloroform/light petroleum giving 1-(o-nitrophenyl)indole m.p. 82-83$^\circ$, yellow needles. Yield: 5.96 g; 50%.

(ii) m-Bromonitrobenzene. The reaction of m-chloronitrobenzene was carried out with indole in dimethylformamide in a manner similar to that for pyrazole and imidazole, but no 1-(m-nitrophenyl)indole could be isolated.

The reaction between indole (2.92 g) and m-bromonitrobenzene (5.05 g) in pyridine (10 ml) and cupric oxide (0.125 g) was carried out over a period of 48 hrs. as with $o$-chloronitrobenzene. The residue, obtained on removal of the solvent from the combined filtrate and chloroform extract, was chromatographed over alumina with benzene as the eluting solvent. The first few fractions on removal of the solvent left a residue m.p. 59-61$^\circ$. This on crystallisation from ethanol gave yellow needles of 1-(m-nitrophenyl)indole m.p. 67-68$^\circ$. Yield: 5.14 g; 79.6%.

(iii) p-Chloronitrobenzene. The reaction between indole (5.85 g) and p-chloronitrobenzene (7.35 g) was carried out in the same fashion
as with γ-chloronitrobenzene. The total reflux period was 19 hrs.
Chromatography over alumina with benzene as the eluting solvent
gave a residue which was crystallised twice from chloroform/light
petroleum giving 1-(γ-nitrophenyl)indole, yellow crystals m.p.
133-134°. Yield: 1.78 g; 14.9%.

Indole (1.6 g) was also recovered from the chromatography.

(iv) 2-Bromopyridine. The reaction between indole (2.93 g)
and 2-bromopyridine (4 g) was carried out over a reaction period of
17 hrs. in the usual manner. Chromatography over alumina with benzene
as eluting solvent gave a residue when the eluents were freed of
the solvent. The residues from the various fractions were collected
together and distilled under reduced pressure giving 2-(indol-1'-yl)-
pyridine b.p. 167-169°/0.5 mm. Yield: 3.83 g; 79.1%.

(v) 3-Bromopyridine. The reaction between indole (5.85 g) and
3-bromopyridine (7.9 g) was carried out over a reflux period of
24 hrs. The reaction mixture was worked up as in the case of the
reaction of indole and 2-bromopyridine. The distillation of the
product gave 3-(indol-1'-yl)pyridine b.p. 141-143/0.35 mm. Yield:
5.56 g; 75.4%.
(vi) 4-Chloropyridine hydrochloride. A mixture of indole (5.85 g), 4-chloropyridine hydrochloride (7.5 g) and anhydrous potassium carbonate (14 g) in pyridine (25 ml) was heated under reflux and to this cupric oxide (0.25 g) was added. The mixture was allowed to reflux for 20.5 hrs., cooled and filtered. The residue was extracted with benzene and chloroform. The combined extract was treated with charcoal, filtered, and the solvents removed from the filtrate. Chromatography over alumina gave only tars.

The reaction was repeated with a reaction time of only 40 hrs. Working up of the reaction mixture left tars and no clean identifiable product was isolated.

In another experiment 4-chloropyridine was liberated from its salt (7.5 g) by 5% sodium carbonate solution and taken up in chloroform. This chloroform solution was dried and filtered and to this solution indole (5.85 g), pyridine (10 ml), cupric oxide (0.25 g) and anhydrous potassium carbonate (7 g) was added and heated under reduced pressure (aspirator vacuum) on a water bath for 20 hrs. Chloroform was allowed to escape during the reaction. The reaction mixture was cooled, filtered, and extracted with chloroform. The solvent was removed from the combined extract and filtrate. The residue thus obtained was distilled under reduced pressure when only
Indole was recovered from the distillate b.p. 95-96°/5 mm. m.p. 52-54° (mixed m.p. 52-54° with indole).

The reaction of indole (5.35 g), 4-chloropyridine hydrochloride (7.5 g), cupric oxide (0.25 g) in dimethylformamide (50 ml) was carried out in the usual manner over a period of 22 hrs. The reaction mixture was cooled and filtered. The filtrate was added to stirring water (250 ml), allowed to stand for a few hours and filtered off. The precipitate obtained was dissolved in chloroform and mixed with the chloroform extract of the residue from the reaction mixture. The combined chloroform extracts were dried and filtered. The solvent was removed from the filtrate and the residual liquid distilled under reduced pressure, when from the distillate only indole was obtained (identical m.p. and mixed m.p.). The residue from this distillate was taken up in chloroform and treated with charcoal and filtered. On removal of the solvent a small amount of viscous liquid was obtained. This was very similar to the 2- and 3-(indol-1′-y1)-pyridines in its infrared and ultraviolet spectra. This small amount of the sticky substance was chromatographed over alumina using benzene as the eluting solvent. The first fraction gave a very small amount of indole b.p. 76-78°/0.7 mm (identical m.p. and mixed m.p.) followed by a few fractions which left a syrupy liquid on evaporation of benzene from the eluents. The various fractions were combined giving
4-(indol-1'-yl)pyridine. Yield: 0.25 g; 2.6%. Picrate m.p. 209-211°, recrystallised from ethanol, needles m.p. 212-213°. Anal. calcd. for C_{19}H_{13}N_{5}O: C, 54.0; H, 3.1; N, 16.6%. Found: C, 54.1; H, 3.3; N, 16.3%.

The reaction in dimethylformamide was repeated but again a very small amount of 4-(indol-1'-yl)pyridine was obtained.

(vii) 2-Chlorobenzonitrile. The Ullmann condensation between indole (5.85 g) and 2-chlorobenzonitrile (6.35 g) was carried out over a reflux period of 50 hrs. The reaction mixture was cooled and filtered. The residue was extracted with chloroform. The solvents were evaporated and the residue was chromatographed over alumina. The first few fractions obtained on elution with benzene were combined. The latter fractions gave unreacted indole. The first few fractions obtained from chromatography were rechromatographed over alumina using benzene as eluting solvent. The fractions which eluted first were freed of benzene and then treated with hot light petroleum (to remove any indole) and filtered. The residue m.p. 106-108° left after extracting with light petroleum was crystallised from chloroform/light petroleum to give 2-(indol-1'-yl)-benzonitrile m.p. 109-110°. Yield: 0.2 g; 3.6%.

(viii) 3-Bromobenzonitrile. The reaction of indole (2.925 g) and 3-bromobenzonitrile (4.55 g) with cupric oxide (0.125 g) was carried out as usual in pyridine (10 ml) over a period of 113 hrs. After this
period the reaction mixture was cooled and filtered. The residue was extracted with chloroform and the solvents were removed from the combined filtrate. The residue thus left was dissolved in benzene when a portion of the residue m.p. 175-177° was found to be insoluble in benzene and this (Residue A) was filtered off. The benzene soluble portion was chromatographed over alumina and the residues from the different fractions, obtained after removal of benzene, were collected together and distilled under reduced pressure. Distillation gave 3-(indol-1-yl)benzonitrile b.p. 190-192°/2 mm crystallised from aqueous ethanol in colourless needles m.p. 37-38°. Yield: 3.04 g; 55.9%.

Residue A, m.p. 175-177° was crystallised from ethanol giving crystals, m.p. 181-182°. Yield: 0.4 g; 6.6%. This was assigned the structure m-(indol-1-yl)benzamide on the basis of its elemental analysis and infrared spectrum.

(ix) 4-Bromobenzonitrile. The reaction between indole (2.925 g) and 4-bromobenzonitrile (4.55 g) was performed in a similar manner to the reaction of 3-bromobenzonitrile. Heating under reflux was carried out for 39 hrs. Chromatography over alumina was performed with benzene as the eluting solvent when a very small amount of unchanged 4-bromobenzonitrile was recovered. Further elution with benzene gave a
residue m.p. 89-92° on evaporation of the solvent from the eluents. This was crystallised from chloroform/light petroleum giving 4-(indol-1'-yl)benzonitrile m.p. 95-96°. (This depressed the m.p. of 4-bromo-benzonitrile). Yield: 4.2 g; 77.1%.

The residue, left after the extraction of the reaction mixture with chloroform, was extracted with water. This aqueous extract was acidified with hydrochloric acid and then extracted with ether. The ether extract was dried and filtered. The solvent was removed from the extract giving a very small amount of impure acid m.p. 192-207°, probably 2-(indol-1-yl)benzoic acid.

(x) α-Bromacetophenone. The reaction between indole (2.925 g) and α-bromacetophenone (5 g) was carried out in pyridine (10 ml) in the presence of anhydrous potassium carbonate (7 g) and cupric oxide (0.25 g). The mixture was heated under reflux for 24 hrs. The reaction mixture was worked up as usual and the residue thus obtained was chromatographed on alumina with benzene as eluting solvent. The eluents on removal of benzene left a syrupy liquid which was distilled under reduced pressure. α-(Indol-1-yl)acetophenone, pale yellow liquid b.p. 163-164°/0.25 mm was obtained. Yield: 4.35 g; 74%. Semicarbazone m.p. 198-199° (aqueous ethanol). Anal. calcd. for C_{17}H_{16}N_{4}O: C, 69.9; H, 5.5; N, 19.2%. Found: C, 70.0; H, 5.5; N, 17.5%. (See p.31.)
(xi) m-Bromoacetophenone. The reaction of indole (2.925 g) and m-bromoacetophenone (5 g) was carried out as for p-bromoacetophenone over a period of 30 hrs. and worked up in the same way. The liquid, obtained from the chromatography over alumina with benzene as eluting solvent, was distilled under reduced pressure when m-(indol-1-yl)acetophenone b.p. 181-182°/0.25 mm was obtained. Yield: 3.5 g; 60.2%. Semicarbazone m.p. 171-172° (aqueous ethanol). Anal. calcd. for C₁₇H₁₆N₄O: C, 69.9; H, 5.5; N, 19.2%. Found: C, 68.5; H, 5.3; N, 20.0%. (See p.31.)

(xii) p-Bromoacetophenone. The reaction between indole (2.925 g) and p-bromoacetophenone (5 g) was carried out over a period of 45 hrs. in a similar manner to that for the meta isomer. From the chromatography using benzene as the eluting solvent, residue m.p. 72-75° was obtained on removal of the solvent from the eluents. On crystallisation from chloroform/light petroleum p-(indol-1-yl)acetophenone m.p. 85-87° was obtained. Yield: 5.45 g; 92.8%. Semicarbazone m.p. 214-215° (aqueous ethanol). Anal. calcd. for C₁₇H₁₆N₄O: C, 69.9; H, 5.5; N, 19.2%. Found: C, 69.5; H, 5.7; N, 18.4%.

(xiii) p-Iodosobenzoic acid. A mixture of indole (2.925 g), p-iodobenzoic acid (5.7 g) and anhydrous potassium carbonate (7 g) in pyridine (30 ml) was heated under reflux and to this refluxing mixture
cupric oxide (0.125 g) was added. The reaction mixture was allowed to reflux for 50 hrs., cooled and filtered. The residue was extracted with chloroform and the combined filtrate and extract freed of the solvent. No identifiable products could be obtained from this. The residue, left after extraction with chloroform, was extracted with hot water and the aqueous extract treated with charcoal, filtered and the filtrate cooled and acidified with hydrochloric acid. The precipitated acid was crystallised from hot water when crystals m.p. 161-163° (mixed m.p. with o-iodobenzoic acid 110-128°) of o-(indol-1-yl)benzoic acid were obtained. Recrystallisation from aqueous ethanol gave crystals m.p. 164-165°. Yield: 1.8 g; 30%.

An attempt to cyclise o-(indol-1-yl)benzoic acid with polyphosphoric acid failed.

Ullmann Condensation of Benzimidazole.

Ullmann condensations of benzimidazole with various haloaryls (underlined) are described below.

(i) o-Chloronitrobenzene. The reaction between benzimidazole (5.9 g) and o-chloronitrobenzene (7.85 g) was carried out over a reflux
period of 7 hrs. in a manner similar to that of other azoles described previously. The reaction mixture was worked up in the usual manner. The extracts were treated with charcoal and filtered. The residue obtained from the evaporation of the solvent from the filtrate was chromatographed over alumina. When benzene was used as eluting solvent some o-chloronitrobenzene (2.9 g) was recovered unchanged from the column. Elution with 50% chloroform/benzene gave a sticky residue on removal of the solvent. This sticky residue on trituration with light petroleum gave 1-(o-nitrophenyl)benzimidazole m.p. 80-82°, lit. m.p. 82° (47). Yield: 5.4 g; 45.3%.

(ii) m-Bromonitrobenzene. The reaction between benzimidazole and m-chloronitrobenzene in either pyridine or dimethylformamide under the usual conditions failed to produce 1-(m-nitrophenyl)benzimidazole. The only product isolated was unreacted m-chloronitrobenzene.

The reaction of benzimidazole (2.95 g) and m-bromonitrobenzene (5.05 g) was carried out over a period of 46 hrs. The reaction mixture was processed in the usual way. Chromatography on alumina with benzene as eluting solvent gave unchanged m-bromonitrobenzene (1.73 g). Elution was continued with 50% chloroform/benzene and on evaporation of the solvent from the various fractions solid m.p. 143-150° was obtained. This on crystallisation from chloroform/light
petroleum gave 1-(m-nitrophenyl)benzimidazole m.p. 151-152°. lit. m.p. 149.5° (47). Yield: 0.48 g; 8.1%.

(iii) p-Chloronitrobenzene. The reaction between benzimidazole (5.9 g) and p-chloronitrobenzene (5.9 g) was carried out as with 3-chloronitrobenzene for a total reflux period of 3.5 hrs. The reaction mixture was worked up in the usual manner. Chromatography over alumina with benzene as the solvent gave unchanged p-chloronitrobenzene (4 g). The eluting solvent was then changed to 50% chloroform/benzene. On evaporation of the solvent from the eluents 1-(p-nitrophenyl)benzimidazole m.p. 181-183° (mixed m.p. with benzimidazole 140-160°) was obtained. lit. m.p. 182° (47). Yield: 3.28 g; 27.5%. Elution of the column with ethyl acetate gave unchanged benzimidazole (0.55 g).

(iv) 2-Bromopyridine. A mixture of benzimidazole (5.9 g), 2-bromopyridine (7.9 g) and anhydrous potassium carbonate (7 g) in pyridine (10 ml) with cupric oxide (0.125 g) was heated under reflux over a period of 19 hrs. The reaction mixture was worked up as usual. The chloroform extract and the filtrate were treated with charcoal and filtered. The solvent was removed from the filtrate, giving a residue. This residue was chromatographed over alumina. The chromatography column was eluted with 50% chloroform/benzene and various fractions
collected. The solvent was removed from these eluents and the residues obtained were combined and distilled under reduced pressure. The fraction b.p. 186-188°/31.5 mm was collected. This fraction was redistilled giving 2-(benzimidazol-1′-yl)pyridine b.p. 177-178°/1 mm, shining plates m.p. 59-60° (chloroform/light petroleum). Yield: 4.54 g; 46.5%.

(v) 3-Bromopyridine. The reaction between benzimidazole (5.9 g) and 3-bromopyridine (7.9 g) was carried out over a reflux period of 24 hrs. as in the case of 2-bromopyridine. The reaction mixture was allowed to cool and filtered. The residue was extracted with chloroform. The solvents were removed from the combined filtrate and extracts. The residue thus obtained was extracted with hot benzene and filtered, the residue from this filtration was found to be identical with benzimidazole (identical m.p., mixed m.p.). The filtrate (benzene extract) on removal of benzene gave solid m.p. 105-107°. This was crystallised from chloroform/light petroleum giving prisms of 3- (benzimidazol-1′-yl)pyridine m.p. 107-108°. Yield: 3.25 g; 33.3%.

(vi) 4-Chloropyridine hydrochloride. The reaction between 4-chloropyridine hydrochloride (7.5 g) and benzimidazole (5.9 g) was carried out over a reflux period of 19.5 hrs. in the presence of
anhydrous potassium carbonate (14 g) and cupric oxide (0.25 g) in pyridine (25 ml). The reaction mixture was cooled and filtered. The residue obtained was extracted with chloroform. The filtrate and the chloroform extracts were combined and the solvents removed from it leaving a residue which was dissolved in hot benzene. The benzene solution was treated with charcoal and filtered. Benzene was evaporated from the filtrate and the residue thus obtained was chromatographed over alumina. The chromatography column was eluted with 25% chloroform/benzene. The solvent was removed from the eluents leaving a residue. This residue gave 4- (benzimidazol-1'-yl)-pyridine m.p. 119-120° (chloroform/light petroleum), identical with a synthetic sample. Yield: 2 g; 20.8%.

