The Interaction of Amines and α Halogeno-ketones.

T H E S I S

presented by

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Papers.

The Interaction of Amines and

α Halogeno-ketones.

Molecular Compounds of Certain

Thio-derivatives.

C O N T E N T S.

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GENERAL INTRODUCTION.

(A). Abnormal Reaction of ∝ bromo-ketones.

Stevens & McGeoch (1) discovered that w-bromo-w-benzyl acetophenone when treated with aniline yielded two isomeric products,

$$C_6H_5.CO.CH.(Br).CH_2.C_6H_5 \rightarrow \begin{cases} C_6H_5.CO.CH.(NH.C_6H_5).CH_2.C_6H_5 \\ C_6H_5.CH_2.CO.CH.(NH.C_6H_5).C_6H_5. \end{cases}$$

An analogous anomaly can be perceived in the reaction of ∝ -bromo ischexophenone with p-toluidine described by Wedekind & Bruch (2) where two isomeric products were isolated. One has been proved to be the corresponding p-toluidino isohexophenone, while the other, m.p. 112°C., has not yet been identified. Attempted reduction (3) failed to produce the expected ketone, the compound being quite stable to such treatment.

(B). Object of the Work.

Recently, however, I have discovered that this abnormal result reported by Stevens & McGeoch was not a function of the ∝ -bromo-ketone but a rearrangement of the ∝ -anilino ketone,

$$R'.CH.(NH.C_6H_5).CO.R \rightleftharpoons R'.CO.CH.(NH.C_6H_5).R$$

after its formation from the ∝ -bromo compound.

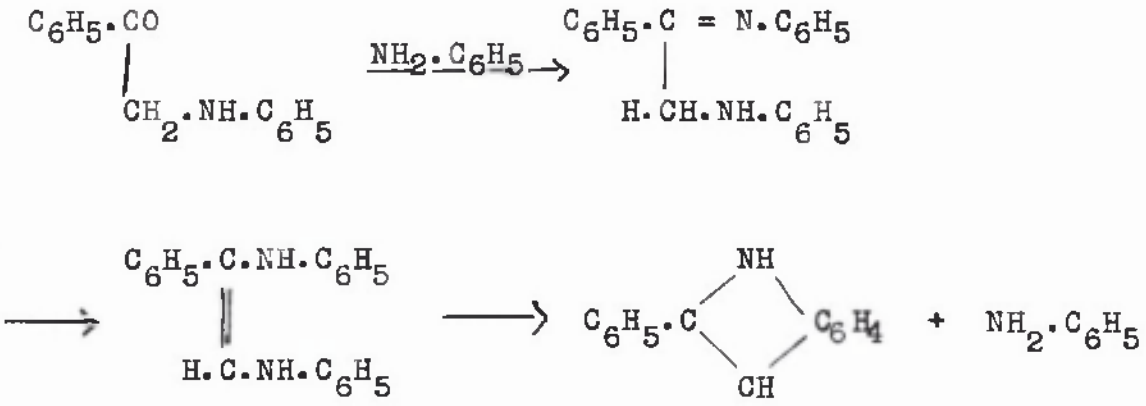
Consequently, by selecting suitable compounds and investigating them from different aspects governing

rearrangement, I have endeavoured to elucidate the mechanism of the reaction and, if possible, isolate intermediate products.

This has resulted in the division of the description of the work into chapters, outlined at the beginning, each having its own short introduction and discussion, leading to a general co-ordination of the principal experimental findings at the end.

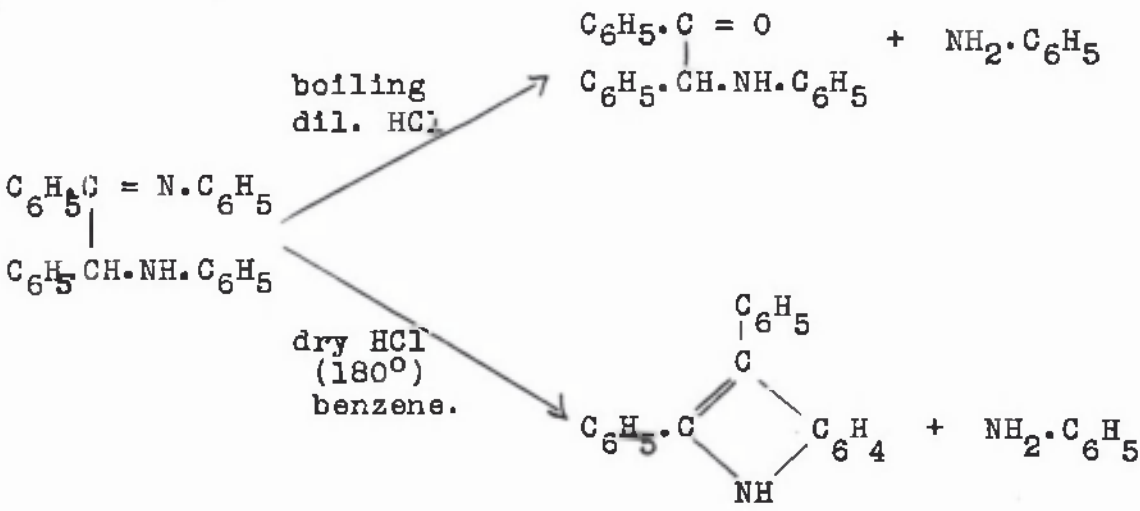
(C). Relation with Anil-anilides.

The apparently close relationship existing between this extraordinary phenomenon of rearrangement and the familiar behaviour of phenacyl aniline, by the intermediate formation of an anil-anilide, in giving 2 phenyl indole,



as postulated by Bischler (4), has been demonstrated by Strain (5). He showed that α-anilino desoxybenzoin

and 2:3 diphenyl indole could emanate from the same intermediate product (benzoin anil-anilide $C_6H_5.C = (N.C_6H_5).CH.(NH.C_6H_5).C_6H_5$) with loss of aniline by minute modification of the reaction conditions.

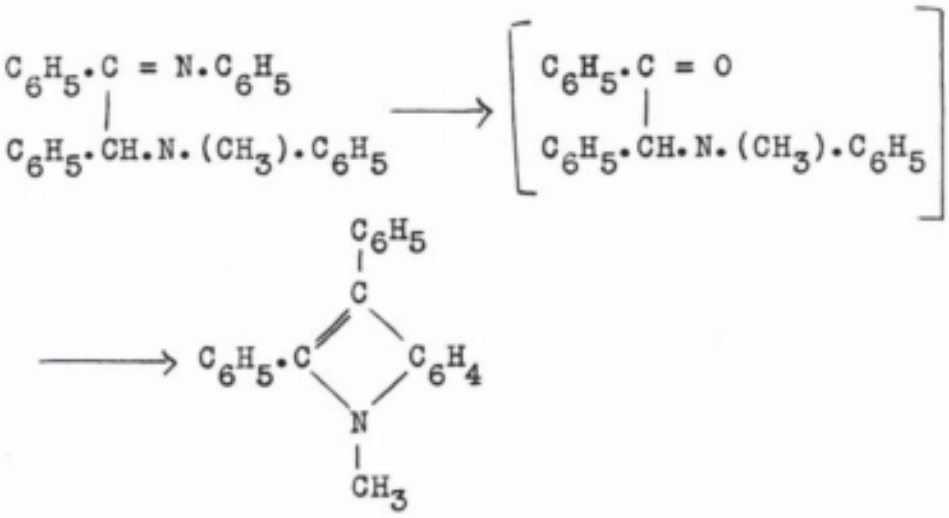


and deduced that a tautomeric parallel existed between these ammono benzoins (a) and the aquo-benzoins (benzoin) (b)

a) $C_6H_5.C = N.C_6H_5$ | $C_6H_5.CH.NH.C_6H_5$ ⟶ $C_6H_5.C.NH.C_6H_5$ ‖ $C_6H_5.C.NH.C_6H_5$ ⟶ $C_6H_5.CH.NH.C_6H_5$ | $C_6H_5.C = N.C_6H_5$

(b) $C_6H_5.C = O$ | $C_6H_5.CH.OH$ ⟶ $C_6H_5.C.OH$ ‖ $C_6H_5.C.OH$ ⟶ $C_6H_5.CH.OH$ | $C_6H_5.C = O$

Moreover, the work reported by Montagne & Garry (6) is significant in showing the production of α-methyl anilino ketone from benzoin anil-methyl anilide,



although the formation of 1 methyl 2:3 diphenyl indole might easily be dependent on the primary formation of amino ketone.

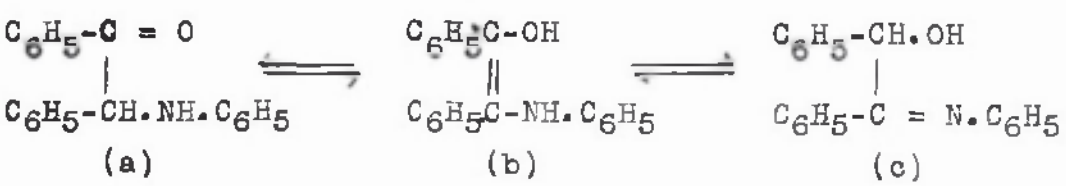
∝ Anilino p Methoxy Desoxybenzoin Series.

Introduction.

For some time there have been differences of opinion about the preparation and formulation of ∝ anilino desoxybenzoins. For example, Voigt (7), from benzoin and primary benzenoid amines, prepared desylanilides which he called "benzoinanidils" and formulated as the anils of benzoin ($C_6H_5.CH(OH)C(=NR).C_6H_5$).

Compounds possessing similar chemical and physical characteristics and believed to have the structure of anilides were prepared by Bischler and Fireman (8) from desyl chloride and primary aromatic amines by an analogous method to the one used by Mohlau (9) for the preparation of phenacyl aniline.

Japp & Murray (10) then noticed the close relationship which existed between these desyanilides of Bischler and the "benzoinanils" of Voigt. Accordingly they synthesised these compounds by the two respective methods and discovered that they were indistinguishable, formulating them as desyl-anilides (a) in agreement with their formation from desyl bromide.



On the other hand Lachowicz (11), like Voigt, believes that these compounds should have the structure represented by formula (c), while Strain (12) predicts that these two formulae are related by the transition formula (b), any one of them being derived from the other by the shift of a hydrogen atom analogous to the change which takes place in the keto-enol isomerism of aceto-acetic ester.

As a matter of fact, in the following experimental work, not only proof of the existence of tautomerism in these compounds has been obtained and their structure identified, but also a new conception of the mechanism of the formation of ∝ anilino ketones from ∝ hydroxy ketones and aniline has been established.

Later work on the preparation of desylanilides from ∝ hydroxy desoxybenzoins and primary benzenoid amines is due to Reddelien (13) who introduced a trace of zinc chloride to facilitate this condensation and to Knoevenagel (14) who used iodine as a catalyst in the reaction.

Experimental.

(A) Preparation from ∝ Halogeno-ketones and Amines.

As the method of preparing ∝ anilino ketones from ∝ halogeno ketones and aniline has been applied generally in this chapter, a complete outline of the method will be given at the beginning: thereafter, only brief reference will be made to it.

∝ Anilino p methoxy benzyl phenyl ketone (1) has been prepared from p methoxy benzyl phenyl ketone by the following series of reactions:-

$$CH_3O.C_6H_4.CH_2.CO.C_6H_5 \xrightarrow[\text{in ether}]{Br_2} CH_3O.C_6H_4.CH.(Br)CO.C_6H_5$$

$$\xrightarrow{NH_2.C_6H_5} CH_3O.C_6H_4.CH.(NH.C_6H_5).CO.C_6H_5$$
(1)

p Methoxy benzyl phenyl ketone.

Numerous syntheses of this compound were tried before any reasonable advance was made with the investigation. The chief difficulty was the persistently low yields of ketone from long laborious preparations, even the method used (15) displaying this feature. Nor did the pure compound itself decrease the difficulties already present, as it invariably darkened on standing (16), even in a stoppered bottle.

The reduction of benzanisoin (17) with tin and

hydrochloric acid in alcohol solution described by Buck & Ide (18) and repeated with less success by Jenkins (17), resulted in an even smaller yield of product usually contaminated by unchanged starting material, while the preparation by a Friedel & Crafts' reaction from p methoxy phenyl acetyl chloride and benzene (compare Buck & Ide (19)) was hampered by the failure to obtain p methoxy phenyl aceto-nitrile. Attempted preparation of this material from p methoxy benzyl chloride (20) and potassium cyanide in alcohol solution (compare Adams & Thal (21)) gave a colourless mobile liquid, b.p.$_{20\ mm.}$ 125 - 127°C., believed to be p methoxy benzyl ethyl ether. No reaction was observed when the solvent was eliminated.

A small yield of p methoxy phenyl acetic acid was obtained by reducing ∝ bromo p methoxy mandelic acid (22), but the quantity was quite inadequate for the continuation of the synthesis.

∝ Bromo p methoxy benzyl phenyl ketone.

To p methoxy benzyl phenyl ketone (13 g.) in ether (120 c.c.) containing a trace of $AlCl_3$ was added bromine (3 c.c.), gradually at first until the reaction started, more quickly when the solution was cooled. On complete addition of bromine the solution, after standing (30 min.), was shaken with water to remove the dissolved

hydrogen bromide. The separated ethereal layer was dried with sodium sulphate and the solvent removed at the pump. The crude product crystallised as white matted needles, m.p. 93°C. from petrol ether (b.p., 60 - 80°C.). The yield was 92%.

This material was originally prepared by Jenkins (23) in carbon tetrachloride solution using a 500 watt tungsten lamp.

The ∝ bromo compound (1 mol.) when heated with aniline (2 mols.) on the water bath for a few minutes, gave ∝ anilino p methoxy benzyl phenyl ketone (I). It was isolated by extraction of the reaction mixture with benzene, the precipitated aniline hydrogen bromide being filtered off. After distillation of the benzene at the pump the crude product crystallised from alcohol as pale yellow laminae, m.p. 135 - 136°C. They were sparingly soluble in alcohol, more soluble in benzene. Treatment in the former solvent with dilute hydrogen chloride gave soft white needles of amine hydrochloride which were insoluble in water. Analysis gave, 4.55% N; $C_{21}H_{19}O_2N$ requires, 4.41% N.

∝ p toluidino p methoxy benzyl phenyl ketone (II) was obtained from the ∝ bromo compound by treatment with p toluidine. It crystallised from alcohol in greenish yellow prisms, m.p. 119 - 120°C., which formed a hydrochloride, insoluble in water. Analysis gave, 4.42% N;

$C_{22}H_{21}O_2N$ requires, 4.23% N.

