169. *The Mechanism of Indole Formation from Phenacylarylamines. Part II. The Stability and Reactions of Phenacyl-N-alkylarylamines.*

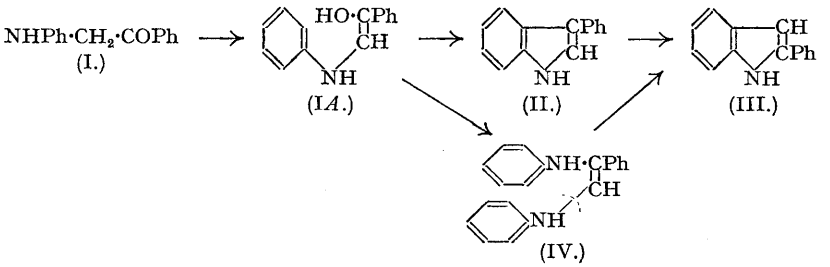
By Fred Brown and Frederick G. Mann.

A detailed study has been made of the conditions under which the phenacyl derivatives of *N*-alkylanilines undergo conversion into indoles. It is shown that a phenacylarylamine of type $NRPh{\cdot}CH_2{\cdot}COPh$, where R is an alkyl group, has considerable stability when pure, but when boiled with alcoholic zinc chloride gives a 3-aryl-1-alkylindole, when fused with zinc chloride gives a 2 (or 3)-aryl-1-alkylindole, and when boiled with the amine NHRPh in the presence of acids gives a mixture of 2-arylindole and 2 (or 3)-aryl-1-alkylindole. The origin of the 3-aryl-1-alkylindoles and the 2-arylindoles is elucidated: the mechanism by which 2-aryl-1-alkylindoles are formed is apparently similar to that by which 2-arylindoles arise from phenacylarylamines of type $NHPh{\cdot}CH_2{\cdot}COPh$. The study of the latter reaction is reserved for Part III.

In Part I (Crowther, Mann, and Purdie, *J.*, 1943, 58) a considerable volume of experimental evidence concerning the conditions under which phenacylarylamines undergo conversion into arylindoles was described, and the possible mechanism of such conversion was discussed. Among the numerous points which emerged, the following are the most important. (*a*) Phenacylaniline, $NHPh{\cdot}CH_2{\cdot}COPh$, could be distilled unchanged at *ca.* 20 mm., but underwent decomposition when heated at 760 mm.: no indole could be detected among the several products of this thermal decomposition. (*b*) When phenacylaniline was heated to 180° with a minute proportion (for example, 0·01 g.-mol.) of aniline hydrobromide or hydriodide, or of many other compounds which could produce hydrogen bromide or iodide under these conditions, it underwent rapid and smooth conversion into 2-phenylindole. These properties were shown to be general for a number of phenacyl primary arylamines. (*c*) Phenacyl secondary amines were not so readily susceptible to this action of acidic catalysis, but when, for example, phenacyl-*N*-ethylaniline, $NEtPh{\cdot}CH_2{\cdot}COPh$, was fused with zinc chloride it gave 3-phenyl-1-ethylindole. Only one example of the production of a 2-aryl-1-alkylindole was detected: phenacyl-*N*-methylaniline furnished 3-phenyl-1-methylindole when boiled with alcoholic zinc chloride, but 2-phenyl-1-methylindole when fused with anhydrous zinc chloride. This property appeared to be governed in part by the nature of the aryl group, since *p*-chlorophenacyl-*N*-methylaniline, $NMePh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4Cl$, when either boiled with alcoholic zinc chloride or fused with zinc chloride gave 3-*p*-chlorophenyl-1-methylindole. With this one exception of phenacyl-*N*-

methylaniline, the indolisation of all the phenacyl secondary amines studied gave the corresponding 3-aryl-1-alkylindoles and appeared therefore to proceed by simple cyclisation of their *enol* forms. In this respect the phenacyl secondary amines differed markedly from the phenacyl primary amines.

Two reaction mechanisms had previously been suggested for the conversion of phenacyl primary amines into 2-arylindoles. The first (or isomerisation) theory, originally suggested by Fischer and Schmidt (*Ber.*, 1888, **21**, 1071, 1811) presumed that phenacylamine (I), in its *enol* form (I*A*), underwent simple cyclisation to 3-phenylindole (II), which then in turn underwent



isomerisation to 2-phenylindole (III). In Part I, however, it was shown that many 3-arylindoles are unaffected by the conditions which produce 2-arylindoles from the corresponding phenacylamines, and that they cannot therefore be intermediate compounds in this process.

The second (or diamine) theory was put forward by Bischler (*Ber.*, 1892, **25**, 2868) who prepared the 2-arylindoles by boiling the corresponding phenacyl bromide with excess of aniline without isolating the intermediate phenacylamine. He presumed that this phenacylamine in its *enol* form (I*A*) condensed with a second molecule of aniline to give the diamine (IV), which then underwent cyclisation by loss of the *initial* aniline residue, the corresponding 2-arylindole being thus produced. Bischler supported this theory by showing, for instance, that phenacylaniline (I) when boiled with *p*-toluidine (10 mols.) furnished 2-phenyl-5-methylindole.

In Part I, however, it was shown that aniline condenses with pure phenacylaniline to give the triamine, *NN*-di-(2-phenylamino-1-phenylvinyl)aniline (V), and no diamine of Bischler's type could be isolated from phenacyl primary amines. Furthermore, phenacylaniline (I), when boiled with excess of, for example, pure *o*-toluidine (VI), undergoes a slow double decomposition with the formation of phenacyl-*o*-toluidine (VII) and aniline. The two phenacylamines undergo no further change under these conditions. If, however, a trace of acid is present, the phenacylamines undergo the usual catalysed indolisation, and the indole formed in greater

NHPh·CH:CPh
>NPh
NHPh·CH:CPh
(V.)

$$\underset{\text{(VI.)}}{\text{Ph·NH·CH}_2\text{·COPh}} + o\text{-C}_6\text{H}_4\text{Me·NH}_2 \rightleftarrows \underset{\text{(VII.)}}{o\text{-C}_6\text{H}_4\text{Me·NH·CH}_2\text{·COPh}} + \text{Ph·NH}_2$$

proportion (2-phenylindole or 2-phenyl-7-methylindole) will depend on the excess of *o*-toluidine in the original mixture and on the time of heating. These double decompositions therefore invalidate Bischler's deductions.

Neither the isomerisation nor the diamine theory explains the necessity for the presence of traces of acid.

To explain both the formation of 2-phenylindole and the rôle of the acid during indolisation of phenacylaniline, Crowther, Mann, and Purdie (*loc. cit.*) tentatively suggested a mechanism by which a phenacyl ion attached itself to the ortho-carbon atom of an aniline molecule: loss of a hydrogen atom as a proton then gave phenyl *o*-aminobenzyl ketone which was known to cyclise readily to 2-phenylindole.

We have investigated this problem further in order to elucidate more completely the mechanism of the various reactions involved. For this purpose our work has fallen into two main sections. In the first section (described in this Part), we have re-investigated the indolisation of phenacyl secondary amines in order to determine in what circumstances a compound of type NRPh·CH_2·CO·C_6H_4R′(*p*) would undergo indolisation to a 3-aryl-1-alkylindole and/or a 2-aryl-1-alkylindole, and, in the latter case, to what extent the production of the 2-aryl-1-alkylindole rather than its 3-aryl isomer was determined by the alkyl group R and by the *p*-substituent R′. Furthermore, it was necessary to know, when a 2-aryl-1-alkylindole was formed, whether the mechanism of this reaction was essentially the same as that by which

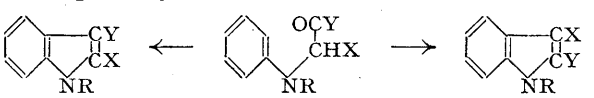
2-arylindoles are formed from phenacyl primary amines. The origin of a number of significant by-products also required investigation.

Our second section (described in Part III) has been devoted to a further study, on rather different lines from those adopted in Part I, of the main problem, namely the indolisation of phenacyl primary amines to 2-arylindoles, a reaction which is clearly the most fundamentally important of all those arising in this investigation. In this second section, we had been interested in the evidence recorded in a brief note by McGeoch and Stevens (*J.*, 1935, 1032) that the bromo-

$$\underset{\text{(VIII.)}}{Ph{\cdot}CH_2{\cdot}CHBr{\cdot}COPh} \longrightarrow \underset{\text{(IX.)}}{NHPh{\cdot}CH(CH_2Ph){\cdot}COPh} + \underset{\text{(X.)}}{NHPh{\cdot}CHPh{\cdot}CO{\cdot}CH_2Ph}$$

ketone (VIII) when heated with 2 mols. of aniline at 60° for 4 days gave a mixture of isomeric anilides, namely the yellow 1-benzylphenacylaniline (IX), m. p. 106°, and the colourless α-anilinodibenzyl ketone (X), m. p. 125°. This implied that under suitable conditions phenacyl primary amines might be interconvertible: if these conditions obtained in our experiments an entirely new light would be thrown on the mechanism of these reactions, since isomerisation of our phenacylamines might precede indolisation and thus determine the ultimate position of the aryl group in the final indole.