(vii) 2-Chlorobenzonitrile. The reaction was carried out as usual with benzimidazole (5.9 g), and 2-chlorobenzonitrile (6.85 g). The total reflux period was 52 hrs. The reaction mixture was worked up as usual by extracting with chloroform. The solvent was removed from the extracts. The residue thus obtained was subjected to chromatography over alumina with benzene as the eluting solvent. A small amount of unchanged 2-chlorobenzonitrile was obtained. The eluting solvent was then changed from benzene through 25-50% chloroform/benzene. The different fractions obtained were combined and the solvents evaporated giving a solid m.p. 106-109°. This solid on
crystallisation from chloroform/light petroleum gave 2-(benzimidazol-1'-yl)benzonitrile m.p. 110-111°. Yield: 1.34 g; 12.2%.

(viii) 3-Bromobenzonitrile. The reaction between benzimidazole (2.95 g) and 3-bromobenzonitrile (4.55 g) was carried out over a reflux period of 39 hrs. in the usual manner. The residue obtained on removal of the solvent from the chloroform extract and filtrate was chromatographed over alumina. A small amount of 3-bromobenzonitrile was obtained on elution with benzene. Elution with 50% chloroform/benzene gave a syrupy liquid which on crystallisation from aqueous ethanol gave 3-(benzimidazol-1'-yl)benzonitrile m.p. 67-68°. Yield: 1.68 g; 30.7%. Anal. calcd. for C_{14}H_{9}N_{3}: C, 76.7; H, 4.1; N, 19.2%. Found: C, 73.1; H, 4.7; N, 17.9%. Picrate m.p. 205-207° (from ethanol). Anal. calcd. for C_{20}H_{12}N_{6}.O: C, 53.6; H, 2.7; N, 18.8%. Found: C, 53.0; H, 2.8; N, 18.3%.

A small portion of the benzonitrile was dissolved in benzene and dry HCl gas was passed through the solution when the hydrochloride was precipitated. This was crystallised from ethanol giving 3-(benzimidazol-1'-yl)benzonitrile hydrochloride m.p. 252-254°. Anal. calcd. for C_{14}H_{10}N_{3}Cl: C, 65.8; H, 3.9; N, 16.4; Cl, 13.9%. Found: C, 65.1; H, 4.1; N, 16.2; Cl, 13.7%.
(ix) 4-Bromobenzonitrile. The reaction was carried out over a period of 101 hrs. in a manner similar to that of 3-bromobenzonitrile. Benzimidazole (2.95 g) and 4-bromobenzonitrile (4.55 g) was used. Chromatography over alumina was performed with benzene as eluting solvent. Some unchanged 4-bromobenzonitrile (1.1 g) was obtained. The solvent was then changed to 50% chloroform/benzene and the various fractions obtained were collected. The solvent was removed leaving a residue m.p. 132-133°C. This residue was crystallised from chloroform/light petroleum giving 4-(benzimidazol-1'-yl)-benzonitrile m.p. 134-135°C. Yield: 2.3 g; 41.6%.

(x) o-Bromoacetophenone. The reaction between benzimidazole (2.95 g) and o-bromoacetophenone (5 g) was carried out over a reflux period of 46 hrs. The reaction mixture was extracted with chloroform. On removal of the solvents from the extract a solid m.p. 134-136°C (mixed m.p. with benzimidazole 140-145°C) was obtained. A small sample crystallised from hot water giving crystals m.p. 223-224°C. This gave a negative iodoform test and lacked the usual carbonyl absorption of an acetophenone in the infrared absorption spectrum. Yield: 4.9 g; 83.1%. The compound analysed for C_{15}H_{12}N_{2}O. Anal. calcd.: C, 76.3; H, 5.1; N, 11.9; O, 6.8%. Found: C, 76.1; H, 5.1; N, 11.8; O, 7.3%. Ultraviolet absorption: $\lambda_{\text{max}}$ 236, 287 sh., 323 and 335 mμ (log $\varepsilon$ : 4.31, 3.57, 3.96 and 3.98).
The reaction was repeated with a heating time of only 3 hrs. The reaction mixture was worked up as for the preceding experiment. The residue on chromatography over alumina with benzene as eluting solvent gave some unchanged \( \alpha \)-bromoacetophenone (1.36 g). The solvent was then changed to 25\% chloroform/benzene and from the various fractions \( \alpha \)-(benzimidazol-1-yl)acetophenone, a syrupy liquid was obtained. Yield: 2.7 g; 46\%. (73.4\% based on the recovery of \( \alpha \)-bromoacetophenone).

Further elution of the column with 50\% chloroform/benzene and chloroform gave solid residue on evaporation of the solvents. This residue gave benzimidazole (probably mixed with a small amount of material, m.p. 223-224\(^\circ\), obtained in the previous reaction).

\( \alpha \)-(Benzimidazol-1-yl)acetophenone semicarbazone m.p. 212-214\(^\circ\), (aqueous ethanol). Anal. calcd. for \( \text{C}_\text{16} \text{H}_{15} \text{N}_5 \text{O} \): C, 65.5; H, 5.1; N, 23.9\%. Found: C, 64.1; H, 5.4; N, 22.6\%. \( \text{C}_\text{16} \text{H}_{15} \text{N}_5 \text{O}_2 \cdot \frac{1}{2}\text{H}_2\text{O} \) requires: C, 63.6; H, 5.3; N, 23.2\%). Picrate m.p. 182-183\(^\circ\) (from ethanol).
Anal. calcd. for \( \text{C}_\text{12} \text{H}_{15} \text{N}_5 \text{O}_3 \): C, 54.2; H, 3.2; N, 15.1\%. Found: C, 54.3; H, 3.5; N, 15.0\%.

\( \text{(xi)} \) \( \mu \)-Bromoacetophenone. The reaction of benzimidazole (2.95 g) and \( \mu \)-bromoacetophenone (5 g) was carried out in a similar manner as for \( \alpha \)-bromoacetophenone. The total reaction period was 45 hrs. The
reaction mixture was worked up as usual by extraction of the reaction mixture with chloroform. The residue obtained on removal of the solvent was subjected to chromatography on alumina. With benzene as eluting solvent unchanged m-bromoacetophenone (2.4 g) was obtained. The solvent was then changed to 25% chloroform/benzene and from the various fractions collected the solvent was removed and thus a semi solid material was obtained. The semi solid material from the different fractions was combined and dissolved in benzene. The benzene solution was treated with charcoal and filtered. The solvent was evaporated from the filtrate. The residue thus obtained was chromatographed on alumina with 25% chloroform/benzene as eluting solvent. The residues from these chromatographic fractions gave m-(benzimidazol-1-yl)-acetophenone m.p. 77-78°, needles from chloroform/light petroleum. Yield: 1.1 g; 18.8%.

(xii) p-Bromoacetophenone. The reaction of benzimidazole (2.95 g) with p-bromoacetophenone (5 g) was carried out in the same manner as the above two reactions. The total reaction time was 30 hrs. From the chromatography over alumina with benzene as eluting solvent unchanged p-bromoacetophenone (2.1 g) m.p., mixed m.p. 50-51° was recovered. On elution with 25% chloroform/benzene fractions were obtained which on removal of the solvent gave a solid m.p. 127-131°.
From this \( \text{p-}(\text{benzimidazol-1-yl})\text{acetophenone} \) m.p. 136-137° was obtained as shining plates (chloroform/light petroleum). Yield: 2.8 g; 47.9%.

Semicarbazone m.p. 229-230° (decomp.) (from aqueous ethanol). Anal. calcd. for \( \text{C}_{16}\text{H}_{15}\text{N}_{5}\text{O} \): C, 65.5; H, 5.1; N, 23.9%. Found: C, 64.7; H, 5.3; N, 23.2%.

**Ullmann Condensation of Carbazole.**

Some condensations of carbazole were carried out with the following haloaryls (underlined):

(i) **o-Chloronitrobenzene.** The reaction between carbazole (4.18 g) and \( \text{o-chloronitrobenzene} \) (3.9 g) was carried out over a period of 16 hrs. under the usual conditions. The reaction mixture was cooled and filtered. The residue was extracted with hot benzene. The combined filtrate and the benzene extract was treated with charcoal, filtered and the solvents evaporated leaving behind a residue m.p. 138-140°. This residue was recrystallised from chloroform/light petroleum giving \( 9-(\text{o-nitrophenyl})\text{carbazole} \) m.p. 156-158°. lit. 156° (12). Yield: 6.5 g; 89.7%.

(ii) **m-Bromonitrobenzene.** From the reaction between carbazole and \( \text{m-chloronitrobenzene} \) in dimethylformamide no \( 9-(\text{m-nitrophenyl})\text{-carbazole} \) could be obtained.
A mixture of m-bromonitrobenzene (5.05 g), carbazole (4.175 g), anhydrous potassium carbonate (3.5 g) in pyridine (10 ml) was heated under reflux and to this refluxing mixture cupric oxide (0.25 g) was added. The mixture was allowed to reflux over a period of 26 hrs. The reaction mixture was cooled and filtered. The residue was extracted with chloroform. The solvents were removed from the combined filtrate and extract. The residue thus obtained was chromatographed over alumina with benzene as the eluting solvent. The first few fractions obtained were combined, the latter fractions yielded unchanged carbazole. The combined fractions were rechromatographed over alumina using benzene as solvent. The first few eluents gave unchanged m-bromonitrobenzene (1.5 g) followed by a mixture which after removal of benzene was washed several times with light petroleum to remove m-bromonitrobenzene (present as impurity). The residue on crystallisation from chloroform/light petroleum gave 9-(m-nitrophenyl)carbazole, yellow needles, m.p. 132-133°. Yield: 3.9 g; 53.7%.

(iii) p-Chloronitrobenzene. The reaction between carbazole (4.18 g) and p-chloronitrobenzene (3.9 g) was carried out over a period of 18 hrs. The reaction mixture was worked up as usual and chromatographed over alumina. Unchanged p-chloronitrobenzene (2.85 g) was obtained on elution with benzene. Further elution with benzene
gave 9-(p-nitrophenyl)carbazole m.p. 211-213° (from chloroform/light petroleum), lit. m.p. 209-211° (13). Yield: 0.015 g; 0.2%.

(iv) 2-Bromopyridine. The Ullmann condensation between carbazole (4.175 g) and 2-bromopyridine (4 g) was carried out in the usual manner in pyridine (10 ml) over a period of 26 hrs. The reaction mixture was cooled and filtered. The residue was extracted with chloroform and the combined extract and filtrate was freed of the solvents. The residue thus obtained was exhaustively extracted with light petroleum. The solvent was removed from the combined extracts giving a residue. This residue was chromatographed over alumina using benzene as the eluting solvent. On removal of benzene from the eluents a material m.p. 70-73° was obtained, which on crystallisation from light petroleum gave 9-(α-pyridyl)carbazole m.p. 73-74°. Yield: 3.6 g; 59.3%. Anal. calcd. for C₁₁H₁₂N₂: C, 83.6; H, 4.9; N, 11.5%. Found: C, 83.4; H, 5.1; N, 11.5%.

The material m.p. 70-73° was left for 3 weeks and the m.p. was redetermined when it was found that the m.p. has raised to 92-93°. This was identical in all respects (m.p., mixed m.p., infrared and ultraviolet spectra) with a sample of Gilman and Honeycutt (22). It seems that the material m.p. 72-73° is either one of the polymorphic forms of 9-(α-pyridyl)carbazole or retained some solvent which evaporated on keeping for three weeks.
Intramolecular Condensation of o-Bromoacetophenone-p-Nitrophenyl-Hydrazone.

(a) o-Bromoacetophenone-p-nitrophenylhydrazone.

A mixture of o-bromoacetophenone (1 g) and p-nitrophenyl-hydrazine (1 g) in ethanol (20 ml) with five drops of acetic acid was heated under reflux for 0.5 hr. A few drops of water were added and the mixture cooled in an ice bath. The crystallised p-nitrophenyl-hydrazone of o-bromoacetophenone, m.p. 162-164° was filtered off and dried (mixed m.p. with p-nitrophenylhydrazine 130°). Yield: 0.88 g; 52.4%.

(b) 1-(p-Nitrophenyl)-2-methylindazole.

A mixture of o-bromoacetophenone-p-nitrophenylhydrazone (0.88 g) and anhydrous potassium carbonate (0.5 g) in pyridine (5 ml) was heated under reflux and to this refluxing mixture a very small amount (a few milligrams) of cupric oxide was added. The mixture was allowed to reflux for 7 hrs. The reaction mixture was allowed to cool and filtered. The residue was extracted with benzene and the solvents were removed from the combined filtrate and extracts. The residue obtained was dissolved in ethyl acetate, treated with charcoal and
filtered. The filtrate was concentrated giving 1-(p-nitrophenyl)-3-methylindazole m.p. 147-148°. Yield: 0.17 g; 24.9%. lit. m.p. 150° (104). This compound showed absorption in the infrared and ultraviolet spectra, identical to that reported for 1-(p-nitrophenyl)-3-methylindazole (104).

UNSUCCESSFUL CONDENSATIONS.

The following condensations under Ullmann conditions (as exploratory experiments) were attempted, but only starting materials could be isolated: 1,2,4-triazole with bromobenzene; 1,2,4-triazole with iodobenzene; 1,2,4-triazole with p-bromonaphthalene; 1,2,4-triazole with p-bromocinnamaldehyde; 1,2,4-triazole with 4-chlorobiphenyl in dimethyl formamide, and 1,2,4-triazole with 1-bromonaphthalene.
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CHAPTER II

NEBREWIA AVIATIENSIS
Meerwein and his co-workers (1) discovered the arylation of alkenic compounds by the decomposition of diazonium salts in acetone in the presence of a copper salt. This reaction has recently been reviewed by Røndestvedt jr. (2). The Meerwein arylation is favoured when the double bond is activated by an electron attracting group $X$, such as carbonyl, cyano or aryl. The aryl group from the diazonium salt is substituted at the $\beta$-carbon atom either directly or by addition of $Ar$ and $Cl$ to the double bond:

$$ArN_2Cl + RCH=CRX \quad \xrightarrow{\text{copper salt}} \quad ArCR=CRX + ArCHR=O(R)CIX$$

Both ionic and free radical mechanisms have been postulated to explain the products of the reaction. However, the cationic

$$ArN_2^+ \quad \xrightarrow{RCH=CRX} \quad Ar^+ + N_2$$
$$Ar^+ + RCH=CRX \quad \longrightarrow \quad ArCH(R)^+ CRX$$
$$ArCH(R)^+ CRX + Cl^- \quad \longrightarrow \quad ArCH(R)CCLI\text{RX} \quad \longrightarrow \quad ArC(R)=CRX + H^+$$

mechanism fails to account for some features: the double bond must be activated by an electron-attracting group and the diazonium salts...
bearing electron-attracting substituents usually give better results than those possessing electron releasing substituents. The normal polarisation of the alkenes renders the $\beta$-carbon positive,

$$\text{CH}_2=\text{CH}-\text{C}=\text{O} \rightleftharpoons \left[ \text{CH}_2\overline{\text{CH}}-\text{C}=\text{O} \right] \rightleftharpoons \text{CH}_2\overline{\text{CH}}-\text{C}=\text{O}^-$$

as demonstrated by the following additions:

$$\text{ROH}^+ + \text{CH}_2=\text{CHCN} \xrightarrow{\text{Base}} \text{ROCH}_2\text{CH}_2\text{CN}$$

$$\text{H}^+\text{Cl}^- + \text{CH}_2=\text{CHCO}_2\text{H} \rightarrow \text{CICH}_2\text{CH}_2\text{CO}_2\text{H}$$

Alternatively, one must invoke an abnormal polarisation $\text{CH}_2\overline{\text{CH}}\text{C}=\text{O}^+$ to explain why the hypothetical cation attacks the $\beta$-carbon atom. An ionic mechanism involving an aryl anion is equally difficult to accept, for the existence of aryl anions in the aqueous acid medium is highly unlikely (1).