∝ Methyl anilino p methoxy benzyl phenyl ketone (III) was prepared from the corresponding ∝ bromo ketone by heating on the water bath with methyl aniline for 10 minutes. The crude product crystallised from alcohol as white needles, m.p., 118 - 119°C. Analysis gave, 4.31% N; $C_{22}H_{21}NO_2$ requires, 4.23% N.

∝ Anilino benzyl p methoxy phenyl ketone (IV) was prepared from ∝ bromo benzyl p methoxy phenyl ketone by heating with aniline. White needle crystals, m.p., 144 - 145°C., were deposited from alcohol solution.

$$CH_3O.C_6H_4.CO.CH(Br).C_6H_5 \xrightarrow{NH_2.C_6H_5} \underset{(IV)}{CH_3O.C_6H_4.CO.CH(NH.C_6H_5)C_6H_5}$$

The ∝ bromo benzyl p methoxy phenyl ketone (23) was obtained by brominating benzyl p methoxy phenyl ketone (19) in ether solution in the presence of $AlCl_3$ (vide supra).

∝ p Toluidino benzyl p methoxy phenyl ketone (V) prepared from the above ∝ bromo ketone and p toluidine, crystallised from alcohol as white prismatic needles, m.p., 142 - 143°C. Analysis gave, 4.34% N; $C_{22}H_{21}NO_2$ requires, 4.23% N.

∝ Methyl anilino benzyl p methoxy phenyl ketone (VI) formed by heating the corresponding ∝ bromo ketone with methyl aniline, crystallised from alcohol as long white

prisms, m.p., 160 - 161°C. Analysis gave 4.52% N; $C_{22}H_{21}NO_2$ requires, 4.23% N.

Chlorination of Benzanisoin.

$$CH_3O.C_6H_4.CO.CH.(OH).C_6H_5 \xrightarrow{SOCl_2} CH_3O.C_6H_4.CO.CH.(Cl).C_6H_5$$

To thionyl chloride (8 g.) in a cooled container was added gradually with stirring finely powdered benzanisoin (10 g.). After the reaction had subsided the mixture was poured into water and the product extracted with ether. On removal of the ether at the pump a brown syrup was obtained, which failed to crystallise. Nor did the customary methods of purification induce crystallisation, while distillation under reduced pressure decomposed the product.

However, treatment in the cold with twice the theoretical quantity of aniline produced (IV), proved by admixture. The yield was 50% of the theoretical.

(B). Preparation from ∝ Hydroxy Ketones and Amines.

Preparation of (I).

$$CH_3O.C_6H_4.CO.CH(OH).C_6H_5 \xrightarrow[P_2O_5]{NH_2.C_6H_5} CH_3O.C_6H_4.CH(NH.C_6H_5).CO.C_6H_5$$

Benzanisoin (cf. page 7) was heated with aniline (5 g.) and P_2O_5 (0.5 g.) for 1½ hours on the water bath, when the brown syrup gradually solidified to a yellow mass.

This was dissolved in alcohol, the insoluble phosphorous compounds being separated by filtration. On cooling, the filtrate deposited yellow nodules which, after washing with caustic soda (dilute), crystallised from alcohol as yellow laminae, m.p., 135 - 136°C. Admixture with (I) proved them to be identical. The yield was 95% of the theoretical.

N.B. This convenient method of preparation of (I) was finally adopted in preference to the more laborious and somewhat uncertain synthesis from the ∝ bromo ketone and aniline already described (page 7).

Preparation of (II).

(II) was prepared from benzanisoin and p toluidine by an analogous synthesis

$$CH_3O.C_6H_4.CO.CH(OH).C_6H_5 \xrightarrow[P_2O_5]{NH_2.C_6H_4.CH_3} CH_3O.C_6H_4.CH(NH.C_6H_4.CH_3).CO.C_6H_5$$
(II)

It crystallised from alcohol as greenish yellow prisms, m.p., 118 - 119°C. Admixture proved this compound to be identical with (II), synthesised from the ∝ bromo ketone and aniline.

Preparation of (III).

Attempted preparations of this compound from benzanisoin and methyl aniline with P_2O_5 were unsuccessful, the starting product being recovered after each operation. Temperatures at intervals of 20° to a maximum of 170°C. were used.

However, a more convenient method of preparation was found to replace the present protracted synthesis (page 10).

$$CH_3O.C_6H_4.CH(NH.C_6H_5).CO.C_6H_5 \xrightarrow{(CH_3)_2SO_4} CH_3O.C_6H_4.CH.\underset{(III)}{(N.(CH_3).C_6H_5)}.C_6H_5.$$

6 g. of (I), prepared from benzanisoin, were heated on the water bath with dimethyl sulphate (3 g.) in benzene (10 c.c.). At short intervals small portions of solid Na_2CO_3 were added until effervescence ceased (2 hours), the final mixture being poured into ice cold water, when a greenish yellow benzene layer was obtained. On separation of this layer and drying with anhydrous Na_2SO_4, followed by removal of the benzene at the pump, an oil, which readily crystallised from alcohol as white needles, m.p., 118 - 119°C., was obtained. Admixture with a pure sample of (III) showed no depression of the melting point.

Preparation of (IV).

$$CH_3O.C_6H_4.CH(OH).CO.C_6H_5 \xrightarrow[P_2O_5]{NH_2.C_6H_5} CH_3O.C_6H_4.CO.CH.(NH.C_6H_5).C_6H_5.$$
(IV)

Anisbenzoin, prepared as described by Asahina & Terasake (24) from p methoxy mandelonitrile and phenyl magnesium bromide, was treated with aniline in the presence of P_2O_5 (vide supra), when white needle crystals, m.p., 142 - 144°C. were deposited from alcohol. Mixed melting point determination proved them to be identical with (IV), synthesised from the corresponding ∝ bromo ketone and aniline.

(C). Reduction.

Reduction of (I).

$$CH_3O.C_6H_4.CH.(NH.C_6H_5).CO.C_6H_5 \xrightarrow[H_2SO_4]{Zn\ \&} CH_3O.C_6H_4.CH_2.CO.C_6H_5.$$
(I)

(I) was heated for 2 - 3 hours on the water bath with zinc dust and 20% H_2SO_4 and the solution was filtered hot. On cooling, the filtrate was extracted several times with ether, the combined ethereal layers being dried with anhydrous Na_2SO_4. On removal of the solvent at the pump the remaining dark oil crystallised

from alcohol as white plates, m.p., 93 - 94°C. These showed no depression on admixture with a pure sample of p methoxy benzyl phenyl ketone (15). The yield was 50% of the theoretical.

Reduction of (IV).

$$CH_3O.C_6H_4CO.CH(NH.C_6H_5).C_6H_5 \xrightarrow{Zn + H_2SO_4} CH_3O.C_6H_4.CO.CH_2.C_6H_5.$$
(IV)

(IV) was reduced by the same method as described above. White glistening plates, m.p., 75 - 76°C., which showed no depression on admixture with pure p methoxy phenyl benzyl ketone (20), were obtained from alcohol solution.

This method of reduction could not only be applied to the preparation of isomeric p methoxy desoxybenzoins from their corresponding ∝ anilino compounds, but also could be used as a means of determining their structure.

Discussion.

A New Conception of the Mechanism of the Formation of ∝ Anilino Ketones from ∝ Hydroxy Ketones and Amines.

It is generally known that symmetrical benzoins when treated with primary benzenoid amines under suitable conditions produce ∝ anilino desoxybenzoins (cf. page 5), and it seems that there is some doubt as to the mechanism of condensation.

Recently, however, I have found that the reaction of aniline with benzanisoin takes place at the keto group thus:-

$$CH_3O.C_6H_4CO.CH(OH)C_6H_5 \xrightarrow{NH_2C_6H_5} CH_3O.C_6H_4CH(NH.C_6H_5).CO.C_6H_5$$
(I)

to give (I), whose structure has been proved by reduction to p methoxy benzyl phenyl ketone,

$$CH_3O.C_6H_4.CH(NH.C_6H_5).CO.C_6H_5 \xrightarrow[zinc + H_2SO_4]{reductn.} CH_3O.C_6H_4.CH_2.CO.C_6H_5$$
(I)

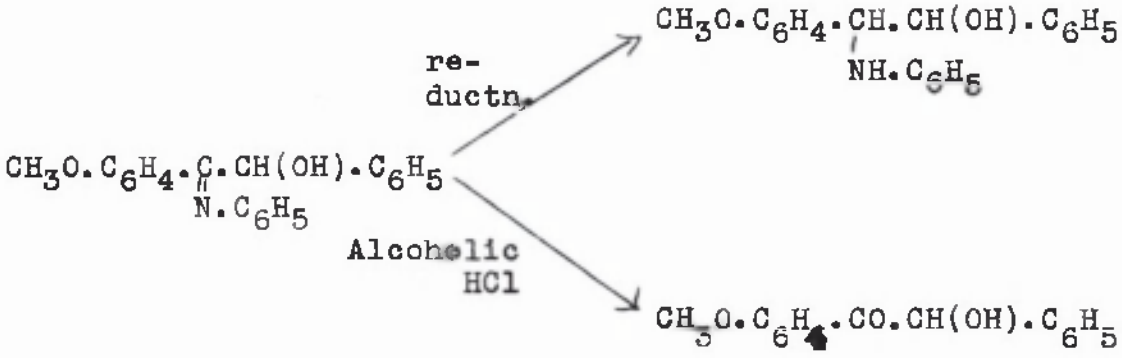
and by synthesis from ∝ bromo p methoxy benzyl phenyl ketone and aniline

$$CH_3O.C_6H_4.CH(Br).CO.C_6H_5 \xrightarrow{NH_2C_6H_5} CH_3O.C_6H_4.CH(NH.C_6H_5).CO.C_6H_5$$
(I)

It is formulated as an ∝ anilino ketone (8), (10), a fact which is further substantiated by its facile formation of

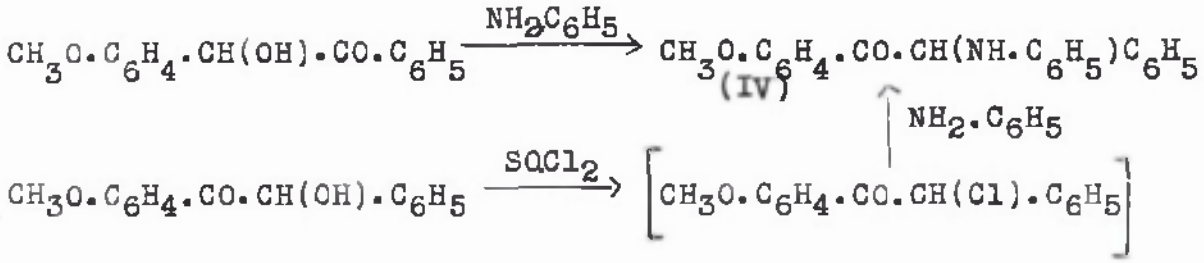
an insoluble hydrochloride.

If it were an anil-alcohol, (7), (11), of the formula as shown herewith,

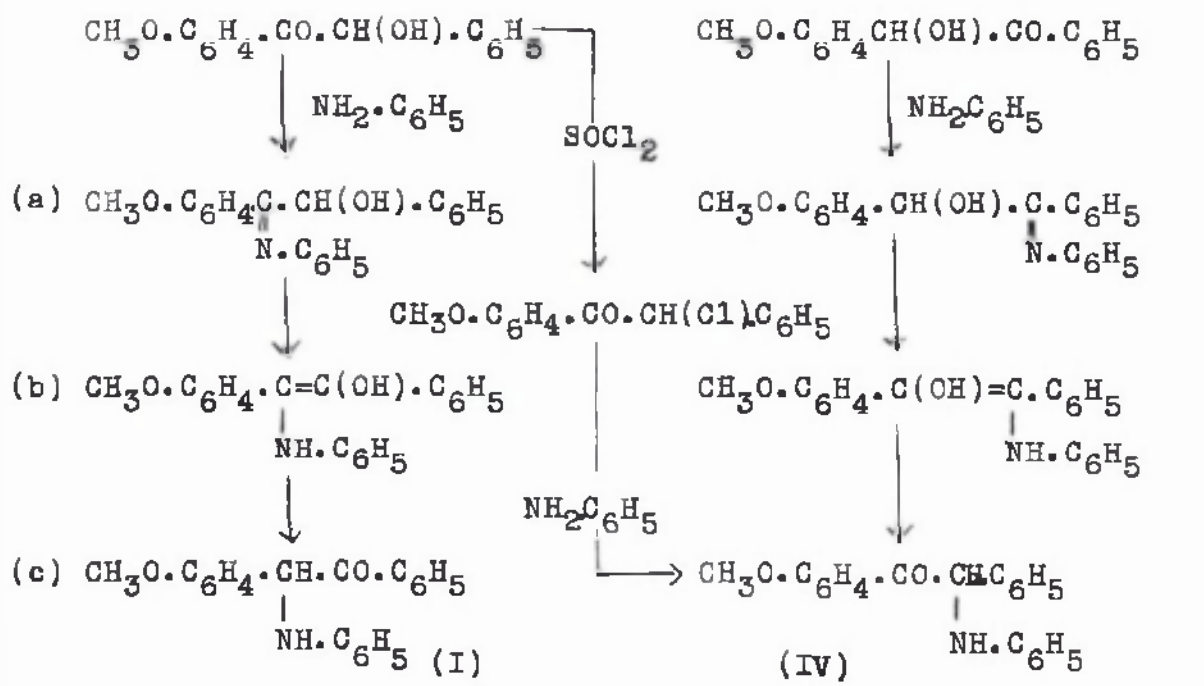


reduction might take place primarily at the C = N group, while aqueous alcoholic hydrogen chloride treatment would produce hydrolysis to the original ketone. As already stated, neither of these predictions have been fulfilled experimentally. At the same time, however, the existence of imino-enamine, keto-enol tautomerism cannot be excluded.