The greater part of our work on these subjects had been completed when the published work of two other groups of workers came (very belatedly owing to war conditions) into our hands. Verkade and Janetzky (*Rec. Trav. chim.*, 1943, **62**, 763, 775) confirmed the findings of Crowther, Mann, and Purdie (*loc. cit.*) that phenacylaniline was unchanged on boiling with aniline: they showed, however, that it gave 2-phenylindole on fusion with zinc chloride and when heated with one equivalent of aniline hydrochloride. Furthermore, phenacyl-*N*-methylaniline, $NMePh{\cdot}CH_2{\cdot}COPh$, when heated with an equal weight of *N*-methylaniline hydrochloride at 170° gave a high yield of 3-phenyl-1-methylindole and a small proportion of 2-phenyl-1-methylindole. They also investigated the cyclisation of compounds of type (XI) in which X and Y were aryl and alkyl substituents respectively, and showed that in certain circumstances indolisation



(XII*A*.) (XI.) (XII*B*.)

occurred by "true ring closure" to give indoles of type (XII*A*), and sometimes by "rearrangement" or "apparent ring closure" to give isomeric indoles of type (XII*B*), although no detailed mechanism was suggested. Later communications by Verkade *et al.* have since appeared (*ibid.*, 1945, **64**, 129, 139, 289; 1946, **65**, 193, 691).

More significant and decisive evidence has been produced by Julian, Meyer, Magnani, and Cole (*J. Amer. Chem. Soc.*, 1945, **67**, 1203), who have shown that both α-bromopropiophenone and α-bromobenzyl methyl ketone on treatment with aniline give a mixture of the isomeric anilides,* namely the yellow α-anilinopropiophenone (XIII), m. p. 102°, and the white α-anilino-

$$\underset{}{MeCHBr{\cdot}COPh} \longrightarrow \underset{\text{(XIII.)}}{NHPh{\cdot}CHMe{\cdot}COPh} + \underset{\text{(XIV.)}}{NHPh{\cdot}CHPh{\cdot}COMe} \longleftarrow \underset{}{Ph{\cdot}CHBr{\cdot}COMe}$$

benzyl methyl ketone (XIV), m. p. 90°. They claimed that these isomeric anilides underwent interconversion when heated in alcohol solution with aniline hydrobromide, and that both when heated with a mixture of aniline and aniline hydrochloride gave 2-phenyl-3-methylindole. Each of other similar pairs of isomeric anilides, however, gave a mixture of isomeric indoles; for example, both α-anilinodibenzyl ketone, $Ph{\cdot}CH(NHPh){\cdot}CO{\cdot}CH_2Ph$, and α-anilino-β-phenylpropiophenone, $Ph{\cdot}CO{\cdot}CH(NHPh){\cdot}CH_2Ph$, on cyclisation gave a mixture of 3-phenyl-2-benzylindole and 2-phenyl-3-benzylindole. These workers incline to the view that the Bischler diamine theory if suitably modified will apply to certain cases of indole formation from phenacylamines. They assert that the interaction of an α-bromo-ketone and an arylamine is a complicated system that "may involve simultaneously" seven different reactions.

In the first main section of our work—that on the stability and reactions of phenacyl secondary amines—we have first prepared a series of such compounds in which the phenacyl group carried in turn the *p*-methyl, *p*-chloro-, and *p*-phenyl group as substituent. The *p*-chloro-

* It is unfortunate that this pair of isomers (and certain others) were not characterised by either analyses or molecular weight determinations. This is particularly to be regretted as Crowther, Mann, and Purdie (*loc. cit.*) have shown that phenacylamines may form bimolecular polymers: others, moreover, pass readily into anhydrides, which have been mistaken for true phenacylamines.

group was investigated, because our work in Part I (*loc. cit.*) indicated that the *p*-chlorophenyl group enhanced the stability both of phenacylamines and of 3-*p*-chlorophenylindoles obtained from them. The *p*-methyl and *p*-phenyl groups were chosen as the simplest alkyl and aryl substituent respectively. The condensation of *p*-methylphenacyl bromide, $Br{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4Me$, with highly purified *N*-methyl- and *N*-ethyl-aniline in turn furnished p-*methylphenacyl*-N-*methylaniline*, $NMePh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4Me$, and its N-*ethyl* homologue. The use of *p*-chlorophenacyl bromide gave *p*-chlorophenacyl-*N*-methylaniline and its *N*-ethyl homologue (Crowther, Mann, and Purdie, *loc. cit.*), and the use of *p*-phenylphenacyl bromide gave *p*-phenylphenacyl-*N*-methylaniline, $NMePh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4Ph$, and its N-*ethyl* homologue. Each of these phenacylamines was carefully purified, and in particular all traces of ionic halogen were completely eliminated (see p. 855).

The object of the first series of experiments was to determine the behaviour of these phenacylamines when boiled with alcoholic zinc chloride until no further perceptible reaction occurred. For this purpose, 5—6 mols. of zinc chloride were employed and the boiling continued usually for 6 hours. The low solubility in boiling alcohol of the *p*-phenyl compounds, however, necessitated a much greater volume of the solvent, and hence a much greater proportion of zinc chloride was used so that the concentration of the chloride in the alcoholic solutions should be approximately the same in all the experiments: for the *p*-phenyl compounds, moreover, a considerably longer time of heating was employed. The results are summarised in Table I.

TABLE I.

Action of Boiling Alcoholic Zinc Chloride on p-*Substituted Phenacyl Secondary Amines*, $NRPh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R'$.

R.	R′.	Product.	R.	R′.	Product.
Me	Me	3-*p*-Tolyl-1-methylindole	Et	Me	3-*p*-Tolyl-1-ethylindole
,,	Cl	3-*p*-Chlorophenyl-1-methylindole	,,	Cl	3-*p*-Chlorophenyl-1-ethylindole
,,	Ph	3-*p*-Phenylyl-1-methylindole	,,	Ph	3-*p*-Phenylyl-1-ethylindole

In each case, the indole formed was identified both by analysis and by direct comparison with the isomeric 2-aryl-1-alkylindoles prepared by Fischer's synthesis. It is clear from these results that alcoholic zinc chloride causes indolisation by direct cyclisation, and consequently the 3-arylindole is always obtained.

The action of fused zinc chloride on these phenacylamines was next studied. For this purpose, an intimate powdered dry mixture of the phenacylamine and the zinc chloride was plunged into a bath already heated to the required temperature and then stirred gently for the time noted. This technique was employed (unless otherwise stated) for all zinc chloride fusions described in Parts II and III of this work: it was found to give consistent results, which sometimes differed from those recorded by Crowther, Mann, and Purdie (*loc. cit.*), who, however, usually placed their mixtures of amine and zinc chloride in a cold bath which was then heated to the required temperature. The latter method might clearly allow a rapid reaction to proceed to completion with the formation of a stable product below the final temperature of the bath: our present technique reduces this possibility to a minimum. The results of these experiments are collected in Table II.

TABLE II.

Action of Fused Zinc Chloride on p-*Substituted Phenacyl Secondary Amines*, $NRPh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R'$.

R.	R′.	Temp.	*M*.	*t*.	Product.
Me	Me	250°	5	45	2-*p*-Tolyl-1-methylindole
,,	Cl	200	10	30	2-*p*-Chlorophenyl-1-methylindole
,,	,,	250	10	30	Extensive decomposition
,,	Ph	140	2	15	3-*p*-Phenylyl-1-methylindole
,,	,,	200	5	30	,, ,, ,,
,,	,,	250	11	40	2-*p*-Phenylyl-1-methylindole
Et	Me	200	9	120	2-*p*-Tolyl-1-ethylindole
,,	,,	230	10	*	,, ,,
,,	Cl	200	10	30	3-*p*-Chlorophenyl-1-ethylindole
,,	,,	250	10	30	Extensive decomposition
,,	Ph	150	5	30	3-*p*-Phenylyl-1-ethylindole
,,	,,	200	12	30	2-*p*-Phenylyl-1-ethylindole

(*M* = mols. of $ZnCl_2$; *t* = time of heating, in minutes.)

