170. *The Mechanism of Indole Formation from Phenacylarylamines. Part III. The Conditions and Mechanism of the Isomerisation and Indolisation of Phenacylarylamines.*

By Fred Brown and Frederick G. Mann.

It is shown that a phenacylarylamine of type NHPh·CHR·COR′, where R and R′ are both aryl groups, may have considerable stability in the pure state. When heated to moderate temperatures in the presence of small quantities of acid, however, it may readily isomerise to the phenacyl compound NHPh·CHR′·COR, and at higher temperatures, also in the presence of acids, may then indolise: the indole thus obtained from either of the isomeric phenacylamines will therefore be the 2-R′ : 3-R-indole formed by cyclisation of the second and more stable phenacylamine. If an *N*-alkyl group R″ is inserted in the phenacylamines, the two resulting isomers, NR″Ph·CHR·COR′ and NR″Ph·CHR′·COR, do not undergo detectable interconversion, and consequently undergo indolisation almost invariably by direct cyclisation.

The bearing of these results and of those described in Part II (preceding paper) upon the general problem of the indolisation of phenacylanilines is discussed, and a reaction mechanism for the above isomerisation and the indolisation is suggested.

In reconsidering the various possible mechanisms for the indolisation of phenacyl primary arylamines and similar compounds, we were impressed by the fact that most of the published evidence was derived from compounds of the type NHPh·CH_2·COR, where R was an aryl or alkyl group, or from compounds of type NHPh·CHR′·COR, where R was aryl and R′ alkyl or vice versa. It appeared to us that decisive evidence for the mechanism of the indolisation, and even more for that of the isomerisation of the phenacylamines themselves, would more probably be obtained if the use of the comparatively mobile alkyl groups were avoided, and compounds of the type NHPh·CHR′·COR, where both R and R′ were aryl groups, were alone employed: for this purpose it was clearly desirable that the groups R and R′ should be closely alike so that if possible neither should exert a dominant influence over the course of subsequent reactions. (For identification of the ultimate position of each of these two groups, they clearly had to be different.)

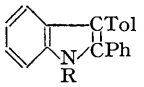
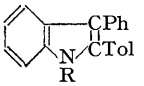
For this purpose, *p*-tolyl benzyl ketone was prepared by the action of phenylacetyl chloride on toluene, and then brominated to give p-*tolyl α-bromobenzyl ketone*, Ph·CHBr·COTol.* This compound readily reacted with aniline in boiling alcoholic solution to give 1-*phenyl*-p-*methyl-phenacylaniline* (I), m. p. 137°. In the isomeric series, phenyl *p*-methylbenzyl ketone was

* Throughout this paper, the symbol " Tol " is employed to denote the *p*-tolyl group.

similarly prepared by the action of *p*-tolylacetyl chloride on benzene, and then brominated to *phenyl α-bromo*-p-*methylbenzyl ketone*, Tol·CHBr·COPh. When this compound was boiled with

(I.) NHPh·CHPh·COTol NHPh·CHTol·COPh (II.)

aniline in alcoholic solution, however, a viscous syrup was obtained, from which ultimately the crystalline compound (I) was significantly obtained. When, however, equimolecular quantities of the bromo-ketone and aniline were shaken in cold alcoholic solution with potassium carbonate for 18 hours, the pure 1-p-*tolylphenacylaniline*, (II), m. p. 71°, was isolated. These reactions in themselves indicated strongly that (II) might undergo conversion into the isomeric compound (I) under suitable conditions : the stability and reactions of each of these phenacylamines were therefore studied in considerable detail. Again, the identity of each indole obtained in this section of the work was confirmed both by analysis and by direct comparison with authentic indoles prepared by Fischer's synthesis. It will be noted that 1-phenyl-*p*-methylphenacylaniline (I), if it underwent indolisation by direct cyclisation, would give 2-*phenyl*-3-p-*tolylindole*

(III.)   (IV.)

(III, R = H), whereas the isomeric 1-*p*-tolylphenacylaniline (II) would similarly give 3-*phenyl*-2-p-*tolylindole* (IV, R = H).

The properties and reactions of the phenacylamine (I) are summarised in Table I.

TABLE I.

Reactions of 1-*Phenyl*-p-*methylphenacylaniline*, NHPh·CHPh·COTol (I).

(1) Heated alone, 195—200°, 30 mins.	Unchanged
(2) Fused + $ZnCl_2$ (11 mols.), 180°, 15 mins.	,,
(3) Fused + $ZnCl_2$ (11 mols.), 220°, 15 mins.	Extensive decomp.
(4) Heated + NH_2Ph,HBr (0·006 mol.), 195—200°, 30 mins.	Converted into 2-phenyl-3-*p*-tolylindole
(5) Boiled + NH_2Ph (15·5 mols.) + NH_2Ph,HBr (1 mol.), 1 hr.	,, ,, ,, ,,

It will be seen that the pure phenacylamine (I) has considerable stability : moreover it does not show the comparatively ready indolisation with fused zinc chloride that, for example, phenacylaniline, NHPh·CH_2·COPh, undergoes (cf. p. 869). On the other hand, it is clearly very susceptible to the action of traces of acids, and then undergoes indolisation *by direct cyclisation*. (The term " direct cyclisation " is employed here to denote cyclisation without isomerisation at any stage, irrespective of the mechanism involved.) The result of Expt. 5 indicated that *p*-tolyl α-bromobenzyl ketone, Ph·CHBr·COTol, when boiled with excess of aniline should also give 2-phenyl-3-*p*-tolylindole, and experiment confirmed this deduction.

The fact that only the indole obtained by direct cyclisation was found in the above reactions also indicated that the corresponding phenacyl secondary amines, namely, 1-*phenyl*-p-*methylphenacyl*-N-*methylaniline*, NMePh·CHPh·COTol, and its N-*ethyl* homologue, would similarly indolise when treated either with alcoholic or with fused zinc chloride, although certain of our earlier phenacyl secondary amines gave different types of indolisation under these two conditions (cf. Part II, Tables I and II). The results recorded in Table I*A* show that in all cases indolisation by direct cyclisation has now occurred, producing 2-*phenyl*-3-p-*tolyl*-1-*methyl*- and 2-*phenyl*-3-p-*tolyl*-1-*ethyl-indole* (III, R = Me and Et).

TABLE I*A*.

Reactions of 1-*Phenyl*-p-*methylphenacyl*-N-*alkylanilines*, NRPh·CHPh·COTol.

R = Me.—	(1) Boiled + alcoholic $ZnCl_2$ (23 mols.), 5 hrs.	Converted into 2-Ph-3-Tol-1-Me-indole
	(2) Fused + $ZnCl_2$ (11·5 mols.), 200°, 30 mins.	,, ,, ,, ,,
R = Et.—	(3) Boiled + alcoholic $ZnCl_2$ (12 mols.), 5 hrs.	Converted into 2-Ph-3-Tol-1-Et-indole
	(4) Fused + $ZnCl_2$ (12 mols.), 200°, 30 mins.	,, ,, ,, ,,

Our preparation of the two isomeric phenacylamines (I) and (II) indicated that the second compound, 1-*p*-tolylphenacylaniline (II), was much the less stable. Its properties and reactions were therefore studied in considerable detail (Table II). Expts. 1—8 in Table II were performed in pure *n*-butyl alcohol : this alcohol was used instead of ethyl alcohol in order to obtain a higher temperature and also the more readily to secure anhydrous conditions.

TABLE II.

Reactions of 1-p-*Tolylphenacylaniline*, NHPh·CHTol·COPh (II).

(1)	Heated alone, 195—200°, 30 mins.	Unchanged
(2)	Boiled in BuOH, alone, 30 mins.	,,
(3)	,, ,, + NH_2Ph (1 mol.), 30 mins.	,,
(4)	,, ,, + NH_2Ph,HBr (0·07 mol.), 30 mins.	Largely unchanged
(5)	,, ,, + NH_2Ph,HBr (1 mol.), 30 mins.	Isomerised to (I)
(6)	,, ,, + NHEtPh,HBr (1 mol.), 30 mins.	Largely unchanged
(7)	,, ,, + HBr–HOAc soln.* (0·05 c.c.), 30 mins.	Mixture of (I) and (II)
(8)	,, ,, + HBr–HOAc soln.* (0·05 c.c.), 5 hrs.	Isomerised to (I)
(9)	,, in NH_2Ph (15·5 mols.), alone, 1 hr.	Unchanged
(10)	,, in NH_2Ph (15·5 mols.) + NH_2Ph,HBr (1 mol.), 1 hr.	Converted into 2-Ph-3-Tol-indole †
(11)	Heated + NH_2Ph,HBr (0·017 mol.), 195—200°, 30 mins.	,, ,, ,, ,, †

* This solution contained 50 g. HBr/100 c.c. soln.

† Both these products were initially impure and may have contained both 2-phenyl-3-*p*-tolyl- and 3-phenyl-2-*p*-tolyl-indole: only the former could be isolated.