Further conclusive evidence which has definitely established the conception of the mechanism of the formation of these ∝ anilino ketones was obtained when anisbenzoin, the isomer of benzanisoin, was condensed with aniline to give (IV), while direct chlorination of benzanisoin with thionyl chloride, followed by treatment with aniline, produced the same secondary base,

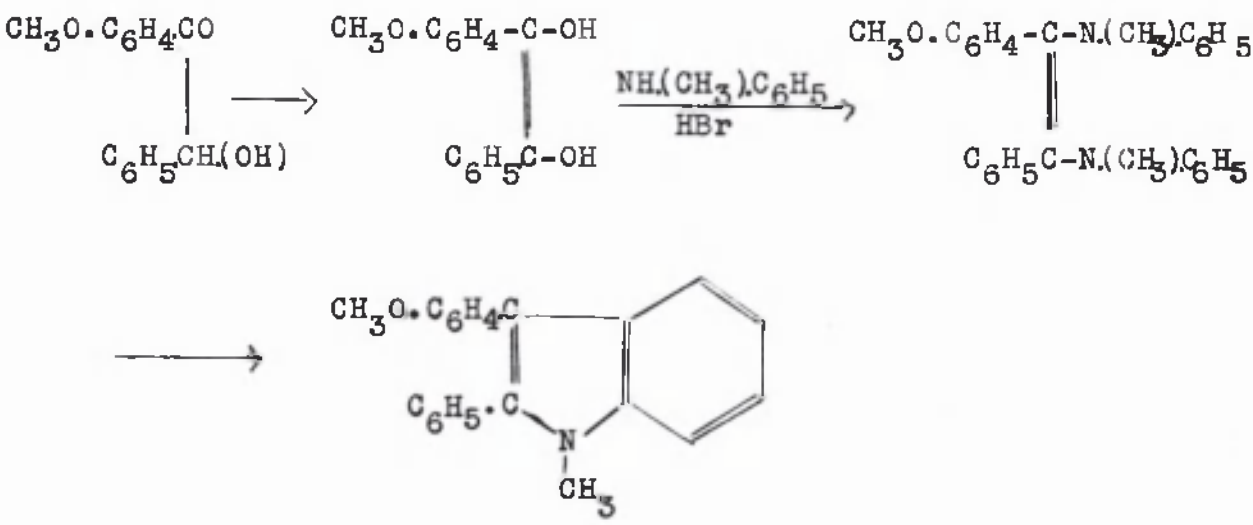


The mechanism by which these condensations occur can be readily explained by assuming that the anil-alcohol (a) after formation, undergoes an imino-enamine change to produce the ∝ anilino β hydroxy p methoxy stilbene (b) which on keto-enol isomerism forms the ∝ anilino ketone (c).

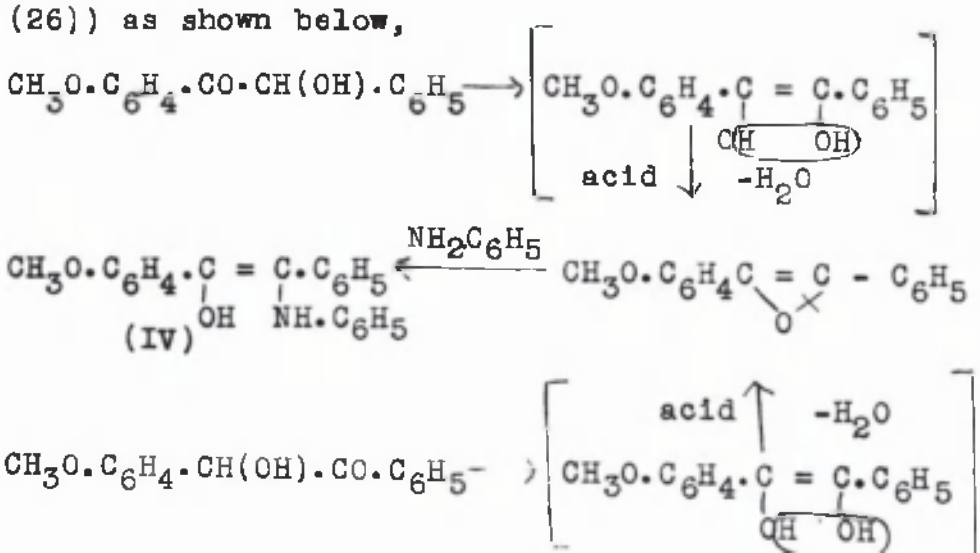


This aspect of the condensation also explains why benzanisoin does not react with methyl aniline, even at higher temperatures (170°C.), to give the respective

tertiary base. The formation of the respective methyl indole (page 42) could be caused by the primary isomerism to $\alpha\beta$ dihydroxy p methoxy stilbene, preceded by di-anilide formation, which on losing methyl aniline gives 1 methyl 2 phenyl 3 p methoxy phenyl indole.



Attempts to use the alternative conception that benzanisoin and anisbenzoin respectively enolise first, followed by the loss of water to produce the same oxide ring (compare (25)) which reacts with aniline (compare (26)) as shown below,



to give either (IV) or the same mixture of (I) and (IV) is disproved by the isolation of different bases (I) and (IV) exclusively from benzaniscin and anisbenzoin respectively.

Appendix.

Preparation of ω Bromo Acetophenone.

$C_6H_5.CO.CH_3 + Br_2 \longrightarrow C_6H_5.CO.CH_2.Br + HBr.$

To a solution of 200 g. of acetophenone in 200 c.c. of sodium dried ether contained in a dry pressure flask, cooled in ice, are added first 0.5 g. aluminium chloride, then 267 g. bromine. The bromine is added gradually from a dropping funnel at the rate of 1-2 c.c. per minute with occasional shaking. Throughout the bromine is decolourised and hydrogen bromide given off, although towards the end of the reaction the solution is coloured pink.

On complete addition the ether and absorbed hydrogen bromide are removed at the pump in a stream of air, when the phenacyl bromide comes out as a solid mass of brownish yellow crystals. These on shaking with a mixture of water and petroleum ether (20 c.c. each) are rendered white immediately and are filtered off. The yield is 320 g. (97 - 98%) and the m.p. 48 - 50°C.

This method has been applied successfully to the bromination of the isomeric p methoxy desoxybenzoins and α benzyl benzyl p methoxy phenyl ketone.

Methods of Preparation.

W bromo acetophenone has been prepared from bromine and acetophenone (27) in CS_2 solution (28), (29), in acetic acid solution (30), (31), (32), and in aqueous solution (33). It has also been prepared from bromo acetyl chloride and benzene by a Friedel & Crafts' reaction (34) and from benzoyl bromide and diazomethane (35). The present method is based on the method of preparing bromo-desoxybenzoin from bromine and desoxybenzoin (36).

Rearrangement of ∝ Anilino p Methoxy Desoxybenzoins.

Introduction.

In the following experimental survey it will be found that the investigation of the rearrangement of ∝ anilino p methoxy benzyl phenyl ketone (I)

$$\underset{\text{(I)}}{CH_3O.C_6H_4.CH(NH.C_6H_5).CO.C_6H_5} \xrightarrow{NH_2.C_6H_5} \underset{\text{(IV)}}{CH_3O.C_6H_4.CO.CH(NH.C_6H_5)C_6H_5}$$

to ∝ anilino benzyl p methoxy phenyl ketone (IV) has been pursued from three closely associated aspects,

(A) the rearrangement of labile amine (I) to its stable isomer (IV),

(B) the rearrangement of labile amine (I) and displacement of base to produce an isomeric homologue (V)

$$\underset{\text{(I)}}{CH_3O.C_6H_4.CH.(NH.C_6H_5).CO.C_6H_5} \xrightarrow{NH_2.C_6H_4.CH_3} \underset{\text{(V)}}{CH_3O.C_6H_4.CO.CH.(NH.C_6H_4.CH_3).C_6H_5}$$

(C) the rearrangement by an intramolecular mechanism.

At the same time, no theoretical predictions are assumed by this convenient arrangement: it can best be regarded as a means of classification for ease of reference and discussion.

Moreover, since the method of isolation of the products from the various reactions can be applied generally, due to the closely associated chemical characteristics of these compounds, and since the conditions of rearrangement cited in the first instance will be adopted as a standard for purposes of comparison, only necessary important variations from this data will be duly reported in the course of the monograph.

Experimental.

(A). Rearrangement of (I).

$$CH_3O.C_6H_4.CH.(NH.C_6H_5).CO.C_6H_5 \xrightarrow[115^\circ C.]{NH_2.C_6H_5} CH_3O.C_6H_4.CO.CH.(NH.C_6H_5).C_6H_5$$

(I) (IV)

1 mol. of (I) was heated with aniline (3 mols.) and aniline hydrobromide (½ mol.) for 3 hours at 115 - 120°C. The reaction mixture on cooling was treated with dilute hydrochloric acid and extracted with ether; the combined acid layers on standing depositing long needle crystals of amine hydrochloride. The free base, m.p., 115 - 125°C., was regenerated by treatment with alcoholic ammonia and on crystallisation from alcohol gave white needles, m.p., 143 - 144°C. Admixture with a pure sample of (IV) proved them to be identical.

It reduced with zinc dust and 20% H_2SO_4 to p methoxy phenyl benzyl ketone (page 14).

The total yield of (IV) isolated was 85%: no trace of (I) could be found in the mother liquors.

By dissolution of the original reaction mixture in alcohol the final product could be readily obtained but the yield was much smaller, quite insufficient for confirmatory evidence of the irreversibility of the reaction.

Attempted rearrangement of (IV).

$$CH_3O.C_6H_4.CO.CH.(NH.C_6H_5).C_6H_5 \xrightarrow[170^{\circ}C.]{NH_2.C_6H_5} \text{(IV) unchanged}$$
(IV)

When (IV) was heated with aniline, aniline hydrobromide for 3 hours at 115 - 120°C. no evidence of rearrangement was observed, the starting material being recovered unchanged.

Graduated increase at intervals of 10°C. to a maximum of 170°C. failed to produce any change. When the temperature was raised above 170°C. indolisation (page 41) began and complicated the issue.

Rearrangement of (II).

$$CH_3O.C_6H_4.CH.(NH.C_6H_4.CH_3).CO.C_6H_5 \xrightarrow[115^{\circ}C.]{NH_2.C_6H_4.CH_3}$$
(II)

$$CH_3O.C_6H_4.CO.CH.(NH.C_6H_4.CH_3).C_6H_5$$
(V)

(II) rearranged to (V) when heated in p toluidine p toluidine hydrobromide solution at 115°C. for 3 hours, proved by admixture with a pure sample of (VI) and reduction with zinc dust and 20% H_2SO_4 to p methoxy phenyl benzyl ketone (page 14). No trace of starting material was observed in the mother liquors, 85% of product being isolated.

Attempted rearrangement of (V).

(V), like its homologue (IV), failed to rearrange even when heated to 170°C. for prolonged periods. In each instance the starting material was recovered.

Attempted rearrangement of (III).

$$CH_3O.C_6H_4.CH.(N.(CH_3).C_6H_5).CO.C_6H_5 \xrightarrow[170^\circ C.]{HN.(CH_3).C_6H_5} \text{(III) unchanged.}$$
(III)

When (III) was heated with methyl aniline, methyl aniline hydrobromide no rearrangement occurred. Increase of temperature to 170°C. for prolonged periods merely produced tarry products from which unchanged product (III) was with difficulty isolated.

Attempted rearrangement of (VI).

$$CH_3O.C_6H_4.CO.CH(N(CH_3).C_6H_5)C_6H_5 \xrightarrow[170^\circ C.]{HN.(CH_3).C_6H_5} \text{(VI) unchanged}$$
(VI)

Like its isomer (III), (VI) did not rearrange when heated with methyl aniline, methyl aniline hydrobromide. The maximum temperature was limited to 170°C. by the formation of indole.

α Methyl mesidino p methoxy benzyl phenyl ketone.

By the substitution of methyl groups in the ortho position to the N atom in the amine nucleus, it was hoped that indolisation would be prevented and permit the

investigation of tertiary amines at higher temperatures than those already experienced by the ∝ methyl anilino p methoxy desoxybenzoins, (III) and (VI).

For this purpose the labile ∝ methyl mesidino compound was synthesised from ∝ bromo p methoxy benzyl phenyl ketone and methyl mesidine (37).

$$CH_3O.C_6H_4.CH.(Br).CO.C_6H_5 \xrightarrow{NH.(CH_3).C_6H_2(CH_3)_3} CH_3O.C_6H_4.CH.\left[N.(CH_3).C_6H_2.(CH_3)_3\right]CO.C_6H_5$$

It crystallised from alcohol as white needle crystals, m.p., 89 - 90°C. Analysis gave, 4.00% N; $C_{25}H_{27}NO_2$ requires, 3.83% N.

When heated with methyl mesidine, methyl mesidine hydrobromide at 170°C. for 5 - 6 hours, the compound was unaffected. However, by prolonged heating (6 hours) at 190°C. a non-nitrogenous product was isolated from the ethereal extract. The crude material crystallised from alcohol in white glistening laminae, m.p., 96 - 98°C. The absence of nitrogen in this compound was determined qualitatively as well as quantitatively.

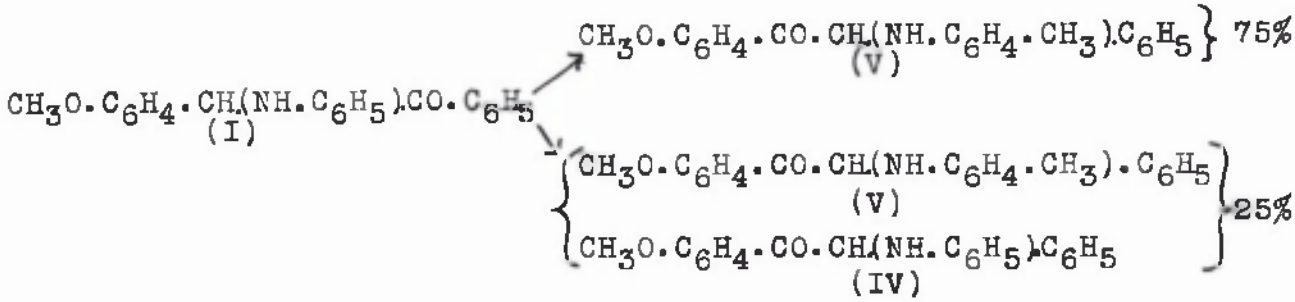
This unfortunate result coupled with the difficulty of obtaining a small quantity of degradation product sufficient for a complete analysis were decisive factors in abandoning the investigation of the rearrangement of tertiary amines using this compound.

TABLE I.