* This mixture was heated slowly to 230° and maintained there for 10 minutes.

Although these results do not show any close correlation between the nature of the product and that of the *p*-substituent R′, they clearly show that the production of 2-aryl-1-alkylindoles is more frequent than hitherto supposed, and they also show clearly the effect of the temperature of the fusion on the structure of the resultant indole. Furthermore they provide the first examples of the conversion of a phenacyl-*N*-ethylaniline into a 2-aryl-1-ethylindole: the previous rare examples of the production of 2-aryl-1-alkylindoles were solely from phenacyl-*N*-methylanilines.

It will be seen from Table II that 2-aryl-1-alkylindoles are usually obtained from the phenacylamines at higher temperatures than those which produce the isomeric 3-aryl-1-alkylindoles. The question arises whether the 3-aryl-1-alkylindoles are therefore the first product of the reaction and then isomerise to the 2-aryl-1-alkylindoles. This appeared to be not improbable, for Crowther, Mann, and Purdie (*loc. cit.*) have shown that 3-phenyl-1-methylindole is isomerised to 2-phenyl-1-methylindole by fusion with zinc chloride at 250°. To determine this point, the above 3-aryl-1-alkylindoles were fused with zinc chloride under similar conditions to those employed with the phenacylamines: the results are summarised in Table III. In each case the time of heating was 30 minutes.

TABLE III.

Stability of Indoles Fused with Zinc Chloride.

Indole.	Temp.	Mols. of $ZnCl_2$.	Product.
3-*p*-Tolyl-1-methylindole	250°	8	Isomerised to 2-*p*-tolyl-1-methylindole
3-*p*-Chlorophenyl-1-methylindole...	200	9	Unchanged
,, ,, ,, ...	250	9	Decomp. to indefinite products
3-*p*-Phenylyl-1-methylindole	250	10	Isomerised to 2-*p*-phenylyl-1-methylindole
3-*p*-Tolyl-1-ethylindole	250	8	Unchanged
3-*p*-Chlorophenyl-1-ethylindole ...	200	10	Unchanged
3-*p*-Phenylyl-1-ethylindole	250	11	Mainly unchanged

These results reveal two important points. First, that 3-aryl-1-alkylindoles cannot invariably be intermediate compounds in the conversion of phenacyl secondary amines into 2-aryl-1-alkylindoles. This follows from the fact, for example, that *p*-methylphenacyl-*N*-ethylaniline when heated at 200° with zinc chloride affords 2-*p*-tolyl-1-ethylindole, whereas 3-*p*-tolyl-1-ethylindole is unaffected by zinc cloride at 250°: similarly *p*-phenylphenacyl-*N*-ethylaniline gives 2-*p*-phenylyl-1-ethylindole with zinc chloride at 200°, whereas 3-*p*-phenylyl-1-ethylindole is little affected by the chloride even at 250°. It follows that the formation of 2-aryl-1-alkylindoles from phenacyl secondary amines *must involve an entirely different mechanism* from that of the formation of 3-aryl-1-alkylindoles: the latter are almost certainly formed by direct cyclisation of the phenacylamine. Secondly, 3-aryl-1-ethylindoles are notably more stable than 3-aryl-1-methylindoles, which in turn are more stable than 3-arylindoles: no example of the isomerisation of a 3-aryl-1-ethylindole by zinc chloride has been detected in this work.

Another series of reactions showed that the formation of 2-aryl-1-alkylindoles from phenacyl secondary amines may occur under very similar conditions to that of 2-arylindoles from phenacyl primary amines, and may therefore proceed by a similar mechanism. For this purpose each of our *p*-substituted phenacyl bromides was boiled in turn with excess of *N*-methyl- and *N*-ethyl-aniline. Since in these circumstances the first reaction almost certainly is the formation of the phenacyl secondary amine and the *N*-alkylaniline hydrobromide, similar results should be obtained if the phenacyl secondary amines were boiled with excess of the corresponding *N*-alkylaniline and one equivalent of hydrogen bromide. Inspection of the results recorded in Tables IV and V, summarising the experiments with phenacyl bromides and phenacylamines respectively, shows that this is correct.

Some of the above reactions can occur rapidly: for example, in the first reaction the same products were isolated when the reactants had been boiled together for 20 minutes or for 5 hours.

In the experiments summarised in Table V, an accurate addition of 1 mol. equivalent of anhydrous hydrogen bromide or chloride was obtained by adding 1 mol. equivalent of the pure crystalline *N*-alkylaniline hydrobromide or hydrochloride to the reaction mixture. The number of mols. of secondary amine recorded in Column 4 is therefore the number of mols. of free amine used plus one extra added as the salt.

The following important factors follow from the results collected in Tables IV and V.

(i) It is clear that no indolisation of phenacyl secondary amines occurs in boiling *N*-alkylanilines in the absence of acids (cf. Table V). We have further evidence that acids are essential

TABLE IV.

Products Obtained by Boiling p-*Substituted Phenacyl Bromides*, $Br{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R'$, *with Excess of* N-*Alkylaniline.*

R′.	Amine.	Mols. of amine.	Time of boiling (hrs.).	Products.
Me	NHMePh	6	{0·33 {5	2-*p*-Tolylindole + 2-*p*-tolyl-1-methylindole ,, ,,
Cl	,,	5	2	2-*p*-Chlorophenylindole + 2-*p*-chlorophenyl-1-methylindole
Ph	,,	4	2·5	2-*p*-Phenylylindole + 3-*p*-phenylyl-1-methylindole
Me	NHEtPh	6	5	2-*p*-Tolylindole + 3-*p*-tolyl-1-ethylindole
Cl	,,	5·5	2	2-*p*-Chlorophenylindole + 3-*p*-chlorophenyl-1-ethylindole
Ph	,,	4	2·5	2-*p*-Phenylylindole + 3-*p*-phenylyl-1-ethylindole

TABLE V.

Products Obtained by Boiling p-*Substituted Phenacyl*-N-*alkylanilines*, $NRPh{\cdot}CH_2CO{\cdot}C_6H_4R'$, *with Excess of* N-*Alkylaniline and* 1 *Equivalent of Acid.*

R.	R′.	Amine.	Mols. of amine.	Acid.	Time of boiling (hrs.).	Products.
Me	Me	NHMePh	11	HBr	12	2-*p*-Tolylindole + 2-*p*-tolyl-1-methylindole
Me	Cl	,,	6	,,	1	2-*p*-Chlorophenylindole + 2-*p*-chlorophenyl-1-methylindole
,,	,,	,,	6	HCl	1	,, ,, ,, ,, ,,
Me	Ph	,,	10	HBr	2·5	2-*p*-Phenylylindole + 3-*p*-phenylyl-1-methylindole
Et	Cl	NHEtPh	6	HBr	1	2-*p*-Chlorophenylindole + 3-*p*-chlorophenyl-1-ethylindole
,,	,,	,,	6	HCl	1	,, ,, ,, ,, ,,
Me	Cl	NHMePh	6	None	1	Unchanged phenacylamine
Me	Ph	,,	10	,,	2·5	,, ,, ,,
Et	Cl	NHEtPh	6	,,	1	,, ,, ,,

for this indolisation irrespective of the media, for we have found that *p*-phenylphenacyl-*N*-methylaniline, and its *N*-ethyl homologue, can be distilled unchanged at 18 mm.: the former compound furthermore was unchanged after 3 hours' refluxing in pure *o*-dichlorobenzene. The phenacyl secondary amines require a higher proportion of acid for cyclisation than do phenacyl primary amines, as Crowther, Mann, and Purdie (*loc. cit.*) indicate.

(ii) Hydrogen chloride can be used for cyclisation instead of hydrogen bromide. Crowther, Mann, and Purdie (*loc. cit.*) showed that 0·01 mol. of hydrogen bromide or iodide would induce indolisation of phenacyl primary amines, but that hydrogen chloride in this proportion was inactive. We now find that hydrogen chloride will catalyse the indolisation of phenacyl primary and secondary amines but requires a much higher concentration (cf. p. 869), and this apparent discrepancy is now cleared up.

(iii) When phenacyl secondary amines undergo cyclisation in boiling *N*-alkylanilines, the product always consists of *two* indoles, one of which is invariably a 2-arylindole, whilst the other is either a 3-aryl-1-alkyl- or a 2-aryl-1-alkyl-indole. It is noteworthy that the phenacyl-*N*-ethylanilines always gave 3-aryl-1-ethylindoles, whilst the phenacyl-*N*-methylanilines gave 2-aryl-1-methylindoles (2 examples) or 3-aryl-1-methylindole (1 example).

