# 194. *Molecular Rearrangement and Displacement of Arylamine Residues in α-Arylamino-ketones. Part I.*

By R. M. Cowper and T. S. Stevens.

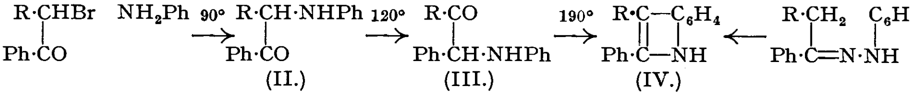
When an arylaminodeoxybenzoin (*e.g.*, II) is heated with a mixture of an arylamine and its hydrobromide, rearrangement may take place (to III); if the arylamine does not correspond to the arylamine residue in the ketone, this residue may be displaced by that of the reagent, with or without simultaneous rearrangement. The observations are only partly explicable by the mechanism proposed by Bischler for the rearrangements and displacements involved in the conversion of phenacylarylamines into arylindoles, and other mechanisms are discussed.

McGeoch and Stevens (*J.*, 1935, 1032) observed that the action of aniline on phenyl 1-bromo-2-phenylethyl ketone afforded an anomalous by-product (I):

$$\mathrm{CH_2Ph{\cdot}CHBr{\cdot}COPh} \longrightarrow \mathrm{CH_2Ph{\cdot}CH(NHPh){\cdot}COPh} + \mathrm{CH_2Ph{\cdot}CO{\cdot}CHPh{\cdot}NHPh} \quad \text{(I.)}$$

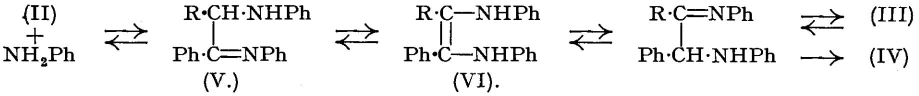
Related reactions of more tractable materials have been studied in detail, and the observations and tentative conclusions are reported now in view of publications by other workers in the same field (Crowther, Mann, and Purdie, *J.*, 1943, 58; Verkade and Janetzky, *Rec. Trav. chim.*, 1943, **62**, 763, 775; Julian, Meyer, Magnani, and Cole, *J. Amer. Chem. Soc.*, 1945, **67**, 1203). The results of the principal series of experiments are summarised in the table.

The α-bromo-derivatives of 4- and 4′-methoxydeoxybenzoin react in the first instance *normally*, by direct displacement, with aniline, *p*-toluidine, or methylaniline (Cowper and Stevens, *J.*, 1940, 347; which see for proofs of constitution of substances described in this paper); but at higher temperatures, in presence of arylamine and arylamine hydrobromide, such transformations as the following may occur (R = *p*-anisyl, throughout):



$$\begin{array}{c}R\cdot CHBr\\ |\\ Ph\cdot CO\end{array}\ NH_2Ph \xrightarrow{90^\circ} \underset{\text{(II.)}}{\begin{array}{c}R\cdot CH\cdot NHPh\\ |\\ Ph\cdot CO\end{array}} \xrightarrow{120^\circ} \underset{\text{(III.)}}{\begin{array}{c}R\cdot CO\\ |\\ Ph\cdot CH\cdot NHPh\end{array}} \xrightarrow{190^\circ} \underset{\text{(IV.)}}{\begin{array}{c}R\cdot C\text{—}C_6H_4\\ \|\quad |\\ Ph\cdot C\text{—}NH\end{array}} \longleftarrow \begin{array}{c}R\cdot CH_2\quad C_6H_5\\ |\qquad |\\ Ph\cdot C{=}N\cdot NH\end{array}$$

The conversion of the base (II) into (III) is sensibly complete, like the thermal transformation (Julian and Passler, *J. Amer. Chem. Soc.*, 1932, **54**, 4756; cf. Luis, *J.*, 1932, 2547) of the corresponding benzoin into its isomeride, $R\cdot CH(OH)\cdot COPh \longrightarrow R\cdot CO\cdot CH(OH)Ph$. It is plausibly explained on the basis of Bischler's mechanism for the formation of 2-phenylindole from anilinoacetophenone (*Ber.*, 1892, **25**, 2860; 1893, **26**, 1336; cf. Strain, *J. Amer. Chem. Soc.*, 1929, **51**, 270):