	Compound	Solvent	Result
(a)	$CH_3O.C_6H_4.CH(NH.C_6H_5).CO.C_6H_5$ (I)	Aniline, aniline hydrobromide	$CH_3O.C_6H_4.CO.CH(NH.C_6H_5).C_6H_5$ (IV)
(b)	$CH_3O.C_6H_4.CO.CH(NH.C_6H_5).C_6H_5$ (IV)	" " "	unchanged (170°) (IV)
(c)	$CH_3O.C_6H_4.CH(NH.C_6H_4.CH_3).CO.C_6H_5$ (II)	p toluidine, p toluidine hydrobromide	$CH_3O.C_6H_4.CO.CH(NH.C_6H_4.CH_3)C_6H_5$ (V)
(d)	$CH_3O.C_6H_4.CO.CH(NH.C_6H_4.CH_3).C_6H_5$ (V)	" "	unchanged (170°) (V)
(e)	$CH_3O.C_6H_4.CH[N.(CH_3).C_6H_5]CO.C_6H_5$ (III)	methyl aniline, methyl aniline hydrobromide	unchanged (170°) (III)
(f)	$CH_3O.C_6H_4.CO.CH.[N.(CH_3)C_6H_5].C_6H_5$ (VI)	" " "	" " (VI)
(g)	$CH_3O.C_6H_4.CH[N(CH_3).C_6H_2(CH_3)_3]CO.C_6H_5$	methyl mesidine, methyl mesidine hydrobromide	unchanged (170°) 190°C. (degradation product)

(B) Rearrangement and Displacement.

(a) Rearrangement and displacement of (I).



When (I) (1 mol.) was heated with p toluidine (3 mols.) and p toluidine hydrobromide (½ mol.) for 3 hours at 115 - 120°C. and the products isolated by acid extraction, two compounds were isolated on fractional crystallisation from alcohol. The first fraction consisted of (V), 75%, m.p., 141 - 142°C., proved by admixture with a pure sample. The remaining 25% was found to be an isomorphous mixture of (IV) and (V), m.p., 115 - 117°C.

Indirect proof of the composition of this isomorphous mixture was obtained by preparing a 50% melt of (IV) and (V) and crystallising it from alcohol. White prisms, m.p., 116 - 117°C., which showed no depression on admixture with the previous compound, were deposited.

(b) Displacement of (IV).

Results which were indistinguishable from those already described were obtained when (IV) was heated with p toluidine, p toluidine hydrobromide. 75% of (V) and an isomorphous mixture of (IV) and (V), 25%, were isolated.

(c) Rearrangement and displacement of (V).

$$CH_3O.C_6H_4.CH(NH.C_6H_4.CH_3).CO.C_6H_5 \rightarrow \begin{cases} CH_3O.C_6H_4.CO.CH(NH.C_6H_5)C_6H_5 \text{ (IV)} & 75\% \\ \left.\begin{matrix} CH_3O.C_6H_4.CO.CH(NH.C_6H_5)C_6H_5 \text{ (IV)} \\ CH_3O.C_6H_4.CO.CH(NH.C_6H_4.CH_3).C_6H_5 \text{ (V)} \end{matrix}\right\} & 25\% \end{cases}$$

When (II) was heated with aniline, aniline hydrobromide, 75% of (IV) and 25% of an isomorphous mixture described above, were isolated from the reaction solution. Admixture proved the identity of the materials.

(d) Displacement of (V).

When (V) was heated with aniline, aniline hydrobromide in the customary manner 75% of (IV) and 25% of an isomorphous mixture of (IV) and (V), the nature of which has already been discussed, was isolated.

(e) Attempted rearrangement and displacement of (III).

Neither rearrangement nor displacement was observed when (III) was heated with aniline, aniline

hydrobromide and p toluidine, p toluidine hydrobromide solutions respectively. Even heating at 170°C. for prolonged periods failed to produce different results. The reaction mixture merely darkened and produced tarry mixtures difficult to purify. In each case the starting material was isolated, decreasing in quantity with rise of temperature.

(f) Similar results were obtained when (VI) was used as the tertiary amine.

(g) Displacement of desyl aniline.

$$C_6H_5.CO.CH(NH.C_6H_5)C_6H_5 \xrightarrow{CH_3.C_6H_4.NH_2} \left\{ \begin{array}{l} C_6H_5.CO.CH(NH.C_6H_5).C_6H_5 \\ C_6H_5.CO.CH(NH.C_6H_4.CH_3).C_6H_5 \end{array} \right\} 50\%$$

When desyl aniline (14) (1 mol.) was heated with p toluidine (2 mols.) and p toluidine hydrobromide ($\frac{1}{2}$ mol.) for 3 hours at 115 - 120°C. an isomorphous mixture of desyl aniline and desyl p toluidine was obtained. Yellow prisms, m.p., 124 - 130°C. were deposited from alcohol solution.

(h) The same isomorphous mixture was obtained when desyl p toluidine (14) was heated with aniline, aniline hydrobromide under the same conditions. Admixture of these two products showed no depression in m.p., (126 - 131°C.).

TABLE II.

No.	Compound	Heated with	Products
(a)	$CH_3O.C_6H_4.CH(NH.C_6H_5)CO.C_6H_5$ (I)	p toluidine, p toluidine hydrobromide	$CH_3O.C_6H_4.CO.CH(NH.C_6H_4.CH_3)C_6H_5$ (V) 75% $CH_3O.C_6H_4.CO.CH(NH.C_6H_5)C_6H_5$ (IV) $CH_3O.C_6H_4CO.CH(NH.C_6H_4.CH_3)C_6H_5$ (V) } 25%
(b)	$CH_3O.C_6H_4.CO.CH(NH.C_6H_5)C_6H_5$ (IV)	" "	ditto
(c)	$CH_3O.C_6H_4.CH(NH.C_6H_4.CH_3)CO.C_6H_5$ (II)	aniline, aniline hydrobromide	$CH_3O.C_6H_4.CO.CH(NH.C_6H_5)C_6H_5$ (IV) 75% $CH_3O.C_6H_4.CO.CH(NH.C_6H_4.CH_3)C_6H_5$ (V) $CH_3O.C_6H_4.CO.CH(NH.C_6H_5)C_6H_5$ (IV) } 25%
(d)	$CH_3O.C_6H_4.CO.CH(NH.C_6H_4.CH_3)C_6H_5$ (V)	" "	ditto
(e)	$CH_3O.C_6H_4.CH[N(CH_3)C_6H_5]CO.C_6H_5$ (III)	" "	unchanged
(f)	$CH_3O.C_6H_4.CO.CH[N(CH_3)C_6H_5]C_6H_5$ (VI)	" "	"
(g)	$C_6H_5.CH(NH.C_6H_5)CO.C_6H_5$	p toluidine, p toluidine HBr	$C_6H_5.CH(NH.C_6H_5)CO.C_6H_5$ $C_6H_5.CH(NH.C_6H_4.CH_3)CO.C_6H_5$ }
(h)	$C_6H_5.CH(NH.C_6H_4.CH_3)CO.C_6H_5$	aniline, aniline HBr	ditto

(C). Intramolecular Rearrangement.

(a) Rearrangement in methyl aniline, methyl aniline hydrobromide solution.

When (I) was heated in methyl aniline, methyl aniline hydrobromide solution, the product isolated was (IV)

$$\underset{\text{(I)}}{CH_3O.C_6H_4CH(NH.C_6H_5).CO.C_6H_5} \xrightarrow{NH(CH_3).C_6H_5} CH_3O.C_6H_4.CO.\underset{\text{(IV)}}{CH(NH.C_6H_5).C_6H_5}$$

This extraordinary result which is contradictory to the theoretical postulations on the mechanism of the reaction was repeated by (II), giving (V)

$$\underset{\text{(II)}}{CH_3O.C_6H_4.CH(NH.C_6H_4.CH_3).CO.C_6H_5} \xrightarrow[+\ HBr]{NH(CH_3).C_6H_5} CH_3O.C_6H_4.CO.\underset{\text{(V)}}{CH(NH.C_6H_4CH_3).C_6H_5}$$

(b) As a matter of fact this peculiar phenomenon suggested the use of pyridine, (b.p. 115°C.) pyridine hydrobromide as a medium in which rearrangement could be accomplished. In this instance the solution was boiled for 3 hours. The results were striking; not only did rearrangement of the above compounds occur but the reaction solution showed little tendency to darken, a property common to both primary and secondary amine media.

(c) Furthermore, rearrangement of (I) and (II) could easily be performed in n butyl alcohol solution (b.p. 118°C.) containing pyridine hydrobromide, or pyridine hydrogen sulphate.

(d) Rearrangement of a mixture of two secondary amines in pyridine, pyridine hydrobromide.

Final and convincing evidence that intramolecular rearrangement was an accomplishment in this series was obtained when a mixture of ∝ anilino p methoxy benzyl phenyl ketone (I) and ∝ (O) carboxy anilino desoxybenzoin were rearranged simultaneously in the same medium without any evidence of the displacement of amine in one, by the amine in the other

$$\left.\begin{matrix} CH_3O.C_6H_4.CH(NH.C_6H_5).C_6H_5 \\ C_6H_5.CO.CH(NH.C_6H_4.COOH).C_6H_5 \end{matrix}\right\} \xrightarrow[\text{pyridine HBr}]{\text{pyridine}} \left\{\begin{matrix} CH_3O.C_6H_4.CO.CH(NH.C_6H_5).C_6H_5 \\ C_6H_5.CO.CH(NH.C_6H_4.COOH).C_6H_5 \end{matrix}\right.$$

1 g. of the former compound was boiled with 1 g. of the latter in pyridine, pyridine hydrobromide solution for 3 hours. When cold, the reaction mixture was dissolved in ether, the separated pyridine hydrobromide being filtered off. The ether solution was first extracted several times with dilute caustic soda to remove the acidic compounds, then with dilute hydrochloric acid to obtain the basic materials.

By acidification of the alkaline layers, a compound which readily crystallised from alcohol as cream plates was obtained. This was proved by admixture to be ∝(o) carboxy anilino desoxybenzoin, melting point, 225 - 227°C., (found, 4.42% N; $C_{21}H_{17}O_3N$ requires 4.23% N), while, on basification of the hydrochloride which crystallised from the acid layer, the rearranged compound (IV) was isolated.

In each case 90% of crude products was isolated. When purified 75 - 80% of pure materials was obtained.

These results were duplicated, using three times the weight of <u>∝ anilino p methoxy benzyl phenyl ketone</u> with respect to the weight of <u>∝ (o) carboxy anilino desoxybenzoin.</u>

<u>∝(o) carboxy anilino desoxybenzoin</u>. prepared from benzoin and anthranilic acid, readily exchanges when heated with aniline, aniline hydrobromide to give partially desyl aniline and partially unchanged starting material.

<u>∝(o) carboxy anilino p methoxy benzyl phenyl ketone</u>,

$$CH_3O.C_6H_4CH(NH.C_6H_4.COOH)CO.C_6H_5 \xrightarrow[\text{aniline HBr}]{\text{aniline}} CH_3O.C_6H_4.CO.CH(NH.C_6H_5)C_6H_5$$

prepared from benzanisoin and anthranilic acid (vide infra),

white needles, m.p., 198 - 199°C. (analysis gave 4.01% N, calculated 3.87% N), showed simultaneous rearrangement and displacement when heated with aniline, aniline hydrobromide.

TABLE III.

	Compounds	heated with	Products.
(a)	$CH_3O.C_6H_4.CH(NH.R).CO.C_6H_5$ [R = phenyl, tolyl]	methyl aniline, methyl aniline hydrobromide	$CH_3O.C_6H_4.CO.CH(NHR).C_6H_5$
(b)	$CH_3O.C_6H_4.CH(NHR)CO.C_6H_5$	pyridine, pyridine hydrobromide	$CH_3O.C_6H_4.CO.CH(NHR).C_6H_5$
(c)	"	n butyl alcohol, pyridine HBr or pyridine hydrogen sulphate	"
(d)	$CH_3O.C_6H_4.CH(NH.C_6H_5).CO.C_6H_5$ + $C_6H_5.CO.CH(NH.C_6H_4.COOH)C_6H_5$	pyridine, pyridine hydrogen bromide	$CH_3O.C_6H_4.CO.CH(NH.C_6H_5).C_6H_5$ + $C_6H_5.CO.CH(NH.C_6H_4.COOH).C_6H_5$ (75-80%)

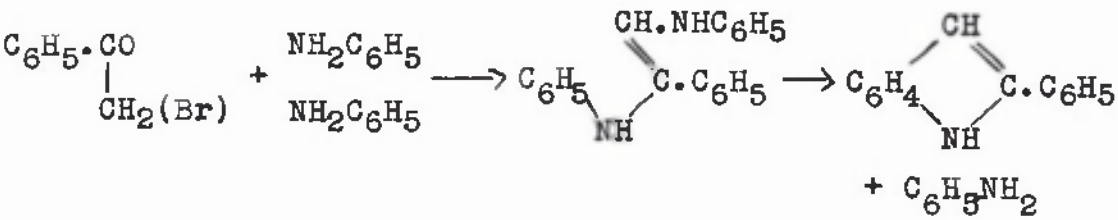
Preparation of Indoles from ∝ Anilino p Methoxy Desoxybenzoins.

Introduction.

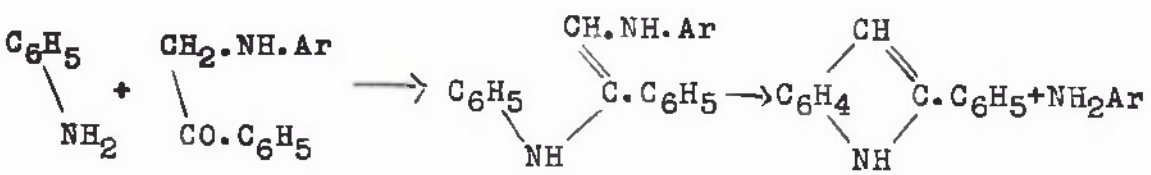
Staedel (38) by the action of ammonia upon phenacyl bromide obtained dihydrodiphenyl pyrazine "isoindole" (39).

However, when treated with aniline this compound gives ∝ phenyl indole (40) not "diphenyl diisoindole" (41) nor even the β isomeride (42) as one might expect.

This curious result was explained by Bischler (43) who believed that an anil anilide was first formed.

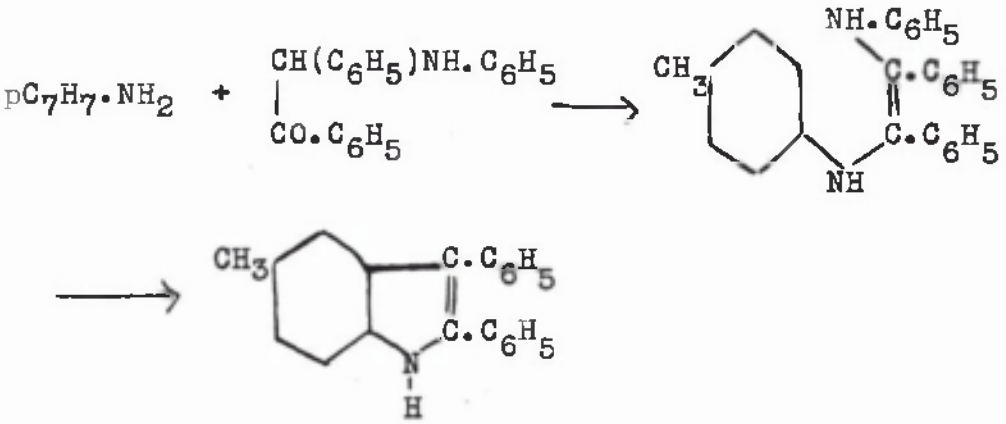


Further confirmation was given to these assumptions when that author showed that phenacyl arylamines, when treated with aniline, all gave the same ∝ phenyl indole, while phenacyl aniline gave ∝ phenyl indoles substituted in the nucleus when heated with substituted primary benzenoid amines.