The origin of 2-arylindoles is of great interest. They cannot arise by de-alkylation of the 2-aryl-1-alkylindoles, because we find that both 2-*p*-tolyl-1-methylindole and 2-*p*-chlorophenyl-1-methylindole are unaffected by boiling with excess of *N*-methylaniline containing 1 mol. equivalent of *N*-methylaniline hydrobromide.

We consider that when a phenacyl bromide is boiled with excess of an *N*-alkylaniline, the following changes occur:

(*a*) $NHRPh + Br{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R' \longrightarrow NRPh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R' + HBr$

(*b*) $NRPh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R' + HBr \rightleftarrows [NHRPh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R']Br \rightleftarrows NHPh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R' + RBr$

(*c*) $NHRPh + RBr \longrightarrow NR_2Ph + HBr$

(*d*) $NHPh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R' \longrightarrow$ 2-arylindole $+ H_2O$

(*e*) $NRPh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R' \longrightarrow$ 2(or 3)-aryl-1-alkylindole $+ H_2O$

Reaction (*a*) is normal formation of phenacyl secondary amine and hydrogen bromide. In Reaction (*b*), these combine to give the phenacyl secondary amine hydrobromide, which in the boiling *N*-alkylaniline can dissociate either into its original components or into the corresponding phenacyl primary amine and alkyl bromide. Of these two dissociations, the former might be expected to be the more prominent, but the latter is promoted by the subsequent reaction of the alkyl bromide with the secondary amine to give the tertiary *N*-dialkylaniline (Reaction *c*). Then follow the familiar acid-catalysed cyclisation of the phenacyl primary amine to give the 2-arylindole (Reaction *d*), and of the phenacyl secondary amine to give the 2(or 3)-aryl-1-alkylindole (Reaction *e*).

We have both direct and indirect confirmation of the existence of the above reactions. We find that when *p*-phenylphenacyl bromide is boiled with excess of *N*-methylaniline (cf. Table IV), *N*-dimethylaniline is formed in addition to the 2-*p*-phenylylindole and the 3-*p*-phenylyl-1-methylindole recorded above. This is precisely what the above series of reactions demands.

As indirect confirmation, it should follow, if the above series of reactions is correct, that a phenacyl bromide when boiled with excess of a tertiary amine such as *N*-dimethylaniline should form ultimately a phenacyl secondary amine and phenyltrimethylammonium bromide by the reactions :

$$NMe_2Ph + Br{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R' \longrightarrow [NMe_2Ph{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R']Br$$
$$[NMe_2Ph{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R']Br \longrightarrow NMePh{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4R' + MeBr$$
$$NMe_2Ph + MeBr \longrightarrow [NMe_3Ph]Br$$

Moreover, since no free acid is available in this system, the phenacyl secondary amine should be stable and in particular should undergo no indolisation. This has proved to be correct, for we find that *p*-phenylphenacyl bromide when boiled with excess of pure *N*-dimethylaniline gave *p*-phenylphenacyl-*N*-methylaniline, but no indole could be detected. Staedel (*Ber.*, 1888, **21**, 2196) had shown that phenacyl bromide reacted with *N*-dimethylaniline to give phenacyl-*N*-methylaniline, but this result has been held of doubtful significance without evidence of the purity of dimethylaniline used : our results show, however, that Staedel's phenacyl-*N*-methylaniline was derived from the dimethylaniline and was not merely a product of *N*-methylaniline that might possibly have contaminated his dimethylaniline.

The first section of our work has therefore elucidated the conditions under which phenacyl secondary amines give rise to 2-arylindoles, 3-aryl-1-alkylindoles, and 2-aryl-1-alkylindoles. It has shown the mechanism by which the precursors of the 2-arylindoles, *i.e.*, the phenacyl primary amines, are derived from the phenacyl secondary amines. It does not, however, give any decisive evidence of the mechanism by which the 2-aryl-1-alkylindoles are formed : it is clear, however, that this mechanism must be closely allied to—and is probably identical with—that by which 2-arylindoles are formed from phenacyl primary amines, which is discussed in Part III. Furthermore, the acid-catalysed direct cyclisation of phenacyl secondary amines to give 3-aryl-1-alkylindoles must undoubtedly proceed by a mechanism parallel to that by which, for example, 1-phenyl-*p*-methylphenacylaniline gives rise to 2-phenyl-3-*p*-tolylindole, which is also discussed in Part III (p. 863).

Experimental.

The names of solvents used for recrystallisation are stated in parentheses after the compounds concerned : when two solvents are named, the form "acetic acid, benzene" indicates recrystallisation from each consecutively in the order given; the form "acetone–alcohol" indicates recrystallisation from the mixed solvents. All phenacyl bromides and indoles were colourless, and all phenacylamines were pale yellow.

Preparation of Pure N-*Alkylanilines.*—To ensure that the *N*-methyl- and *N*-ethyl-aniline used were pure, and in particular entirely free from primary and tertiary amines, the technically pure *N*-alkylaniline was carefully added to a solution of freshly prepared cuprous chloride (1 mol.) in concentrated hydrochloric acid. After the mixture had been cooled, the precipitated complex was collected, washed thrice with water and thrice with alcohol (to remove the more soluble complexes of any aniline or dialkylaniline present), decomposed with concentrated aqueous sodium hydroxide, and then steam distilled. The *N*-alkylaniline was extracted with ether, dried, and distilled. No impurities could be detected in the final product (cf. Jones and Kenner, *J.*, 1932, 714).

Ketones.—*p*-Methylacetophenone was prepared by the action of acetyl chloride on toluene, and after careful fractionation obtained as a colourless liquid, b. p. 100°/13 mm. *p*-Chloroacetophenone and *p*-phenylacetophenone were prepared by the directions given in *Org. Synth.*, Coll. Vol. I, 111, and by Drake and Bronitsky (*J. Amer. Chem. Soc.*, 1930, **52**, 3718), respectively.

Indoles by the Fischer Synthesis.—Certain of our indoles, prepared by the Fischer synthesis, were already available (cf. Part I). We have utilised this synthesis to prepare authentic samples of all the 2-aryl- and 2-aryl-1-alkyl-indoles which arose in our phenacylamine investigations : these authentic samples were thus available for direct comparison by mixed m. p. determinations with our 2-arylindoles and their 3-aryl isomers. All such identifications were confirmed by analysis and often molecular-

weight determinations. For further characterisation of certain of the indoles, their picrates and nitroso-derivatives were prepared, as described in Part I. We have prepared certain 2-aryl-5-methylindoles for additional comparison with the isomeric 2 (and 3)-aryl-1-alkylindoles. In our Fischer synthesis, the indoles were sometimes prepared by the interaction of the ketone with the hydrazine without isolation of the intermediate hydrazone: in other cases the hydrazone was isolated and purified.

2-p-*Tolylindole*. Powdered zinc chloride (100 g.) was rapidly added with stirring to a mixture of *p*-methylacetophenone (13·4 g.) and phenylhydrazine (11·7 g., 1·1 mols.). The mixture became warm and was then heated at 130° for 30 minutes. The cold product was digested with hot dilute hydrochloric acid and the insoluble *indole* collected, washed with water, and recrystallised (alcohol); m. p. 218—219° (Found: C, 86·9; H, 6·4; N, 7·1. $C_{15}H_{13}N$ requires C, 86·0; H, 6·3; N, 6·8%). The 1-*nitroso*-derivative formed orange crystals (alcohol), m. p. 240° (decomp.) (Found: C, 77·0; H, 5·8; N, 12·0. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1; N, 11·9%).

2-p-*Phenylylindole*. A mixture of *p*-phenylacetophenone (20 g.), phenylhydrazine (15 g., 1·5 mols.), and acetic acid (1 g.) was heated slowly to 120°, giving a solid product. The latter when cold was powdered, mixed with pulverized zinc chloride (90 g.), and heated at 200° for 45 minutes. The cold hard mass was powdered, extracted with hot dilute hydrochloric acid, washed with water, and the *indole* recrystallised; cream-coloured crystals (glycol monomethyl ether), m. p. 302—304° (Found: C, 89·4; H, 5·7; N, 5·5. $C_{20}H_{15}N$ requires C, 89·2; H, 5·6; N, 5·2%). The 1-*nitroso*-derivative formed orange crystals (alcohol), m. p. 274—276° (decomp.) (Found: C, 80·4; H, 5·4; N, 9·17. $C_{20}H_{14}ON_2$ requires C, 80·6; H, 4·7; N, 9·4%).