A radical mechanism was proposed by Koclsch and Poekelheide (3) and by Müller (47). It is suggested that at pH 3-5, the diazinium salt solution is in equilibrium with the covalent diazoacetate (from the acetate buffer) or diazochloride, either of which may decompose to give an aryl radical which subsequently adds to the double bond. The alkyl radical is thought to be oxidised by cupric ion to a cation which in turn either acquires a chloride ion or loses a proton to
give the product. The cuprous ion is reoxidised by the acetate (or chloride) radical to cupric ion.

\[
\begin{align*}
\text{ArN}_2^+ + \text{OCOCOH}_3^- & \rightarrow \text{ArN}=\text{N}-\text{OCOCOH}_3 \\
\text{ArN}=\text{N}-\text{OCOCOH}_3 & \rightarrow \text{Ar}^* + \text{N}_2 + \cdot\text{OCOCOH}_3 \\
\text{Ar}^* + \text{RCH}=\text{GRX} & \rightarrow \text{ArCH}(\text{R})\cdot\text{GRX} \\
\text{ArCH}(\text{R})\cdot\text{GRX} + \text{Cu}^{++} & \rightarrow \text{ArCH}(\text{R})^+\text{GRX} + \text{Cu}^+ \\
\text{Cu}^+ + \cdot\text{OCOCOH}_3 & \rightarrow \text{Cu}^{++} + \text{OCOCOH}_3^- 
\end{align*}
\]

The radical mechanism explains the direction of addition to unsymmetrical alkenes. It is believed that the copper salt or another component of the medium functions as an efficient chain transfer agent to prevent the growth of monomer radical \(\text{ArCH}_2\cdot\text{CHX}\), which is converted efficiently to \(\text{ArCH}_2\cdot\text{CHCLX}\) or \(\text{ArCH}=\text{CHX}\). Olefins, which are vinyl monomers and are readily polymerised by authentic radicals, were found to give good yields of products in the Meerwein arylations without appreciable formation of polymers. This led to the inference of the presence of a chain transfer agent in the reaction medium. A more conclusive proof of the aryl radical participation in the Meerwein arylations came from the work of Dickerman et al. (4, 5, 6). It was found that arylation of some arenes under Meerwein conditions gave the same isomer ratio of arylarenes as other reactions of established homolytic character.
Although both cupric and cuprous chloride have successfully been employed in the Meerwein arylation, it has been suggested by Kochi (8) that the cuprous chloride is the effective catalyst. To support this suggestion, experiments were conducted with acetone/cupric chloride system, and it was found that cupric chloride is easily reduced to cuprous chloride by acetone, which is the most commonly employed solvent in the Meerwein arylation.

\[
2 \text{CuCl}_2 + \text{CH}_3\text{COCH}_3 \rightarrow 2 \text{CuCl} + \text{ClCH}_2\text{COCH}_3 + \text{HCl}
\]

Since cuprous chloride is a powerful catalyst for the Sandmeyer reaction and also for Meerwein arylation of styrene and acrylonitrile, it is concluded that the reaction is catalysed by univalent copper, not by divalent copper. This is supported further by the fact that chloroacetone and aryl halides together with normal Meerwein products are formed during the course of many reactions (1).

Rondestvedt and Vogl (7) had earlier suggested that in the Meerwein arylation initially a complex is formed between diazonium salt, olefin and copper chloride which undergoes decomposition by an internal one electron transfer process to give the products. Recently Schrauzer (13) has presented experimental evidence for the significance of copper (I) chloride complexes in the Meerwein arylation reaction: \((\text{CH}_2=\text{CHCN})\text{Ni} \) reacted with \(p\)-chlorobenzene-diazoniumchloride giving the normal Meerwein product; copper (I)
chloride and copper (I) bromide form complexes with acrylonitrile; and metal carbonyls can also function as catalysts in the reaction.

In most of the Meerwein arylations acetone gave the best results. Other solvents, such as acetonitrile, N-methylpyrrolidine, dimethylsulphoxide, sulpholane and dimethylsulpholane have also been successfully employed. In many reactions (as with acrylic acid, maleic acid and furfural) acetone has been found to be harmful (9-12). These compounds are better arylated in aqueous solutions. This suggests that acetone is a useful but not altogether indispensable solvent for Meerwein arylations.

Since 1958 (2) investigations centred on the following compounds: "α,β-unsaturated compounds" (14); diisopropenyl (15); 1,3 pentadiene (16); vinyl and isopropenyl aryl ketones (17); cycloheptatriene (18); aldoximes (19); vinylchlorides (20); styrenes (21); acrylonitriles (19b, 22); acrylic acids and their derivatives (23, 24); furfural (25); 2-furoic acid (26) and some arenes (5, 6). Diamines have also been used in some Meerwein arylations (27).

A number of olefinic compounds have been used as the unsaturated component and a great variety of aromatic amines employed for diazonium salts in the Meerwein arylation reaction (2). There are only a few cases where heteroaromatic amines have been employed (19a, 28) for diazonium salts, or heteroaromatics used as the "unsaturated component" (11, 12, 24, 29). Although the Meerwein arylation of
2-furoic acid has been described in the literature (2, 26) only a small number of aromatic amines have been used to effect arylation. In all the reported Meerwein arylations of 2-furoic acid, 5-substituted 2-furoic acid was found to be the only product formed together with some 5-aryl-furan arising from decarboxylation of the corresponding acid formed during the reaction (26).

The studies reported in this thesis aimed at the preparation of some hitherto unreported 5-aryl-2-furoic acids and then to extend the arylation reaction by using heteroaromatic amines. No work on the Meerwein arylation of methyl 2-furoate has been reported in the literature. Since the arylation and subsequent hydrolysis of the 2-furoic acid esters can also be used as an effective route to 5-aryl-2-furoic acid, Meerwein arylations of methyl 2-furoate were also undertaken. It was also attempted to effect arylation of some of the other "unsaturated components", such as acrylic acid, cinnamic acid, benzoquinone and coumarin, with diazonium salts derived from some heteroaromatic amines.
RESULTS AND DISCUSSION

When the arylation of methyl-2-furoate and 2-furic acid were performed under Meerwein conditions various new compounds were obtained. These compounds are listed in the following table (I).

Table I: NEW COMPOUNDS OBTAINED IN MEERWEIN REACTIONS.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R and Yield (%)</th>
<th>M.p. (°C)</th>
<th>Formula</th>
<th>Analyses (%)</th>
<th>other elements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>O</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>other elements</td>
<td></td>
</tr>
<tr>
<td>1. a-Nitrophenyl</td>
<td>78-79</td>
<td>C_{12}H_{9}NO_5</td>
<td>58.4</td>
<td>3.8</td>
<td>N</td>
</tr>
<tr>
<td>2. m-Nitrophenyl</td>
<td>140-142</td>
<td>&quot;</td>
<td>58.1</td>
<td>3.7</td>
<td>N</td>
</tr>
<tr>
<td>3. p-Chlorophenyl</td>
<td>68-69</td>
<td>C_{12}H_{9}Cl</td>
<td>60.7</td>
<td>4.0</td>
<td>Cl</td>
</tr>
</tbody>
</table>
Table I (contd.)

<table>
<thead>
<tr>
<th>Compound</th>
<th>mp (°C)</th>
<th>C x H y O z Cl</th>
<th>% C</th>
<th>% H</th>
<th>% O</th>
<th>% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. m-Chlorophenyl</td>
<td>81–82</td>
<td>C_{12}H_{9}Cl</td>
<td>60.6</td>
<td>3.9</td>
<td></td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>10.4</td>
<td>(60.9)</td>
<td></td>
<td></td>
<td></td>
<td>(15.0)</td>
</tr>
<tr>
<td>5. m-Chlorophenyl</td>
<td>131–132</td>
<td>&quot;</td>
<td>61.4</td>
<td>3.9</td>
<td></td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td>11.4</td>
<td>(60.9)</td>
<td></td>
<td></td>
<td></td>
<td>(15.0)</td>
</tr>
</tbody>
</table>

\[
\text{R} - \text{O} \quad \text{CO}_2\text{H}
\]

6. o-Nitrophenyl  | 223–224 | C_{11}H_{7}NO_5 | 56.8| 3.1 |     | 5.9  |
| d                | 46.1    | (56.7)         |     | (3.0) |     | (6.0) |

7. o-Chlorophenyl | 220–221 | C_{11}H_{7}Cl | 59.3| 3.4 |     | 15.9 |
| e                | 41.0    | (decomp.)     | (59.3) | (3.1) |     | (16.0) |

8. m-Chlorophenyl | 170–171 | "              | 58.9| 3.4 |     | 16.3 |
| e                | 13.1    | (59.3)         |     | (3.1) |     | (16.0) |

\[
\text{R} - \text{O}
\]

9. o-Chlorophenyl  | f       | C_{10}H_{7}ClO  | 67.2| 4.3 |     | 20.1 |
|                  | 51.1    | (67.2)         |     |     |     | (19.9) |

- a Crystallised from methanol.
- b Crystallised from aqueous methanol.
- c Crystallised from light petroleum.
- d Crystallised from ethyl acetate.
- e Crystallised from aqueous ethanol.
- f B.p. 110–112°/6mm and 91–92°/0.7mm.
- g The figures in parentheses refer to the calculated values.
Arylations of methyl-2-furoate were carried out in aqueous acetone with cupric chloride as the catalyst. From the reaction mixture 5-substituted methyl-2-furoates were obtained together with small quantities of the corresponding acids. These acids were most likely formed during the reaction by the acid hydrolysis of the esters. The yields of these esters varied from 3.9 to 38.5% for different aryl groups. The 5-aryl-2-furoic acids in comparison were obtained in better yields (see Table I). The poor yields of some of the furoic esters obtained in the arylation reactions could be ascribed as due to the separation of methyl-2-furoate during the reaction.

In the case of methyl-5-m-(nitrophenyl)-2-furoate the orientation of substitution was established by the hydrolysis of the ester to the known 5-(m-nitrophenyl)-2-furoic acid (26).

5-(o-Chlorophenyl)-2-furoic acid was found to melt with decomposition. A small amount of this acid was heated in a sausage flask and the liquid which distilled was found to be identical with a sample of 2-(o-chlorophenyl)furan, prepared by Gomberg arylation of furan. The evidence thus obtained points to the thermal decarboxylation of the acid:

\[
\begin{align*}
\text{Cl} & \quad \text{CO}_2\text{H} \quad \Delta \\
\text{Cl} & \quad \text{CO}_2\text{H} \\
\text{Cl} & \quad \text{CO}_2\text{H} \\
\end{align*}
\]
INFRARED SPECTRA.

The esters and acids listed in Table I displayed strong bands in their infrared absorption spectra. These bands could be ascribed to the carbonyl absorption of the esters and acids and the substitution patterns of the benzene rings introduced into the furan ring during arylation. The bands in the region 650-1000 cm\(^{-1}\) may be difficult to assign definitely, due to C-H deformation modes of the benzene ring as the furan also gives absorption peaks in this region (30a). All the esters showed strong absorption in the region 1715-1740 cm\(^{-1}\), due to the C=O stretching frequency of a methyl ester having a C=O group conjugated with C=C bonds. The furan-2-carboxylic esters have been found to absorb at higher frequency (1717-1723 cm\(^{-1}\)) as compared to their thiophene analogues which absorb at 1704-1707 cm\(^{-1}\). This is believed to be due to a direct field effect of furan oxygen atom on the C=O of the ester which is close to the oxygen of furan, and this assumption was supported by the fact that the corresponding 2-thionyl and 2-furyl-acrylic esters (where the C=O is away from the furan oxygen atom) all absorb at 1703 ± 2 cm\(^{-1}\) as expected (30b). It has also been known that esters conjugated with an aromatic ring usually have a strong band near 1280 cm\(^{-1}\) and a second band for esters of primary alcohols near 1120 cm\(^{-1}\) due to ester C-O stretching frequency (31a). All the esters obtained from the arylation of methyl-2-furacate displayed bands due to these frequencies. The characteristic bands for different esters are listed in the following Table II.
Table II: INFRARED ABSORPTION BANDS OF VARIOUS FUROIC ESTERS.

![Structure of 2-furoic acid]

<table>
<thead>
<tr>
<th>R</th>
<th>1715-1740 (C=O stretching)</th>
<th>1300-1100 (Ester C=O stretching)</th>
<th>650-1000 (C=H out of plane deformation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1727 br.</td>
<td>1307</td>
<td>763</td>
</tr>
<tr>
<td>(liquid film)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o-Nitrophenyl</td>
<td>1722</td>
<td>1298</td>
<td>750, 760, 790, 982</td>
</tr>
<tr>
<td>o-Chlorophenyl</td>
<td>1733</td>
<td>1300</td>
<td>755</td>
</tr>
<tr>
<td>m-Chlorophenyl</td>
<td>1710-1718</td>
<td>1302</td>
<td>680, 752, 780, 790</td>
</tr>
<tr>
<td>p-Chlorophenyl</td>
<td>1722</td>
<td>1295</td>
<td>752, 790, 800, 818, 830</td>
</tr>
</tbody>
</table>

In the 5-substituted 2-furoic acids characteristic bands appear between the region 2500-2700 cm\(^{-1}\) due to the C-H stretching frequency of the hydrogen bonded dimer. The carbonyl stretching frequency due to C=O absorption in the region of 1680-1715 cm\(^{-1}\) was also observed as strong bands (31b), except in the case of 5-(p-chlorophenyl)-2-furoic acid which was found to absorb at 1667 cm\(^{-1}\). This acid was prepared...
following the procedure of Mathur and Mehra (26). The bands between 2500-2700 were observed as weak broad bands. The strong bands in the regions are listed in Table III below.

Table III: INFRARED ABSORPTION BANDS OF VARIOUS FURCIC ACIDS.

```

Infrared absorption regions (cm⁻¹)

<table>
<thead>
<tr>
<th></th>
<th>2500-2700</th>
<th>1680-1715</th>
<th>650-1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>(O-H stretching)</td>
<td>(C=O stretching)</td>
<td>(C-H out of plane deformation)</td>
</tr>
<tr>
<td>all weak bands</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Nitrophenyl</td>
<td>2580,2665,2710</td>
<td>1690-1700 br.</td>
<td>696,742,758,780,810,852</td>
</tr>
<tr>
<td>m-Nitrophenyl</td>
<td>2564,2667</td>
<td>1681</td>
<td>675,738,760,805,812</td>
</tr>
<tr>
<td>α-Chlorophenyl</td>
<td>2580,2650-2710</td>
<td>1680-1690 br.</td>
<td>745,758,795</td>
</tr>
<tr>
<td>m-Chlorophenyl</td>
<td>2580,2670-2730</td>
<td>1692</td>
<td>686,758,784</td>
</tr>
<tr>
<td>p-Chlorophenyl</td>
<td>2570,2660</td>
<td>1667</td>
<td>758,805,815</td>
</tr>
</tbody>
</table>
```

The infrared absorption spectrum of 5-(α-nitrophenyl)-2-furaldehyde (prepared according to Oda (11)) was also recorded and
found to give strong bands at 1662 and 1680 cm\(^{-1}\) due to C=O stretching of an aromatic aldehyde. This pattern is similar to that of the carbonyl stretching frequency of furfural observed by Allen and Bernstein (32). The two peaks at 1675 and 1690 cm\(^{-1}\) in the infrared spectrum of furfural arise due to the two rotational isomers, say, A and B, that would arise if conjugation keeps the C=O in the plane of the ring.

![Diagram](A) ![Diagram](B)

Additional strong bands in the region of C-H deformation (682, 742, 805, 850 and 962 cm\(^{-1}\)) were also observed in the infrared spectrum of 5-(p-nitrophenyl)-2-furaldehyde.

A few experiments were performed using heterocyclic amines. Recently Filler and his co-workers (24) attempted arylation of acrylonitrile, acrylic acid and methyl acrylate with various aromatic and heteroaromatic amines with a view to find a suitable route to aromatic a-aminooicids. These workers found that although aromatic amines gave good yields of the Meerwein arylation products, heteroaromatic amines e.g. 3-aminopyridine, 2-aminothiazole, 3-aminquinoline and 3-amino-1,2,4-triazole could not be used for Meerwein arylations. The heteroaromatic amines either failed to react or gave tars or abnormal products (e.g. 3-chloro-1,2,4-triazole when 3-amino-1,2,4-
triazole was employed). In the present studies poor yields of products in impure forms were obtained. It is believed that with some variations on experimental methods and isolation procedures, most of the heteroaromatic amines could satisfactorily be used for arylation. As the experiments with heteroaromatic amines were only of exploratory nature further attempts were not made to purify the products or establish unambiguously their identities. Further progress in that direction may be made in future work.

When 3-amino-1,2,4-triazole was diazotized in hydrochloric acid and added to an aqueous solution of acrylic acid under Meerwein conditions, the only product isolated was 3-chloro-1,2,4-triazole. This 3-chloro-1,2,4-triazole undoubtedly arises either by a fast competitive Sandmeyer reaction or by the decomposition of unstable diazonium chloride during the diazotization of the amine. Thiele and Manchot (33) had earlier obtained 3-chloro-1,2,4-triazole by the diazotization of 3-amino-1,2,4-triazole in conc. hydrochloric acid.

The reaction of 2-thiazolediazoniumchloride with acrylic acid was performed under Meerwein conditions. A very small amount of solid m.p. 192-194° was obtained; 2-thiazoleacrylic acid, lit. m.p. 182-183° (34) and 187-190° (35). The product obtained from the reaction is believed to be 2-thiazoleacrylic acid (m.p. and infrared spectrum). The various bands in the infrared spectrum could possibly be attributed as follows: 1707 cm⁻¹ (s) (νC=O stretching for
\(\alpha,\beta\)-unsaturated acid) and a doublet at 964-975 cm\(^{-1}\) (m) (C-H bending, trans-disubstituted olefinic double bond) (36); 1533 cm\(^{-1}\) (thiazole II band, ring stretching), 1052 cm\(^{-1}\) (v) (2-monosubstituted thiazole), 780 cm\(^{-1}\) (m) (C-H out of plane deformation, thiazole ring breathing?) (30c, 37).