This explanation also shows how Nencki & Berlinerblau (44) obtained methyl ketol from chloroacetone and aniline, and how Berlinerblau obtained indole from aniline and chloroacetaldehyde (45).

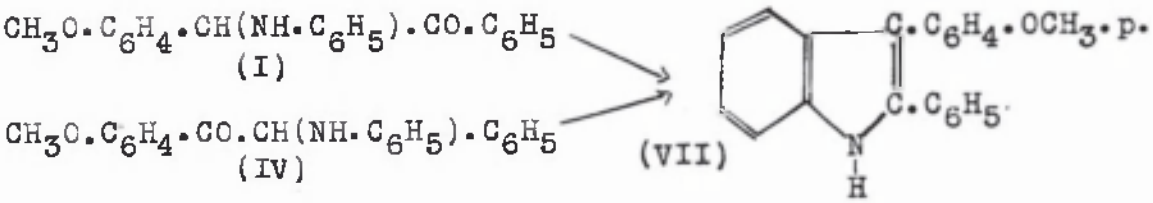
Cullmann (46) obtained 1 methyl 2 phenyl indole from phenacyl bromide and methyl aniline, while Bischler & Fireman (47) and Japp et al.. (48) prepared indoles by heating the anilides and toluidides of benzoin with aryl-amine hydrochloride.



Finally, Bauer & Buhler (49) prepared N benzyl 2 phenyl indole from phenacyl bromide and benzyl aniline in alcohol.

Experimental.

(a) Preparation of 2 phenyl 3 p methoxy phenyl indole.



When (I) was boiled with aniline, aniline hydrobromide (compare Japp & Murray (48)), 2 phenyl 3 p methoxy phenyl indole was obtained. The crude product on distillation under reduced pressure crystallised from alcohol as colourless prisms, m.p., 188 - 190°C. It was found to be identical with the product obtained from (IV). Analysis gave, 4.54% N; $C_{21}H_{17}NO$ requires 4.68% N.

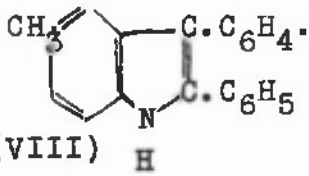
The structure assigned to this compound (VII) was proved by synthesis from p methoxy benzyl phenyl ketone phenylhydrazone, by Fischer's method (40), in alcohol solution containing dilute hydrochloric acid. Admixture with (VII) showed no depression.

The phenylhydrazone was prepared from its components in alcohol acetic acid solution, from which it crystallised as cream plates, m.p., 124 - 125°C. Analysis gave, 8.66% N; $C_{21}H_{20}N_2$ requires, 8.86% N.

(b) Preparation of 2 phenyl 3 p methoxy phenyl 5 methyl indole

$CH_3O.C_6H_4.CH(NH.C_6H_4.CH_3).CO.C_6H_5$ (II)

$CH_3O.C_6H_4.CO.CH(NH.C_6H_4.CH_3).C_6H_5$ (V)



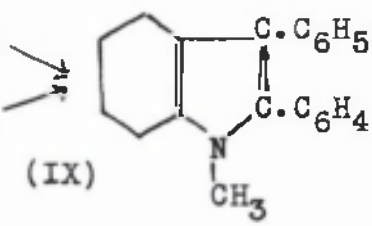
(VIII)

When (II) and (V) respectively were boiled in p toluidine, p toluidine hydrobromide solution the same indole (VIII) was obtained by distillation under reduced pressure. It crystallised from alcohol as long colourless prisms, m.p., 150 - 151°C. Analysis gave, 4.79% N; $C_{22}H_{19}O$ requires, 4.46% N.

(c) Preparation of 1 methyl 2 phenyl 3 p methoxy phenyl indole.

$CH_3O.C_6H_4.CH(N(CH_3).C_6H_5).CO.C_6H_5$ (III)

$CH_3O.C_6H_4.CO.CH(N(CH_3).C_6H_5).C_6H_5$ (VI)



(IX)

When (III) and (VI) respectively were boiled for 3 hours in methyl aniline, methyl aniline hydrobromide the same indole (IX) was obtained, crystallising from alcohol as long colourless needles, m.p., 130 - 131°C. Analysis gave, 4.63% N; $C_{22}H_{19}NO$ requires, 4.46% N.

(d) Partial indolisation by heating (III) at 180 - 185°C. for a prolonged period produced unchanged (III) from the acid layer and (IX) from the ethereal extract.

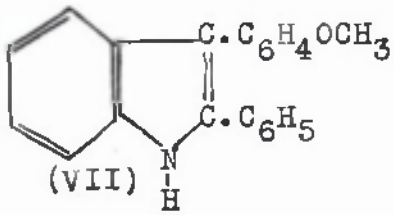
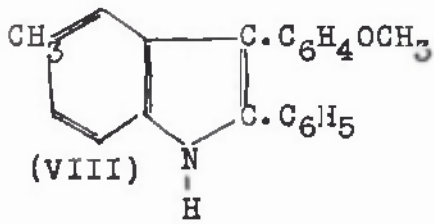
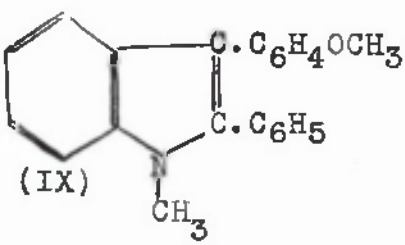
Attempts to indolise (III) and (VI) respectively in aniline solution resulted in the production of a light brown syrup, b.p.$_{12\ mm.}$ 260 - 275°C., which would not crystallise. It appeared to be a mixture of products which could not readily be separated.

(e) Attempted indolisation in pyridine, pyridine hydrobromide solution.

Attempts to indolise (I) and (II) by heating with pyridine, pyridine hydrobromide solution in a sealed tube at 200°C. produced from (I) a compound, m.p., 94 - 96°C., crystallising from alcohol in glistening plates, and from (II) a substance, m.p., 92 - 94°C., which crystallised from alcohol in white plates. Admixture, (79 - 85°C.) showed them to be different.

In each case only a small quantity of material was isolated from the gelatinous mass of the reaction mixture. Nitrogen tests gave a negative result.

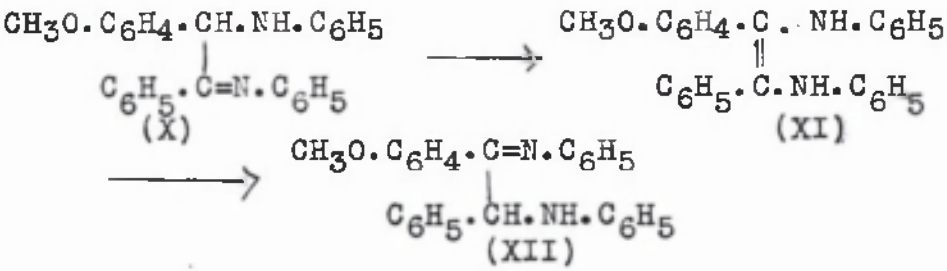
TABLE IV.

	Compounds	Indole
(a)	$CH_3O.C_6H_4.CH(NH.C_6H_5).CO.C_6H_5$ (I) $CH_3O.C_6H_4.CO.CH(NH.C_6H_5).C_6H_5$ (IV)	 (VII)
(b)	$CH_3O.C_6H_4.CH(NH.C_6H_4CH_3).CO.C_6H_5$ (II) $CH_3O.C_6H_4.CO.CH(NH.C_6H_4.CH_3).C_6H_5$ (V)	 (VIII)
(c)	$CH_3O.C_6H_4.CH(N(CH_3).C_6H_5)CO.C_6H_5$ (III) $CH_3O.C_6H_4.CO.CH(N(CH_3)C_6H_5).C_6H_5$ (VI)	 (IX)

Synthesis of Intermediate Products.

Introduction

As it has been postulated that the rearrangement of (I) to its stable isomer (IV) might be readily accomplished by the possible intermediate formation of an anil anilide capable of undergoing tautomeric change as outlined below,



several attempts were made to find a rational synthesis of (X), (XI) and (XII). Failing the isolation of each individual compound from the respective synthesis, due presumably to its labile nature, it was entertained that the consistent production of (XII), the structure which should be possessed by the stable anil anilide, would at least denote the existence of an imino-enamine tautomeric system among these compounds: while further practical considerations to complicate the issue are the ease with which anils hydrolyse in acid media and the sparsity of methods of preparing anil anilides of an unsymmetrical nature. Moreover, those described in the literature are applicable only to the synthesis of symmetrical desoxybenzoin anil anilides.

The most general method is reported by Strain (50) who prepared benzoin anil anilide and benzoin p tolil toluide by an ammono benzoin condensation of benzylidene aniline, and benzylidene p toluidine, respectively, in liquid ammonia with potassium cyanide.

Previously, Schiff (51) had reported the preparation of a compound having the same empirical formula ($C_{26}H_{22}N_2$) and melting point as the latter, obtained by heating benzylidene aniline in a sealed tube.

The same author (52) had also reported the isolation of a compound having the same empirical formula ($C_{28}H_{26}N_2$) and physical properties as the latter, prepared by heating benzylidene p toluidine in a sealed tube.

However, neither Strain (50), Voigt (53) nor v. Miller & Plöchl (54) have been able to duplicate Schiff's results.

The formation of a "dianilide" [$C_6H_5.CH.(NH.C_6H_5)C = (N.C_6H_5).CH_2.C_6H_5$] formulated as dibenzyl ketone anil anilide and prepared from α bromo dibenzyl ketone and aniline has been published by Francis (55). It agrees very closely indeed with α anilino dibenzyl ketone synthesised by Stevens & McGeoch (1), the outstanding anomaly being the good analysis reported by Francis. Moreover, the hydrochloride, m.p., 178-180°C.

prepared by myself from Stevens' specimen compares admirably with the hydrochloride, m.p. 175°C. described by that author. In all probability the compound is ∝ anilino dibenzyl ketone, as such treatment with acid would tend to hydrolyse the anil in preference to the formation of a hydrochloride.

Montagne & Garry (6) have described a benzoin anil methyl anilide, while Lachowicz (48) found that benzoin anil was the sole product of the reaction when he attempted to prepare benzoin anil anilide by the action of aniline on benzoin, the ammonolysis failing to go to completion.

Experimental.

Synthesis of ∝ p toluidino p methoxy benzyl phenyl ketone phenyl hydrazil.

$$CH_3O.C_6H_4.CH(C_6H_5).C{=}O.NH.C_6H_4.CH_3 + NH_2.NH.C_6H_5 \longrightarrow CH_3O.C_6H_4.CH(C_6H_5).C{=}N.NH.C_6H_5.NH.C_6H_4.CH_3$$

∝ p Toluidino p methoxy benzyl phenyl ketone (1.5 g.) and phenyl hydrazine (0.5 g.) were boiled in glacial acetic acid (20 c.c.) containing aqueous alcohol (3 c.c.) for ½ hour. On cooling the solution deposited a black tar which crystallised from aqueous acetic acid as yellow needles, m.p., 168 - 170°C. Analysis gave 8.80% N; $C_{28}H_{27}N_3O$ requires 10.0% N. Boiling dilute alcoholic hydrogen chloride produced no change in this material, the product being recovered unchanged on treatment with dilute ammonia.

It is without doubt ∝ phenyl hydrazino benzyl p methoxy phenyl ketone obtained by rearrangement in acetic acid media

$$CH_3O.C_6H_4.CH(C_6H_5).C{=}N.NH.C_6H_5.NH.C_6H_4.CH_3 \xrightarrow{H\bar{A}} CH_3O.C_6H_4.C{=}O.CH(C_6H_5).NH.NH.C_6H_5$$

$C_{21}H_{20}N_2O_2$ requires 8.43% N.

This compound was prepared by treating ∝ bromo benzyl p methoxy phenyl ketone with phenyl hydrazine in

alcohol solution in the cold.

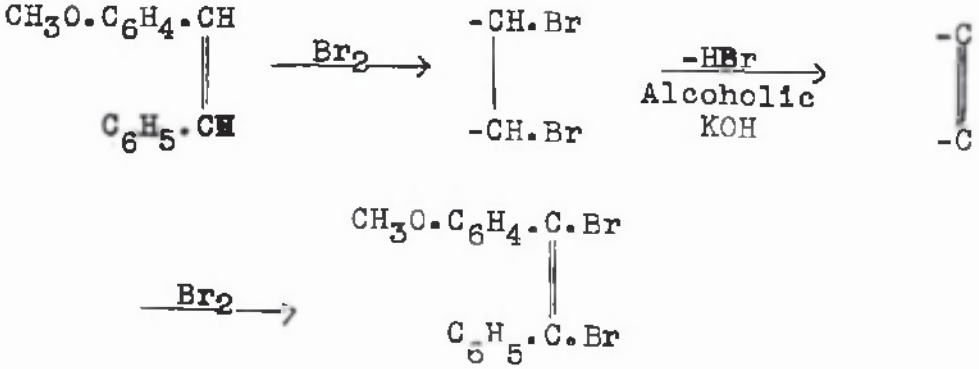
$C_6H_5.CH(Br).CO.C_6H_4.OCH_3 \longrightarrow C_6H_5.CH(NH.NH.C_6H_5).CO.C_6H_4.OCH_3$

The brown tar which deposited on standing was with difficulty purified by several crystallisations from aqueous acetic acid. Yellow needles, m.p., 165 - 168°C., which showed no depression on admixture with the product above, were deposited.

Attempted preparation of p tolan dianilide ($CH_3O.C_6H_4.C.(NH.C_6H_5) = C.(NH.C_6H_5).C_6H_5$).