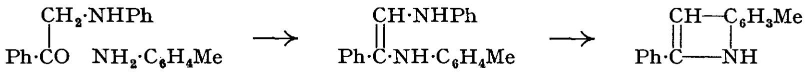


$$\begin{array}{c}\text{(II)}\\ +\\ NH_2Ph\end{array} \rightleftarrows \underset{\text{(V.)}}{\begin{array}{c}R\cdot CH\cdot NHPh\\ |\\ Ph\cdot C{=}NPh\end{array}} \rightleftarrows \underset{\text{(VI).}}{\begin{array}{c}R\cdot C\text{—}NHPh\\ \|\\ Ph\cdot C\text{—}NHPh\end{array}} \rightleftarrows \begin{array}{c}R\cdot C{=}NPh\\ |\\ Ph\cdot CH\cdot NHPh\end{array} \begin{array}{l}\rightleftarrows \text{(III)}\\ \\ \longrightarrow \text{(IV)}\end{array}$$

This explanation does not exclude rearrangement of the *N*-methyl derivative of (II) in presence of methylaniline and its hydrobromide, through direct formation and hydrolysis of the intermediate (as VI); but the process might be expected to be more difficult, in view of the failure of the carbonyl group of benzoins to react with a secondary base (Cowper and Stevens, *loc. cit.*). In fact, no reaction was observed below 170°, higher temperatures leading, not to the methyl derivative of (III), but by indolisation to that of (IV). Indolisation is structurally excluded in *phenyl* α-(N-*methylmesidino*)-p-*methoxybenzyl ketone*, $Ph\cdot CO\cdot CHR\cdot NMe\cdot C_6H_2Me_3$, but when this was heated with methylmesidine and its hydrobromide at 170° it was recovered unchanged, and at 190° the only isolable product was nitrogen-free.

Julian *et al.* (*loc. cit.*) record similar (reversible) rearrangements, *i.e.*, (II; R = Me or $CH_2Ph$) ⟶ (III; R = Me or $CH_2Ph$), and also demonstrate the formation, under similar experimental conditions, of anilinodeoxybenzoin anil (as V) from anilinodeoxybenzoin and aniline.

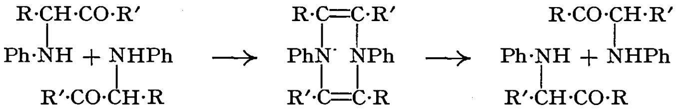
The Bischler mechanism accounts well for the conversion of anilinoacetophenone, by heating with excess of *p*-toluidine and its hydrochloride, into 2-phenyl-5-methylindole, aniline being in effect displaced by toluidine (Bischler, *loc. cit.* For other examples, see Julian *et al.*, *J. Amer. Chem. Soc.*, 1933, **55**, 2105; 1945, **67**, 1203; Verkade and Janetzky, *loc. cit.*):



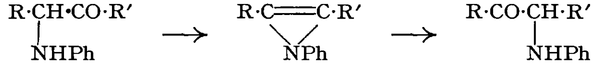
$$\begin{array}{c}CH_2\cdot NHPh\\ |\\ Ph\cdot CO\end{array}\ NH_2\cdot C_6H_4Me \longrightarrow \begin{array}{c}CH\cdot NHPh\\ \|\\ Ph\cdot C\cdot NH\cdot C_6H_4Me\end{array} \longrightarrow \begin{array}{c}CH\text{—}C_6H_3Me\\ \|\quad |\\ Ph\cdot C\text{——}NH\end{array}$$

Such a displacement is not necessarily associated with indolisation; thus when (II) or (III) is heated at 120° with excess of *p*-toluidine and *p*-toluidine hydrobromide the product is the toluidino-analogue of (III), displacement being accompanied in the former case by rearrangement. Further similar results are recorded in the table.