2-p-*Tolyl*-1-*methylindole*. The intermediate hydrazone isolated in this experiment could not initially be induced to crystallise. Ultimately the viscous oil from a small preparation was distilled under reduced pressure, and then readily crystallised, and could be used to seed larger preparations. The mixture obtained by adding a solution of *as*-phenylmethylhydrazine (4·9 g.) in acetic acid (3 g.) containing water (2 g.) to one of *p*-methylacetophenone (5·4 g., 1 mol.) in acetic acid (5 g.) was heated at 70° for 5 minutes and cooled. The oil which separated crystallised on seeding, and gave cream crystals (aqueous alcohol) of the *phenylmethylhydrazone*, m. p. 107° (Found: N, 11·9. $C_{16}H_{18}N_2$ requires N, 11·8%). A mixture of this compound (3 g.) and powdered zinc chloride (6 g.) was heated at 200° for 7 minutes. The cold product was given the usual acid digestion, and the residue then taken up in ether, dried, and distilled at 20 mm. The distillate rapidly solidified and gave white crystals (alcohol) of 2-p-*tolyl*-1-*methylindole*, m. p. 94° (Found: C, 86·5; H, 6·9; N, 6·5; *M*, ebullioscopically in 0·939% alcoholic solution, 225. $C_{16}H_{15}N$ requires C, 86·9; H, 6·8; N, 6·3%; *M*, 221). This compound had the same m. p. alone and mixed with the indole obtained from *p*-methylphenacylmethylaniline.

2-p-*Tolyl*-1-*ethylindole*. A mixture of *p*-methylacetophenone (13·4 g.), *as*-phenylethylhydrazine (13·6 g., 1 mol.), and acetic acid (0·5 g.) was heated at 100° for 5 minutes, cooled, mixed with powdered zinc chloride (100 g.), and then heated slowly in an oil-bath. At 130° a violent reaction occurred and the mass became black. After acid extraction the product was dissolved in ether–benzene, dried, and twice distilled at 0·2 mm. The final product solidified and was crystallised (alcohol); m. p. 48° (Found: C, 87·4; H, 7·2; N, 6·0; *M*, ebullioscopically in 1·31% alcoholic solution, 225. $C_{17}H_{17}N$ requires C, 86·8; H, 7·3; N, 6·0%; *M*, 235).

2-p-*Tolyl*-5-*methylindole*. For this purpose, p-*methylacetophenone* p-*tolylhydrazone* was prepared as above; it formed cream-coloured crystals (alcohol), m. p. 138° (Found: N, 12·0. $C_{16}H_{18}N_2$ requires N, 11·8%), which when set aside for a few days decomposed to a brown tar. The normal fusion with zinc chloride at 130° for 30 minutes furnished the *indole* (alcohol), m. p. 239—240° (Found: C, 86·7; H, 6·8; N, 6·8. $C_{16}H_{15}N$ requires C, 86·9; H, 6·8; N, 6·3%). It gave the 1-*nitroso*-derivative, red crystals (alcohol), m. p. 253° (decomp.) (Found: C, 79·7; H, 6·2; N, 11·8. $C_{16}H_{14}ON_2$ requires C, 76·9; H, 5·6; N, 11·2%); this compound did not depress the m. p. of 1-nitroso-2-*p*-tolylindole.

2-p-*Chlorophenyl*-1-*methylindole*. This indole was prepared in the usual way by heating *p*-chloroacetophenone (7·7 g.), *as*-phenylmethylhydrazine (6·1 g., 1·1 mols.), and acetic acid first to 100° for 5 minutes and subsequently with zinc chloride (20 g.) at 180° for 15 minutes. The crude product after acid digestion and recrystallisation (alcohol, acetic acid) gave the pure *indole*, m. p. 119° (Found: C, 74·3; H, 5·2; N, 5·6; Cl, 14·9. $C_{15}H_{12}NCl$ requires C, 74·5; H, 5·0; N, 5·8; Cl, 14·7%). It gave the 3-*nitroso*-derivative, green crystals (alcohol), m. p. 158° (Found: C, 66·2; H, 4·2; N, 9·95. $C_{15}H_{11}ON_2Cl$ requires C, 66·2; H, 4·1; N, 10·4%).

2-p-*Phenylyl*-1-*methylindole*. The interaction of *p*-phenylacetophenone (7 g.) and *as*-phenylmethylhydrazine (7·7 g., 1·7 mols.) in 50% aqueous acetic acid at 70° readily gave p-*phenylacetophenone phenylmethylhydrazone*, yellow crystals (alcohol containing a small quantity of the hydrazine), m. p. 107° (Found: C, 84·2; H, 6·9; N, 9·4. $C_{21}H_{20}N_2$ requires C, 84·0; H, 6·7; N, 9·3%). The hydrazone (5 g.) and zinc chloride (1 g.) were boiled in acetic acid (15 c.c.) for 1 hour, during which the *indole* began to crystallise. When cold, it was collected, washed with alcohol, and recrystallised (acetic acid, petrol), and then had m. p. 154° (Found: C, 89·4; H, 5·7; N, 4·8. $C_{21}H_{17}N$ requires C, 89·0; H, 6·1; N, 4·9%). This gave the 3-*nitroso*-derivative, green crystals (acetic acid, benzene), m. p. 214° (Found: C, 81·1; H, 5·5. $C_{21}H_{16}ON_2$ requires C, 80·8; H, 5·2%).

2-p-*Phenylyl*-1-*ethylindole*. p-*Phenylacetophenone phenylethylhydrazone* was prepared by the usual method, m. p. 122—123° (alcohol) (Found: N, 9·3. $C_{22}H_{22}N_2$ requires N, 8·9%). The hydrazone (5 g.) and zinc chloride (10 g.) were boiled in acetic acid (50 c.c.) for 1 hour and the solution poured into much dilute hydrochloric acid; the precipitated *indole* after recrystallisation (acetic acid, benzene) had m. p. 134° (Found: C, 89·0; H, 6·4; N, 4·6. $C_{22}H_{19}N$ requires C, 88·8; H, 6·4; N, 4·7%). The 3-*nitroso*-derivative formed green crystals (alcohol), m. p. 164° (Found: C, 81·0; H, 6·0; N, 8·95. $C_{22}H_{18}ON_2$ requires C, 81·0; H, 5·6; N, 9·0%).

2-p-*Phenylyl*-5-*methylindole*. Interaction of *p*-phenylacetophenone (3·9 g.) and *p*-tolylhydrazine (2·5 g., 1 mol.) under the usual conditions readily gave the yellow p-*tolylhydrazone* (acetic acid), m. p. 212—214° (decomp.) (Found: N, 9·4. $C_{21}H_{20}N_2$ requires N, 9·3%). This compound when fused with zinc chloride at 140—150° for 3 hours gave the *indole* (acetic acid, glycol monomethyl ether), m. p. 327—329°

(Found : N, 5·2. $C_{21}H_{17}N$ requires N, 4·9%), which in turn furnished the 1-*nitroso*-derivative, orange crystals (alcohol), m. p. 279—280° (decomp.) (Found : N, 9·3. $C_{21}H_{16}ON_2$ requires N, 9·0%); this nitroso-compound did not depress the m. p. of 1-nitroso-2-*p*-phenylylindole.

Preparation of Phenacyl Bromides.—Phenacyl bromide, when prepared in accordance with *Org. Synth.*, Coll. Vol. II, 480, and then washed with petrol and water, dried, and crystallised (methyl alcohol), had m. p. 48—50° and remained unchanged for many weeks if kept thoroughly dry. The following bromides were prepared according to the reference stated. *p*-Methylphenacyl bromide, m. p. 52·5—53·5°, Kunckell (*Ber.* 1897, **30**, 577) (cf. also *Org. Synth.*, Coll. Vol. II, 480); *p*-chlorophenacyl bromide, m. p. 96—97°, adapted from *Org. Synth.* (*loc. cit.*); *p*-phenylphenacyl bromide, m. p. 125—126°, Drake and Bronitsky (*loc. cit.*).