In another experiment diazotized 3-amino-1,2,4-triazole (in sulphuric acid) was allowed to decompose in an acetone solution of \(\alpha\)-benzoquinone, using acetate buffer. On working up the reaction mixture a very dark brown coloured solid m.p. \(>300^\circ\) was obtained which could not easily be crystallised from various solvents. Analysis of the compound showed it to be an impure triazolylbenzoquinone.

It has been shown that in the Meerwein arylation and other related arylation reactions with coumarin the only product formed is 3-aryl-coumarin (38) and thus the Meerwein arylation could prove to be an excellent procedure for preparing 3-heterocaromatic substituted coumarins. Rondestvedt and Vogl (39) have made a detailed study of the arylation of coumarins under Meerwein conditions, using diazonium salt derived from \(\alpha\)-nitroaniline. Different variables were changed. These included catalysts, solvents, pH and buffers. The most effective catalyst was found to be cupric chloride, acetone the best solvent, pH range of 2-4 and acetate the best buffer for Meerwein arylation. The presence of halide ion is believed to be of great
importance in Meerwein arylations (2) and cupric chloride the best
catalyst, but since diazotized 3- amino-1,2,4-triazole in the presence
of halide ions gives 3-chloro-1,2,4-triazole (see p.183), diazonium
salt prepared from 3-amino-1,2,4-triazole and hydrochloric acid
could not be used. Also, it has been observed that the replacement
of chloride ion by sulphate slows down the reaction, thus needing
vigorous conditions (such as heating the reaction mixture to 60° in
some cases (40)); the yields obtained in some of the present
experiments were very low. Another factor responsible for low
yields of Meerwein arylation products, when diazotized 3-amino-1,2,4-
triazole was employed, could be the formation of complexes between
cupric chloride or other copper salts with triazole ring. This complex
formation will withdraw the catalyst from the reaction mixture, as it
is well known that triazoles even under mild conditions give complexes
with cupric chloride and other copper salts (41). 3-Amino-1,2,4-
triazole was diazotized in sulphuric acid and reaction of the
diazonium salt with coumarin under Meerwein conditions using copper
sulphate gave 3-(1',2',4'-triazol-3'-yl)coumarin. The analysis of the
product showed it to be impure.

An attempts was made to react diazonium salt derived from
3-amino-1,2,4-triazole with cinnamic acid, with a view to prepare
3-styryl-1,2,4-triazole, but no pure product could be isolated.
Arylation of coumarin using 3-aminopyridine under Meerwein conditions gave 3-(3'-pyridyl)coumarin. When cinnamic acid was used as the substrate, pyridine-3-diazonium chloride gave a small amount of β-stilbazole. An attempts to prepare α-stilbazole from 2-aminopyridine and cinnamic acid failed.

**ULTRAVIOLET SPECTRA.**

Ultraviolet absorption spectra of various products obtained from the Meerwein reaction were recorded and are given in Table IV below.

<table>
<thead>
<tr>
<th>Table IV: ULTRAVIOLET ABSORPTION SPECTRA OF MEERWEIN ARYLATION PRODUCTS (IN METHANOL).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R</strong></td>
</tr>
<tr>
<td>α-Nitrophenyl</td>
</tr>
<tr>
<td>m-Nitrophenyl</td>
</tr>
<tr>
<td>α-Chlorophenyl</td>
</tr>
<tr>
<td>m-Chlorophenyl</td>
</tr>
<tr>
<td>p-Chlorophenyl</td>
</tr>
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</table>
Table IV (contd.)

<table>
<thead>
<tr>
<th></th>
<th>COOH</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>o-Nitrophenyl</td>
<td></td>
<td>218 (4.03); 280 (4.14)</td>
<td></td>
</tr>
<tr>
<td>m-Nitrophenyl</td>
<td></td>
<td>217 (4.23); 296 (4.21); 306 sh. (4.10)</td>
<td></td>
</tr>
<tr>
<td>o-Chlorophenyl</td>
<td></td>
<td>216 (4.05); 227 sh. (3.96); 235 sh. (3.91); 288 sh. (4.35); 295 (4.40); 310 sh. (4.22)</td>
<td></td>
</tr>
<tr>
<td>m-Chlorophenyl</td>
<td></td>
<td>216.5 (3.94); 223 in (3.78); 234 sh. (3.69); 290 sh. (4.17); 297 (4.22); 312 sh. (4.09)</td>
<td></td>
</tr>
<tr>
<td>p-Chlorophenyl</td>
<td></td>
<td>216 (3.82); 300 (4.20); 315 sh. (4.09)</td>
<td></td>
</tr>
<tr>
<td>o-Nitrophenyl</td>
<td>GHO</td>
<td>217 (3.96); 236 in (3.68); 342 (4.29)</td>
<td></td>
</tr>
<tr>
<td>p-Chlorophenyl</td>
<td>H</td>
<td>217.5 (4.21); 223 (4.24); 230 (4.17); 278 (4.37)</td>
<td></td>
</tr>
</tbody>
</table>

3-Pyridyl: 216 (4.15); 236 in (3.78); 300 (4.06); 325 (4.00)

3-Pyridyl: 226 (4.04); 292 (4.32); 305 (4.32)
EXPERIMENTAL

General conditions were the same as in the previous chapter (p. 85).

The following starting materials were obtained commercially and used without further purification: furan, m-chloroaniline, 2-aminopyridine and 3-aminopyridine (Halewood Chemicals); 2-furoic acid, cinnamic acid, o-nitroaniline, m-nitroaniline, p-nitroaniline, acrylic acid, 2-aminothiazole and 3-amin-1,2,4-triazole (Light and Co.); o-chloroaniline, p-chloroaniline and coumarin (B.D.H.); and benzoquinone (May and Baker). Furfural (Hopkins and Williams) was redistilled before using. Cupric chloride (B.D.H.) and copper sulphate (May and Baker) were also obtained commercially.

Methyl 2-furoate b.p. 181° was prepared in 78.5% yield from the esterification of 2-furoic acid by methanol following the method of Afrikian and Grigorian (42). 5-p-Chlorophenyl-2-furoic acid m.p. 191-193° was prepared by the method of Mathur and Mehra (26) and 5-p-(nitrophenyl)-2-furaldehyde m.p. 209-211° · (33.5%) by the method of Gda (11); lit. m.p. 203-204° (11).

2-(p-Chlorophenyl)fur. The method used was due to Johnson (43). p-Chloroaniline (12.8 g) was dissolved in conc. hydrochloric acid
(32 ml) and water (18 ml) and then diazotized in the usual manner by the addition of a solution of sodium nitrite (9 g) in water (20 ml). The filtered diazonium salt solution was added to furan (50 ml) and stirred vigorously at 0-5° while a solution of sodium acetate (32 g in 30 ml water) was added. The stirring was continued for 48 hrs. at ambient temperature. The furan layer was separated and the aqueous layer was extracted with benzene. The combined furan and benzene extract was washed with water, dried and filtered. The filtrate was treated with charcoal and filtered. The solvent was removed from the filtrate under reduced pressure (aspirator) on a water bath. The residuus was distilled under reduced pressure when 2-(o-chlorophenyl)-furan b.p. 90-92°/0.7 mm was obtained. Yield: 9.1 g; 51.1%.

ARYLATIONS OF 2-FUROIC ACID.

Meerwein arylations of 2-furoic acid were carried out with the following amines (underlined):

(i) o-Nitroaniline. o-Nitroaniline (9 g) was diazotized in hydrochloric acid (20 ml) and water (20 ml) at 0-5° by the addition of a solution of sodium nitrite (6 g) in water (12 ml). The diazotized solution was added to a solution of 2-furoic acid (9 g) in water
(100 ml) at 20-30° followed by the addition of a solution of cupric chloride (3 g). The mixture was stirred for 12 hrs. and then distilled in steam. The residue from this steam distillation gave a solid (11 g) m.p. 219-220°. This crude material was dissolved in ethyl acetate, treated with charcoal and filtered. The filtrate was concentrated and allowed to crystallise. Crystals of 5-\((\alpha\)-nitrophenyl\)-2-furoic acid m.p. 223-224° were deposited (5.3 g). The mother liquor yielded another crop (1.7 g) of crystals m.p. 223-224°. Yield: 7 g; 46.1%.

(ii) \(\alpha\)-Chloroaniline. \(\alpha\)-Chloroaniline (8 g) was diazotized in a similar manner to that used for the diazotization of \(\alpha\)-nitroaniline in the preceding experiment. The diazotized solution was filtered through glass wool and added to a solution of 2-furoic acid (9 g) in acetone (100 ml) at 20-30° followed by the addition of cupric chloride (3 g) in water. The mixture was stirred for 21.5 hrs. and distilled in steam. The residue was taken up in ether and the ethereal solution extracted with a 5% solution of sodium bicarbonate and the extract was acidified with hydrochloric acid. The precipitated acid was filtered off and dried (vacuum desiccator) giving 5-(\(\alpha\)-chlorophenyl)-2-furoic acid m.p. 212-213° (decomp.). A portion was recrystallised from aqueous ethanol raising the m.p. to 220-221° (decomp.). Yield: 5.73 g; 41%. 
A small amount of the acid was heated in a sausage flask when the acid melted with decomposition. Heating was continued and the liquid which distilled over was collected in the side arm. This liquid was found to be identical (infrared and ultraviolet spectra) with a synthetic sample of 2-(o-chlorophenyl)furan (see p.164).

(iii) m-Chloroaniline. The diazotized solution from m-chloroaniline (8 g) was added to a solution of 2-furoic acid (9 g) in acetone followed by a solution of cupric chloride as described in the previous experiment. The mixture was stirred for 13 hrs. and then distilled in steam. The residue from the steam distillation was extracted with ethyl acetate. The extract was dried and filtered. The filtrate was treated with charcoal and filtered. The solvent was removed from the filtrate and the residue taken up in ether. The ethereal solution was extracted with a saturated solution of sodium bicarbonate. The sodium bicarbonate extract was acidified with hydrochloric acid and the precipitated acid was filtered off and dried. 5-(m-Chlorophenyl)-2-furoic acid m.p. 159-160° was obtained. A small portion was crystallised from aqueous ethanol giving pure product m.p. 170-171°. Yield: 1.34 g; 13.1%.

The filtrate left after removal of precipitated 5-(m-chlorophenyl)-2-furoic acid, was extracted with ether. On removal of ether from the extract unchanged 2-furoic acid (4 g) was recovered.
(iv) 3-Aminopyridine. A preliminary reaction was carried out using diazotized 3-aminopyridine but no identifiable products could be obtained.

ARYLATIONS OF METHYL 2-FUROATE.

Arylations of methyl 2-furoate under Meerwein conditions were carried out for various amines (underlined) and are described below.

(i) \(\alpha\)-Nitroaniline. \(\alpha\)-Nitroaniline (9 g) was diazotized in the usual manner in hydrochloric acid (20 ml) and water (15 ml) at 0-5° with sodium nitrite (6 g in 12 ml water). The diazotized solution was added to a solution of methyl 2-furoate (10 g) in acetone (50 ml) and water (25 ml) followed by dropwise addition of a solution of cupric chloride (3 g) at 20-30°. The mixture was allowed to stir for 11 hrs. at ambient temperature and then distilled in steam. The residue from the steam distillation was extracted with methanol. The methanol extract was concentrated and allowed to crystallise. Crystals of methyl 5-(\(\alpha\)-nitrophenyl)-2-furoate m.p. 78-79° (0.98 g) were obtained. A further crop of 0.32 g was isolated from the mother liquor. Yield: 1.30 g; 8\%.
The mother liquor left after isolation of the ester was further concentrated. 5-(o-Nitrophenyl)-2-furoic acid m.p. 217-219° was obtained. This was identical (mixed m.p. and infrared spectrum) with a sample of the acid obtained in the Meerwein arylation of 2-furoic acid by diazotized o-nitroaniline. Yield: 0.28 g; 1.8%.

(ii) m-Nitroaniline. The reaction between diazotized m-nitroaniline (9 g) and methyl 2-furoate in the presence of cupric chloride (3 g) was carried out as described for the reaction of o-nitroaniline. The reaction mixture was stirred for 18 hrs. at 20-30° and then distilled in steam. The first fraction from the steam distillate was found to be unchanged methyl 2-furoate since it afforded 2-furoic acid m.p. 124-126° on hydrolysis with ethanolic potassium hydroxide. The steam volatile material was rejected and the residue was extracted with ethyl acetate. The ethyl acetate extract was treated twice with charcoal and filtered. The solvent was evaporated from the filtrate giving a residue. The residue on crystallisation from methanol gave methyl 5-(m-nitrophenyl)-2-furoate m.p. 146-148°. Yield: 0.63 g; 3.9%.

From the mother liquor 5-(m-nitrophenyl)-2-furoic acid m.p. 235-236° was obtained, which was recrystallised from methanol m.p. 249-250°. This was identical (mixed m.p., infrared spectrum) with the hydrolysis product of the ester. Yield: 0.13 g; 0.8%.
Methyl 5-(m-nitrophenyl)-2-furoate (0.435 g) was heated under reflux for 1.5 hrs. with an ethanolic solution of potassium hydroxide (0.28 g in 7 ml ethanol). The alcohol was removed under reduced pressure (aspirator) on a water bath. The residue thus obtained was extracted with ether and the ether extract discarded. The residue left after extraction with ether was dissolved in water and acidified with 5% hydrochloric acid. The acidified solution was extracted with ether (250 ml). The ether extract on removal of the solvent gave 5-(m-nitrophenyl)-2-furoic acid m.p. 250-251°. Lit. m.p. 244° (26), and 245-246° (25). Yield: 0.26 g; 63.9%.

(iii) p-Nitroaniline. The reaction between diazotized p-nitroaniline and methyl 2-furoate was carried out but no identifiable product was isolated.

(iv) p-Chloroaniline. The reaction of methyl 2-furoate (10 g) and diazotized p-chloroaniline (8 g) in the presence of cupric chloride was carried out as described for the reaction of p-nitroaniline. The reaction mixture was stirred for 18 hrs. at a temperature of 25-35° and then distilled in steam. First 200 ml of the steam distillate (containing mainly p-dichlorobenzene) was rejected. The next 500 ml of the steam distillate was extracted with ethyl acetate ("Extract A"). The residue from the steam distillation was extracted with ethyl
acetate ("Extract B"). "Extract B" was washed with 5% sodium bicarbonate solution and then water. The "Extract B" after washing with sodium bicarbonate and water was dried and filtered. The filtrate was treated with charcoal and filtered. The filtrate was freed of the solvent giving methyl 5-(ω-chlorophenyl)-2-furoate m.p. 68-69° (5.1 g). The "Extract A" on removal of the solvent gave a further yield of the ester m.p. 68-69°. A small amount was crystallised from aqueous methanol giving ester m.p. 68-69°.

Yield: 5.72 g; 38.5%.

The sodium bicarbonate extract from the "Extract B" was acidified with hydrochloric acid giving impure 5-(ω-chlorophenyl)-2-furoic acid m.p. 206-208°. This was identical (mixed m.p. and infrared spectrum) with a sample of the acid obtained in the arylation of 2-furoic acid by diazotized ω-chloroaniline. Yield: 0.1 g; 0.7%.

(v) m-Chloroaniline. The reaction between methyl 2-furoate (10 g) and diazotized m-chloroaniline (8 g) was carried out as with ω-chloroaniline. The mixture was stirred for 20 hrs. and then distilled in steam. The residue from the steam distillation was extracted with ethyl acetate. The ethyl acetate solution was washed with 5% sodium bicarbonate solution. The ethyl acetate extract was treated with charcoal and filtered. The solvent was evaporated
from the filtrate. The residue thus obtained was subjected to distillation under reduced pressure and the fraction b.p. 132-138°/0.4 mm was collected and left in the freezer. After two days it was found to have solidified. This was triturated with a small amount of light petroleum giving crystals m.p. 74-77°. A small portion of this crystalline material was dissolved in benzene and treated with charcoal, filtered and benzene was evaporated from the filtrate. The residue was recrystallised from light petroleum giving methyl 5-(m-chlorophenyl)-2-furoate, needles, m.p. 81-82°. Yield: 1.55 g; 10.4%.

The sodium bicarbonate washings were acidified with hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extract was filtered. The filtrate was freed of the solvent. The residue thus obtained was dissolved in hot water and filtered. On cooling, the filtrate gave a small amount of crystals m.p. 163-164°, identical (mixed m.p., infrared spectrum) with a sample of 5-(m-chlorophenyl)2-furoic acid.