Certain very important deductions arise from these results.

(i) The phenacylamine (II) has clearly considerable stability in the pure state or in neutral solution, and under these conditions gives no indication of isomerisation to the phenacylamine (I) even at high temperatures (Expts. 1, 2, 3, 9).

(ii) In the presence of acids and at moderate temperatures, however, it may undergo a rapid and often apparently complete isomerisation to the phenacylamine (I) (Expts. 4—8). For this purpose, aniline hydrobromide is apparently a more active catalyst than hydrogen bromide, for we find that 1-p-*tolylphenacylaniline hydrobromide* when boiled in butyl alcohol for 30 minutes was unchanged: this is equivalent of course to the phenacylamine (II) plus 1 mol. of hydrogen bromide, yet in Expt. 5, the phenacylamine (II) plus 1 mol. of aniline hydrobromide under otherwise identical conditions underwent isomerisation to (I).

(iii) In the presence of acids but at higher temperatures (Expts. 10, 11) the phenacylamine (II) undergoes indolisation, but the nature of the indole produced indicates strongly that now *isomerisation precedes indolisation*, since the indole obtained is that which is known to be formed by the indolisation of the phenacylamine (I) under identical conditions (Table I). To prove this point, 3-*phenyl*-2-p-*tolylindole* (IV, R = H), *i.e.*, the indole which would be formed by direct cyclisation of the phenacylamine (II), was prepared by Fischer's synthesis and its stability investigated. It proved to be unchanged when fused with zinc chloride at 200° for 30 minutes, and also when boiled in aniline containing 1 mol.-equiv. of aniline hydrobromide for 30 minutes. It is clear therefore that this indole could not have been an intermediate in the formation of the isomeric indole (III, R = H) in Expts. 10 and 11, and that the latter indole almost certainly had been formed by isomerisation of the phenacylamine (II) followed by indolisation of (I) by direct cyclisation. The nature of the crude initial product obtained in Expts. 10 and 11 indicated that possibly direct cyclisation of (II) to give the stable indole (IV) occurred initially to a small extent, but that the main reaction was isomerisation to (I) followed by indolisation to (III).

A further important fact in this connection is that the pure dry 1-*p*-tolylphenacylaniline hydrobromide when heated alone at 205—210° for 10 minutes underwent considerable decomposition, giving phenyl *p*-methylbenzyl ketone, Tol·CH_2·COPh, but no isomerisation or indolisation could be detected. This confirms the (unpublished) results of Crowther, Mann, and Purdie (cf. Part I., *J.*, 1943, 58), who found that pure phenacylaniline hydrobromide on being heated underwent decomposition without detectable indolisation. This remarkable difference between the pure hydrobromide and the phenacylamine mixed with a much smaller proportion of hydrogen bromide must be considered in any reaction mechanism.

In view of the labile nature of 1-*p*-tolylphenacylaniline (II), the stability and reactions of the corresponding 1-p-*tolylphenacyl*-N-*methylaniline*, NMePh·CHTol·COPh, and its N-*ethyl* homologue were clearly of considerable importance. These are summarised in Table II*A*.

This Table also reveals some important factors.

(i) Neither of the above *N*-alkylphenacylamines gave any direct evidence of isomerisation to the corresponding compounds of formula NRPh·CHPh·COTol.

(ii) The two *N*-alkyl compounds showed one remarkable difference, in that the *N*-ethyl compound under the influence of either alcoholic or fused zinc chloride underwent indolisation by direct cyclisation, whereas the *N*-methyl compound behaved similarly only under the influence of alcoholic zinc chloride, but under the influence of fused zinc chloride gave the

TABLE II*A*.

Reactions of 1-p-*Tolylphenacyl*-N-*alkylanilines*, NRPh·CHTol·COPh.

R = Me.—	(1) Boiled in BuOH + NH_2Ph,HBr (1 mol.), 30 mins.	Unchanged
	(2) ,, ,, + NHMePh,HBr (1 mol.), 30 mins.	,,
	(3) ,, ,, + NHMePh,HBr (1 mol.), 4 hrs.	,, *
	(4) Boiled + alcoholic $ZnCl_2$ (11·5 mols.), 5 hrs.	Converted into 3-Ph-2-Tol-1-Me-indole (IV, R = Me)
	(5) Fused + $ZnCl_2$ (11·5 mols.), 200°, 30 mins.	Converted into 2-Ph-3-Tol-1-Me-indole (III, R = Me) †
R = Et.—	(6) Boiled in BuOH + NH_2Ph,HBr (1 mol.), 30 mins.	Unchanged
	(7) ,, ,, + NHEtPh,HBr (1 mol.), 30 mins.	,,
	(8) Boiled + alcoholic $ZnCl_2$ (12 mols.), 5 hrs.	Converted into 3-Ph-2-Tol-1-Et-indole (IV, R = Et)
	(9) Fused + $ZnCl_2$ (12 mols.), 200°, 30 mins.	,, ,, ,, †

* Yield of pure unchanged product from crude product was low.
† Yield of indole was low.

isomeric 2-phenyl-3-*p*-tolyl-1-methylindole (III, R = Me). This indole could not have arisen by the intermediate formation and subsequent isomerisation of 3-*phenyl*-2-p-*tolyl*-1-*methylindole* (IV, R = Me), because we find that the latter indole, after fusion with zinc chloride at 200° for 30 minutes, can be recovered almost entirely unchanged. It should be noted, however, that crude product obtained in Expts. (5) and (9) required a long purification resulting in a low yield of the final component, and the possibility of the presence of the isomeric indole in the crude product from each experiment cannot be precluded.

It follows that any mechanism for the indolisation of phenacylamines, when applied to our compounds, must account for the following main factors :

(*A*) The pure phenacylamines (I) and (II) are stable up to 200°.

(*B*) The phenacylamine (II) is readily isomerised to (I) by acid catalysts at moderate temperatures, but when *N*-alkylated is not thus isomerised. Aniline hydrobromide is a more effective catalyst than hydrogen bromide. The reverse isomerisation, from (I) to (II), was never detected and therefore cannot occur to more than a negligible extent.

(*C*) The phenacylamine (I) is cyclised to the normal indole by acid catalysts at higher temperatures, but the phenacylamine (II) under these conditions is apparently first isomerised to (I) and therefore gives the same indole.

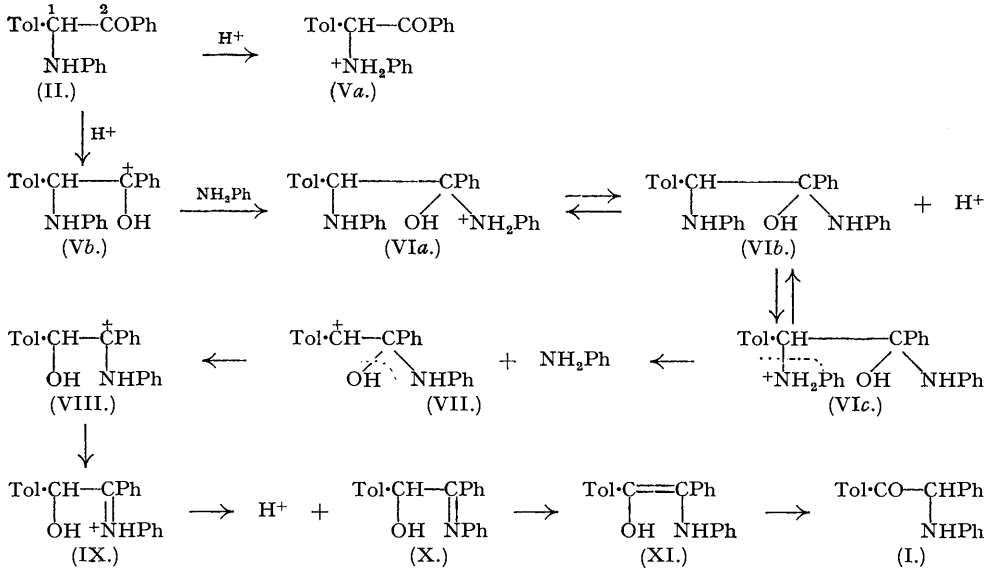
(*D*) The phenacylamine (I) when *N*-methylated or -ethylated always gives the normal indole by direct cyclisation. The phenacylamine (II) when *N*-ethylated also gives the normal indole by direct cyclisation, but when *N*-methylated does so under the influence of alcoholic zinc chloride but gives the isomeric indole under the influence of fused zinc chloride.

(*E*) The pure dry hydrobromide of the phenacylamine (II) when heated decomposes without perceptible isomerisation or indolisation.

The fundamental factor here is the mechanism of the acid-catalysed isomerisation of the phenacylamine (II) to (I) : if this is a general process, the products of indolisation could be readily explained; for example, it would follow that the production of 2-phenylindole from phenacylaniline, NHPh·CH_2·COPh, might occur by the initial conversion of this compound into the isomer NHPh·CHPh·CHO, which would then undergo direct cyclisation.