Preparation of Phenacylamines.—The detailed preparation of one of these compounds suffices for all. It must be emphasised that each phenacylamine when first collected on the filter was washed in turn with a small quantity of alcohol and with water, and then suspended in water (*ca.* 1 l.) and vigorously stirred for several hours; it was again collected, washed, and recrystallised until it had a sharp m. p. and was entirely free from ionic halogen.

p-*Methylphenacyl*-N-*methylaniline*. A mixture prepared by adding *p*-methylphenacyl bromide (16 g.) and *N*-methylaniline (17 c.c., 2 mols.) to alcohol (40 c.c.) was refluxed for 1 hour and cooled. The *phenacyl* derivative which had crystallised was collected, purified as above, and recrystallised (alcohol); m. p. 87° (Found : C, 77·9; H, 7·0; N, 6·1. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·1; N, 5·9%). The N-*ethyl* homologue had m. p. 76° (alcohol, petrol) (Found : C, 80·5; H, 7·6; N, 5·4. $C_{17}H_{19}ON$ requires C, 80·6; H, 7·6; N, 5·5%).

p-Chlorophenacyl-*N*-methylaniline and its *N*-ethyl homologue were prepared as above, whereas Crowther, Mann, and Purdie (*loc. cit.*) used calcium carbonate to neutralise the hydrogen bromide formed by the interaction of the bromide and the amine.

p-*Phenylphenacyl*-N-*methylaniline* was prepared as above, but using 2·5 mols. of *N*-methylaniline; m. p. 152° (alcohol–acetone) (Found : C, 83·9; H, 6·0; N, 4·9. $C_{21}H_{19}ON$ requires C, 83·7; H, 6·4; N, 4·7%). The N-*ethyl* homologue had m. p. 114° (alcohol) (Found : C, 84·6; H, 6·7. $C_{22}H_{21}ON$ requires C, 84·0; H, 6·6%).

Reaction of Phenacylamines with Alcoholic Zinc Chloride (cf. Table I).*—The description of one experiment suffices for all, except in the *p*-phenylphenacyl series, where certain solubility factors entered. (i) *p*-Methylphenacyl-*N*-methylaniline (2·7 g.) and powdered zinc chloride (8 g., 5 mols.) were rapidly added in turn to alcohol (15 c.c.), and the mixture refluxed for 5 hours. The solution was then poured into excess of ice-cold dilute hydrochloric acid, and the precipitated pale brown tar when collected and recrystallised (alcohol) gave white crystals of 3-p-*tolyl*-1-*methylindole*, m. p. 63° (Found : C, 86·6; H, 6·7; N, 6·5. $C_{16}H_{15}N$ requires C, 86·9; H, 6·8; N, 6·3%). (ii) *p*-Methylphenacyl-*N*-ethylaniline, similarly treated, gave 3-p-*tolyl*-1-*ethylindole*, colourless needles (methyl alcohol), m. p. 63° (Found : C, 86·0; H, 7·4; N, 5·8; *M*, ebullioscopically in 1·02% alcoholic solution, 241. $C_{17}H_{17}N$ requires C, 86·8; H, 7·3; N, 6·0%; *M*, 235). (iii) *p*-Chlorophenacyl-*N*-methylaniline similarly gave 3-*p*-chlorophenyl-1-methylindole (alcohol), m. p. 96°. (iv) *p*-Chlorophenacyl-*N*-ethylaniline gave 3-*p*-chlorophenyl-1-ethylindole, m. p. 79° (alcohol). Experiments (iii) and (iv) were thus performed under closely similar conditions to those of Crowther, Mann, and Purdie (*loc. cit.*), and confirm their results. (v) The solubility of *p*-phenylphenacyl-*N*-methylaniline in boiling alcohol is low. If the usual proportion of phenacylamine to zinc chloride had been employed, the concentration of the chloride in the alcohol would have been very low : consequently the amount of chloride employed was considerably increased to ensure that the phenacylamine should be exposed to approximately the same concentration of zinc chloride as in the above experiments. A considerably longer time of boiling was also required to ensure absence of unchanged material in the final product. A mixture of *p*-phenylphenacyl-*N*-methylaniline (3 g.) and zinc chloride (106 g.) in alcohol (200 c.c.) was refluxed for 27 hours. The hot filtered solution was poured into ice-cold dilute hydrochloric acid (2·5 l.), and the cream-coloured precipitate was collected and dried. Recrystallisation of this crude material was difficult : it separated from an acetic acid solution over a period of several days, and was then more readily recrystallised from alcohol : ultimately it furnished 3-p-*phenylyl*-1-*methylindole*, m. p. 134° (Found : C, 89·4; H, 6·0; N, 5·2; *M*, cryoscopically in 0·73% ethylene dibromide solution, 287. $C_{21}H_{17}N$ requires C, 89·0; H, 6·1; N, 4·9%; *M*, 283). In another experiment, the phenacylamine (3 g.) and zinc chloride (15 g., 11 mols.) were dissolved in the minimum volume of boiling alcohol, and the solution refluxed for 30 hours, evaporated to small bulk, and then poured into cold dilute acid. The yellow precipitate when repeatedly crystallised from acetic acid now furnished *p*-phenylbenzoic acid, m. p. 221·5—222·5° (Found : C, 79·4; H, 5·5. Calc. for $C_{13}H_{10}O_2$; C, 78·9; H, 5·1%). Similarly, a solution of the phenacylamine (2·8 g.) and zinc chloride (10 g., 8 mols.) in glycol monomethyl ether (40 c.c.) was heated at 100° for 24 hours. The solution was poured into cold acid, and the yellow precipitate collected, dried, and extracted (Soxhlet) with petrol (b. p. 80—100°). Evaporation of the petrol extract gave a yellow product which after repeated recrystallisation (petrol, *cyclo*hexane) also furnished *p*-phenylbenzoic acid, m. p. 220·5—223°, not depressed by admixture with previous sample (Found : C, 78·6; H, 5·3%). This (atmospheric) oxidation of the phenacylamine to the corresponding acid recalls the ready atmospheric oxidation of *p*-chlorophenacyl-*N*-ethylaniline to *p*-chlorobenzoic acid recorded by Crowther, Mann, and Purdie (*loc. cit.*). (vi) *p*-Phenylphenacyl-*N*-ethylaniline (10 g.) and zinc chloride (250 g., 60 mols.) were dissolved in the minimum amount of boiling alcohol (*ca.* 750 c.c.) and refluxed for 24 hours. The cold solution was poured into excess of cold dilute acid, and the white precipitate, when collected, washed, and recrystallised (acetic acid), furnished 3-p-*phenylyl*-1-*ethylindole*, m. p. 111° (Found : C, 89·2; H, 6·3; N, 4·9. $C_{22}H_{19}N$ requires C, 88·8; H, 6·4; N, 4·7%).

Reactions of Phenacylamines with Fused Zinc Chloride (cf. Table II).—(i) A mixture of

* For brevity of presentation, in this and the following section the order in which the experiments are described is not that in which they appear in Tables I and II.