(vi) \( p \)-Chloroaniline. The diazonium salt solution from \( p \)-chloroaniline (8 g) was allowed to react with methyl 2-furoate (10 g) in a similar manner to that used for the \( o \)-chloroaniline reaction. The reaction mixture was stirred for 22.5 hrs. and then distilled in steam. The residue from the steam distillation was
dissolved in ethyl acetate. The ethyl acetate solution was extracted with sodium bicarbonate solution (5%). The ethyl acetate extract was treated twice with charcoal and filtered. The solvent was evaporated from the filtrate giving crude material which was washed with a small amount of methanol giving crystals of methyl 5-(p-chlorophenyl)-2-furoate m.p. 124-126°. On recrystallisation from methanol the m.p. was raised to 131-132°. Yield: 1.71 g; 11.4%.

The sodium bicarbonate extract on acidification yielded a small amount of a little impure 5-(p-chlorophenyl)-2-furoic acid m.p. 174-178°. Lit. m.p. 194° (26).

ARYLATION OF ACRYLIC ACID.

The arylation reactions of acrylic acids were performed with the following two amines (underlined):

(i) 3-Amino-1,2,4-triazole. The method used was due to Rai and Mathur (9). 3-Amino-1,2,4-triazole (2.1 g) was diazotised at 0-5° by treatment with 25 ml of 1:1 hydrochloric acid, 15 g of ice and 7 ml of 30% aqueous sodium nitrite. The filtered diazonium solution was added to a solution of acrylic acid (2 g), sodium acetate (5.8 g) and cupric chloride (1 g) in water (80 ml). The reaction mixture was
stirred at ambient temperature for 12 hrs. and then extracted with ethyl acetate ("Extract A"). "Extract A" was washed with 5% sodium bicarbonate solution. The sodium bicarbonate washings were acidified with dilute sulphuric acid and extracted with ethyl acetate ("Extract B"). "Extract B" was dried and filtered. The solvent was evaporated from the filtrate leaving residue m.p.160-162°. The "Extract A" was dried and filtered. The solvent was evaporated from the filtrate leaving a solid identical (m.p., mixed m.p. and infrared spectrum) with the residue m.p. 160-162° of "Extract B". The infrared spectra of the two residues lacked absorption due to carbonyl of an acid. Thus 3-chloro-1,2,4-triazole was obtained. Lit. m.p. 167° (33). This was found to be identical with a sample prepared according to the method of Thiele and Manchot (33). Yield: 1.45 g; 56.3%.

(ii) 2-Aminothiazole. 2-Aminothiazole (5 g) was diazotized at 5-10° as in the preceding experiment by treatment with 50 ml of 1:1 hydrochloric acid, 20 g of ice and 14 ml of 30% aqueous sodium nitrite. The filtered diazonium solution was added to a solution of acrylic acid (4 g), sodium acetate (11.6 g) and cupric chloride (2 g) in water (150 ml). Stirring was continued for 10 hrs. at ambient temperature. At the end of this period the reaction mixture was extracted with ethyl acetate, and the extract was dried and filtered.
The solvent was evaporated from the filtrate, under reduced pressure, on a water bath. The liquid residue thus obtained could not be crystallised and was left in the freezer. After standing for two months a small amount of 2-thiazoleacrylic acid m.p. 192-194° was deposited. Lit. m.p. 187-190° (35).

**ARYLATION OF BENZOQUINONE WITH 3-AMINO-1,2,4-TRIAZOLE.**

The method used was essentially of Kvalnes (44). 3-Amino-1,2,4-triazole (4.2 g) was diazotized at 5-10° by treatment with 20 ml 1:1 sulphuric acid and 30% aqueous sodium nitrite solution (20 ml). The diazonium solution was added to a cold (10°) stirring solution of p-benzoquinone (6 g) in acetone (100 ml) and water (60 ml) containing 15 g sodium acetate. A vigorous reaction set in and the temperature rose to 20°. It was cooled and stirred at room temperature for 3 hrs. The solvent was removed at room temperature under reduced pressure and the reaction mixture was filtered. The residue was washed thoroughly with water followed by a little ethyl acetate (to remove unchanged benzoquinone). The residue (3.5 g) was dark brown in colour and did not melt till > 300°. 2-(1',2',4'-Triazol-3'-yl)benzoquinone C_9H_5N_3O_2 calcd.: C, 54.9; H, 2.9 and N, 24.0%. Found: C, 38.3; H, 3.9; N, 19.4%. The product could not be purified and was left impure.
ARYLATION OF COUMARIN.

Arylation of coumarin with 3-amino-1,2,4-triazole and 3-amino-pyridine was carried out. These arylations are described below.

(i) 3-Amino-1,2,4-triazole. 3-Amino-1,2,4-triazole (4.2 g) was diazotized in sulphuric acid as in the preceding reaction. The diazonium solution was added to a cold (5°) solution of coumarin (7.7 g) in acetone (120 ml), followed by a saturated solution of sodium acetate (15 g). The temperature of the reaction rose to 15°. A few crystals of copper sulphate were added and the mixture was stirred at ambient temperature (20-22°) till the evolution of nitrogen ceased (18 hrs.). Acetone was removed by evaporation under reduced pressure. The residue thus obtained was treated with 5% sodium bicarbonate solution and filtered. The residue was thoroughly washed with benzene. These benzene washings were used to extract the filtrate. The benzene washings were collected, dried and filtered. The solvent was evaporated from the filtrate. The residue thus obtained was crystallised from chloroform/light petroleum giving crystals m.p. 206-208°. 3-(1',2',4'-Triazol-3'-yl)coumarin

C_{11}H_7N_3O_2  calcd.: C, 62.0; H, 3.3 and N, 19.7%. Found: C, 58.3;
H, 3.5 and N, 18.2%. Yield: 0.31 g; 2.9%. 
(ii) 3-Aminopyridine. 3-Aminopyridine (4.7 g) was diazotized by treatment with 1:1 hydrochloric acid (28.5 ml), ice and a saturated aqueous solution of sodium nitrite (10 ml), taking the usual precautions. The pH was brought to 3-4 by the addition of a saturated solution of sodium acetate. This solution of diazotized 3-aminopyridine was then added to a cold solution (5%) of coumarin (7.7 g) in acetone (120 ml) followed by cupric chloride (1.33 g). The reaction mixture was stirred at ambient temperature for 18 hrs. and then filtered. The solvent was evaporated from the filtrate. The residue thus obtained was dissolved in a minimum quantity of benzene and passed through a column of alumina. The column on elution with benzene gave unchanged coumarin. The eluting solvent was then changed to 25% chloroform/benzene and fractions were collected. On removal of the solvent from these combined eluents a residue m.p. 157-159° was obtained. The residue from the filtration of the reaction mixture was repeatedly extracted with boiling benzene. On evaporation of the solvent a further crop of solid m.p. 157-159° was obtained. This material was combined with that obtained from the chromatography. The solid m.p. 157-159° was dissolved in chloroform, treated with charcoal and filtered. The solvent was evaporated from the filtrate and the residue was crystallised from chloroform/light petroleum giving 3-(3'-pyridyl)-coumarin m.p. 165-165.5°. Lit. m.p. 167.7-169° (45) and 163-164° (48). Yield: 1.2 g; 11%.
ARYLATION OF CINNAMIC ACID.

The arylation of cinnamic acid was carried out with the following amines (underlined):

(i) 3-Aminopyridine. 3-Aminopyridine (4.7 g) was diazotized in the same manner as used for the preceding experiment. The diazonium solution was added to a cold stirring solution of cinnamic acid (7.4 g) in acetone (400 ml), followed by a saturated solution of sodium acetate (20 g) and cupric chloride (2.1 g). The reaction mixture was stirred for 24 hrs. at ambient temperature and then for 3 hrs. at 32°. After this period the reaction mixture was filtered and the solvent evaporated from the filtrate. The residue thus obtained was made alkaline by treatment with 5% sodium hydroxide solution and extracted with five 100 ml portions of benzene. The benzene extract was dried and filtered. The solvent was evaporated leaving a small amount of residue. The residue was extracted with light petroleum. Removal of the solvent left crystals m.p. 77-79°. On recrystallisation from light petroleum the melting point was raised to 78-80°. The residue left from the benzene extract after extraction with light petroleum was chromatographed over alumina. On elution with 25% chloroform/benzene an additional amount of material m.p. 78-80° was obtained. This was identified as β-stilbazole m.p. 78-80°. Lit. m.p. 80° (46). Yield: 0.02 g; 0.2%.
(ii) 3-Amino-1,2,4-triazole. 3-Amino-1,2,4-triazole was diazotized in sulphuric acid and the reaction was carried out with cinnamic acid in a similar manner to that used for pyridine. Copper sulphate was used as the catalyst in place of cupric chloride. The reaction mixture was stirred for 45 hrs. The reaction mixture was worked up in a manner similar to the preceding experiment, but no arylation product could be isolated.

(iii) 2-Aminopyridine. 2-Aminopyridine was diazotized in sulphuric acid in the usual manner. The diazotized solution was added to an acetone solution of cinnamic acid. Copper sulphate was used as the catalyst for the reaction. The reaction was carried out in a similar manner as that for the reaction of cinnamic acid with 3-aminopyridine. The reaction mixture was also worked up in a similar manner, but no α-stilbazole could be obtained.
REFERENCES


27. F. Bell and C.J. Oliver, Chem. and Ind., 1558 (1965).


40. Ref. 2 p. 217.


CHAPTER III

GOMBERG ARYLATIONS
The literature on homolytic aromatic substitution has been extensively documented (1-3) and recently a review on free radical substitution in heteroaromatics has also appeared (4). It has previously been established that the free radical arylation of benzene and other aromatics by diacyl peroxides proceeds through arylcyclo-hexadienyl radicals which undergo disproportionation and dimerization to give the arylation products (5, 6). The arylation follows the scheme:

(a) In moderately concentrated solution -

\[
\begin{align*}
(Ar\text{CO}_2)_2 & \rightarrow 2Ar\text{CO}_2^* \\
Ar\text{CO}_2^* & \rightarrow Ar^* + CO_2 \\
Ar\text{CO}_2^* + PhH & \rightarrow (Ar\text{CO}_2\text{PhH})^* \\
(Ar\text{CO}_2\text{PhH})^* + Ar\text{CO}_2^* & \rightarrow Ar\text{CO}_2\text{Ph} + Ar\text{CO}_2\text{H} \\
Ar^* + PhH & \rightarrow (Ar\text{PhH})^* \\
(Ar\text{PhH})^* + Ar\text{CO}_2^* & \rightarrow Ar\text{Ph} + Ar\text{CO}_2\text{H}
\end{align*}
\]

(b) In dilute solution -

\[
Ar^* + PhH \rightarrow \text{ArPh}
\]
Various methods have been used to effect aryllations (3); of these the Gomberg-Bachmann reaction, commonly referred to as the Gomberg reaction, is one of the oldest. The reaction was developed by Gomberg and Bachmann (7) and has been reviewed by Bachmann and Hoffmann (8), and by Dermer and Edmison (2). The reaction is carried out by diazotizing an aromatic amine at a temperature of 0-5°C, and allowing the diazotized amine to decompose in a liquid aromatic compound in the presence of alkali or sodium acetate. A diaryl compound is produced thus:

\[
\text{ArN}_2^+ + \text{NaOH} + \text{Ar'H} \rightarrow \text{ArAr'} + \text{N}_2 + \text{NaX} + \text{H}_2\text{O}
\]

The reaction is heterogeneous and the success of the reaction depends on the diazohydroxide (or diazoacetate) - formed during the reaction - being extracted from the aqueous into the organic phase as fast as it is formed. The yields of diaryls are low, rarely above 30% (3). The process is more efficient when the organic compound (Ar'H) is water soluble, for example pyridine (9). A modified reaction condition has also been employed for Gomberg arylation where the diazotization is effected by amyl nitrite, thus providing a homogenous system (59). It has already been established
that the entity effecting arylation during the Comberg reaction is
an aryl radical, since the isomer distribution of substituted
diaryls obtained is the same as that observed when aryl radicals are
produced by other means (10). Recently Gragerov and Turkina (11)
have confirmed the radical nature of the reaction by decomposing
benzenediazonium chloride in an aqueous solution of a base in the
media $C_6D_6 + C_6H_6$ and $C_6H_{12}$.

The reaction has been known for more than forty years and
various mechanisms have been proposed. It has been suggested that
a covalent diazohydroxide is formed during the reaction and this
diazohydroxide decomposes into radicals in the non aqueous phase.
This mechanism (15) could not account for the production of the $^1OH$
radical during the reaction:

$$\text{Ar-}N==N\text{-OH} \quad \rightarrow \quad \text{Ar}^* + N_2 + ^1\text{OH}$$

since no products arising from hydroxyl radicals have been isolated.

Since in the Comberg and in the related acylarylnitrosamine
reaction no dihydrobiaryls or their dimerisation products could be
detected, it was believed that the reaction takes a different course.
A "cage reaction" was suggested to be operating (14), but later this
concept was dropped as evidence against such a reaction was
accumulated (16, 17). Recently Rüchardt and his co-workers (18, 19)
have postulated a mechanism of acylaryl nitrosamine decomposition and the Gomberg reaction. They propose (19) that, instead of decomposing directly to aryl and hydroxyl free radicals, the diazohydroxide loses a proton, forming the corresponding diazotate ion. This diazotate ion in turn reacts with unchanged diazonium salt to yield diazoanhydride. It is the diazoanhydride that is the source of the aryl free radical (and nitrogen); hydroxyl radicals are not involved, instead the radical PhN=NO is produced in the decomposition of a diazonium salt under Gomberg conditions (20, 70). The latter radical Ph-N=N-O is rather stable and thus, like Ph-C, accumulates in quite higher stationary state concentration. This radical (Ph-N=N-O) acts as an efficient scavenger for the arylcyclohexadienyl radicals, produced by the attack of aryl radicals on to the aromatics (e.g. benzene), and thus prevents dimerization and disproportionation of arylcyclohexadienyl radicals. Artylhexadienyl radicals are converted to arylbenzene and Ar-N=N-OH. The latter then loses a proton to give the diazotate ion thus propagating a chain reaction. The whole mechanism is depicted in the following scheme:
The kinetic study of the reaction was carried out by Richardt and his co-workers (20). The rate of nitrogen evolution was followed and the reaction was found to be of second order. These workers maintain that if the diazonium salt decomposition followed the path where the diazohydroxide forms aryl and hydroxy radicals, the reaction would be unimolecular. They found that the rate of nitrogen evolution is fastest when the equilibrium mixture contains equimolar quantities of the diazonium and diazotate ions.
Diazooanhydrides, postulated as the aryl radical generators, have previously been isolated (21) and characterised (22) and found to decompose violently on attempted dissolution in organic solvents.

Recently Eliel and Saha (23) have supported this mechanism. These workers proposed that if the mechanism of Nöhradikt and his co-workers is operative it would lack the following criteria: dihydrobiaryl formation, apparent isotope effects, and the appearance of dideuterated biaryls. Eliel and Saha carried out Gomberg reactions of benzene-d with p-methyl-, p-methoxy- and p-chloro-benzenediazoium salts. Their results suggested the presence of an efficient radical scavenger in the intermediate stages of the reaction and thus were in complete agreement with Nöhradikt's postulated mechanism.

Grieve and Hey (12) had earlier developed decomposition of acylaryl nitrosamines as source of aryl radicals. That the decomposition proceeds via rearrangement to the diazoesters:

\[
\text{ArN(NO)}-\text{COCH}_3 \rightarrow \text{ArN}^+ - \text{COCH}_3 \rightarrow \text{Ar}^+ + \text{N}_2 + \text{COOCH}_3
\]

has been demonstrated by Huisgen and his co-workers (13). A puzzling feature of the decomposition of the nitrosamines by this mode, however, is that the presumed acyloxy radical fails to evolve \( \text{CO}_2 \), and can generally be recovered as the corresponding acid rather than becoming
involved in further radical processes (24). A "cage reaction" was also postulated for this reaction (14), but was later rejected (16, 17). The mechanism proposed by Rüchardt and Freudenberg (18) seems to be the most plausible one since it incorporates all the experimental observations (for example lack of dihydrobiaryl formation and formation of acetic acid). The mechanism of Rüchardt and Freudenberg proposes diazo-anhydride as the radical producing entity similar to that of the Gomberg reaction. The diazohydroxide ([Ar-N=N-OH]) produced during the formation of biaryl from the arylcyclohexadienyl radical reacts with the nitrosamine (or rather its rearrangement product (25), the diazoacetate) to give acetic acid and regenerates [Ar-N=N-O-N=N-Ar].