To account for the isomerisation of the phenacylamine (II) to (I), we tentatively suggest the following considerations. Since the phenacylamine (II) undergoes no reactions in the absence of acids, the first stage must be proton addition. This might occur at the nitrogen atom to give the cation (V*a*) and at the oxygen atom to give the cation (V*b*), although the first process must strongly predominate. Since, however, the hydrobromide of (II), which must contain the cation (V*a*), does not show either isomerisation or indolisation, this cation is clearly inactive. Consequently the cation (V*b*) must be that involved, in spite of its low concentration : it would of course be expected to possess a very much greater reactivity than (V*a*). Now it is significant that aniline hydrobromide is a more effective catalyst than hydrogen bromide : moreover, aniline must always be present in the acid-catalysed system, as the acid would react to some extent with any phenacylaniline to give the phenacyl bromide and aniline. Consequently the next stage is probably direct addition of aniline to (V*b*) to give the cation (VI*a*), which will certainly be in dynamic prototropic equilibrium with the amine (VI*b*) produced by normal dissociation of the salt, and with the isomeric cation (VI*c*). Now if the cation (VI*c*) is to be converted into the phenacylamine (I), this process must involve at some stage (i) loss of the aniline residue attached to carbon atom 1, (ii) migration of the OH group from carbon atom 2 to carbon atom 1, (iii) the final loss of a proton, although these three processes may not necessarily

occur in this order. We suggest that (i) occurs first, producing aniline and the very reactive cation (VII), and is immediately followed by (ii) to give the cation (VIII). The conversion of this cation into the phenacylamine (II) would then rapidly proceed by normal electronic and

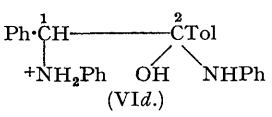


tautomeric changes, namely, loss of a proton through the intermediate formation of the cation (IX) to give the anil (X), followed by tautomerisation through (XI) to the phenacylamine (I).

This mechanism if correct must provide a reasonable interpretation of the main factors (A)—(E) outlined above. To consider them in order :

(*A*) The pure phenacylamines (I) and (II) are stable up to 200° because reaction involves proton addition.

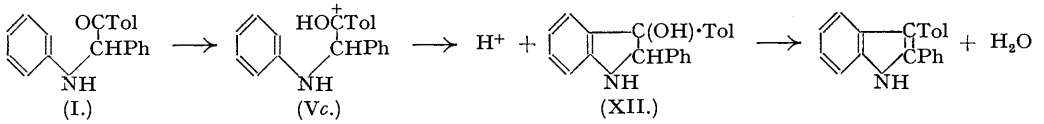
(*B*) The critical point is why the phenacylamine (II) is isomerised to (I) and not vice versa. This implies by our mechanism that loss of the positively-charged aniline residue attached to carbon atom 1 in the cation (VI*c*) must be more ready than the loss of that attached to carbon atom 2 in the cation (VI*d*) which would be formed in the conversion by an identical mechanism of the phenacylamine (I) into the isomer (II). It must be borne in mind, however, that this predominant stability of one phenacylamine over its isomer is not general. For example, Julian *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 1203) have shown that both α-anilinodibenzyl ketone, Ph·CH(NHPh)·CO·CH_2Ph, and its isomer α-anilino-β-phenylpropiophenone, Ph·CO·CH(NHPh)·CH_2Ph, when heated with a mixture of aniline and aniline hydrobromide give a mixture of 3-phenyl-2-benzyl- and 2-phenyl-3-benzyl-indole. This would entail that in this series the two isomeric cations, corresponding to our cations (VI*c*) and (VI*d*), must have approximately equal stability, and each loses its positively changed aniline residue, so that a mixture of the two indoles results. To explain why in our phenacylamines the isomerisation apparently goes solely from (II) to (I), it must be noted that during the conversion of the cation



(VI*c*) into (VII), *i.e.*, during the fission Tol·CH(·$\overset{+}{N}H_2$Ph)$^-$ ⟶ NH_2Ph + Tol·$\overset{+}{C}$H$^-$, the electrons forming the bond between the nitrogen atom and carbon atom 1 remain with the nitrogen, and the C1 atom acquires a positive charge until the migration of the hydroxyl group from C2 to C1 transfers this charge to C2 in the cation (VIII). Clearly, therefore, this fission will be promoted by a high electron density at C1, or by the ability of the atom C1 to carry a positive charge. These conditions will occur in the cation (VI*c*), by virtue of the polar effect of the *p*-methyl group in the tolyl radical, to a much greater extent than in the cation (VI*d*), and it is apparently this stage that determines the direction of the isomerisation. It would therefore be of great interest to study the stabilising effect of competing *p*-substituents, for example $^-$Cl and $^-$Br, in the two aryl groups R and R′ in isomeric phenacylamines of type (I) and (II).

(*C*) Although the conversion of the phenacylamine (II) into the more stable isomer (I)

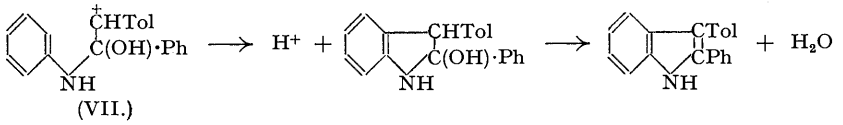
under the influence of acids can thus be explained, it is still necessary to explain why this stable isomer also requires an acid to promote indolisation by direct cyclisation. We suggest that here again it is the cation of type (V*b*) which is the active intermediate, since it is known that cations of type (V*a*) give neither isomerisation nor indolisation. The more stable 1-phenyl-*p*-methylphenacylaniline (I) would therefore by proton addition give the cation (V*c*), identical in type with (V*b*), and this cation would then lose a proton to give the 3-hydroxyindoline (XII), which



(I.) (V*c*.) (XII.)

would undergo ready dehydration to 2-phenyl-3-*p*-tolylindole. A similar mechanism could clearly be applied to the acid-catalysed direct cyclisation of phenacyl-*N*-alkylanilines to 3-aryl-1-alkylindoles (cf. Part II).

Although this may well be the acid-catalysed mechanism by which a " stable " phenacylamine (*i.e.*, a phenacylamine not showing isomerisation) undergoes cyclisation to an indole, it is not necessarily the only mechanism of indole formation. We have discussed a possible mechanism by which the phenacylamine (II) when heated with acids at moderate temperatures undergoes isomerisation to the phenacylamine (I). When, however, the phenacylamine (II) is heated at higher temperatures with acids (Expts. 10, 11; Table II), it undergoes ultimately conversion into 2-phenyl-3-*p*-tolylindole. It is impossible to say whether this process consists first in the complete isomerisation of (II) to (I), followed by the acid-catalysed cyclisation of (I) to the indole as indicated above, or whether the intermediate cation (VII), which at the lower temperature rearranged to the cation (VIII), now at the higher temperature undergoes direct

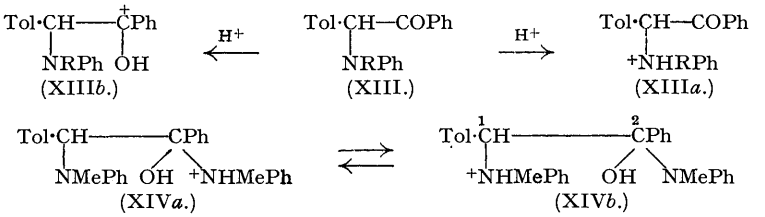


(VII.)

cyclisation (with loss of a proton) to the 2-hydroxyindoline, which then furnishes the 2-phenyl-3-*p*-tolylindole.

(*D*) Phenacyl-*N*-alkylanilines require in general much more vigorous conditions for indolisation than the unalkylated phenacylanilines, and almost invariably indolise by direct cyclisation : the formation of the isomeric indole by zinc chloride fusion is occasionally observed with *N*-methylphenacylanilines but only very rarely with the *N*-ethyl homologues (cf. Part II). The most striking difference in this behaviour is shown by 1-*p*-tolylphenacylaniline (II) and its *N*-alkyl derivatives, and this compound will therefore be selected to illustrate the application of our mechanism.

It has been shown by Hall and Sprinkle (*J. Amer. Chem. Soc.*, 1932, **54**, 3469) that the strength as bases of the *N*-methylated anilines increases in the order NH_2Ph, NHMePh, NMe_2Ph, but that the introduction of an *N*-ethyl group into aniline has an even greater effect, so that the difference in basic strength between NHEtPh and NHMePh is greater than that between NHMePh and NH_2Ph : furthermore, the introduction of an *N*-ethyl group into a secondary amine causes an exceptionally large increase in basic strength. Consequently it follows that the difference in basic strength between a phenacyl-*N*-ethylaniline and a phenacyl-*N*-methylaniline will be even greater than that between the latter compound and the corresponding unalkylated phenacylamine. When therefore a 1-*p*-tolylphenacyl-*N*-



(XIII*b*.) (XIII.) (XIII*a*.)