p-methylphenacyl-*N*-methylaniline (4·8 g.) and powdered zinc chloride (13·6 g., 5 mols.) was heated at 250° for 45 minutes with occasional stirring. The cold product was then thoroughly digested with hot dilute hydrochloric acid. The dark oil which floated on the acid solidified on cooling, and was then dried, powdered, and extracted (Soxhlet) with petrol (b. p. 60—80°). The extracts on evaporation left a yellow residue which after recrystallisation (petrol, alcohol) (charcoal) afforded 2-*p*-tolyl-1-methylindole, m. p. 94—95° (alone and mixed) (Found: C, 87·1; H, 7·0; N, 6·7%). (ii) A similar mixture of *p*-methylphenacyl-*N*-ethylaniline (5 g.) and zinc chloride (25 g., 9 mols.) was heated at 200° for 2 hours. The crude brown product after acid digestion could not be crystallised: it was therefore dissolved in ether, dried, and distilled at 2 mm. The distillate readily solidified, and after three recrystallisations (alcohol) afforded 2-*p*-tolyl-1-ethylindole, m. p. 48° (alone and mixed) (Found: C, 86·7; H, 7·0; N, 6·1%). (iii) A mixture of *p*-chlorophenacyl-*N*-methylaniline (5 g.) and zinc chloride (25 g., 10 mols.) was heated at 200° for 30 minutes with frequent stirring. The product after acid digestion and repeated recrystallisation (alcohol) gave colourless crystals of 2-*p*-chlorophenyl-1-methylindole, m. p. 117·5—119° (alone and mixed) (Found: C, 74·7; H, 4·9; N, 5·6; Cl, 14·6%). In Part I, a similar experiment afforded the 3-*p*-chlorophenyl isomer, and the different result is to be attributed to the different technique of fusion (p. 850). When the above experiment was repeated with 30 minutes' fusion at 250°, a crude product was obtained from which no pure compound could be isolated. (iv) Expt. (iii) was repeated using the *N*-ethyl homologue, and the crude product after repeated crystallisation (acetic acid, alcohol) afforded 3-*p*-chlorophenyl-1-ethylindole, m. p. 79—80°: this result tallies with that described in Part I. Repetition of the experiment with fusion at 250° for 30 minutes gave a crude product from which no pure component could be isolated. (v) A mixture of *p*-phenylphenacyl-*N*-methylaniline (5 g.) and zinc chloride (5 g., 2 mols.) was heated at 140° for 15 minutes with continuous stirring. Acid digestion, followed by repeated recrystallisation (acetic acid, alcohol), ultimately furnished 3-*p*-phenylyl-1-methylindole, m. p. 134° (Found: C, 89·05; H, 6·1; N, 4·9. Calc. for $C_{21}H_{17}N$: C, 89·0; H, 6·1; N, 4·9%). When a similar mixture containing zinc chloride (5 mols.) was slowly heated to 200° and there maintained for 30 minutes with stirring, extraction ultimately furnished the same indole, m. p. 131—133° (Found: C, 88·65; H, 6·1; N, 5·0%). When, however, the mixture of the phenacylamine (3 g.) and zinc chloride (15 g., 11 mols.) was heated at 250° for 40 minutes, the usual extraction followed by repeated recrystallisation (acetic acid, petrol, acetic acid) gave 2-*p*-phenylyl-1-methylindole, m. p. 153° (alone and mixed) (Found: C, 88·5; H, 6·2; N, 5·1%). (vi) When *p*-phenylphenacyl-*N*-ethylaniline (5 g.) and zinc chloride (10 g., 5 mols.) were heated with stirring at 150° for 30 minutes, the product ultimately furnished 3-*p*-phenylyl-1-ethylindole (acetic acid), m. p. 110° (Found: C, 88·4; H, 6·3; N, 4·9. Calc. for $C_{22}H_{19}N$: C, 88·8; H, 6·4; N, 4·7%). When, however, the proportion of zinc chloride was increased to 12 mols., and the fusion conducted at 200° for 30 minutes, the crude product after repeated recrystallisation (acetic acid) furnished 2-*p*-phenylyl-1-ethylindole, m. p. 133—134·5° (alone and mixed) (Found: C, 89·2; H, 6·5; N, 4·75%).

Stability of Certain Indoles when fused with Zinc Chloride (cf. Table III).—(i) A mixture of 3-*p*-tolyl-1-methylindole (2·6 g.) and powdered zinc chloride (13 g., 8 mols.) was heated at 250° for 30 minutes with frequent stirring. The cold product was digested with hot dilute hydrochloric acid, and the sticky insoluble product, when collected and recrystallised (acetic acid, alcohol), afforded 2-*p*-tolyl-1-methylindole, m. p. 95—96° (alone and mixed) (Found: C, 87·3; H, 6·5; N, 6·5%). (ii) 3-*p*-Chlorophenyl-1-methylindole (5 g.) and zinc chloride (25 g., 9 mols.) were mixed and heated at 200° for 30 minutes. After acid digestion, the residue was recrystallised (alcohol) and afforded the unchanged indole, m. p. 96—97° (alone and mixed). Repetition of this experiment at 250° gave a crude product from which no pure component could be isolated. (iii) 3-*p*-Phenylyl-1-methylindole (3 g.) and zinc chloride (15 g., 10 mols.) were mixed and heated at 250° for 30 minutes with continuous stirring. The product after the usual treatment afforded 2-*p*-phenylyl-1-methylindole (benzene, acetic acid), m. p. 148·5—151·5° (alone and mixed). (iv) 3-*p*-Tolyl-1-ethylindole (3·7 g.) and zinc chloride (18 g., 8·5 mols.) when similarly heated at 250° for 30 minutes gave after acid extraction a tar which could not be crystallised. Evaporation under reduced pressure of an alcoholic solution of the tar gave crystals which after further recrystallisation (alcohol) gave the unchanged indole, m. p. 62—63° (alone and mixed). (v) 3-*p*-Chlorophenyl-1-ethylindole (5 g.) and zinc chloride (25 g., 9·5 mols.), fused at 200° for 30 minutes, gave a final product which on recrystallisation (alcohol) afforded the unchanged indole, m. p. 78·5—80° (alone and mixed). (vi) 3-*p*-Phenylyl-1-ethylindole (3 g.) and zinc chloride (15 g., 11 mols.) were heated at 250° for 30 minutes with stirring. The product after acid digestion was recrystallised (benzene, glycol monomethyl ether) and afforded a small quantity of 2-*p*-phenylylindole, m. p. 301—304° (alone and mixed). Evaporation of the benzene mother-liquors gave a much greater residue, which when thrice recrystallised (acetic acid) afforded the unchanged 3-*p*-phenylyl-1-ethylindole, m. p. 109—111° (alone and mixed). The results in Experiments (iii) and (v) confirm those of Crowther, Mann, and Purdie (*loc. cit.*).

A mixture of 2-*p*-tolyl-1-methylindole (2·2 g.), *N*-methylaniline hydrobromide (1·9 g. 1 mol.), and *N*-methylaniline (10·4 c.c., 10 mols.) was refluxed for 12 hours. Acid digestion of the cold product gave an insoluble residue which on recrystallisation (alcohol) furnished the unchanged indole. Similar results were obtained when 3-*p*-chlorophenyl-1-methylindole was used.

p-Methylphenacyl bromide (5 g.) and pure aniline (25 c.c., 12 mols.) were refluxed for 5 hours. The crystals which separated from the cold mixture were collected, washed with a small quantity of alcohol, and then copiously with dilute hydrochloric acid and water. Recrystallisation (alcohol) afforded 2-*p*-tolylindole, m. p. 219—220° (alone and mixed) (Found: C, 86·8; H, 6·4; N, 7·1%). *p*-Phenylphenacyl bromide (10 g.) and aniline (50 c.c., 15 mols.) were refluxed for 1·75 hours. The crystals which separated were washed as before, and when recrystallised (glycol monomethyl ether) furnished 2-*p*-phenylylindole, m. p. 302—305° (alone and mixed) (Found: C, 89·65; H, 5·4; N, 5·8%).

Interaction of p-*Substituted Phenacyl Bromides with* N-*Alkylanilines* (cf. Table IV).—(i) *p*-Methylphenacyl bromide (6·4 g.) and *N*-methylaniline (18·8 c.c., 6 mols.) were refluxed for 20 minutes, and the cold mixture then poured into cold dilute hydrochloric acid (300 c.c.). The solid precipitate was