Binsch and Härichardt (60) determined the esr spectrum of the stable radical, obtained in the decomposition of N-nitroso-acetanilide in benzene and interpreted that radical (I) is responsible for this spectrum. Härichardt and his co-workers had earlier postulated (I) to be the radical responsible for scavenging (cf. Scheme I p.198). More recently Chalfont and Perkins (61) have redetermined the esr spectrum of the stable radical produced in the decomposition of N-nitrosoacetanilide in benzene and found it to be identical in all
respects with the spectrum of the product obtained by mixing benzene solutions of nitrosobenzene and N-bromoacetonilide. This evidence has led Chalfont and Perkins to propose that the radical responsible for the esr spectra from the two reactions is (II) and not (I) as had been proposed earlier (18, 60).

\[
\text{PhNOOCH}_3 + \text{PhN}=0 \rightarrow \text{II}
\]

In the reaction of nitrosobenzene and N-bromoacetonilide, II is considered to arise by the addition of the nitrogen centred radical \( \text{PhNOOCH}_3 \) to nitrosobenzene:

The reaction of N-bromo-\( \text{p} \)-chloroacetanilide with nitroso-benzene was also found to give a radical whose esr spectrum was found to be indistinguishable from that of II (61) and is consistent with the hypothesis of negligible splitting by the ring B protons. In the light of the above evidence Chalfont and Perkins have postulated a
modified mechanism for the N-nitrosoacetanilide reaction (Scheme II).

\[
\begin{align*}
\text{PhN} = \text{NOCOCH}_3 & \quad \rightarrow \quad \text{Ph}^* + \text{N}_2 + \cdot \text{COOCH}_3 \\
\text{Ph}^* + \text{Ph-N-OCOCH}_3 & \quad \rightarrow \quad \text{II} \\
\text{Ph}^* + \text{PhH} & \quad \rightarrow \quad \text{Ph} \quad \text{H} \\
\text{Ph} & \quad + \quad \text{II} \\
\text{PhN} = \text{NOCOCH}_3 + \text{Ph-N-OH} & \quad \rightarrow \quad \text{II} + \text{Ph}^* + \text{N}_2 + \text{ACOH}
\end{align*}
\]

SCHEME II

In a very recent communication (71) Cadogan and his co-workers have reported the formation of an adduct with 2,3,4,5-tetraphenylcyclopentadienone (t.p.c.p.) in the decomposition of N-nitrosoacetanilide in benzene in the presence of t.p.c.p., only 0.02% of biphenyl was formed. While in the absence of t.p.c.p. the same reaction gave 50% yield of biphenyl without any adduct formation,
it is believed that the intermediate in the decomposition of
\( \text{H-nitrosoacetanilide} \) is not benzyn itself but that it is
benzynoid in the sense that it gives 'benzyn adducts' with the more
reactive dienes, but not with furan." (71)

The substituent effects on the relative rates of arylation
have been studied (26, 27). It was found that in a Gomberg reaction
when benzene competes with chlorobenzene or nitrobenezene for phenyl
radicals, the substituted benzene reacts more readily than the
unsubstituted one. Augood, Hey and Williams (28) studied the
competitive phenylation of benzene, nitrobenezene, chlorobenzene and
pyridine. The activating or deactivating influence of the group \( X \)
was expressed by the quantity \( \frac{\text{PhX}}{\text{PhH}} K \), the rate of attack of the phenyl
radical on PhX compared with the rate of attack on benzene (PhH).
The relative rate for the phenylation of nitrobenezene and benzene on
\( \frac{\text{PhNO}}{\text{PhH}} 2K \) was found to be 4 (28). If the phenyl radical is substituted
by an electron withdrawing group, the relative ratio \( \frac{\text{PhX}}{\text{PhH}} K \) is
decreased. The decrease in this ratio is explained by assuming that
as the radical nucleus becomes more electron deficient it becomes
more difficult for it to react with the electron deficient substituted
benzene. The reverse, of course, is true if one of the substituents
either on benzene or on the aryl radical is electron donating and the
other electron withdrawing. This postulate was supported by the
experimental observations of Weingarten (27), when he obtained the following relative rates for the arylation of a mixture of benzene and chlorobenzene by different radicals: phenyl, 1.35; o-chlorophenyl, 1.02 and 3,4-dichlorophenyl, 0.73 ± 0.03.

The steric effects in the Gomberg reaction have also been investigated (29). It was concluded that, while ortho-halo-substitution in a Gomberg reaction might give rise to an unfavourable dipolar repulsion in the transition state, steric effects were relatively unimportant. o-, and m-Dichlorobenzenes were used as the substrates and the radicals used were phenyl, p-chlorophenyl, o-chlorophenyl, o-bromophenyl and o-tolyl. A transition state with a long "W-like" bond was proposed where the direction to the forming C-C bond is nearly perpendicular to the plane of o-dichlorobenzene ring. The plane of the radical bearing ring approximately bisects the o-dichlorobenzene ring at the carbon to which it is becoming attached. The direction of the C-H bond at the carbon, undergoing substitution is only slightly modified. In this transition state the carbon halogen dipoles are able to interact, while steric interaction between the substituent groups is minimal. The substituent X is pictured as being away from the o-dichlorobenzene ring.
The influence of electronic and steric effects mentioned in the preceding paragraphs has also been observed by Abramovitch and Saha (30) who support Weingarten's suggestion of the mode of attack of aryl radicals. They further observed that the ratio of isomers formed in the Gomberg arylation of pyridine was relatively unaffected by the presence of oxygen.

Because of the easy accessibility of aromatic amines and the comparatively simpler technique of arylation, the Gomberg arylation reaction has been widely used. A number of aromatic and heteroaromatic amines have been employed (2, 4). The yields are usually low due to the heterogenous character of the reaction, and rarely exceed 30% (8).

Gomberg arylations and nitrosoamine reactions of heteroaromatics have been reviewed earlier (2,4,8). A very brief review of the literature on these reactions of heteroaromatics (appeared since the last review (4)) is attempted in the following. The arylations were accomplished either by the reaction of diazotized (or nitrosated) heteroaromatic amines on aromatics or by the reaction
of diazotized (or nitrosated) aromatic amines on heteroaromatics. The Gomberg arylation of heteroaromatics followed the general pattern of Gomberg arylation of aromatic compounds.

**Pyridines.** The Gomberg arylation of pyridine was effected by phenyl and ortho-substituted phenyl radicals (30). In the o-nitrophenylation of pyridine 3-(o-nitrophenyl)pyridine was found to be the main isomer (50% of total aryalted product). A new type "ortho-effect" was postulated to rationalise the product formation: a repulsion between the ortho-methyl group of the attacking radical and the lone pair of electrons of pyridine nitrogen in the transition state takes place. Similarly an attraction between the ortho-nitro group of the attacking radical and the pyridine nitrogen lone pair in the transition state takes place. The effect of diazonium salt solution concentration on the arylation of pyridine has also been studied (63). It was found that the arylation of pyridine with a dilute solution of diazonium salt from p-nitroaniline gave the following isomer ratio: 2-, 44.6%; 3-, and 4-, 45.4%. In concentrated solution the ratio was found to be: 2-, 27.5%; 3-, 55.5% and 4-, 17%. In the phenylation of 3-, and 4-picolone under Gomberg conditions (62) the methyl group of the two picolines was found to activate the nucleus towards phenylation. The most abundant isomer obtained in these
phenylations was found to be the one in which the phenyl group enters ortho- to the methyl group.

**Thiophenes.** The Comberg reaction of diazotized aniline with thiophene gave 2-phenylthiophene as the main product of phenylation (31). Other products isolated were: 3-phenylthiophene; 2,3-diphenylthiophene; 2,5-diphenylthiophene; 3-xenylthiophene and 5-phenyl-2-xenylthiophene. The reaction of N-nitrosoacetanilide with thiophene was found to give the same products (31). The Comberg reaction of diazotized methyl 5-amino-2-thenoate with benzene gave 8% yield of methyl 5-phenyl-2-thenoate (64).

**Thiazoles.** J. Vitry (32) obtained phenylthiazoles only in 2% yield by the Comberg reaction of benzenediazonium chloride on thiazole. The series of reactivity was found to be 2 > 4 > 5 with 2-isomer predominating. The same pattern of substitution was obtained when phenylation of thiazole was carried out by benzoyl peroxide (32). Arylation of 4,5-dimethylthiazole by p-nitro-benzenediazonium chloride and p-methoxybenzenediazonium chloride under Comberg conditions gave respective yields of 35% and 12% of the corresponding 2-arylated isomer. Vernin and Metzger, in addition to 2-, 4-, and
5-phenyl-thiazole, obtained 2,2-dithiazolyl, biphenyl, phenol and isomeric 2-dithiazolyl in the Gomberg phenylation of thiazole by benzenediazonium chloride. The isomer ratio was found to be 2-, 80%; 4-, and 5-, 20% and the reactivity of position 2 > 5 > 4.

Isothiazoles. The reaction of diazotized 4-amino-3-methylisothiazole and 5-amino-3-methylisothiazole with benzene gave the corresponding 4-, and 5-phenyl-3-methylisothiazole in yields of 36% and 26% respectively (36). The diazotization of the amines was effected by isopentyl nitrite.

1-Methylpyrazole. The reaction of 1-methylpyrazole with N-nitroso-acetanilide at 40° was found to give phenylated products in a yield of 12-20% (34). The isomer ratio was 5-, 94%; 3-, 5% and 4-, 1%.

1-Methylimidazole. 1-Methylimidazole when reacted with N-nitroso-acetanilide at 40° gave 10-20% yield of 1-methyl-(X)-phenylimidazoles (34). The isomer ratio was found to be: 2-, 67% and 5-, 33%.

Competition experiments with benzene showed the reactivity of 1-methylimidazole towards phenylation to be 1.2 ± 0.2 times that of benzene (34). Phenylation of 1-methylimidazole with benzenediazonium
tetrafluoroborate was also carried out (35) and it was observed that low concentration of diazonium salt gave phenylation closely similar to those obtained using other phenylating sources. When the concentration of diazonium salt was increased the isomer ratio was found to change appreciably. Using a molar ratio of diazonium salt 1:250 the isomer ratio of 1-methyl-(X)-phenylimidazole was 2-, 61%; 4-, and 5-, 39%. Changing the molar ratio to 1:29 and 1:4 gave 2-, 80%; 4- and 5-, 20% and 2-, 81%; 4-, and 5-, 19% respectively. The abnormal isomer distributions and enhanced reactivities are ascribed to the occurrence of attack of phenyl radical on the 3-phenylazo-1-methylimidazolium ions initially formed by the electrophilic addition of the diazonium ion to a ring nitrogen similar to that demonstrated earlier (30) in the Comberg phenylation of pyridine.

RESULTS AND DISCUSSION

During the course of present investigations some new compounds were synthesised. These compounds are listed in the following table (I).
Table I: NEW COMPOUNDS OBTAINED IN COMBERG ARYLATIONS.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R and Yield</th>
<th>m.p. °C</th>
<th>Formula</th>
<th>Analyses a %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>g</td>
</tr>
<tr>
<td>1.</td>
<td></td>
<td>162-164</td>
<td>C₆H₈N₆</td>
<td>43.5</td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td>71-72</td>
<td>C₁₄H₁₁N₃</td>
<td>75.9</td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td>83-84</td>
<td>&quot;</td>
<td>76.3</td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td>130-131</td>
<td>&quot;</td>
<td>76.0</td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td>208-210</td>
<td>C₆H₉NCl (decomp.)</td>
<td>48.8</td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td>160-162</td>
<td>C₁₄H₁₁N₃</td>
<td>75.8</td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td>137-138</td>
<td>&quot;</td>
<td>74.6</td>
</tr>
</tbody>
</table>
Table I (contd.)

<table>
<thead>
<tr>
<th></th>
<th>p-Biphenylc</th>
<th>221-222</th>
<th>C_{14}H_{11}N_3</th>
<th>75.5</th>
<th>5.0</th>
<th>18.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.</td>
<td></td>
<td>(76.0)</td>
<td></td>
<td>(5.0)</td>
<td>(19.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>o-Aminophenyl</th>
<th>135-136</th>
<th>C_{8}H_{8}N_4</th>
<th>60.8</th>
<th>5.3</th>
<th>34.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.</td>
<td></td>
<td>(60.0)</td>
<td></td>
<td>(5.0)</td>
<td>(35.0)</td>
<td></td>
</tr>
</tbody>
</table>

\[\text{a} \] The figures in parentheses refer to the calculated values.

\[\text{b} \] 1,2-Di(1',2',4'-triazol-1'-yl)ethane.

\[\text{c} \] Crystallised from ethyl acetate.

\[\text{d} \] Crystallised from light petroleum (b.p. 40-60°).

\[\text{e} \] Obtained from the Gomberg arylation reaction. (See experimental p. 235.)

\[\text{f} \] Crystallised from chloroform/light petroleum (b.p. 60-80°).

\[\text{g} \] The crude amine was obtained as a syrupy liquid (Yield 56.8%).

\[\text{h} \] Crystallised from ethanol.

\[\text{i} \] Crystallised from chloroform/light petroleum (b.p. 40-60°).

In the present study of Gomberg arylation, heteroaromatic and aromatic amines were used. As diazotisation of 3-amino, 1,2,4-triazole gives 3-chloro, 1,2,4-triazole (37), it was found necessary
to avoid the presence of any halide ions in the reaction medium.

The diazotizations of 3-amino-1,2,4-triazole were carried out either in sulphuric acid or in nitric acid. The results are shown in the following Table II.

**Table II: COMBERG ARYLATIONS.**

<table>
<thead>
<tr>
<th>Amine</th>
<th>Substrate</th>
<th>Yield of arylated products (%)</th>
<th>Products and Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Amino-1,2,4-triazole</td>
<td>Benzene</td>
<td>15.4</td>
<td>3-Phenyl-1,2,4-triazole</td>
</tr>
<tr>
<td></td>
<td>Nitrobenzene</td>
<td>38.8</td>
<td>3-(p-Nitrophenyl)-1,2,4-triazole (25.8%) and 3-(p-nitrophenyl)-1,2,4-triazole (8.6%) isolated; rest not identified.</td>
</tr>
<tr>
<td></td>
<td>Bromobenzene</td>
<td>15.5</td>
<td>3-((x)Bromophenyl)-1,2,4-triazole. Not identified.</td>
</tr>
<tr>
<td>3-Amino-5-phenyl-1,2,4-triazole</td>
<td>Benzene</td>
<td>6</td>
<td>3,5-Diphenyl-1,2,4-triazole</td>
</tr>
<tr>
<td>5-Aminotetrazole</td>
<td>Benzene</td>
<td>29.1</td>
<td>5-Phenyltetrazole</td>
</tr>
<tr>
<td>1-Methyl-1,2,4-triazole</td>
<td></td>
<td>-</td>
<td>No reaction</td>
</tr>
</tbody>
</table>
Table II (contd.)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Product</th>
<th>Yield (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aniline</td>
<td>1,2,4-Triazole in acetone</td>
<td>-</td>
</tr>
<tr>
<td>1-Methyl-1,2,4-triazole</td>
<td>-</td>
<td>No reaction</td>
</tr>
<tr>
<td>p-Nitroaniline</td>
<td>1,2,4-Triazole</td>
<td>-</td>
</tr>
<tr>
<td>4-(p-Aminophenyl)-Benzene</td>
<td>1,2,4-triazole</td>
<td>0.5</td>
</tr>
<tr>
<td>1-(p-Aminophenyl)-Benzene</td>
<td>1,2,4-triazole</td>
<td>10.0</td>
</tr>
<tr>
<td>1-(p-Aminophenyl)-Benzene</td>
<td>1,2,4-triazole</td>
<td>23.9</td>
</tr>
<tr>
<td>3-Amino-4-phenyl-Benzene</td>
<td>1,2,4-triazole</td>
<td>-</td>
</tr>
</tbody>
</table>

In some of the reactions N-nitrosoacetanilide was used as a source of phenyl radical. Using 1-methyl-1,2,4-triazole as substrate a small amount of 1-methyl-5-phenyl-1,2,4-triazole was obtained. Reaction of N-nitrosoacetanilide with 4-phenyl-1,2,4-triazole either in ethylacetate or in acetic acid failed, only unchanged 4-phenyl-1,2,4-triazole was recovered from the reaction mixtures.
The above results show that 1,2,4-triazole-3-diazonium salts behave like typical aryldiazonium salts in their decomposition and possibly decompose by a similar mechanism as depicted in Scheme I (p. 198), where

\[
\text{Ar} = \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\]

It has been shown (3) that in homolytic aromatic substitution all substituents regardless of their polar nature activate the aromatic ring, especially at the ortho- and the para-position. The substitution pattern for the arylation of nitrobenzene by diazotized 3-amino-1,2,4-triazole in the Comber reaction is in keeping with the above mentioned facts and is quite different from that found in the electrophilic substitution of nitrobenzene. The isomer ratio in the present study is on the basis of isolable products, and no attempts was made to determine the accurate isomer ratio, which would conclusively support the homolytic pattern of substitution. However, the isolation of isomers in the arylation of nitrobenzene (o-, 37.1 and p-, 12.5% of the mixture) indicates the homolytic nature of the reaction. The generally observed ortho-para orientation suggests that the major factor controlling the orientation of the entering group is the degree of stabilisation of the transition state due to
the delocalisation of the odd electron. Thus when the addition of
an aryl radical occurs at the ortho or the para position to a
substituent, the odd electron, in the transition state, can conjugate
with the substituent group through the electron system of the
aromatic nucleus; consequently the substituent contributes to the
stabilisation of the transition state. Rondestvedt and Blanchard
(38) propose that since the greatest electron density, in the
substrate with electron withdrawing substituents, is at the
substituent itself (e.g. nitro−), the association of the incoming
radical with the substituent sets up a preliminary complex which
can most readily rearrange to the ortho-σ-complex.