(XIV*a*.) (XIV*b*.)

alkylaniline (XIII) is converted into a salt, its strongly basic character will cause the cation to exist almost entirely in the inactive form (XIII*a*) and only a very small proportion of the active

isomeric cation (XIII*b*) will be formed. Since, however, it is only the latter cation that can indolise, this process will be slower and demand more vigorous conditions than in the unalkylated phenacylanilines, where the corresponding cations of type (V*b*) must be formed more readily and in a proportion which, although still small, is greater than in the *N*-alkyl series. These more vigorous conditions, however, cause the very reactive cation (XIII*b*) to undergo direct indolisation by the mechanism already described, with the formation of 3-phenyl-2-*p*-tolyl-1-alkylindole. The only exception is the action of fused zinc chloride on the *N*-methyl derivative at 200°, giving 2-phenyl-3-*p*-tolyl-1-methylindole. In these circumstances, the hydrogen chloride inevitably present must cause some disproportionation to the 1-chloro-ketone and *N*-methylaniline: the latter may then add on to the cation (XIII*b*) to give the cation (XIV*a*) which again will be in prototropic equilibrium with the isomeric cation (XIV*b*). On the basis of our previous scheme (p. 862), it will be the latter cation which loses the positively charged methylaniline from the C1 atom, and thus gives the 2-phenyl-3-*p*-tolyl-1-methylindole. In the more strongly basic *N*-ethyl series, the cation of type (XIII*b*) is formed in very small quantity, and at the high temperature undergoes immediate direct cyclisation without appreciable formation of by-products of the type of (XIV*a*) and (XIV*b*). Our mechanism does explain therefore why the formation of the isomeric indole from a phenacylaniline will occur only occasionally in the more basic *N*-methyl series and very rarely in the far more basic *N*-ethyl series.

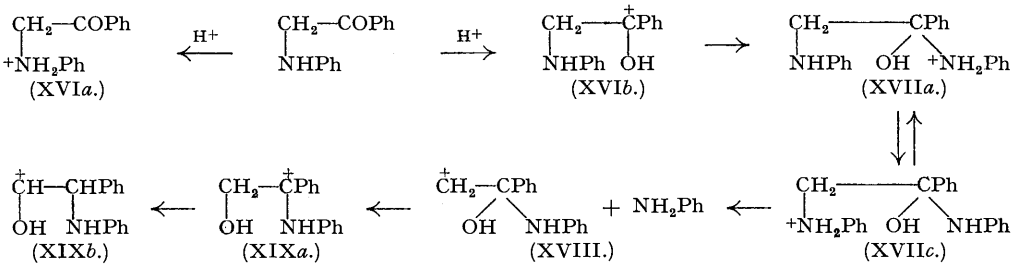
(*E*) The reason why pure dry phenacylaniline hydrobromides do not give indoles on heating becomes clear on our mechanism, namely that in these compounds the cation exists almost solely in the form (V*a*), and the active cation of type (V*b*) is therefore present in negligible proportion: consequently thermal decomposition occurs more readily than indolisation.

The fact that aniline hydrobromide is a much more effective catalyst for indolisation than aniline hydrochloride (cf. Parts I and II) is also now explained. The aniline hydrochloride, being the salt of a stronger acid, is less dissociated under the conditions employed than the hydrobromide, and therefore provides a lower concentration of the protons required for the first stage of this process.

Certain further points deserve brief discussion. Our reaction mechanism explains why the phenacylamine (II) in boiling butyl alcohol is readily isomerised by one molecular equivalent of aniline hydrobromide but much less readily by one equivalent of *N*-ethylaniline hydrobromide (cf. Expts. 5, 6; Table II). The latter salt will be less dissociated and consequently will give a lower concentration of protons. Moreover, the cation formed by addition of *N*-ethylaniline and corresponding to (VI*a*) will now be (XV*a*), and because of comparative basic strengths this

cation will be formed to the almost complete exclusion of the isomeric cation (XV*b*). But the cation (XV*a*) can lose only its positively-charged amine residue and hence can only revert to the original cation (V*b*). Formation of the indole (III, R = H) must therefore await liberation of aniline by disproportionation followed by the sequence of reactions already described (p. 862).

An explanation of the ready conversion of phenacylaniline into 2-phenylindole under acid-catalysed conditions is also now available. This simple compound differs from those employed in the mechanism-scheme on p. 862 in that only the C2 atom is directly joined to an aryl group. Consequently, in the absence of an aryl group joined to the C1 atom, the active

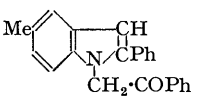


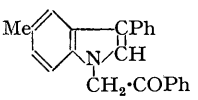
cation (XVI*b*) is formed in an unusually high proportion to the inactive cation (XVI*a*), because the positive charge on the C2 atom in (XVI*b*) is partly stabilised by the direct linkage of this

atom to the phenyl group. This cation is therefore available for direct addition of aniline to give the cation (XVII*a*) which in turn is in equilibrium with the cation (XVII*c*). The latter then loses the positively charged aniline residue on the Cl atom, to form the reactive cation (XVIII) which owing to high reactivity can have only a transient existence. It either undergoes direct cyclisation with loss of a proton to give the 2-hydroxyindoline which then loses water to give the indole, or the isomerisation process goes one stage further to form the cation (XIX*a*); this is in prototropic equilibrium with (XIX*b*), *i.e.*, with the cation that the isomeric phenacylamine, namely anilinophenylacetaldehyde, CHPh(NHPh)·CHO, must form for acid-catalysed cyclisation to 2-phenylindole. This promotion of the formation of reactive cations of type (XVI*b*) will apply to all phenacylanilines of type NHPh·CH_2·COR, *i.e.*, to those in which the aryl substituent is attached solely to the C2 atom.

We are not claiming that the above reaction mechanisms are necessarily correct or complete : we claim solely that they appear to us to conform more closely to the considerable volume of experimental evidence, and to be chemically more probable, than any of the other reaction schemes that we have considered. They supersede the mechanism which was suggested in Part I (*J.*, 1943, 62), and which was based on considerably less knowledge than is now available.

There is one novel and striking reaction of certain phenacylanilines that lies outside the above scheme of reactions. In the course of the work described in Part I, Crowther, Mann, and Purdie (*loc. cit.*) had found that phenacyl-*p*-toluidine, NHTol·CH_2·COPh, when heated with aniline hydrobromide (0·01 mol.) at 180° for 10 minutes gave a colourless crystalline compound of formula $C_{23}H_{19}ON$. This reaction was a notable exception to that of all the other phenacylanilines previously studied, which under the influence of the aniline hydrobromide readily gave the simple 2-arylindoles. We have investigated this reaction further, and it is highly probable that the product is either 1-phenacyl-2-phenyl-5-methylindole (XX) or its 3-phenyl isomer (XXI). 1-Phenacylindoles have not previously been recorded, and it was of interest to elucidate what groups in a substituted phenacylaniline determine this abnormal type of indolisation, and also by what mechanism these 1-phenacylindoles are formed. On the

(XX.) 



(XXI.)

first point we find that *phenacyl*-p-*ethylaniline*, C_6H_4Et·NH·CH_2·COPh, similarly gives 1-*phenacyl*-2(or 3)-*phenyl*-5-*ethylindole*. On the other hand, *phenacyl*-3 : 4-*dimethylaniline*, $C_6H_3Me_2$·NH·CH_2·COPh, and *phenacyl*-p-*chloroaniline*, C_6H_4Cl·NH·CH_2·COPh, under similar conditions are converted normally into 2-*phenyl*-4 : 5 (or 5 : 6)-*dimethylindole* and 5-*chloro*-2-*phenylindole* respectively. Although there is insufficient evidence for generalisation, it would appear that this reaction proceeds only if the aniline residue in the phenacylaniline has only one substituent, and that substituent must be a *p*-alkyl group.