The preparation of this product from p methoxy tolan dibromide was unsuccessful because of the unreactivity of the dibromide to primary aromatic amines. Boiling aniline produced no change, the starting material being recovered, while heating at 170°C. for 3 hours with aniline magnesium bromide followed by decomposition of the reaction mixture with ice-cold ammonium chloride gave negative results. The dibromide was isolated from the ethereal extract.

p Methoxy tolan dibromide was prepared as follows:-



p Methoxy stilbene (56) gave the dibromide, m.p., 136°C. when treated with bromine in ether solution (57). Analysis by Stepanow's method gave 43.01% Br_2; $C_{15}H_{14}OBr_2$ requires 43.24% Br_2.

Elimination of 2 molecules of hydrogen bromide by heating with alcoholic caustic soda (57) formed p methoxy tolan, m.p., 99 - 100°C., crystallising from alcohol as white needle clusters. Analysis gave 86.21% C, 5.93% H; $C_{15}H_{12}O$ requires 86.53% C, 5.76% H. Addition of bromine in ether produced p methoxy tolan dibromide, m.p., 167 - 169°C., crystallising as white needles from alcohol. Analysis gave 43.29% Br_2; $C_{15}H_{12}OBr_2$ requires 43.48% Br_2.

Attempted preparation of ∝ p toluidino p methoxy benzyl phenyl ketone diethyl acetal.

The ease of formation of anils by treating the acetals of ketones with amines (58) suggested the preparation of ∝ p toluidino p methoxy benzyl phenyl ketone anil by this method. Failure to produce the diethyl acetal, however, altered this decision.

The hydrochloride of (II) (8 g.) and ethyl orthoformate (10 c.c.) were made into a thick paste and heated gently on the water bath. A reaction began, the paste dissolving to a yellow viscid solution. Titration

with sodium ethoxide solution (phenolphthalein as indicator) removed the hydrochloric acid, while solution in benzene precipitated the sodium chloride which was filtered off. The solvent was distilled under reduced pressure, when the thick syrup crystallised to a yellow mass. Crystallisation from benzene gave white prisms, m.p., 143 - 144°C. Analysis gave, 4.09% N; $C_{26}H_{31}NO_3$ requires, 3.56% N.

It is unaffected by treatment with dilute acid contrary to the behaviour of acetals. The compound is probably the formyl derivative ($CH_3O.C_6H_4.CH.(N.(CHO)C_6H_4.CH_3).CO.C_6H_5$); $C_{23}H_{21}NO_3$ requires, 4.08% N.

Attempted preparation of 4 dimethyl amino anil ∝ anilino p methoxy benzyl phenyl ketone.

Vogtherr (59) has recorded the preparation of desoxybenzoin p dimethyl amino anil by heating desoxybenzoin with dimethyl amino aniline. Attempts to repeat this condensation with (I) were unsuccessful. The starting product was recovered unchanged from the tarry mass.

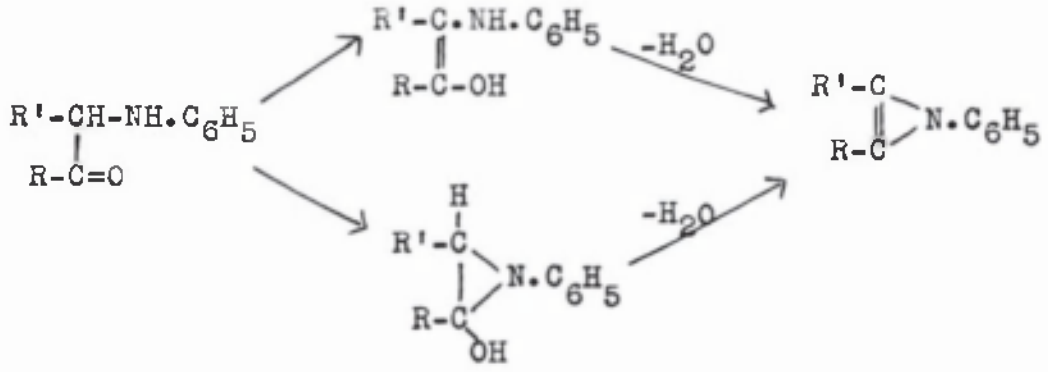
Variations in the condensation using p toluidine as a substitute for p dimethyl amino aniline with P_2O_5 as a dehydrating agent were of no avail. Equimolecular proportions of the constituents were heated at 130 - 140°C. for 3 - 4 hours.

Iodine was also used to induce condensation, but without result. The starting product was recovered unchanged. Not even rearrangement could be accomplished by these conditions.

∝ Anilino Camphor Series.

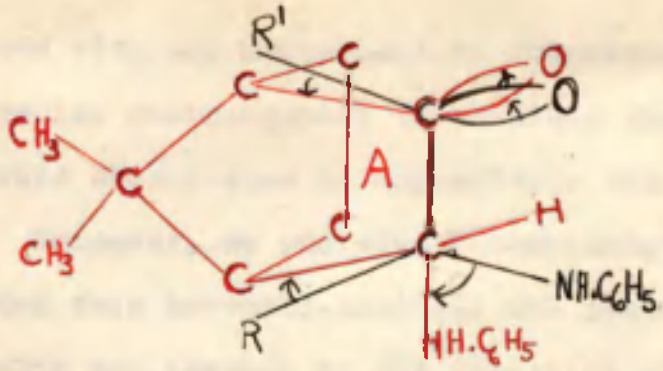
Introduction.

As it has been verified experimentally that intramolecular rearrangement is an obvious accomplishment in the ∝ anilino p methoxy desoxybenzoin series and that it might readily be performed by the formation of a 3 membered ring as outlined below,



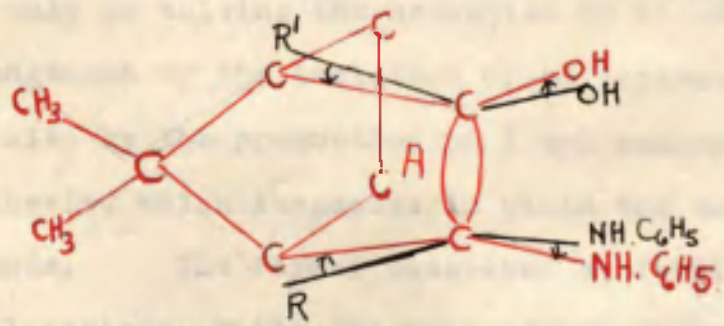
every effort was made to obtain some practical evidence of this assumption.

For this purpose the ∝ anilino camphor series was chosen. Here, in contrast to the above system where only the customary strain of formation of a 3 membered ring is involved, there is a still further increase in strain to be overcome. This additional impeding force, as can be seen from the following contrast of the two systems,



is produced by the formation of the adjacent 5 membered skewed-ring system [A] of the camphor molecule, which deflects the C-N, C=O bonds from the same plane and from their normal angles, orienting them in different planes with greater angles to the C-C bond common to both.

If we allow enolisation to occur in the two systems, however,



a more distinctive contrast can be drawn, as in each example the C-OH&C-N bonds are in the same plane.

These minor structural differences therefore should reflect substantial variations in the conditions of intramolecular rearrangement from those already

experienced with the desoxybenzoin compounds, whereas if intermolecular rearrangement is possible the conditions in each case should show no appreciable change.

Moreover, an additional consideration which recommended this investigation was the possibility of synthesising epi camphor by the reduction of ∝ anilino epi camphor formed by rearrangement. Nevertheless, no predictions could be made that ∝ anilino camphor was the labile isomer, or that it would rearrange integrally to its isomeric compound, the determining factors of a successful synthesis of epi camphor.

It will be seen, however, that the experimental results have fully justified the investigation, resulting not only in solving the mechanism of intermolecular rearrangement by the isolation of an intermediate product, but also by the production of l epi camphor by a new synthesis, which surpasses in yield the two existing methods. The former described by Perkin (60) is long and laborious, while the more recent by Bredt & co-workers (61) entails the separation of two isomeric hydroxy camphors, ∝ hydroxy camphor and β hydroxy camphor, with the use of only the latter product to complete the synthesis.

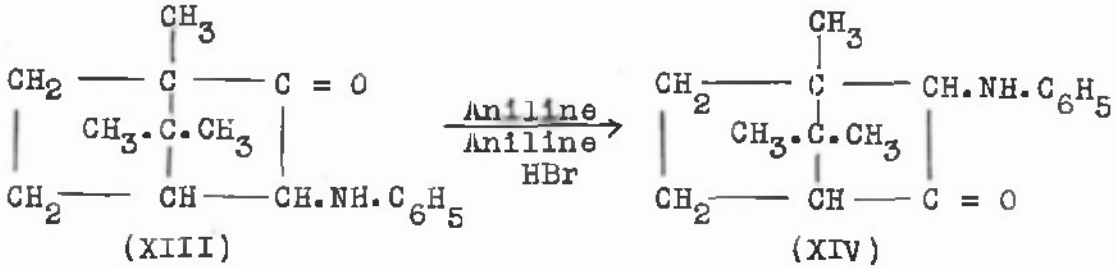
Experimental.

(a) Preparation of ∝ Anilino Camphor.

∝ Anilino camphor (62) was prepared from camphor quinone (63) and aniline via camphor quinone mono-anil.

A method of synthesis from ∝ bromo camphor (64) and aniline was unsuccessful. Even boiling aniline failed to react with the bromo compound. In each case the bulk of starting material was recovered unchanged.

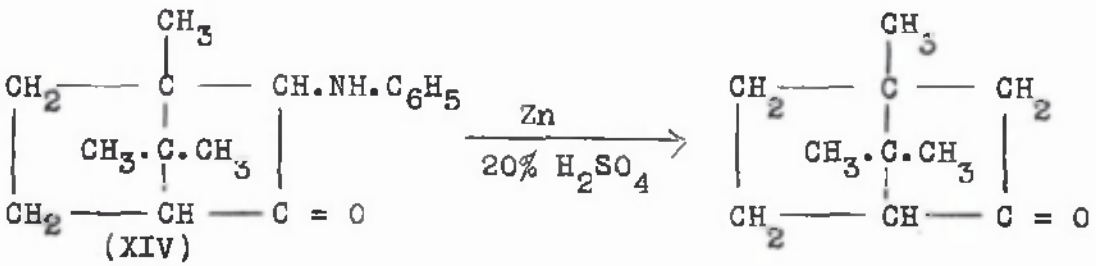
(b) Rearrangement of ∝ Anilino Camphor (XIII).



(XIII) (1 mol.) was heated with aniline (3 mols.) and aniline hydrobromide (0.5 mol.) for 3 hours at 125 - 130°C. On cooling, the reaction solution was dissolved in petrol ether (b.p. 40 - 60°C.), the insoluble aniline hydrobromide being filtered off, the filtrate being extracted several times with very dilute hydrochloric acid. The ∝ anilino epi camphor (XIV) remained in the ether

layer as it formed an unstable hydrochloride. By dilution of the acid extracts with water and extraction with more petrol ether a further supply of product was obtained. The combined ether layers were then dried, the ether removed on the water bath and the product crystallised from dilute alcohol. Long colourless needles, m.p., 168 - 170°C. were obtained. The yield was 75%. A sample showed $[\alpha]^{20^\circ}_{5461}$ +35.46° (C, 4.85 g. in chloroform). Analysis gave, 78.65% C; 8.63% H; $C_{16}H_{21}NO$ requires 79% C, 8.64% H.

(c) Reduction of (XIV) to epi camphor.

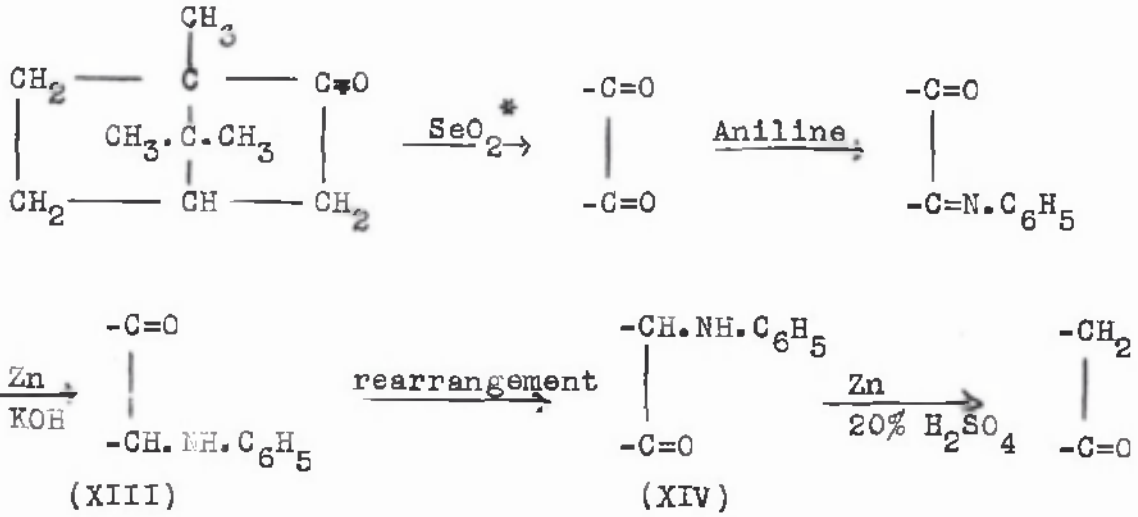


(XIV)

(XIV) (1 g.) was heated for 2 hours on the water bath with 20% H_2SO_4 (15 c.c.) and zinc dust in a long-necked flask fitted with an internal cooling system. The product condensed on the cold surface from which it could be readily collected. It melted at 180 - 181°C., and showed $[\alpha]^{20}_{D}$ -44.5° (C, 4.59 g. in methyl alcohol). Tschugazew (65) records $[\alpha]^{20}_{D}$ -45.5° (C, 9.7 g. in

CH_3OH solution). The yield was 75% of the theoretical.

Hence by employing the following series of reactions l epi camphor can be readily prepared in 45 - 50% yield from d camphor.



(d) Preparation of ∝ p toluidino camphor (XV).

(XV) was prepared by the same method as described for (XIII). It crystallised from dilute alcohol as colourless cubes, m.p., 87 - 88°C. Analysis gave, 5.41% N; $C_{17}H_{23}NO$ requires, 5.44% N, while a sample showed $[\alpha]^{20}_{5461}$ +106.4° (C, 5.624 g. in absolute alcohol).

Camphor quinone p tolil crystallised from petrol ether (b.p. 60 - 80°C.) as yellow laminae, m.p., 102 - 103°C.