collected and twice recrystallised (alcohol): it then had m. p. 85—185°. Further recrystallisation (benzene, alcohol) gave 2-*p*-tolylindole, m. p. 219—219·5° (alone and mixed) (Found: C, 86·6; H, 6·4; N, 7·3; *M*, ebullioscopically in 0·814% benzene solution, 224; in 1·38% solution, 223. Calc. for $C_{15}H_{13}N$: *M*, 207). The benzene mother-liquors were evaporated, and the residue when twice recrystallised (alcohol) gave 2-*p*-tolyl-1-methylindole, m. p. 94—95·5° (alone and mixed). Repetition of this experiment using 5 hours' refluxing gave identical results. (ii) *p*-Chlorophenacyl bromide (9·2 g.) and *N*-methylaniline (10·4 c.c., 5 mols.) were refluxed for 2 hours and poured into acid as above. The crude product after repeated crystallisation (acetic acid) afforded 2-*p*-chlorophenyl-1-methylindole, m. p. 118—119° (alone and mixed). The earlier acetic acid mother-liquors were evaporated under reduced pressure, and the residue when recrystallised (benzene, alcohol), gave 2-*p*-chlorophenylindole, m. p. 205° (alone and mixed) (Found: C, 73·4; H, 4·5; N, 6·1; Cl, 15·2. Calc. for $C_{14}H_{10}NCl$: C, 73·8; H, 4·4; N, 6·2; Cl, 15·6%). (iii) *p*-Phenylphenacyl bromide (4·75 g.) and *N*-methylaniline (7 c.c., 4 mols.) were refluxed for 2·5 hours. After cooling, the copious precipitate was collected, washed in turn with alcohol, dilute hydrochloric acid, and water, and when repeatedly recrystallised (glycol monomethyl ether) afforded 2-*p*-phenylylindole, m. p. 300—303° (alone and mixed). The original filtrate was then poured into much dilute hydrochloric acid, and the precipitate recrystallised from benzene: the crude crystals thus obtained were discarded, but the benzene mother-liquor on evaporation gave a residue which after repeated recrystallisation (acetic acid) gave 3-*p*-phenylyl-1-methylindole, m. p. 131·5—132·5° (alone and mixed). The hydrochloric acid from which this indole separated was concentrated, basified, and steam-distilled. The distillate when extracted with ether gave an oil which was purified by boiling with acetic acid–acetic anhydride. After removal of acetyl derivatives, the residue was again basified and steam-distilled. The *N*-dimethylaniline thus obtained was identified by (*a*) conversion of a portion into the picrate, yellow needles (alcohol), m. p. 161—163° (alone and mixed) (Found: C, 48·1; H, 4·2; N, 15·9. Calc. for $C_8H_{11}N,C_6H_3O_7N_3$: C, 48·0; H, 4·0; N, 16·0%), (*b*) conversion of a second portion into *p*-nitrosodimethylaniline. (iv) Expt. (i) was repeated, using *N*-ethylaniline (22·6 c.c., 6 mols.) and 5 hours' heating. The solid precipitate when recrystallised (alcohol) gave a first crop, m. p. 59—63°, and a later crop, m. p. 60—170°. The first crop when recrystallised (alcohol) gave 3-*p*-tolyl-1-ethylindole, m. p. 63—63·5° (alone and mixed) (Found: C, 86·5; H, 7·4; N, 6·05%), and the second crop, repeatedly recrystallised (alcohol) gave 2-*p*-tolylindole, m. p. 218·5—219·5° (alone and mixed) (Found: C, 86·7; H, 6·4; N, 7·1%). (v) Expt. (ii) was repeated using *N*-ethylaniline (28 c.c., 5·5 mols.). The solution after refluxing was dissolved in benzene (300 c.c.), and then thoroughly extracted with dilute hydrochloric acid, washed with water, dried, and evaporated. The crude solid residue was recrystallised from benzene. The colourless crystals so obtained when further recrystallised (alcohol) gave 2-*p*-chlorophenylindole, m. p. 204—205° (alone and mixed). The benzene mother-liquor was evaporated, and the solid residue on crystallisation (acetic acid, alcohol) afforded 3-*p*-chlorophenyl-1-ethylindole, m. p. 78—79° (alone and mixed). (vi) Expt. (iii) was repeated, using *N*-ethylaniline (9 c.c., 4 mols.). The copious precipitate was again collected and when washed with alcohol and recrystallised (glycol momomethyl ether) gave 2-*p*-phenylylindole, m. p. 304—306° (alone and mixed). The filtrate from the original precipitate was poured into dilute hydrochloric acid, and the solid which separated was recrystallised from benzene. The crystals which now separated were clearly a mixture and were discarded. The benzene mother-liquor was evaporated to dryness and recrystallised (acetic acid): the first crop which separated was still impure and was also discarded, but the second crop, which separated slowly, when again recrystallised (acetic acid) afforded 3-*p*-phenylyl-1-ethylindole, m. p. 107·5—109·5° (alone and mixed). In both expts. (iii) and (vi) the low solubilities of the two phenylylindoles produced made their separation much more difficult than that of the indoles arising in the other experiments.

These results explain Culmann's isolation of 2-phenylindole by the interaction of phenacyl bromide and *N*-methylaniline (*Ber.*, 1888, **21**, 2595), which in Part I (*loc. cit.*) had been attributed to the use of impure *N*-methylaniline.

Interaction of p-*Substituted Phenacyl*-N-*alkylanilines with* N-*Alkylanilines in the Presence of Acids* (cf. Table V).—These experiments were similar to those in the previous section, and only the first is given in detail. In the other experiments, the separation of the two indoles was not significantly different from that in the corresponding experiment in the previous section and is consequently not described. The identity of each indole isolated was confirmed by a mixed m. p. with an authentic sample: in no case was a depression observed. (i) A mixture of *p*-methylphenacyl-*N*-methylaniline (4 g.), *N*-methylaniline hydrobromide (3 g., 1 mol.), and *N*-methylaniline (16·5 c.c., 10 mols.) was refluxed for 12 hours, and the cold product poured into excess of dilute hydrochloric acid. The brown precipitate after two recrystallisations (alcohol) had m. p. 90—168°. It was then recrystallised from benzene and again from alcohol, and afforded 2-*p*-tolylindole, m. p. 218·5—219·5°. The benzene mother-liquors were evaporated, and the residue when recrystallised (alcohol) gave 2-*p*-tolyl-1-methylindole, m. p. 94—96°. (ii) *p*-Chlorophenacyl-*N*-methylaniline (4 g.), *N*-methylaniline hydrobromide (2·7 g., 1 mol.), and *N*-methylaniline (10 c.c., 6 mols.) were refluxed for 1 hour and then afforded 2-*p*-chlorophenylindole, m. p. 204—205°, and 2-*p*-chlorophenyl-1-methylindole, m. p. 119—120°. Repetition of this experiment using *N*-methylaniline hydrochloride (2 g., 1 mol.) in place of the hydrobromide afforded the same two indoles. Repetition of the experiment with the omission of the hydrobromide gave a product which when recrystallised (alcohol) afforded the unchanged phenacylamine, m. p. 109° (alone and mixed). (iii) *p*-Phenylphenacyl-*N*-methylaniline (3 g.), *N*-methylaniline hydrobromide (1·9 g., 1 mol.), and *N*-methylaniline (10 c.c., 10 mols.) when refluxed for 2·5 hours afforded 2-*p*-phenylylindole, m. p. 304—306°, and 3-*p*-phenylyl-1-methylindole, m. p. 132—133·5°. Repetition of this experiment with omission of the hydrobromide gave the unchanged phenacylamine (alcohol), m. p. 153·5—154·5° (alone and mixed). (iv) *p*-Chlorophenacyl-*N*-ethylaniline (4 g.), *N*-ethylaniline hydrobromide (2·6 g., 1 mol.), and *N*-ethylaniline (10 c.c., 6 mols.) when refluxed for 1 hour gave 2-*p*-chlorophenylindole, m. p. 204—205°, and 3-*p*-chlorophenyl-1-ethylindole, m. p. 79—80°. Repetition of this experiment using *N*-ethylaniline hydrochloride (2·0 g., 1 mol.) in place of the hydrobromide gave the same product.

Repetition of the experiment with omission of the hydrobromide gave ultimately the unchanged phenacylamine.

A mixture of *p*-phenylphenacyl bromide (5 g.) and *N*-dimethylaniline (15 c.c., 6·5 mols.) was heated at 100° for 30 minutes, by which time a crystalline deposit had formed, and was then refluxed for 7 hours, cooled, and poured into excess of dilute hydrochloric acid. The precipitate when collected, washed, and recrystallised (alcohol) afforded *p*-phenylphenacyl-*N*-methylaniline, m. p. 153—155° (alone and mixed). The same product was obtained when a mixture of *p*-phenylphenacyl-*N*-dimethylanilinium bromide, $[\overset{+}{N}PhMe_2 \cdot CH_2 \cdot CO \cdot C_6H_4 \cdot Ph]\bar{B}r$ (2 g.), and *N*-dimethylaniline (8 c.c.) was refluxed for 7 hours and then treated as above.

To illustrate the stability of the phenacylamines in absence of acid, the following experiments were performed with *p*-phenylphenacyl-*N*-methylaniline. (*a*) The compound was distilled at 18 mm. The distillate readily solidified and when recrystallised (alcohol) afforded the unchanged material, m. p. 151·5—153·5°. (*b*) The compound was heated in a sealed tube at 180° for 5 hours. Recrystallisation again gave the pure unchanged material. (*c*) A mixture of the compound (2 g.) and *o*-dichlorobenzene (5 c.c.) was refluxed for 3 hours. After cooling, the crystalline deposit was collected and recrystallised (alcohol–acetone), and gave the unchanged material. Experiment (*a*) was repeated using *p*-phenylphenacyl-*N*-ethylaniline, and recrystallisation of the solid distillate again gave the unchanged compound.

3-p-*Phenylyl*-1-*methylindole Dipicrate*.—The composition of this picrate is exceptional, and the presence of the second molecule of picric acid may be due to the general aromatic influence of the *p*-phenylyl group. Cold saturated alcoholic solutions of the indole and of excess of picric acid were mixed and evaporated under reduced pressure at room temperature until a dark crystalline deposit formed. This was collected and twice recrystallised (alcohol containing free picric acid), and afforded the *dipicrate* as a dark brown crystalline powder, m. p. 135—136° (Found: C, 53·5; H, 3·2; N, 13·4. $C_{21}H_{17}N,2C_6H_3O_7N_3$ requires C, 53·5; H, 3·1; N, 13·2%). The salt tends to dissociate in solution, and recrystallisation should preferably be carried out from the almost cold solution.

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