Since pure phenacyl-*p*-toluidine was unchanged by being heated at 180° for 10 minutes, it is probable that the mechanism by which the 1-phenacyl-2(or 3)-phenyl-5-methylindole arises is first by the action of the hydrogen bromide forming the phenacylamine hydrobromide (Reaction *a*), which then dissociates to *p*-toluidine and phenacyl bromide (*b*), and the latter then reacts with more phenacylamine to form diphenacyl-*p*-toluidine and hydrogen bromide (*c*). The diphenacyl-*p*-toluidine under the influence of the acid catalyst gives the usual ready indolisation (*d*). In confirmation of this, we find

(*a*) NHTol·CH_2·COPh + HBr ⟶ [NH_2Tol·CH_2·COPh]Br
(*b*) [NH_2Tol·CH_2·COPh]Br ⟶ NH_2Tol + Br·CH_2·COPh
(*c*) NHTol·CH_2·COPh + Br·CH_2·COPh ⟶ NTol(CH_2·COPh)$_2$ + HBr
(*d*) NTol(CH_2·COPh)$_2$ ⟶ 1-Phenacyl-2(or 3)Ph-5-Me-Indole + H_2O

reaction (*c*) does occur very readily when the two reactants are boiled in alcoholic solution, and that the pure dry diphenacyl-*p*-toluidine when heated with a trace of *p*-toluidine hydrobromide at 200° is readily converted into the phenacylated indole. We have not, however, established decisively the position of the phenyl group in the final 2(or 3)-phenyl-5-methylindole. This compound does not form a picrate or a nitroso-derivative, is unaffected by boiling alcoholic hydrogen chloride, and on oxidation gives indefinite products. We have made many attempts to phenacylate both 2-phenyl- and 3-phenyl-5-methylindole, but all our experiments gave

either unchanged indole or an intractable product from which no pure component could be isolated.*

EXPERIMENTAL.

The names of solvents are cited as in Part II (p. 853); *N*-alkylanilines were purified as described in Part II. All phenacyl bromides and indoles were colourless and all phenacylamines were yellow. All molecular weight determinations, unless otherwise stated, were ebullioscopic.

Ketones.—*p*-Tolyl benzyl ketone was prepared by the action of phenylacetyl chloride on toluene in the presence of aluminium chloride (cf., Mann, *Ber.*, 1881, **14**, 1645) and then recrystallised; colourless crystals, m. p. 109—110°. Mann (*loc. cit.*) gives m. p. 107·5°, and Strassmann (*Ber.*, 1889, **22**, 1231) gives 109°. Phenyl *p*-methylbenzyl ketone, similarly prepared by the action of *p*-tolylacetyl chloride on benzene and recrystallised (alcohol), had m. p. 90—92°: Strassmann (*loc. cit.*) gives m. p. 94°.

Indoles by the Fischer Synthesis.—Alcoholic hydrogen chloride in place of zinc chloride was employed for the conversion of the phenylhydrazones into the indoles in order to ensure the mildest conditions and consequently least likelihood of isomerisation. No indication of such isomerisation during the Fischer synthesis was ever detected.

2-*Phenyl*-3-p-*tolylindole* (III, R = H). A solution of phenyl *p*-methylbenzyl ketone (5 g.) and phenylhydrazine (4 g., 1·5 mols.) in alcohol (50 c.c.) was boiled for 10 minutes, cooled, and saturated alcoholic hydrogen chloride (5 c.c.) cautiously added. When the vigorous reaction had subsided, the mixture was refluxed for 30 minutes, cooled, and filtered to remove precipitated chlorides. The solid residue obtained by evaporating the filtrate was extracted with boiling dilute hydrochloric acid, and the insoluble residue collected, dried, and recrystallised (alcohol, alcohol–water). The *indole* formed colourless crystals, m. p. 134° (Found: C, 88·6; H, 6·1; N, 5·15; *M*, in 0·821% alcoholic solution, 267. $C_{21}H_{17}N$ requires C, 89·1; H, 6·0; N, 4·9%; *M*, 283). When cold saturated alcoholic solutions of the indole and of picric acid were mixed and concentrated, the black crystalline *picrate*, m. p. 153°, separated (Found: N, 10·9. $C_{21}H_{17}N,C_6H_3O_7N_3$ requires N, 10·9%). 2-*Phenyl*-3-p-*tolyl*-1-*methylindole* (III, R = Me) was prepared as the previous indole using *as*-phenylmethylhydrazine (5 g., 1·7 mols.). The final alcoholic reaction mixture when cooled deposited a copious crystalline deposit, which was collected, washed with a small quantity of alcohol and then water, and recrystallised (alcohol); it formed colourless crystals, m. p. 157° (Found: C, 88·3; H, 6·1; N, 4·6. $C_{22}H_{19}N$ requires C, 88·9; H, 6·4; N, 4·7%). 2-*Phenyl*-3-p-*tolyl*-1-*ethylindole* (III, R = Et), similarly prepared using *as*-phenylethylhydrazine (5·3 g., 1·5 mols.), had m. p. 125° (Found: C, 89·0; H, 7·05; N, 4·65. $C_{23}H_{21}N$ requires C, 88·7; H, 6·8; N, 4·5%).

3-*Phenyl*-2-p-*tolylindole* (IV, R = H) was prepared similarly to its isomer above, using *p*-tolyl benzyl ketone (5 g.). The alcoholic reaction mixture was poured with stirring into water (1 l.), and the sticky precipitate, which rapidly solidified, on recrystallisation (alcohol) gave the indole, m. p. 117° (Found: C, 89·4; H, 6·1; N, 5·05; *M*, in 1·33% alcoholic solution, 263. $C_{21}H_{17}N$ requires C, 89·1; H, 6·0; N, 4·9%; *M*, 283); the *picrate* formed very dark brown (almost black) crystals, m. p. 137—138° (Found: N, 10·9. $C_{21}H_{17}N,C_6H_3O_7N_3$ requires N, 10·9%). 3-*Phenyl*-2-p-*tolyl*-1-*methylindole* (IV, R = Me), prepared as its isomer above but using *p*-tolyl benzyl ketone, had m. p. 122° (Found: C, 88·5; H, 6·2; N, 5·0. $C_{22}H_{19}N$ requires C, 88·9; H, 6·4; N, 4·7%). 3-*Phenyl*-2-p-*tolyl*-1-*ethylindole* (IV, R = Et) had m. p. 126° (Found: C, 88·3; H, 6·8; N, 4·8. $C_{23}H_{21}N$ requires C, 88·7; H, 6·8; N, 4·5%). A mixture of this indole and its isomer (III, R = Et) had m. p. 100—105°. The identity of indoles arising from phenacylamines and described later was always confirmed by mixed m. p. determinations with these authentic samples, as well as by analysis.

Bromo-ketones.—p-*Tolyl* α-*bromobenzyl ketone*, Ph·CHBr·CO·Tol. Bromine (2·5 c.c., 1 mol.) was added dropwise during 30 minutes to a well-stirred solution of *p*-tolyl benzyl ketone (10·5 g.) in chloroform (25 c.c.). Bromination was initiated by gentle warming and then proceeded at room temperature. The mixture was set aside for 30 minutes, concentrated to half-bulk, and cooled. The copious crystalline deposit when collected and recrystallised (alcohol) gave the α-*bromo-ketone*, m. p. 86·5—87° (Found: C, 62·2; H, 4·6. $C_{15}H_{13}OBr$ requires C, 62·3; H, 4·5%).

Phenyl α-*bromo*-p-*methylbenzyl ketone*, Tol·CHBr·CO·Ph. This compound was prepared as the above isomer, and evaporation of the chloroform under reduced pressure gave a viscous oil which readily crystallised on being seeded. Recrystallisation (methyl alcohol) gave the α-*bromo-ketone*, m. p. 56—57° (Found: C, 62·3; H, 4·9. $C_{15}H_{13}OBr$ requires C, 62·3; H, 4·5%). The oil obtained in the first preparation of this compound could not at first be crystallised, but when set aside solidified in about a fortnight and was used to seed subsequent preparations.

Phenacylamines.—1-*Phenyl*-p-*methylphenacylaniline* (I). A solution of *p*-tolyl α-bromobenzyl ketone (8·7 g.) and aniline (5·7 g., 2 mols.) in alcohol (30 c.c.) was gently refluxed for 15 minutes and then cooled. The crystalline deposit was collected, thoroughly washed with water, and recrystallised (alcohol); m. p. 137° (Found: C, 83·7; H, 6·5; N, 4·7; *M*, in 1·22% alcoholic solution, 290. $C_{21}H_{19}ON$ requires C, 83·7; H, 6·4; N, 4·7%; *M*, 301). The N-*methyl* homologue, similarly prepared using

* *Note added in Proof.*—Since this and the preceding paper were submitted for publication, a short communication on "Molecular Rearrangement and Displacement of Arylamine Residues in α-Arylaminoketones. Part I," by Cowper and Stevens (*J.*, 1947, 1041), has appeared. These authors consider that a phenacylamine, when heated with a base and its salts, can react in two independent ways: (*a*) by the intermediate formation of a Bischler diamine, and (*b*) by an intramolecular rearrangement, probably involving an intermediate compound of the type R·C═CR′ (with both carbons bridged by NPh).

It should be noted, however, that there is no decisive evidence for either of these mechanisms, and much evidence against the first, whilst the second is stereochemically improbable. Furthermore, neither mechanism explains either the necessity for acid catalysis or the direction of the rearrangement.