The reactions of rearrangement and/or displacement so far discussed can be accommodated by the Bischler–Strain scheme; alternatively, a somewhat similar mechanism could be envisaged, involving as an intermediate stage a product of the type $(NHAr\cdot CR{:}CPh)_2NAr$, discovered by Crowther, Mann, and Purdie (*loc. cit,*); but it is not clear why the *N*-methyl derivatives of (II) and (III) are unaffected by aniline–aniline hydrobromide up to 170°; and most surprising that (II), with methylaniline and its hydrobromide, readily affords (III) by rearrangement *without displacement.* The rearrangement of (II) is, moreover, smoothly effected by boiling with pyridine hydrobromide in pyridine or in butyl alcohol, a result explicable on Bischler's hypothesis only if part of the initial material furnishes free aniline by decomposition. This remote possibility was examined, and the strictly *intramolecular* character of the rearrangement indicated, by heating a mixture of two arylamino-ketones with pyridine hydrobromide in pyridine and seeking evidence for an exchange of arylamine residues. For experimental convenience, one selected initial substance was desylanthranilic acid, Ph·CO·CHPh·NH·$C_6H_4$·$CO_2H$, rearrangement of which is concealed by symmetry but from which aniline readily displaces anthranilic acid. The second initial material was (II), and the only products, isolated in good yield, were (III) and desylanthranilic acid. The result also discredits such a mechanism as the following (cf. Gabriel, *Ber.*, 1908, **41**, 1146) :



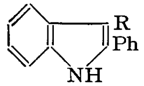
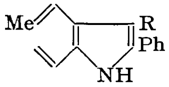
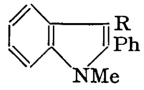
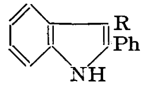
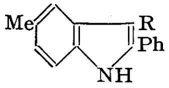
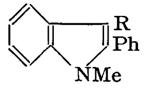
A strictly intramolecular rearrangement can be formulated in conventional structural terms only by postulating an intermediate having a three-membered ring :



For unsaturated $C_2N$ rings compare Neber and Burgard (*Annalen*, 1932, **493**, 281).

Attempts were also made to effect the *displacement* of one arylamine by another, where the Bischler mechanism could be excluded. When *α-anilinophenylacet*-p-*chloroanilide*, NHPh·CHPh·CO·NH·$C_6H_4$Cl, is heated at 200° with *p*-toluidine hydrobromide in *p*-toluidine, the aniline residue only is displaced; here the Bischler intermediate would be a tautomeric amidine, NHPh·CHPh·C(:NPh)·NH·$C_6H_4$Cl $\rightleftharpoons$ NHPh·CHPh·C(NHPh):N·$C_6H_4$Cl, and its formation and decomposition would lead to extensive displacement of chloroaniline also. The high temperature necessary for the reaction, however, forbids the inference that a direct displacement is likely with arylamino-ketones at 120°. Under the same energetic conditions *p*-toluidine displaces aniline from benzylaniline; but benzhydryl-*p*-toluidine, which might have been expected to be very reactive, was unaffected by aniline–aniline hydrobromide at 150°.

It would appear, in sum, that in presence of a base and its salt an arylamino-ketone can react in two independent ways : (*a*) according to the Bischler–Strain scheme made very probable by Julian and his co-workers, leading in appropriate cases to arylamine displacement, to indolisation, and possibly to rearrangement; and (*b*) a strictly intramolecular rearrangement, perhaps by the mechanism suggested above.

| Initial material. | Action of base + salt at 120° : | | | Product of indolisation. |
|---|---|---|---|---|
| | $NH_2Ph$. | $NH_2·C_7H_7$. | NHPhMe. | |
| R·CH·COPh<br>NHPh | Rearr. | Rearr.<br>+<br>Displ. | Rearr. |  |
| R·CH·COPh<br>NH·$C_7H_7$ | Rearr.<br>+<br>Displ. | Rearr. | Rearr. |  |
| R·CH·COPh<br>NMePh | Unch. | Unch. | Unch. |  |
| R·CO·CHPh<br>NHPh | Unch. | Displ. | |  |
| R·CO·CHPh<br>NH·$C_7H_7$ | Displ. | Unch. | |  |
| R·CO·CHPh<br>NMePh | Unch. | Unch. | Unch. |  |

*Indolisation.*—The base (II) and its analogues, each heated at 190—200° with the corresponding arylamine and its hydrobromide, yielded indoles; in all cases the product was that which would have resulted from the direct dehydration of an arylaminobenzyl *p*-anisyl ketone (as