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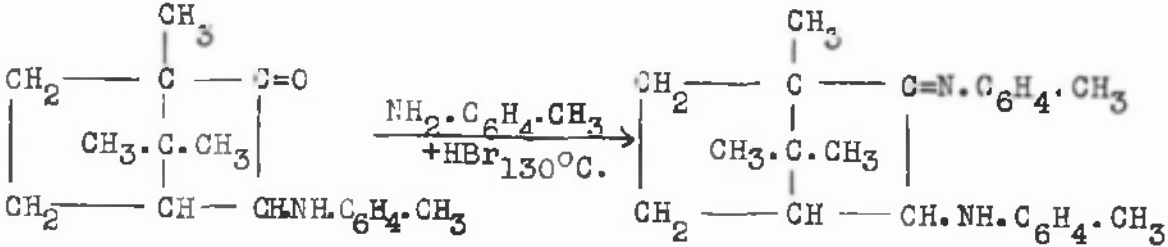
* The selenium dioxide can be readily regenerated from the selenium by oxidation with $CHNO_3$ (cf. Annales de Chemie, 11, (1939), 144 : Guillemonat).

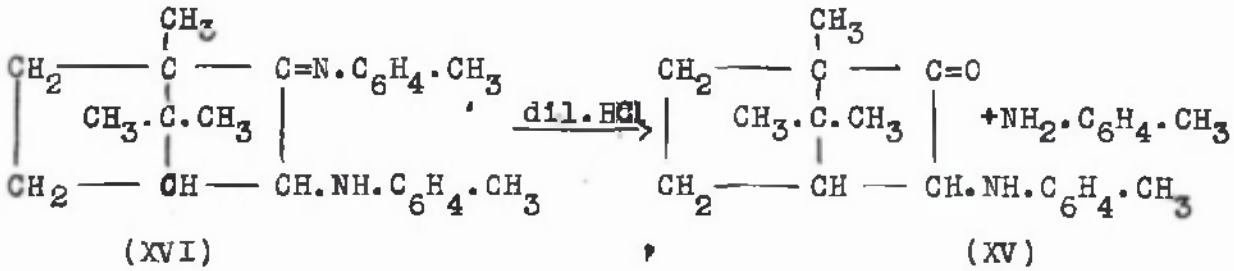

CH3
CH2 — C — C=O
CH3.C.CH3
CH2 — CH — CH.NH.C6H4.CH3
NH2.C6H4.CH3
+HBr 130°C.
CH3
CH2 — C — C=N.C6H4.CH3
CH3.C.CH3
CH2 — CH — CH.NH.C6H4.CH3

Analysis gave, 5.53% N; $C_{17}H_{21}NO$ requires 5.49% N. A sample showed $[\alpha]^{20}_{5461}$ +1174.9° (C, 3.63 g. in $CHCl_3$ solution).

(e) Preparation of ∝ p toluidino camphor p tolil. (XVI).

Attempted rearrangement of ∝ p toluidino camphor (XV) by heating in dry p toluidine, p toluidine hydrobromide solution for 3 - 4 hours at 130 - 135°C. gave a yellow product, isolated from the petrol ether layer after extraction with dilute hydrogen chloride. It crystallised from absolute alcohol as beautiful greenish yellow prisms, m.p., 158 - 160°C. Analysis gave 8.0% N; $C_{17}H_{23}NO$ requires 5.44% N, while a pure sample showed $[\alpha]^{20}_{5461}$ +259.2° (C, 3.75 g. in $CHCl_3$ solution). But these are incongruent with the figures expected for ∝ p toluidino epi camphor. They were more in agreement with the ∝ p toluidino camphor p tolil, $C_{24}H_{30}N_2$ requires 8.7% N. A sample crystallised from petrol ether gave 8.01 % N.

(f) Proof of the structure of ∝ p toluidino camphor p tolil. Hydrolysis to ∝ p toluidino camphor (XV).

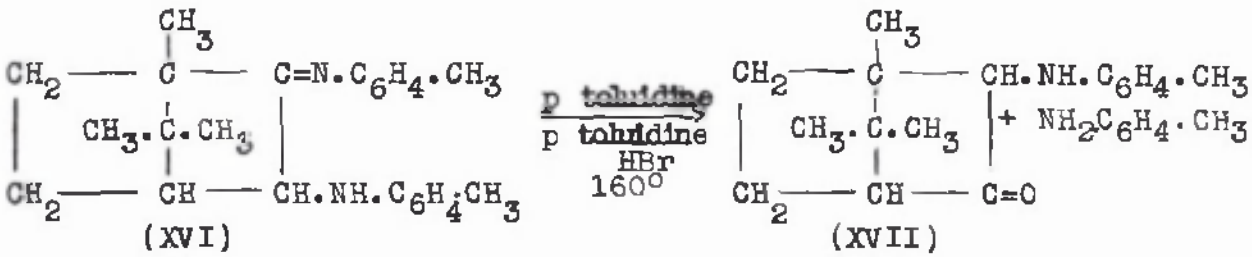


(XVI) (XV)

By boiling (XVI) with dilute hydrochloric acid for a few minutes and basification of the resultant solution, a white product, m.p., 86 - 87°C. separated. This was proved by admixture to be (XV). The alkaline filtrate was then steam distilled and the distillate extracted with ether. On drying and distilling the ether portion, followed by treatment of the remaining yellow oil with acetic anhydride in aqueous solution, a white product, m.p., 147 - 148°C. was obtained. This was proved to be identical with acetyl p toluidine.

This hydrolysis could also be accomplished by heating (XVI) at 130°C. for 3 hours in p toluidine, p toluidine hydrobromide solution containing a trace of water*.

Hydrolysis to ∝ p toluidino epi camphor (XVII).



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* This was found necessary as the p toluidine used in these rearrangements was dried by distilling over BaO.

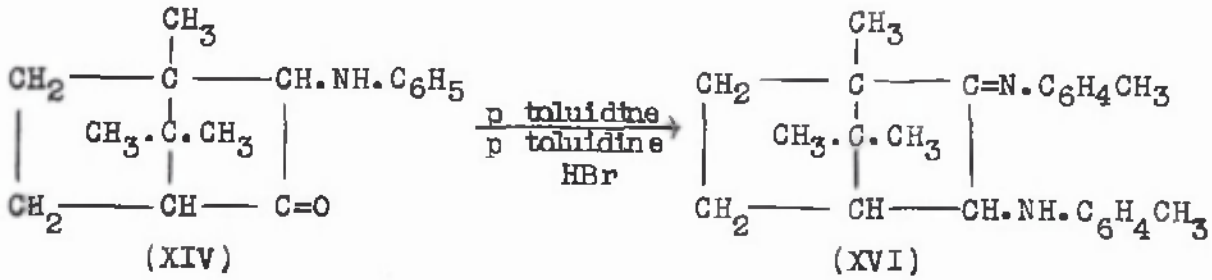
When (XVI), however, was heated at 160°C. for 3 hours in p toluidine p toluidine hydrobromide solution containing a trace of water, (XVII), crystallising from dilute alcohol as white laminae, m.p., 140 - 142°C., was obtained. Analysis gave, 5.37% N; $C_{17}H_{23}NO$ requires 5.44% N. A sample showed $[\alpha]^{20}_{5461}$ +52.0° (C, 1 g. in $CHCl_3$ solution).

Reduction of (XVII) with zinc dust and 20% H_2SO_4 gave l epi camphor, m.p., 181 - 182°C., proved by admixture with d camphor and l camphor respectively. In the former case a depression, m.p., 170 - 173°C. was observed.

By heating at 160°C. for 3 hours with dry p toluidine, p toluidine hydrobromide (XVI) was recovered unchanged.

With p toluidine, p toluidine hydrobromide containing a trace of water, at 150°C. for 3 hours a mixture of the isomeric toluidino camphors (XV) and (XVII) were obtained.

(g) Formation from (XIV).



(XIV) (XVI)

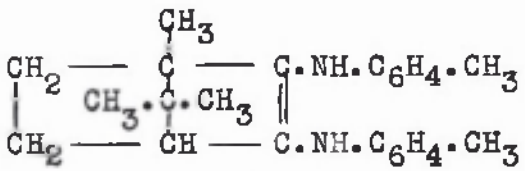
When (XIV) was heated with p toluidine, p toluidine hydrobromide at 160°C. for 3 hours (XVI) was isolated from the reaction mixture in the customary way. The identity of the product was obtained by degradation to (XV) and admixture with a pure sample of (XVI).

The same product was obtained from (XIII).

(h) Discussion on the structure assigned to (XVI).

From the foregoing results the structure of the intermediate product corresponds to ∝ p toluidino camphor p tolil (XVI).

The possibility that the di-toluidide (XVIII)



(XVIII)

is the more appropriate configuration is contradicted by the ease of hydrolysis with dilute hydrochloric acid to (XV). However, in view of the results that (XIII) rearranges integrally to (XIV), it is extraordinary that (XVI) should be the stable intermediate structure isolated from (XIII) and (XIV) respectively.

(i) Intramolecular rearrangement.

Attempts to rearrange (XIII) to (XIV) in pyridine

pyridine hydrobromide solution were unsuccessful. By heating (XIII) in a sealed tube in that media for 3 hours at 200°C., a product crystallising from alcohol as white needle clusters, m.p., 83 - 85°C., was isolated. Analysis proved the absence of nitrogen.

A compound, crystallising from alcohol as white prisms, m.p., 92 - 94°C., was obtained from (XV) when treated under these conditions. Admixture with the product from (XIII) proved them to be different.

So far I have been unable to prove the structures of these compounds or even suggest a possible analogy due to the complexity of the products which could be derived from the fission of either (XIII) or (XV).

Attempts to rearrange (XIII) and (XV) respectively in methyl aniline, methyl aniline hydrobromide at 170°C. were also unsuccessful. The starting material was isolated in each case.

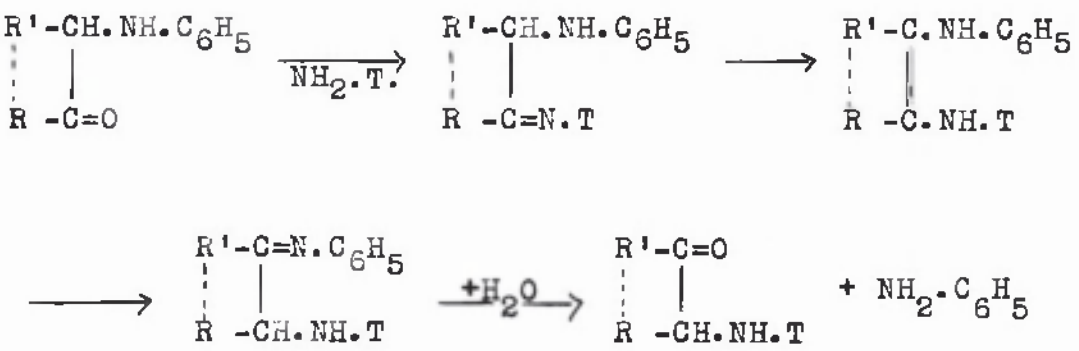
TABLE V.

	Compound	with	Product.
(b)	∝anilino camphor (XIII)	aniline, aniline hydrobromide at 130°C.	∝anilino epi camphor (XIV)
(c)	"	Zinc dust + 20% H_2SO_4	l epi camphor
(e)	∝p toluidino camphor (XV)	p toluidine, p toluidine hydrobromide at 135°C.	∝p toluidino camphor p tolil (XVI)
(f)	∝p toluidino camphor p tolil (XVI)	dilute HCl (boiling) or p toluidine, p toluidine hydrobromide at 130°C.	∝p toluidino camphor (XV)
		p toluidine p toluidine hydrobromide at 160°C.	∝p toluidino epi camphor (XVII)
(g)	∝anilino epi camphor (XIV)	p toluidine p toluidine hydrobromide at 160°C.	∝p toluidino camphor p tolil (XVI)
	∝anilino camphor (XIII)		

Displacement of Amine.

Introduction.

By reviewing the foregoing experimental data two methods of rearrangement become apparent, an intermolecular process, which involves the anil anilide theory,



and an intramolecular mechanism, possibly of the type previously postulated.

Neither of these deductions, however, are comprehensive enough to accommodate certain aspects of displacement, viz., the displacement of primary amine from the stable ∝ anilino p methoxy desoxybenzoin by a homologous base

$$p.CH_3O.C_6H_4.CO.CH(NH.C_6H_5).C_6H_5 \xrightarrow{NH.C_6H_4CH_3} CH_3O.C_6H_4.CO.CH(NH.C_6H_4CH_3)C_6H_5$$

in view of the irreversibility of the rearrangement, or

the absence of displacement in favour of intramolecular rearrangement in methyl aniline, methyl aniline hydrobromide solution.

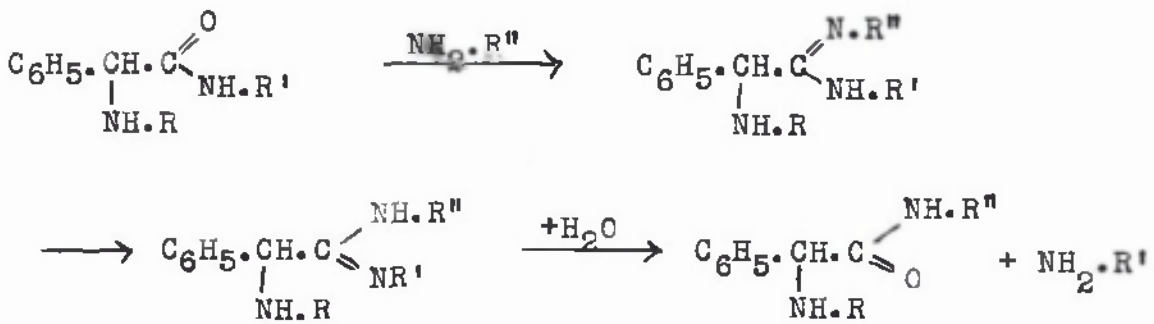
Therefore, in order to explain or refute these anomalies the aspect of displacement was investigated to the exclusion of rearrangement, the compounds being chosen in the hope that they would exert comparable behaviour under similar conditions as those which displayed rearrangement and displacement in the two series already investigated.

Experimental.

Preparation of ∝ anilino phenyl acetic acid p chloro anilide ($C_6H_5.CH.(NH.C_6H_5)CO.NH.C_6H_4.Cl$) (XIX).

This compound was selected to establish the belief that displacement might be a factor concurrent with but not subordinate to rearrangement.