The non-availability of the isomeric 3-bromophenyl-1,2,4-
triazoles has prevented the identification of the reaction products.

1-Methyl-5-phenyl-1,2,4-triazole was the only product (in
low yield) isolated in the phenylation of 1-methyl-1,2,4-triazole.
This can be rationalised in the light of findings of Lynch and
Chang (34). In the free radical phenylation of 1-methylpyrazole
and 1-methylimidazole, by benzoyl peroxide and by N-nitrosoacetanilide
or diazouminobenzene, they obtained 94% of 1-methyl-5-phenylpyrazole
and 67% of 1-methyl-2-, and 33% of 1-methyl-5-phenylimidazole.
They explain the formation of these selective phenylations on the
basis of resonance concepts. Thus species III, resulting from the attack adjacent to the 1-nitrogen atom, is stabilised by conventional odd electron delocalisation (as IIIa), while for species IV, delocalisation necessarily involves a structure (as IVa) which involves charge separation and this is of higher energy.

Lynch and Chang (34) further suggest that these considerations should hold for all five-membered heteroaromatic compounds, and the radicals formed by nuclear attack of phenyl radicals on such compounds should have energies which are markedly dependent upon the position of attack. The results of phenylation of other heteroaromatics, furan (39), pyrroles (40), thiophene (31, 41) and thionaphthene (42) support this suggestion since attack of the radicals takes place predominantly at alpha-positions, while the
pattern of phenylation of thiazole (43) closely resembles that of 1-methylimidazole.

In a similar way the attack of a phenyl radical on 1-methyl-
1,2,4-triazole can lead to species (V), which can be stabilised by

delocalisation of the odd electron (Va).

A few more experiments on the phenylations of 1,2,4-
triazole and better isolation techniques will help to understand
the pattern of homolytic substitution in 1,2,4-triazole. The
evidence so far obtained points to the behaviour of the triazole
nucleus towards free radical attack as being "normal".

In the Gomberg arylation of bromobenzene with diazotized
3-amino-1,2,4-triazole some dibromobenzene m.p. 86-88° was
isolated. Of the three isomeric dibromobenzene (o-dibromobenzene
m.p. 6.7°; m-dibromobenzene, m.p. -7° and p-dibromobenzene m.p.
86.9° (66) only p-dibromobenzene is a solid and has a m.p. (86.9°)
comparable to dibromobenzene isolated from the Gomberg reaction. This compound m.p. 36–38° analysed for C₆H₄Br₂. The formation of p-dibromobenzene in the Gomberg arylation is not surprising since removal of a halogen in radical reactions with halobenzenes has recently been observed: diiodobenzene was formed in the decomposition of o-iodonitrosacetanilide in benzene (67), 3-thenoyl peroxide's reaction with chlorobenzene leads to the formation of a small amount of phenyl-3-thionate which also shows the displacement of a halogen from halobenzene (64); Bunnell and Wamsler (68) obtained p-chloroiodobenzene as the main product from decomposition of bis(p-chloro-benzoyl) peroxide in a benzene solution of iodobenzene; also iodobenzene was the major product from the thermolysis of benzoyl-peroxide in benzene solution of m-chloroiodobenzene. The formation of these products has been accounted for by direct iodine atom abstraction from aryl iodides by aryl radicals.

**INFRARED SPECTRA.**

In Table III below various bands observed in the infrared spectra of biphenylyl triazoles in the region 650–3100 cm⁻¹ are listed. All the biphenylyltriphasyls had medium bands in the region 3000–3100 cm⁻¹ which could be ascribed to aromatic C-H stretchings (65). Strong bands appearing in the region 650–900 cm⁻¹ could be attributed to the following substitution pattern of the benzene ring: 690–710 cm⁻¹ (s) and 730–770 cm⁻¹ (s) (monosubstituted); 735–770 cm⁻¹
(s) (1,2 disubstituted); 680-725 cm$^{-1}$ (m), 750-810 cm$^{-1}$ (s), 860-
900 cm$^{-1}$ (s) (1,3 disubstituted) and 800-860 cm$^{-1}$ (s) (1,4 disubstituted).

Table III: INFRARED ABSORPTION BANDS OF BIPHENYL TRIAZOLES.$^a$

<table>
<thead>
<tr>
<th>R</th>
<th>Infrared absorption bands, cm$^{-1}$</th>
</tr>
</thead>
</table>

\begin{align*}
\text{o-Biphenylyl} & \quad 655(s), 670(s), 702(s), 740(m), 754(s), 765(s), \\
& \quad 786(sh), 860(s), 888(w), 930(w), 960(m), 982(m), \\
& \quad 1030(w), 1060(w), 1080(w), 1122(s), 1162(sh), \\
& \quad 1190(w), 1210(m), 1280(m), 1348(sh), 1360(m), 1442 \\
& \quad (s), 1450(s), 1478(m), 1505(s), 1532(w), 1580(w), \\
& \quad 1650(w), 1715(w), 1768(w), 1840(w), 3070(w), \\
& \quad 3138(m). \\
\text{m-Biphenylyl} & \quad 675(vs), 694(vs), 758(vs), 792(s), 808(s), 890(s), \\
& \quad 969(m), 971(m), 992(s), 1028(s), 1070(m), 1102(w), \\
& \quad 1158(s), 1175(sh), 1237(s), 1283 & 1298 (doublet, \\
& \quad s), 1327(m), 1356(w), 1365(v), 1440(m), 1478(m), \\
& \quad 1513(s), 1578(m), 1592(s), 3100(m), 3120(w). \\
\text{p-Biphenylyl} & \quad 697(s), 720(s), 765(s), 843(s), 885(m), 922(w), \\
& \quad 965(w), 987(m), 1013(w), 1062(w), 1082(w), 1119(w), \\
& \quad 1152(m), 1225(w), 1249(w), 1260(s), 1329(w), 1355 \\
& \quad & \quad \text{& 1365 (doublet, w), 1410(w), 1428(w), 1481(m),} \\
& \quad 1497(m), 1527(m), 1597 & 1604 (doublet, w), 3041 \\
& \quad (w), 3096(m). 
\end{align*}
Table III (contd.)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Spectral Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-Biphenyl</td>
<td>667(s), 703(s), 740(s), 765(s), 779(sh), 869(m), 922(w), 930(w), 1001(m), 1089(m), 1127(m), 1223(m), 1251(w), 1264(w), 1311(w), 1508(m), 3112(m).</td>
</tr>
<tr>
<td>m-Biphenyl</td>
<td>670(sh), 691(vs), 753(vs), 794(s), 861(m), 893 &amp; 903 (doublet, s), 920(m), 961(m), 982(w), 1013(m), 1029(m), 1105(vs), 1158(w), 1187(w), 1259(vs), 1268(sh), 1296(m), 1377(w), 1453(w), 1481(w), 1518(vs), 1578(m), 1594(sh), 1610(s), 3070(w), 3108(m).</td>
</tr>
<tr>
<td>p-Biphenyl</td>
<td>705(s), 720(m), 772(s), 842(m), 876(w), 947(w), 999(m), 1087(s), 1233(s), 1254(w), 1279(w), 1296(w), 1336(w), 1371(m), 1420(w), 1497(m), 1530(m), 3117(m), 3137(w).</td>
</tr>
</tbody>
</table>

\* v, weak; m, medium; s, strong; vs, very strong; sh, shoulder.

ULTRAVIOLET SPECTRA.

Ultraviolet absorption spectra of various compounds obtained during these investigations were also recorded and are presented in the following Table IV.
Table IV: ULTRAVIOLET ABSORPTION SPECTRA OF VARIOUS TRIAZOLES (in methanol).

<table>
<thead>
<tr>
<th>R</th>
<th>$\lambda_{max}$, $\mu$ (log ε)</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-Biphenyl</td>
<td>$\lambda_{max}$, $\mu$ (log ε)</td>
</tr>
<tr>
<td>m-Biphenyl</td>
<td>$\lambda_{max}$, $\mu$ (log ε)</td>
</tr>
<tr>
<td>p-Biphenyl</td>
<td>$\lambda_{max}$, $\mu$ (log ε)</td>
</tr>
<tr>
<td>a-Aminophenyl, hydrochloride</td>
<td>$\lambda_{max}$, $\mu$ (log ε)</td>
</tr>
</tbody>
</table>
Table IV (contd.)

<table>
<thead>
<tr>
<th>Phenylation</th>
<th>240 (3.95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-Nitrophenyl</td>
<td>225 (3.86); 290 infl. (3.40)</td>
</tr>
<tr>
<td>p-Nitrophenyl</td>
<td>217 (3.82); 292 (3.99)</td>
</tr>
</tbody>
</table>

Phenylation | 210 (3.64); 240 (4.05) |

---

a. In water.
General conditions were the same as in Chapter I (p. 85).

3-Amino-1,2,4-triazole used was obtained from Light & Co.; 1,2,4-triazole m.p. 118-120° from Dr. Th. Schuchardt, Munich; samples of 3-phenyl-1,2,4-triazole; 3,5-diphenyl-1,2,4-triazole, 3,4-diphenyl 1,2,4-triazole, 1,3-diphenyl-1,2,4-triazole, 1,5-diphenyl-1,2,4-triazole and 3-(( o- and m-nitrophenyl)-1,2,4-triazole were kindly supplied by Dr. E.J. Browne of this department.

1-Methyl-1,2,4-triazole b.p. 178° was prepared following the method of Atkinson and Polya (44). 5-Aminotetrazole m.p. 206° was prepared by the method of Herbst and Garrison (45).

In the preparation of N-nitrosoacetanilide m.p. 51-53° (decomp.), Bachmann and Hoffmann's improved method (8) was used and the nitrosoacetanilide was obtained in 82% yield. This was used without further purification.

1-Benzyl-1,2,4-triazole m.p. 57-59° was obtained using Jones and Ainsworth's method (46).

N,N',Diformylhydrazine m.p. 156-160° was prepared following the method of Ainsworth and Jones (47) using hydrazine hydrate and formamide. 3,4'-Bitriazole m.p. 295-296° was prepared in 48.8% yield by Wiley and Hart's method (48).
2-Nitro Biphenyl (m.p. 33-34°); 3-nitro biphenyl (m.p. 56-58°) and 4-nitro biphenyl (m.p. 112-114°) were prepared by the Gomberg reaction of isomeric nitroanilines and benzene (49). 3-Amino-5-phenyl-1,2,4-triazole m.p. 188-190° was obtained using the method of Atkinson, Komzak, Parkes and Polya (50). 2-Aminobiphenyl m.p. 46-48°, 3-aminobiphenyl m.p. 30°, and 4-aminobiphenyl m.p. 61-62° were obtained in nearly theoretical yield by the reduction of the corresponding nitro biphenyls by tin and hydrochloric acid (51). 3-Amino-4-phenyl-1,2,4-triazole m.p. 214-215° was prepared in small yield by the method of Raison (52).

4-Phenyl-1,2,4-triazole. A mixture of diformyl hydrazine (105 g; 1.2 mole) and aniline (111 g, 1.2 mole) was heated in an oil bath at 120° for 1 hour and then at 180-185° for 3 hours. The material was distilled under reduced pressure (aspirator vacuum) and the fraction b.p. 224-234° was collected and recrystallised from chloroform/light petroleum. 4-Phenyl-1,2,4-triazole m.p. 122° was thus obtained. Yield: 85.8 g, 49.5%. lit. m.p. 121° (53).

In another experiment when a mixture of diformyl hydrazine and aniline was heated on a heating mantle, the major product isolated was 1,2,4-triazole, which is probably formed by self condensation of diformyl hydrazine with its breakdown products.
1,2-Di(1',2',4'-triazol-1'-yl)ethane (VI). A mixture of 1,2,4-triazole (6.0 g), sodium (2.2 g) and 1,2-dibromoethane (12.6 g) in ethanol (18 ml) was heated under reflux for 19 hrs. The mixture was allowed to cool to room temperature and filtered. The filtrate was freed of ethanol and the residue thus obtained was recrystallised from ethylacetate. 1,2-Di(1',2',4'-triazol-1'-yl)ethane m.p. 162-164° was obtained. Yield: 1.2 g; 16.9%.

1-Phenyl-1,2,4-triazole was prepared according to the method of H. Gold (54). Cyanuric chloride (18.5 g, 0.1 mole) was added to dimethylformamide (60 ml, 0.2 mole). The reaction started within ten minutes with the evolution of heat. The temperature of the reaction was controlled at 50-60°. The adduct thus formed lost carbon dioxide when heated to a temperature of 90°. The reaction mixture was cooled and stirred with cool acetone (150 ml) and filtered through a Büchner funnel at 15°. The residue was washed with a little cool acetone and the "aza salt" (3-dimethylamino-2-azaprop-2-en-1-ylidendimethylammonium chloride) thus obtained was dried in vacuum over activated charcoal and sodium hydroxide.
A mixture of "aza salt" (16.3 g, 0.1 mole) and phenylhydrazine (10.8 g, 0.1 mole) was heated on a water bath at 60° for 10 minutes and then at 90° for 30 minutes. Dimethylamine was evolved during heating. The reaction mixture on cooling was extracted with ether (200 ml, 50 ml portions); the ether extract was washed with water and dried. The solvent was evaporated and the residue thus obtained was distilled. The fraction b.p. 260-270° was collected and this, on chilling, gave 1-phenyl-1,2,4-triazole m.p. 46-48°. Yield: 5.4 g; 37.1%.

1-(x)-Biphenylyl-1,2,4-triazoles. These were prepared by a method similar to that used for the preparation of 1-phenyl-1,2,4-triazole. The appropriate aminobiphenyls were diazotised and reduced to the corresponding hydrazinobiphenyls using stannous chloride (55). The hydrazines were then condensed with the "aza salt" (as obtained in the previous reaction (p.225)) on a water bath at 90° for 1 to 3 hours, and extracted with ether. The ethereal extract was dried and filtered and the solvent was evaporated from the filtrate. The product was isolated from the residue either by distillation under reduced pressure or by chromatography on alumina. The biphenylyl-1,2,4-triazolos were recrystallised from chloroform/light petroleum. A small amount of biphenyl (identical m.p., mixed m.p. and infrared
spectra with an authentic sample) was obtained in all three reactions. 2-Hydrazinobiphenyl failed to give 1-(p-biphenyl)-1,2,4-triazole. Instead, carbazole (identical m.p., mixed m.p. and infrared spectra with an authentic sample) and biphenyl were obtained. The two biphenyl-1,2,4-triazoles obtained from these syntheses are listed in Table I (p.210).

4-(x)-Biphenyl-1,2,4-triazoles. These were prepared from the condensations of respective aminobiphenyls with diformyl hydrazine as employed in the preparation of 4-phenyl-1,2,4-triazole. A mixture of 0.1 mole of aminobiphenyl and 0.1 mole of diformylhydrazine was heated at 100° for 1 hr. and then the temperature was raised to 180° and kept at this temperature for a further period of two hours. On cooling, the reaction mixture was boiled with 20% solution of sodium hydroxide for 1 hr., cooled and extracted with ethyl acetate; the ethyl acetate extract was treated twice with decolorising charcoal and filtered. The solvent was evaporated and the residue thus obtained was either crystallised directly from chloroform/light petroleum (m-, and p-isomers), or distilled under reduced pressure, subjected to chromatography on alumina and recrystallised from benzene/light petroleum. In the case of the p-isomer the chromatography on alumina, with benzene as eluting solvent, gave a small quantity of carbazole.
4-(o-Biphenylyl)-1,2,4-triazole was eluted with 50% chloroform/benzene. The results are listed in Table I (p.210).

Decomposition of diazotized 3-amino-1,2,4-triazole in benzene.

3-amino-1,2,4-triazole (4.2 g, 0.05 mole) was diazotized in sulphuric acid (1:1, 20 ml) at 5°C. The solution of the diazonium salt was stirred at 7°C with chilled benzene (200 ml) while a saturated solution of sodium acetate tri-hydrate was added to bring the pH of the reaction mixture to nearly 5. The stirring was continued for 20 hrs. and the reaction mixture was allowed to come to room temperature. It was then heated for 4 hrs. on a water bath. The benzene layer was separated, dried and filtered. The solvent was evaporated (reduced pressure) from the filtrate. Thus a residue was obtained. Yield: 1.1 g; 15.4%. A small amount of this residue was chromatographed on alumina, with 5% ethanol in benzene. On removal of the solvent from the eluents a residue was obtained which was crystallised twice from light petroleum (b.p. 100-120°C) giving 3-phenyl-1,2,4-triazole, m.p. 118°C, identical with an authentic sample of 3-phenyl-1,2,4-triazole. This, however, depressed the m.p. of triazole (mixed m.p. 80°C).