III), the stable type when simple rearrangement can be effected. Attempted indolisation of (II) and of its *p*-toluidino-analogue in pyridine–pyridine hydrobromide gave as sole definable product a trace of nitrogen-free material, different in the two cases. This failure is not general (see Crowther, Mann, and Purdie, *loc. cit.*), and so not clearly significant as to the mechanism of Bischler synthesis. This investigation as a whole, however, shows that many of the anomalies recorded in this synthesis may be due to demonstrable transformations of the arylamino-ketones before cyclisation, and not to an *ortho*-migration as postulated by Crowther, Mann, and Purdie :

## EXPERIMENTAL.

*Rearrangement*.—The following experiment is typical. Phenyl α-anilino-*p*-methoxybenzyl ketone (II) was heated with aniline (3 mols.) and aniline hydrobromide (0·5 mol.) at 115—120° for 3 hours. The mixture was treated with dilute hydrochloric acid and ether; the combined acid layers deposited long needles of the hydrochloride of (III), which with alcoholic ammonia gave the free base (85%), identified by mixed m. p. and by reduction to *p*-methoxyphenyl benzyl ketone. No unchanged (II) could be recovered.

The same result followed when (II) was boiled for 3 hours with pyridine hydrobromide in pyridine, or with pyridine hydrobromide or sulphate in *n*-butyl alcohol. It was recovered unchanged after 2·5 hours' heating with *p*-toluidine alone at 130°.

*Phenyl* N-*methylmesidino*-p-*methoxybenzyl ketone*, prepared from the related bromo-ketone and methylmesidine (Ullmann, *Annalen*, 1903, **327**, 110) in the usual way (Cowper and Stevens, *loc. cit.*), crystallised from alcohol in colourless needles, m. p. 89—90° (Found : N, 4·0. $C_{25}H_{27}O_2N$ requires N, 3·8%). It was unchanged after 5—6 hours' heating with methylmesidine and its hydrobromide at 170°; after 6 hours at 190° the only isolable product was a little nitrogen-free material, white, glittering laminæ from alcohol, m. p. 96—98°.

*Displacement*.—Phenyl α-anilino-*p*-methoxybenzyl ketone (II) or *p*-methoxyphenyl α-anilinobenzyl ketone (III) was heated at 115—120° for 3 hours with *p*-toluidine (3 mols.) and *p*-toluidine hydrobromide (0·5 mol.). Fractional crystallisation of the product from alcohol yielded in each case 75% of *p*-methoxyphenyl α-*p*-toluidinobenzyl ketone, m. p. and mixed m. p. 141—142°, and 25% of material, m. p. 115—117°, indistinguishable from a mixture of the toluidino-ketone with an equal quantity of (III).

*Simultaneous Rearrangement of* (II) *and Desylanthranilic Acid*.—The acid, from benzoin and anthranilic acid (Weckowicz, *Ber.*, 1908, **41**, 4144), crystallised from alcohol in cream-coloured plates, m. p. 225—227° (Found : N, 4·4. Calc. for $C_{21}H_{17}O_3N$ : N, 4·2%). Heated with aniline and aniline hydrobromide, it rapidly yielded desylaniline with some unchanged material. Equal weights of desylanthranilic acid and the ketone (II) were boiled for 3 hours in pyridine with pyridine hydrobromide. After addition of ether the filtered solution was extracted successively with sodium hydroxide solution and hydrochloric acid. The extracts yielded respectively desylanthranilic acid and the ketone (III), each in 90% yield, with no evidence of any other product. Three parts of (II) to one of desylanthranilic acid were used in another experiment with similar results. For comparison, *phenyl* α-(o-*carboxyanilino*)-p-*methoxybenzyl ketone*, $MeO{\cdot}C_6H_4{\cdot}CHBz{\cdot}NH{\cdot}C_6H_4{\cdot}CO_2H$, was prepared from benzanisoin and anthranilic acid : white needles, m. p. 198—199° (Found : N, 4·0. $C_{22}H_{19}O_4N$ requires N, 3·9%). With aniline and aniline hydrobromide it yielded (III).