N-methylaniline (6·2 g., 2 mols.) and recrystallised, had m. p. 154° (Found: C, 83·6; H, 6·9; N, 4·5. $C_{22}H_{21}ON$ requires C, 83·8; H, 6·7; N, 4·45%). The N-*ethyl* homologue, similarly prepared using *N*-ethylaniline (7·2 g., 2 mols.), formed needles (alcohol), m. p. 121° (Found: C, 84·0; H, 7·15; N, 4·5. $C_{23}H_{23}ON$ requires C, 83·9; H, 7·05; N, 4·26%).

1-p-*Tolylphenacylaniline* (II). Owing to the ready isomerisation of this compound, the following method of preparation was necessary. Anhydrous potassium carbonate (12 g.) was suspended in a solution of phenyl α-bromo-*p*-methylbenzyl ketone (12 g.) in cold alcohol (50 c.c.). Aniline (5 c.c., 1 mol.) was added to the stirred suspension, which was then shaken mechanically for 18 hours. The solution was then concentrated to about 10 c.c. in a vacuum desiccator. The solid deposit was collected, washed with a small amount of alcohol and then with water, and finally recrystallised (alcohol); the *phenacyl* compound (II) was thus obtained as yellow crystals (rather paler in colour than those of its isomer), m. p. 70—71° (Found: C, 83·6; H, 6·4; N, 4·9; *M*, in 1·04% alcoholic solution, 310. $C_{21}H_{19}ON$ requires C, 83·7; H, 6·4; N, 4·7%; *M*, 301).

The N-*methyl* homologue was prepared by dissolving the bromo-ketone (2·1 g.) and *N*-methylaniline (1·5 g., 2 mols.) in alcohol (6 c.c.). The solution was set aside at room temperature for 2 hours and then vigorously stirred; the copious crystalline deposit which then separated was collected, washed with water, and recrystallised (alcohol); m. p. 92° (Found: C, 84·2; H, 6·95; N, 4·5. $C_{22}H_{21}ON$ requires C, 83·8; H, 6·7; N, 4·45%). The N-*ethyl* homologue was prepared by refluxing a solution of the bromo-ketone (5·5 g.) and *N*-ethylaniline (5 c.c., 2 mols.) in alcohol (15 c.c.) for 15 minutes; after cooling, the crystalline deposit was collected and recrystallised (alcohol); m. p. 84° (Found: C, 83·5; H, 7·1. $C_{23}H_{23}ON$ requires C, 83·9; H, 7·05%).

Great care was taken to ensure that all the above phenacylamines were ultimately entirely free from ionic bromine.

Reactions of 1-*Phenyl*-p-*methylphenacylaniline* (I) (cf. Table I).—(1) The compound (I) was heated at 195—200° for 30 minutes. The molten material showed no chemical change and when cooled, solidified, and recrystallised (alcohol–acetone) gave the unchanged substance, m. p. 136—137° (alone and mixed). (2) A mixture of (I) (2 g.) and powdered zinc chloride (10 g.) was heated at 180° for 15 minutes. The cold product was digested with cold dilute hydrochloric acid, but the dark coloured residue could not be readily crystallised; ultimately, however, its solution in petrol (b. p. 60—80°) was filtered and evaporated, and the resultant yellow syrup crystallised when triturated with ether–petrol. This solid when recrystallised (alcohol) gave the unchanged substance, m. p. 134·5—135·5° (alone and mixed). (3) Repetition of this experiment with heating at 220° gave a crude product from which no pure component could be isolated. (4) A mixture of (I) (2 g.) and aniline hydrobromide (0·02 g., 0·006 mol.) was heated at 195—200° for 30 minutes, a brisk effervescence occurring in the early stages of the heating. The cold syrupy residue was dissolved in petrol (b. p. 100—120°) and the filtered solution allowed to evaporate spontaneously. The crystalline deposit when recrystallised (aqueous alcohol) afforded 2-phenyl-3-*p*-tolylindole (III, R = H), m. p. 133·5—134°, unchanged by admixture with the authentic indole, depressed to 100—107° by admixture with the original compound (I), and depressed to 98—104° by admixture with 3-phenyl-2-*p*-tolylindole (IV, R = H). (5) A mixture of (I) (1 g.), aniline (5 c.c., 15·5 mols.), and aniline hydrobromide (0·6 g., 1 mol.) was refluxed for 1 hour, and the cold product poured into dilute hydrochloric acid. The sticky precipitate when collected and recrystallised (alcohol) gave a white powder, m. p. 110—116°. This was extracted with boiling *cyclo*hexane, and the filtered extract evaporated; the residue so obtained gave correct analyses for a phenyltolylindole (Found: C, 89·3; H, 5·9; N, 4·9. Calc. for $C_{21}H_{17}N$: C, 89·1; H, 6·0; N, 4·9%), but had m. p. 112—117°. When its alcoholic solution was treated with alcoholic picric acid, however, brownish-black crystals of the picrate of 2-phenyl-3-*p*-tolylindole, m. p. 150·5—152·5°, separated.

A mixture of *p*-tolyl α-bromobenzyl ketone (5 g.) and aniline (10 c.c., 6·3 mols.) was refluxed for 1 hour, coooled, and poured into excess of dilute hydrochloric acid. The sticky precipitate when twice recrystallised from alcohol and once from aqueous alcohol afforded 2-phenyl-3-*p*-tolylindole, m. p. 134—134·5° (Found: C, 88·9; H, 6·1; N, 4·9%).

Reactions of 1-*Phenyl*-p-*methylphenacyl*-N-*alkylanilines* (cf. Table I*A*).—(1) A solution of the *N*-methyl derivative (0·5 g.) and zinc chloride (5 g.) in alcohol (7·5 c.c.) was refluxed for 5 hours and allowed to cool. The copious crystalline deposit when collected and recrystallised (alcohol) gave 2-phenyl-3-*p*-tolyl-1-methylindole (III, R = Me), m. p. 156—157°. (2) A mixture of the *N*-methyl derivative (1 g.) and powdered zinc chloride (5 g.) was heated at 200° for 30 minutes. Acid digestion of the cold product gave a sticky solid which was dried and extracted with boiling petrol (b. p. 60—80°). Evaporation of the filtered extract gave a yellow glassy residue which crystallised when rubbed with acetic acid, and when then recrystallised (acetic acid) gave the above indole (III, R = Me), m. p. 155—156°. (3) A solution of the *N*-ethyl derivative (1 g.) and zinc chloride (5 g.) in alcohol (15 c.c.) was refluxed for 5 hours, and the cold solution poured into dilute hydrochloric acid. The white precipitate when recrystallised (alcohol) afforded 2-phenyl-3-*p*-tolyl-1-ethylindole (III, R = Et), m. p. 123—125°, unchanged by admixture with an authentic sample, but depressed to 98—105° by admixture with the isomeric indole (IV, R = Et). (4) Experiment (2) was repeated with the *N*-ethyl derivative (2 g.); evaporation of the petrol extract gave an oil which readily solidified and which on recrystallisation (alcohol) gave the indole (III, R = Et), m. p. 121—122°.

Reactions of 1-p-*Tolylphenacylaniline* (II) (cf. Table II).—(1) The compound (II) (0·5 g.) was heated at 195—200° for 30 minutes; the cold solid product when recrystallised (alcohol) gave the unchanged substance, m. p. 69·5—70·5°. (2) A solution of (II) (0·5 g.) in *n*-butyl alcohol (3 c.c.) was refluxed for 30 minutes; on cooling, the unchanged material, m. p. 69—70°, crystallised out. (3) Repetition of expt. (2) with the addition of aniline (0·2 c.c., 1 mol.) to the solution also gave the unchanged material, m. p. 70—71°. (4) A solution of (II) (0·5 g.) and aniline hydrobromide (0·02 g., 0·07 mol.) in butyl alcohol (3 c.c.) was refluxed for 30 minutes. Cooling deposited the unchanged crystalline (II) which, after being washed with alcohol, had m. p. 66—68·5°. (5) Repetition of expt. (4) using the hydrobromide (0·3 g., 1 mol.) gave on cooling a crystalline deposit which when collected