Using nitric acid instead of sulphuric acid for the diazotization of 3-amino-1,2,4-triazole similar results were obtained.
Decomposition of diazotized 3-amino-1,2,4-triazole in nitrobenzene.

3-Amino-1,2,4-triazole (4.2 g, 0.05 mole) was diazotized in a similar manner as used for the diazotization in the preceding experiment. The resulting diazotized solution was stirred with chilled nitrobenzene (200 ml) at 7° while buffering the reaction mixture with sodium acetate. The stirring was continued for 21 hrs. during which period the reaction mixture came up to room temperature. This was further heated on a water bath for 3 hrs. with stirring. The reaction mixture was allowed to cool and then acidified with sulphuric acid and distilled in steam to remove excess nitrobenzene. The residue was made alkaline by sodium hydroxide and then extracted with benzene giving 3-(p-nitrophynyl)-1,2,4-triazole (0.54 g), m.p. 218-221°, mixed m.p. with an authentic sample 220°. The alkaline solution was neutralised with dilute sulphuric acid and extracted with benzene. The benzene extract on standing overnight deposited a further amount (0.3 g) of 3-(p-nitrophynyl)-1,2,4-triazole. The benzene extract, freed of the solvent by evaporation under reduced pressure, gave a residue (1.2 g), which on crystallisation from benzene gave crystals m.p. 142-149°; the m.p. remained unchanged even after five crystallisations. The basic solution of the residue was also extracted with ether giving 0.7 g of residue after evaporation of ether and from this residue another small amount of crystals m.p. 218°.
was obtained. Thus a mixture of arylation products was obtained.
Yield: 3.7 g; 38.8%. From this mixture 0.3 g (8.6%) of 3-(\(p\)-nitrophenyl)-1,2,4-triazole and 0.9 g (25.8%) of compound m.p. 142-149° was isolated. The compound m.p. 142-149° analysed for a mononitrophenyltriazole. Anal. calcd. for C\(_6\)H\(_6\)N\(_4\)O\(_2\): C, 50.5; H, 3.2; N, 29.5%. Found: C, 50.0; H, 3.2 and N, 28.6%. This was identical with an authentic sample of 3-(\(p\)-nitrophenyl)-1,2,4-triazole. The identity of the rest of the residue was not established.

Decomposition of diazotized 3-amino-1,2,4-triazole in bromobenzene.
3-Amino-1,2,4-triazole (8.4 g, 0.1 mole) was diazotized in sulphuric acid and allowed to decompose in the usual manner using chilled bromobenzene (300 ml). The reaction mixture was allowed to stir for 70 hrs. and then extracted with benzene. The benzene extract was dried and filtered. The solvent was evaporated on a water bath (reduced pressure). Excess bromobenzene was removed by distillation at 54°/8 mm and the residue thus obtained 4.2 g (15.5%) was fractionally distilled giving 0.7 g of material b.p. 80°/7 mm. This gave crystals m.p. 86-88° which analysed for a dibromobenzene, \(p\)-dibromobenzene m.p. 86.9° (66). Anal. calcd. for C\(_6\)H\(_4\)Br\(_2\): C, 30.5; H, 1.7; Br, 67.8%. Found: C, 31.2; H, 2.0; Br, 65.6%.
The other two fractions b.p. 196-200°/6 mm and 206-210°/6 mm gave crystals m.p. 115-132°. These fractions were combined and twice recrystallised from acetone/light petroleum giving crystals m.p. 160-164°, which analysed for a monobromophenyltriazole. Anal. calcd. for C₈H₆N₃Br: C, 42.9; H, 2.7; N, 18.8; Br, 35.7%. Found: C, 43.8; H, 2.8; N, 19.1; Br, 33.3%. No other compound could be isolated from the mixture.

Decomposition of diazotised 3-amino-5-phenyl-1,2,4-triazole in benzene.

3-Amino-5-phenyl-1,2,4-triazole (5 g, 0.031 mole) was diazotised in sulphuric acid (1:1, 35 ml) at 5-10° by the addition of sodium nitrite (2.2 g) in water (10 ml). The diazotised solution was filtered through a sintered glass funnel (the residue in the funnel exploded on drying!). Chilled benzene (200 ml) was added to the filtered solution followed immediately by sodium acetate (10 g) in water (25 ml). The mixture was stirred vigorously for 8 hrs. at room temperature. The benzene layer was separated and the aqueous layer was repeatedly extracted with benzene (100 ml) and ethyl acetate (500 ml in 100 ml portions). The combined extract was dried and filtered. The solvent was evaporated from the filtrate giving 3,5-diphenyl-1,2,4-triazole m.p. 201-203° (from ethyl acetate). lit. m.p. 189-191° (56). Yield: 0.4 g; 6%. Anal. calcd. for C₁₄H₁₁N₃: C, 76.0; H, 5.0; N, 19.0%. Found: C, 75.1; H, 5.0; N, 18.8%. 

\[ \text{cm} \]
Decomposition of diazotized 5-aminotetrazole in benzene. 5-Aminotetrazole (5 g, 0.035 mole) was diazotized at $5^\circ$ in sulphuric acid (5%; 100 ml) with a saturated solution of sodium nitrite. Chilled benzene (250 ml) was added to the diazotized solution followed by a saturated solution of sodium acetate and the mixture was stirred for 24 hrs. at room temperature. The benzene layer was separated, dried and filtered. The filtrate on removal of the solvent gave a small amount of residue. The aqueous layer was extracted with ethyl acetate (500 ml in 3 portions). The ethyl acetate extract was dried and filtered. The filtrate was freed of the solvent leaving the residue. Yield: 1.5 g; 29.1%. From this residue needle shaped crystals of 5-phenyltetrazole (from water) were obtained, m.p. 216$^\circ$. lit. m.p. 217-218$^\circ$ (57). Anal. calcd. for $C_7H_6N_4$: C, 57.5; H, 4.1; N, 38.4%. Found: C, 56.8; H, 4.2; N, 37.2%.

1-p-Nitrophenyl-1,2,4-triazole. The method of Gold (54) was used. A mixture of the "aza-salt" (32.6 g) and p-nitrophenylhydrazine (30.6 g) was heated at 60$^\circ$ for half an hour and then at 90$^\circ$(water bath) for two hours. The reaction mixture was extracted with hot ethyl acetate (200 ml). The ethyl acetate extract was treated with charcoal and filtered. The solvent was evaporated from the
filtrate and the residue thus obtained crystallised from ethanol giving 1-p-nitrophenyl-1,2,4-triazole m.p. 192-195°; lit. m.p. 190° (58). Yield: 14.3 g; 37.6%.

1-p-Aminophenyl-1,2,4-triazole. Hydrochloric acid (conc. 25 ml) was added with caution to a mixture of 1-p-nitrophenyl-1,2,4-triazole (4.5 g) and granulated tin (5.5 g). The mixture was cooled in an ico bath since the reaction became too vigorous. The mixture was then heated under reflux for 8 hrs., cooled and then neutralised with sodium hydroxide (60 ml; 33% solution). The basified solution was extracted with ethyl acetate. The ethyl acetate extract was washed, dried and filtered. The solvent was evaporated from the filtrate leaving 1-p-aminophenyl-1,2,4-triazole m.p. 140-142°. lit. m.p. 140° (58). Yield: 3.5 g; 92.9%. Ainsworth et al. (58) had obtained 1-p-aminophenyl 1,2,4-triazole in 50% yield by reduction of 1-p-nitrophenyl-1,2,4-triazole with Raney nickel. The infrared spectrum: \( \nu_\text{NH}_2, 3450, 3320 \text{ cm}^{-1} \) asym. and sym.; 3207 cm\(^{-1}\) bonded NH; NH\(_2\) bending, 1639 cm\(^{-1}\); 1:4 disubstituted benzene, 1614, 1521 and 827 cm\(^{-1}\).

Decomposition of diazotized 1-p-aminophenyl-1,2,4-triazole in benzene. 1-p-Aminophenyl-1,2,4-triazole was diazotized in sulphuric acid (1:1; 23 ml) by sodium nitrite (1.7 g in 10 ml water) at 0-5° with the
usual precautions. Chilled benzene (250 ml) was added to the diazonium solution followed by a saturated solution of sodium acetate (110 g). The mixture was stirred for 34 hrs. at room temperature. The benzene layer was separated and the aqueous layer was extracted with more benzene (300 ml; 100 ml portions). The combined benzene extracts were treated with charcoal and filtered. The solvent was evaporated from the filtrate giving residue m.p. 120-122°. Yield: 1.1 g; 23.9%. The residue on crystallisation from ethyl acetate afforded crystals m.p. 130-131°, identical (m.p., mixed m.p. and infrared spectrum) with 1-p-biphénylyl-1,2,4-triazole m.p. 130-131° obtained from the reaction of 4-hydrazinobiphenyl and the "aza-salt" (p.226). A portion was recrystallised from chloroform/light petroleum giving shining plates m.p. 130-131°. Anal. calcd. for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>: C, 76.0; H, 5.0; N, 19.0. Found: C, 75.3; H, 4.9; N, 18.9%.

1-o-Aminophenyl-1,2,4-triazole. 1-(o-Nitrophenyl)-1,2,4-triazole was reduced following the method of Petrow and Saper (69). 1-(o-Nitrophenyl)-1,2,4-triazole (1.7 g), degreased iron filings (3.7 g), ethanol (18 ml), water (4 ml) and conc. hydrochloric acid (0.25 ml) were heated under reflux for 1.5 hrs. on a water bath. The mixture was filtered hot and the residue was washed with hot ethanol. The filtrate and the washings were combined and from this, ethanol was removed under reduced
pressure (aspirator vacuum). The residue thus obtained was extracted with ether. The ethereal extract was freed of the solvent leaving 1-(α-aminophenyl)-1,2,4-triazole as a viscous liquid. Yield: 0.8 g; 56.8%. This viscous liquid was identical (infrared spectrum) with the product obtained (in 91.6% yield) from the reduction of 1-(α-nitrophenyl)-1,2,4-triazole with tin and hydrochloric acid. The infrared spectrum (liquid film): $\nu_{NH_2}$, 3425, 3333 cm$^{-1}$ asym. and sym.; 3205 bonded NH; 1:2-disubstituted benzene, 1613, 1493 and 746-752 (br.) cm$^{-1}$.

The viscous liquid could not be induced to crystallise and was dissolved in ether and dry HCl gas passed through the ethereal solution when a white solid precipitated out. This solid was filtered off and crystallised from ethanol giving white shining plates of 1-(α-aminophenyl)-1,2,4-triazole hydrochloride, m.p. 208-210°C (decomp.).

Decomposition of diazotized 1-(α-aminophenyl)-1,2,4-triazole in benzene.

1-(α-Aminophenyl)-1,2,4-triazole (6.14 g) was diazotized in hydrochloric acid (15 ml) and water (10 ml) as usual by the addition of sodium nitrite (2.7 g) in water (7 ml). The diazonium salt solution was added to precooled benzene (200 ml) followed by sodium acetate (20 g in 25 ml water). The mixture was stirred for 20 hrs. at ambient temperature. The benzene layer was separated and the aqueous layer
was extracted with more benzene. The combined benzene extracts were dried, filtered and the filtrate was treated with charcoal and filtered. The solvent was evaporated from the filtrate. The viscous residue thus obtained was dissolved in a minimum quantity of benzene and subjected to chromatography on alumina. The eluting solvent was gradually changed from benzene to 25% chloroform/benzene. The eluents left a white solid on removal of the solvent. This solid was twice crystallised from chloroform/light petroleum giving 1-(α-biphenylyl)-1,2,4-triazole m.p. 71-72°. Yield: 0.85 g; 10.0%.

Decomposition of diazotized 4-(α-aminophenyl)-1,2,4-triazole in benzene. 4-(α-Aminophenyl)-1,2,4-triazole (3.36 g) (p. 89) was dissolved in hydrochloric acid (10 ml) and water (10 ml) and diazotized in the usual manner by the addition of sodium nitrite (1.6 g) solution in water (5 ml). The diazonium salt solution was added to precooled benzene (200 ml) followed by a saturated solution of sodium acetate (25 g). The reaction mixture was stirred at ambient temperature for 14 hrs. The benzene layer was separated and the aqueous layer was extracted with several portions of benzene. The combined benzene extracts were treated with charcoal and filtered. The filtrate was freed of benzene and the residue thus obtained was chromatographed on alumina. The eluting solvent was gradually changed from benzene
to 50% chloroform/benzene. From the eluents (from 50% chloroform benzene) the solvent was evaporated giving a small amount of residue m.p. 150-152°. On recrystallisation from chloroform/light petroleum the m.p. was raised to 159-160°. This residue was identical with an authentic sample of 4-(α-biphenyl)-1,2,4-triazole. Yield: 0.23 g; 0.5%.

Further elution of the column with 50% chloroform/benzene yielded 4-phenyl-1,2,4-triazole (0.11 g).

Decomposition of N-nitrosoacetanilide in 1-methyl-1,2,4-triazole.
N-Nitrosoacetanilide (5 g) was allowed to decompose in 1-methyl-1,2,4-triazole (17.3 g) for 70 hrs. at room temperature and then for 2 hrs. at 70°. The reaction mixture was allowed to cool and then 1-methyl-1,2,4-triazole was distilled off under reduced pressure. A small amount of triazole was obtained from the distillate at 128°/3 mm. The residue from the distillation was subjected to chromatography on alumina using 50% benzene/light petroleum (b.p. 60-80°) for developing the column; elution with benzene gave a few crystals of unidentified material m.p. 50°. Using 1% ethanol in benzene, crystals m.p. 52-54° were obtained (11 mg) on evaporation of the solvent from the eluents. This material was identified as 1-methyl-5-phenyl-1,2,4-triazole as it did not depress the m.p. of
an authentic sample of 1-methyl-5-phenyl-1,2,4-triazole (m.p. 57-58°) (56). The infrared spectra were also identical. Anal. calc. for C₉H₉N₃: C, 67.9; H, 5.7; N, 26.4%. Found: C, 68.4; H, 5.9; N, 24.7%.

No other identifiable product was obtained.
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SUMMARY

C- and N- arylation of various heterocyclic compounds were effected using Ullmann condensation and Meerwein and Gomberg arylation reactions.

The Ullmann condensation between pyrazole, imidazole, 1,2,4-triazole, indole, benzimidazole and carbazole were effected by using various aryl halides. Aryl halides employed were: halonitrobenzenes, halopyridines, halobenzonitriles, bromoacetophenones and halobenzoic acids. All the condensations gave normal N-aryl substituted azoles in good yields. In the arylation of pyrrole by p-chloronitrobenzene 1-(p-nitrophenyl)pyrrole was obtained in only 1% yield; arylation by p-chloronitrobenzene failed. In the arylation of 1,2,4-triazole by all the aryl halides except halopyridines only 1-substituted aryltriazoles were obtained. Arylation of 1,2,4-triazole by halopyridines gave predominantly the 1-isomer together with small quantities of the corresponding 4-isomer. Arylation by halobenzonitriles gave N-azolylbenzonitriles accompanied by very small amounts of the corresponding acid and in the case of two arylation (1,2,4-triazole with 4-bromobenzonitrile and indole with 3-bromobenzonitrile) azolylbenzamides were also obtained.
Cupric oxide was used as catalyst and pyridine as solvent in these condensations. Dimethylformamide was also found to be a useful solvent in these condensations. A number of hitherto unreported compounds were obtained from these condensations and are reported in this thesis. The product formation in these condensations has been rationalised in terms of a tentative mechanism.

The Meerwein arylation of 2-furoic acid and methyl 2-furoate by various aromatic amines was also carried out and the corresponding 5-arylfuroic acids and esters were obtained. The arylation of methyl 2-furoate also gave corresponding acids in small yields. Arylation of acrylic acid was effected by diazotized 2-aminothiazole and of benzoquinone by diazotized 3-amino-1,2,4-triazole. Coumarin and cinnamic acid were also arylated by diazotized 3-aminopyridine under Meerwein conditions.

The Gomberg arylation of benzene, nitrobenzene and bromobenzene was carried out using diazotized 3-amino-1,2,4-triazole and the arylated products isolated. Decomposition of the following diazotized amines in benzene was also carried out: 3-amino-5-phenyl-1,2,4-triazole; 5-amino-tetrazole; 1-(p-aminophenyl)-1,2,4-triazole; 1-(p-aminophenyl)-1,2,4-triazole; and 4-(p-aminophenyl)-1,2,4-triazole,
and the corresponding phenylated products were isolated. In the phenylation of 1-methyl-1,2,4-triazole by N-nitrosoacetanilide the only product isolated was 1-methyl-5-phenyl-1,2,4-triazole.

Infrared and ultraviolet absorption spectra of all the new compounds obtained during the present investigations are also reported.
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