"*Direct*" *Displacement of Arylamine Residues*.—Ethyl α-anilinophenylacetate (Stöckenius, *Jahresber.*, 1878, 780) was unaffected by boiling *p*-chloroaniline, but when *p*-chloroaniline and the ester were added successively to ethylmagnesium bromide in ether at room temperature (compare Hardy, *J.*, 1936, 398), α-*anilinophenylacet*-p-*chloroanilide* was obtained : long prisms from alcohol, m. p. 157—158° (Found : N, 8·6; Cl, 10·4. $C_{20}H_{17}ON_2Cl$ requires N, 8·3; Cl, 10·5%). The anilide was boiled for 3 hours with *p*-toluidine hydrobromide (0·5 mol.) in *p*-toluidine (3 mols.), and the mixture treated with ether and dilute hydrochloric acid. The tarry mass deposited by the acid layer afforded, after several crystallisations from ammoniacal alcohol, white needles, m. p. 183—185°. These were identical with α-p-*toluidinophenylacet*-p-*chloroanilide*, prepared in the same way as the anilino-compound (Found : N, 7·9. $C_{21}H_{19}ON_2Cl$ requires N, 8·0%). When methylaniline was used in place of *p*-toluidine, much non-basic material was formed and no individual product could be isolated.

Benzylaniline hydrobromide was boiled under reflux with *p*-toluidine (5 mols.) for 4 hours, and the basified mixture distilled in steam. The non-volatile material, with benzenesulphonyl chloride in pyridine, gave benzenesulphonbenzyl-*p*-toluidide (mixed m. p.) which depressed the m. p. of benzenesulphonbenzylanilide. Benzhydryl-*p*-toluidine (Busch and Rinck, *Ber.*, 1905, **38**, 1768) was unchanged by 3 hours' heating with aniline and aniline hydrobromide at 150°; treatment at 180—190° afforded an oil, b. p. 239—245°/15 mm., which gave no crystalline derivative.

*Indolisation*.—The ketone (II) was heated at 200° for 2·5 hours with aniline (3 mols.) and aniline hydrobromide (0·5 mol.), and the crude non-basic material distilled in a vacuum and crystallised from alcohol. 2-*Phenyl*-3-p-*methoxyphenylindole* (IV) formed colourless prisms, m. p. 188—190° (Found : N, 4·5. $C_{21}H_{17}ON$ requires N, 4·7%). The same product was obtained in small yield by heating (II) with pyridine hydrobromide (0·1 mol.) at 180° for 30 mins.; and was also synthesised by boiling with alcoholic hydrochloric acid *phenyl* p-*methoxybenzyl ketone phenylhydrazone*, prepared in alcohol–acetic acid as cream-coloured plates, m. p. 124—125° (Found : N, 8·7. $C_{21}H_{20}ON_2$ requires N, 8·8%).

The method first described was applied to the preparation of 2-*phenyl*-3-p-*methoxyphenyl*-5-*methylindole*, long prisms, m. p. 150—151° (Found : N, 4·8. $C_{22}H_{19}ON$ requires N, 4·5%), and of 2-*phenyl*-

3-p-*methoxyphenyl*-1-*methylindole*, needles, m. p. 131—133° (Found : N, 4·6%). The former was also synthesised by boiling phenyl *p*-methoxybenzyl ketone with *p*-tolylhydrazine in alcoholic hydrochloric acid for 3 hours; and for comparison 3-*phenyl*-2-p-*methoxyphenylindole* was prepared in like manner from *p*-methoxyphenyl benzyl ketone: needles, m. p. 140—142°, depressed by admixture with its isomeride (Found : N, 4·3%). The latter was synthesised by methylating (IV) as follows : To the indole (0·4 g.) in lukewarm acetone (6 c.c.) were added excess of powdered potassium hydroxide and, portionwise, methyl sulphate (1 c.c.). After 45 mins., the mixture was treated with water, and the product extracted with benzene and crystallised from alcohol.

When (II) was heated with pyridine hydrobromide in pyridine in a sealed tube at 200°, the only isolable product crystallised from alcohol in nitrogen-free plates, m. p. 94—96°; the related *p*-toluidinoketone similarly gave a nitrogen-free substance, m. p. 92—94°, mixed m. p. with its analogue, 79—85°.

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