washed with water, and recrystallised (alcohol) afforded the isomeric phenacylamine (I), m. p. 136—137°, unchanged by admixture with an authentic sample. (6) A solution of (II) (0·5 g.) and of *N*-ethylaniline hydrobromide (0·3 g., 1 mol.) in butyl alcohol (3 c.c.) was boiled for 30 minutes; on cooling, the unchanged material was deposited, m. p. 68—69° after being washed with alcohol. (7) In this and the following expt. a solution of hydrogen bromide in glacial acetic acid containing 50 g. bromide/100 c.c. solution was employed. This solution (0·05 c.c.) was added to one of (II) (0·5 g.) in butyl alcohol (3 c.c.) and the mixture refluxed for 30 minutes. On cooling, the solution gave a crystalline deposit which was collected; the mother-liquors when set aside slowly gave a second deposit in very small quantity. The first deposit, m. p. 65—68°, on recrystallisation gave the pure unchanged (II), m. p. 67·5—68°. The second deposit when washed with alcohol afforded the isomeric compound (I), m. p. 129—133°, unchanged by admixture with an authentic sample. (8) Expt. (7) was repeated with 5 hours' refluxing. The solution on cooling deposited crystals which after recrystallisation (alcohol) gave the pure isomeric compound (I), m. p. 135·5—136·5°. (9) A mixture of (II) (1 g.) and aniline (5 c.c., 15·5 mols.) was refluxed for 1 hour, cooled, and poured on a mixture of ice and dilute hydrochloric acid. The yellow precipitate on recrystallisation (alcohol) afforded the unchanged material, m. p. 69·5—70·5°. (10) When expt. (9) was repeated with the addition of aniline hydrobromide (0·6 g., 1 mol.), cold acid digestion of the crude product followed by recrystallisation (alcohol) gave a cream-coloured powder, m. p. 109—114°. This was extracted with boiling *cyclo*hexane, the filtered extract evaporated, and the residue twice recrystallised (aqueous alcohol); it then had m. p. 114—116°, depressed to 107—110° by admixture with 3-phenyl-2-*p*-tolylindole (IV, R = H). It was therefore almost certainly 2-phenyl-3-*p*-tolylindole (III, R = H) contaminated with a small proportion of (IV, R = H) (Found: C, 88·7; H, 6·2; N, 5·2. Calc. for $C_{21}H_{17}N$: C, 89·1; H, 6·0; N, 4·9%). This was confirmed by treating an alcoholic solution of this product with alcoholic picric acid; brownish-black crystals of the picrate of 2-phenyl-3-*p*-tolylindole, m. p. 151—152·5°, were deposited. (11) A powdered mixture of (II) (1 g.) and aniline hydrobromide (0·01 g., 0·017 mol.) was heated at 195—200° for 30 minutes with continuous stirring. The product was extracted with cold petrol (b. p. 100—120°), the filtered extract evaporated, and the residue recrystallised (methyl alcohol). The white crystals had m. p. 118—121°, and recrystallisation from several solvents made no appreciable change. The final product, m. p. 114—118°, gave analyses for a phenyltolylindole as in expt. 10 (Found: C, 88·7; H, 6·0; N, 4·8%). As before, when an alcoholic solution of this product was treated with alcoholic picric acid, brownish-black crystals of the picrate of 2-phenyl-3-*p*-tolylindole, m. p. 150—152°, were deposited. When this experiment was repeated with aniline hydrobromide (0·6 g., 1 mol.) the same result was obtained.

Phenyl α-bromo-*p*-methylbenzyl ketone (1 g.) was added to aniline (5 c.c., 15·5 mols.); it dissolved with heat evolution and was replaced by a crystalline deposit. The mixture was refluxed for 1 hour, cooled, and poured into excess of dilute hydrochloric acid. The grey powdery precipitate was collected and dissolved in alcohol; this filtered solution was evaporated, and the residue when twice recrystallised (aqueous alcohol) afforded 2-phenyl-3-*p*-tolylindole (III, R = H), m. p. 133·5—134·5°.

1-p-*Tolylphenacylaniline Hydrobromide.—Preparation.* A solution of the base (II) in acetic acid was chilled in ice-water and stirred whilst a solution of hydrogen bromide (*ca.* 2 mols.) in acetic acid was added. Ether was then added to the stirred solution until an emulsion formed. Vigorous stirring caused this emulsion to deposit crystals, and more ether was now added until crystallisation was complete. The *hydrobromide* was collected, washed thrice with anhydrous ether, and dried thoroughly; m. p. 185—186° (Found: C, 65·9; H, 5·45; N, 3·6. $C_{21}H_{19}ON,HBr$ requires C, 66·0; H, 5·2; N, 3·7%).

Reactions. (1) The hydrobromide (2 g.) was heated at 205—210° for 10 minutes, a slight effervescence occurring. The product could not be satisfactorily crystallised, and it was therefore extracted with boiling petrol (b. p. 100—120°) (100 c.c.), and the filtered extract allowed to evaporate spontaneously. The partly crystallised oily residue was mixed with alcohol (4 c.c.) to complete the solidification, and the crystalline deposit when recrystallised (methyl alcohol) afforded phenyl *p*-methylbenzyl ketone, m. p. 93—94° (alone and mixed) (Found: C, 86·5; H, 7·3. Calc. for $C_{15}H_{14}O$: C, 85·8; H, 6·7%). (2) A mixture of the hydrobromide (0·7 g.) and *n*-butyl alcohol (3 c.c.) was refluxed for 30 minutes. The cold solution remained clear, but cautious addition of ether gave an emulsion which rapidly deposited crystals. Addition of ether was then continued until deposition was complete; the crystals when collected and washed with ether were the pure unchanged hydrobromide, m. p. 182—184° (alone and mixed).

Stability of 3-*Phenyl*-2-p-*tolylindole* (IV, R = H).—(1) A mixture of the indole (2 g.) and powdered zinc chloride (9·6 g., 10 mols.) was heated at 200° for 30 minutes. The cold product after acid digestion and recrystallisation (alcohol) gave the unchanged indole, m. p. 115·5—116·5° (alone and mixed). (2) A mixture of the indole (3 g.), aniline (5 g., 5 mols.), and aniline hydrobromide (1·8 g., 1 mol.) was refluxed for 30 minutes, cooled, and poured into dilute acid. The precipitated material when recrystallised (alcohol) gave the unchanged indole, m. p. 116—117° (alone and mixed). Expt. (1) was repeated with 3-phenyl-2-*p*-tolyl-1-methylindole, and the unchanged indole, m. p. 120—121·5° (alone and mixed) was again recovered.

Reactions of 1-p-*Tolylphenacyl*-N-*alkylanilines* (cf. Table II*A*).—(1) A mixture of the *N*-methyl derivative (0·5 g.), aniline hydrobromide (0·3 g., 1 mol.), and *n*-butyl alcohol (3 c.c.) was refluxed for 30 minutes. The clear solution on cooling deposited crystals of the unchanged methyl derivative, m. p. 90—91° (alone and mixed). (2) Repetition of expt. (1) with *N*-methylaniline hydrobromide (0·3 g., 1 mol.) also gave the unchanged derivative, m. p. 89·5—91°. (3) Repetition of expt. (2) with 4 hours' refluxing also gave the unchanged derivative, m. p. 89·5—91°, but the yield was now very low. (4) A mixture of the *N*-methyl derivative (0·5 g.), powdered zinc chloride (2·5 g.), and alcohol (8 c.c.) was refluxed for 5 hours, cooled, and poured into dilute acid. The sticky precipitate was collected and stirred vigorously with a small quantity of alcohol. Ready crystallisation ensued, and the product when recrystallised (alcohol, aqueous alcohol) furnished 3-phenyl-2-*p*-tolyl-1-methylindole (IV, R = Me), m. p. 120·5—122·5°. (5) An intimate mixture of the *N*-methyl derivative (1 g.) and powdered zinc chloride (5 g.) was heated at 200° for 30 minutes with occasional stirring. The crude product was

digested with hot dilute hydrochloric acid, giving an oil which solidified on cooling. This material was extracted with boiling petrol (b. p. 60—80°) (50 c.c.), and the filtered extract evaporated. The residue crystallised when stirred with petrol, and when crystallised in turn from alcohol, acetic acid, and aqueous acetic acid gave the indole (III, R = Me), m. p. 153—155°. (6) Repetition of expt. (1) with the *N*-ethyl derivative (0·5 g.) gave the unchanged material, m. p. 83—84°. (7) Repetition of expt. (2) with the *N*-ethyl derivative (0·5 g.) and *N*-ethylaniline hydrobromide (0·3 g.) also gave the unchanged derivative, m. p. 83—84°. (8) A mixture of the *N*-ethyl derivative (1 g.), zinc chloride (5 g.), and alcohol (15 c.c.) was refluxed for 5 hours. The solution on cooling deposited colourless crystals of 3-phenyl-2-*p*-tolyl-1-ethylindole (IV, R = Et), m. p. 123·5—124·5° after recrystallisation (alcohol). (9) Repetition of expt. (5) with the *N*-ethyl derivative (1 g.) gave a product which after the acid digestion and petrol extraction was ultimately thrice recrystallised (alcohol) and afforded the indole (IV, R = Et), m. p. 123—124·5°.

Phenacylaniline.—The following experiments, carried out with a highly purified sample, amplify the results recorded in Part I (*loc. cit.*). (1) A mixture of phenacylaniline (4·2 g.) and aniline hydrobromide (0·035 g., 0·01 mol.) was heated at 180° for 5 minutes. The cold product when recrystallised (benzene, alcohol) gave 2-phenylindole, m. p. 182—183°. (2) A mixture of phenacylaniline (5 g.) and aniline hydrochloride (2 g., 0·65 mol.) was heated at 175° for 5 minutes. The product, recrystallised as in expt. (1), furnished 2-phenylindole, m. p. 183—184°. Crowther, Mann, and Purdie (*loc. cit.*) performed this experiment using aniline hydrochloride (0·01 mol.) and obtained only partial conversion into diphenacylaniline. It is clear therefore that a concentration of hydrogen chloride much higher than that of hydrogen bromide is required for effective indolisation. (3) A mixture of phenacylaniline (4·2 g.) and powdered zinc chloride (27 g., 10 mols.) was plunged into a bath at 190° and maintained at this temperature for 15 minutes with continuous stirring. The cold product was digested with hot dilute acid, dried, and extracted with boiling benzene (50 c.c.). The filtered extract was evaporated to small bulk; the crystalline deposit when recrystallised (alcohol) afforded 2-phenylindole, m. p. 183—184°. The experiment was repeated using zinc chloride (1·55 mols.) with heating at 180° for 15 minutes, and 2-phenylindole, m. p. 182·5—183·5°, was again obtained. In Part I (*loc. cit.*) these experiments were recorded as giving only an amorphous powder; the difference is to be attributed to the different technique employed for the zinc chloride fusion (cf. Part II, p. 850). (4) A solution of phenacylaniline (8 g.) in tetralin (80 c.c.) was refluxed for 1 hour, cooled, and extracted with cold concentrated hydrochloric acid. The tetralin was almost free from dissolved organic material, but basification of the acid layer gave unchanged phenacylaniline (alcohol), m. p. 98°. When, however, a solution of phenacylaniline (25 g.) in tetralin (250 c.c.) was refluxed for 14 hours, and the solvent then evaporated under reduced pressure, distillation of the residue at 0·1 mm. gave diphenacyl (alcohol), m. p. 142—143° (Found: C, 81·1; H, 6·05. Calc. for $C_{16}H_{14}O_2$: C, 80·6; H, 5·9%). Since diphenacyl could also be isolated by direct crystallisation (alcohol–ether) of the residue, it was formed during the refluxing and not during the distillation of the residue. (5) Pure phenacylaniline hydrobromide was heated at 180° for 15 minutes and gave a dark red resin from which no pure component could be isolated. Heating at 200° gave the same result. This confirms the results of Crowther, Mann, and Purdie (*loc. cit.*) and also our results with 1-*p*-tolylphenacylaniline hydrobromide (p. 868), namely, that pure dry phenacylaniline hydrobromides do not indolise on heating.

1-*Phenacylindoles* (p. 865).—Phenacyl-*p*-toluidine was prepared by adding finely powdered *p*-toluidine (13 g., 2 mols.) to an agitated solution of phenacyl bromide (12 g.) in alcohol (50 c.c.) chilled in ice–water. After 2 hours' stirring, the precipitated phenacyl-*p*-toluidine was collected, digested thoroughly with a large volume of cold water, and finally recrystallised (alcohol); m. p. 128°. Lellmann and Donner (*Ber.*, 1890, **23**, 167) give m. p. 134°; Bischler (*Ber.*, 1892, **25**, 2866) gives m. p. 127°.

Phenacyl-p-*ethylaniline*. This required a special method of preparation. A mixture of phenacyl bromide (20 g.), *p*-ethylaniline (12 g., 1 mol.), anhydrous sodium carbonate (20 g.), and alcohol (200 c.c.) was vigorously stirred at 50° for 1 hour. Stirring was then continued without heating for 3 hours, the mixture poured into cold water (1 l.), and the stirring continued for 1 hour. The *phenacyl*-p-*ethylaniline* was then collected, washed, dried and recrystallised (alcohol–benzene, alcohol–acetone); m. p. 77—79° (Found: C, 80·1; H, 7·05; N, 6·15. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2; N, 5·9%). When *p*-ethylaniline (14·4 g., 2 mols.) was added to a stirred solution of phenacyl bromide (12 g.) in alcohol (30 c.c.) at 40—50°, a product was obtained which after repeated crystallisation (acetone, glycol monoethyl ether, alcohol) furnished *diphenacyl*-p-*ethylaniline*, m. p. 196—200° (Found: C, 80·1; H, 6·6; N, 4·25. $C_{24}H_{23}O_2N$ requires C, 80·6; H, 6·5; N, 3·9%).

Phenacyl-3 : 4-*dimethylaniline* was prepared similarly to phenacyl-*p*-toluidine and recrystallised (alcohol); m. p. 128—129° (Found: C, 79·9; H, 7·1; N, 6·1. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2; N, 5·9%). *Phenacyl*-p-*chloroaniline* similarly prepared and recrystallised (acetone, benzene) had m. p. 162—164° (Found: C, 68·7; H, 5·2; N, 5·7. $C_{14}H_{12}ONCl$ requires C, 68·4; H, 4·9; N, 5·7%).

Diphenacyl-p-*toluidine*. A mixture of phenacyl-*p*-toluidine (9 g.), phenacyl bromide (8 g., 1 mol.), and alcohol (100 c.c.) was refluxed for 15 minutes and cooled. The copious crystalline deposit was collected and recrystallised (glycol monomethyl ether); m. p. 252—255° (Found: C, 80·3; H, 6·1; N, 4·0. Calc. for $C_{23}H_{21}O_2N$: C, 80·4; H, 6·1; N, 4·1%). Lellmann and Donner (*loc. cit.*) give m. p. 255°.

Indolisation. (1) When phenacyl-*p*-toluidine was heated at 180° for 10 minutes, it was recovered unchanged. When, however, a mixture of phenacyl-*p*-toluidine (8·5 g.) and aniline hydrobromide (0·65 g., 0·1 mol.) was heated at 180° for 10 minutes, and the cold product then recrystallised in turn from benzene, acetone, and alcohol, 1-*phenacyl*-2(or 3)-*phenyl*-5-*methylindole* (XX or XXI) was obtained, colourless crystals, m. p. 204—205° (Found: C, 85·0; H, 6·0; N, 4·5. $C_{23}H_{19}ON$ requires C, 84·85; H, 5·9; N, 4·3%). Repetition of this experiment with *p*-toluidine hydrobromide (0·7 g., 0·1 mol.) gave the same compound, m. p. 202—204° (Found: C, 84·8; H, 6·0; N, 4·4%). (2) When a mixture of phenacyl-*p*-ethylaniline (2 g.) and aniline hydrobromide (0·2 g.) was heated at 185° for 5 minutes, a vigorous effervescence occurred. The resultant tar when repeatedly recrystallised (benzene, acetone)

afforded colourless crystals of 1-*phenacyl*-2(or 3)-*phenyl*-5-*ethylindole*, m. p. 209—210° (Found : C, 84·7; H, 6·1; N, 4·15. $C_{24}H_{21}ON$ requires C, 84·9; H, 6·2; N, 4·1%). (3) A mixture of phenacyl-3 : 4-xylidine (10 g.) and aniline hydrobromide (0·1 g.) was heated at 180° for 5 minutes, a vigorous initial reaction occurring. Recrystallisation (benzene, alcohol–acetone) of the crude product afforded 2-*phenyl*-4 : 5(or 5 : 6)-*dimethylindole*, m. p. 220—221° (Found : C, 87·1; H, 7·0; N, 6·6. $C_{16}H_{15}N$ requires C, 86·9; H, 6·8; N, 6·3%). (4) Phenacyl-*p*-chloraniline similarly treated gave a crude product which when recrystallised (benzene, alcohol, aqueous alcohol) afforded 5-*chloro*-2-*phenylindole*, m. p. 191° (Found : C, 73·4; H, 4·6; N, 6·3; Cl, 16·6. $C_{14}H_{10}NCl$ requires C, 73·8; H, 4·4; N, 6·2; Cl, 15·6%). (5) A mixture of diphenacyl-*p*-toluidine (1·5 g.) and *p*-toluidine hydrobromide (0·02 g.) was heated at 200° for 5 minutes. The product when recrystallised (benzene, alcohol–acetone) gave 1-phenacyl-2(or 3)-phenyl-5-methylindole, m. p. 203—204°, unchanged by admixture with that formed in expt. (1).

Attempted Phenacylation of 2-*Phenyl*-5-*methylindole.*—(1) A mixture of the indole (2·6 g.), phenacyl bromide (2 g., 0·8 mol.), and anhydrous potassium carbonate (4 g.) was heated at 115° for 3 hours with occasional stirring. The cold product when digested with dilute hydrochloric acid and then recrystallised (benzene, alcohol) afforded the unchanged indole, m. p. 210—211° (alone and mixed). (2) A similar mixture containing phenacyl bromide (1·3 mols.) was heated at 130°; a violent reaction then occurred. No pure component could be isolated from the crude material. (3) Many experiments were performed in which the indole in benzene solution was boiled with an ethereal solution of ethylmagnesium bromide, and phenacyl bromide added. In spite of wide variations in the general conditions of these experiments, conducted with this indole or with the isomeric 3-phenyl-5-methylindole, the final product was always either the unchanged indole or an intractable material from which no pure component could be isolated.

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