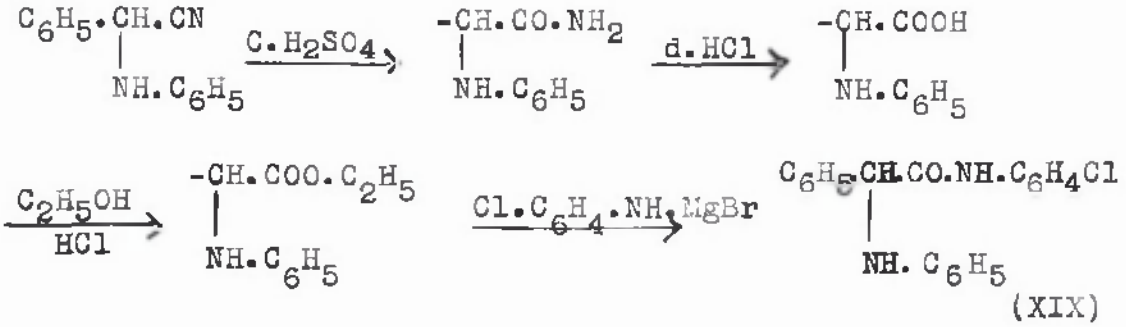
If, before displacement can occur, reaction must be effected at the keto group as advanced by the anil anilide theory (page 65), then with (XIX) such a transformation, if it takes place, will be displayed by the amide group alone,



the ∝ amino group being left intact.

The chloro group was introduced to facilitate the analysis of the structure of the resultant product.

(XIX) was prepared by the following series of reactions:-

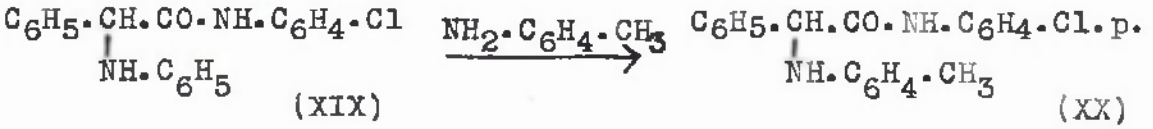


(XIX)

∝ Anilino phenyl aceto nitrile (66) was hydrolysed to ∝ anilino phenyl acetic acid (67). The ester (68) on treatment in ether in the cold with excess p chloro anilino magnesium bromide, gave ∝ anilino phenyl acetic acid p chloro anilide, m.p., 157 - 158°C. It crystallised from alcohol as long white prisms. Analysis gave, 8.58% N; $C_{20}H_{17}N_2O$ requires, 8.32% N.

Attempts to prepare the anilide directly from the ester by boiling with p chloro aniline were unsuccessful, the ester being recovered unchanged.

(a) Displacement in p toluidine solution.



(XIX) (XX)

(XIX) (1 mol.) was boiled for 3 hours with p toluidine (3 mols.) and p toluidine hydrobromide (.5 mol.). When the reaction mixture was cold it was dissolved in ether and dilute hydrochloric acid solution, the

acid layer being separated. It deposited a dark tarry mass which crystallised from ammoniacal alcohol as white needles, m.p., 183 - 185°C. It was ∝ p toluidino phenyl acetic acid p chloro anilide (XX). Analysis gave, 7.85% N; $C_{21}H_{19}N_2OCl$ requires 7.98% N. Several crystallisations were required before a congruent melting point of this material was obtained.

Attempts to duplicate these results at lower temperatures, 115 and 180°C. were unsuccessful.

The structure of the compound was proved by synthesis from ∝ p toluidino phenyl acetic acid according to the scheme already described (page 68), admixture with a pure sample showing no depression.

No evidence of displacement in the amide group was observed.

(b) Attempted displacement in methyl aniline solution.

When (XIX) was boiled for 3 hours in methyl aniline, methyl aniline hydrobromide solution and the mixture treated with dilute hydrochloric acid in the normal manner, a tarry product was isolated. Attempts to crystallise this material, after neutralisation with ammonia, were unsuccessful, no identifiable product being obtained. It was observed, however, that a quantity of non-basic material was extracted in the ethereal layer.

Preparation of ∝ p toluidino diphenylmethane (XXI).

$$C_6H_5.CH{=}N.C_6H_4.CH_3 \xrightarrow{C_6H_5.Mg.Br} (C_6H_5)_2.CH_2.NH.C_6H_4.CH_3$$
(XXI)

This compound was prepared from benzal p toluidine by treatment with phenyl magnesium bromide (64).

(c) Displacement in aniline solution.

(XXI) was heated for 3-4 hours in aniline, aniline hydrobromide solution at 150°C. and the product was isolated by extraction of an ethereal solution with dilute hydrochloric acid. It distilled at b.p.$_{15\ m.m.}$ 236 - 242°C., and crystallised from alcohol as colourless cubes, m.p., 87 - 89°C. Admixture with a pure sample of starting product proved them to be identical.

Increase in temperature to 180 - 190°C. produced a straw coloured oil, b.p.$_{15\ m.m.}$ 239 - 245°C., which would not crystallise from alcohol. Attempted formation of a picrate was a failure; no crystalline derivative could be obtained.

The difficulty encountered here might be the rearrangement discovered by Busch and Rinck (69) proceeding concomitantly.

$$(C_6H_5)_2\cdot CH\cdot NH\cdot C_6H_5 \xrightarrow[C_6H_5\cdot NH_2.HBr]{C_6H_5\cdot NH_2,\ 210^\circ C} (C_6H_5)_2\cdot CH\cdot C_6H_4\cdot NH_2$$
(XXI)

It was originally believed that the displacement would occur at a much lower temperature, 120°C., and exclude this anomaly.

Preparation of ∝ benzyl ∝ anilino benzyl p methoxy phenyl ketone (XXII).

$$C_6H_5\cdot \underset{\displaystyle CH_2\cdot C_6H_5}{\overset{|}{C}}\cdot(Br)\cdot CO\cdot C_6H_4\cdot OCH_3(p) \xrightarrow{C_6H_5\cdot NH_2} C_6H_5\underset{\displaystyle CH_2\cdot C_6H_5}{\overset{|}{C}}\cdot(NH\cdot C_6H_5)CO\cdot C_6H_4\cdot OCH_3(p)$$
(XXII)

∝ Bromo ∝ benzyl benzyl p methoxy phenyl ketone was prepared by brominating ∝ benzyl benzyl p methoxy phenyl ketone (65) in ether solution with aluminium chloride as a catalyst (page 21). It crystallised as soft white needles from alcohol, m.p., 140 - 142°C. (with decomposition). Analysis gave, 20.12% Br; $C_{22}H_{19}O_2Br$ requires 20.26% Br.

(XXII) was obtained by treatment of the bromo derivative with aniline in alcohol solution. White prisms, m.p., 148 - 150°C. were deposited on standing. Analysis gave, 82.86% C, 6.16% H; $C_{28}H_{25}NO_2$ requires, 82.55% C, 6.14% H.

Displacement in p toluidine solution.

$$C_6H_5.C.(NH.C_6H_5).CO.C_6H_4.O.CH_3(p) \xrightarrow{NH_2.C_6H_4.CH_3}$$
$$CH_2.C_6H_5 \quad (XXII)$$

$$C_6H_5.C.(NH.C_6H_4.CH_3).CO.C_6H_4.OCH_3$$
$$CH_2.C_6H_5 \quad (XXIII)$$

When (XXII) was heated with p toluidine, p toluidine hydrobromide displacement of amine occurred giving (XXIII). The product was isolated in the customary manner by dilute hydrogen chloride extraction. However, the yield was very poor. Admixture with a pure specimen synthesised from the α bromo derivative and p toluidine showed no depression. It crystallised from alcohol as white needle clusters, m.p. 140 - 143°C. Analysis gave 83.19% C, 6.15% H; $C_{29}H_{27}NO_2$ requires 82.89% C, 6.41% H.

Displacement in methyl aniline solution.

Attempted displacement by heating with methyl aniline, methyl aniline solution by heating for 3 hours at 120°C. has been unsuccessful, the starting product being recovered unchanged. However, this aspect of the investigation is being continued using higher temperatures.

Displacement of aniline in benzyl aniline.

$$C_6H_5 \cdot CH_2 \cdot NH \cdot C_6H_5(HBr) \xrightarrow{NH_2 \cdot C_6H_4 \cdot CH_3} C_6H_5 \cdot CH_2 \cdot NH \cdot C_6H_4 \cdot CH_3.$$

Benzyl aniline hydrobromide (7 g.) was heated with p toluidine (5 mols.) under reflux for 4 hours, the reaction mixture being steam distilled after making alkaline with caustic soda. The residue was extracted with petrol ether, dried, filtered and the solvent distilled. Treatment of the product with benzene sulphonyl chloride in pyridine, overnight, then boiling 1 hour gave on dilution with water a sticky mass which, after treatment with ether and dilute hydrochloric acid, gave a crystalline product, m.p., 120°C. A pure sample of benzene sulphonyl benzyl p toluidine showed no depression on admixture, while benzene sulphonyl benzyl aniline gave a depression.

TABLE VI.

	Compound	with	Product.
(a)	$C_6H_5.CH.CO.NH.C_6H_4.Cl$ $NH.C_6H_5$ (XIX)	p toluidine, p toluidine HBr (boiling)	$C_6H_5.CH.CO.NH.C_6H_4.Cl$ $NH.C_6H_4.CH_3$ (XX)
(b)	ditto	methyl aniline, methyl aniline hydrobromide	no product isolated.
(c)	$(C_6H_5)_2.CH_2.NH.C_6H_4.CH_3$ (XXI)	aniline, aniline HBr 180 - 190°C.	
(d)	$C_6H_5.C(NH.C_6H_5)CO.C_6H_4.OCH_3$ $CH_2.C_6H_5$ (XXII)	p toluidine, p toluidine HBr at 120°C.	$C_6H_5.C(NH.C_6H_4.CH_3).CO.C_6H_4.OCH_3$ $CH_2.C_6H_5$ (XXIII)
(e)	$C_6H_5.CH_2.NH.C_6H_5(HBr)$	p toluidine, (boiling)	$C_6H_5.CH_2.NH.C_6H_4.CH_3$

Discussion.

Although short discussions have been given in the individual chapters listed at the beginning of this monograph, there is still a large amount of data to be collected and correlated with the main theme.

Rearrangement is displayed by both the ∝ anilino p methoxy desoxybenzoin and the ∝ anilino camphor series, but, whereas two mechanisms - intermolecular and intramolecular - have been established for the former series, only intermolecular interchange is apparent with the latter. The two series, however, agree as their secondary amines rearrange integrally to stable isomeric derivatives in primary amine, amine hydrobromide solution (Table I, a, b, c, d; Table V, b), while no rearrangement occurs with tertiary bases (Table I, e, f).

As regards displacement a uniform scheme can be observed in both series with secondary bases. If primary amines are used as the solvent displacement occurs, the solvent amine displacing the amine already present in the molecule (Table II, a, b, c, d; Table V, g). There is a difference, however, using secondary amine media. Here rearrangement occurs with secondary bases in the p methoxy

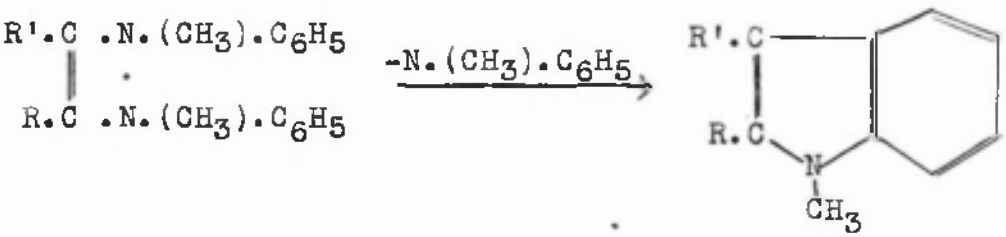
desoxybenzoin series (Table III, a), comparable with intramolecular rearrangement in pyridine, pyridine hydrobromide, etc. (Table III, b, c) with no evidence of displacement, while with ∝ anilino camphor no displacement or rearrangement is observed (page 72). Nor can displacement of amine from tertiary bases be accomplished by heating with primary or secondary amines (Table II, e, f).

On indolisation, both secondary and tertiary isomeric p methoxy desoxybenzoin amines produce the same indole (Table IV) as would be expected. No condensation took place in pyridine, pyridine hydrobromide media (page 43) in agreement with Bischler's hypothesis.

Intermolecular Rearrangement.

By investigating the mechanism of the reaction from the intermolecular aspect, both rearrangement series display normal behaviour. In view of the anil-anilide theory advanced (page 65) and later established in the ∝ anilino camphor series by the isolation of an intermediate product which produced the respective isomers by slight modification of the reaction conditions (page 59), secondary amines would be expected to rearrange, while tertiary bases, which possess only one mobile hydrogen atom (the other being substituted by a methyl group) should exist in two stable non interconvertible forms. The formation

of indole could be interpreted according to Bischler (page 2)



the balance of the reaction favouring indolisation rather than vinyl amine hydrolysis.

The existence of the intermediate product as ∝ p toluidino camphor p tolil (page 59), however, is difficult to explain in view of integral rearrangement of ∝ anilino camphor, to ∝ anilino epi camphor (page 56). Nor does the discrepancy in temperature existing between the formation of ∝ anilino epi camphor and ∝ p toluidino epi camphor (Table V) favour a reasonable explanation.

Nevertheless, in the light of the practical results obtained in this monograph coupled with the practical work of Strain (page 2), it has been definitely established that intermolecular rearrangement occurs by the primary formation of an anil anilide.

Intramolecular Rearrangement.

In spite of this recognition, however, intramolecular rearrangement cannot be refuted. The successful rearrangement of a mixture of two secondary

amines in pyridine, pyridine hydrobromide solution without exchange of amine (page 35) has confirmed such a theory. Moreover, the knowledge that displacement can occur without any relation to rearrangement is more satisfactory evidence for this anomaly of an already anomalous reaction. It can become feasible by the mechanism already postulated (page 53), a theory receiving considerable support from the practical results of Neber (71), who prepared an analogous 3 membered ring system,

$$(NO_2)_2.C_6H_3.CH_2.\underset{\underset{NOH}{\|}}{C}.CH_3 \xrightarrow[C_5H_5N]{CH_3.C_6H_4SO_2Cl} (NO_2)_2.C_6H_3.CH\!<\!\begin{matrix}N\\ \\ \end{matrix}\!>\!C.CH_3$$

$$\xrightarrow{\text{dil. HCl}} (NO_2)_2.C_6H_3.\underset{\underset{NH_2}{|}}{CH} - \underset{\underset{O}{\|}}{C}.CH_3$$

which he easily hydrolysed to an α amino ketone with dilute hydrochloric acid.

Further support to this theory is apparent from the behaviour of α anilino camphor failing to rearrange intramolecularly in pyridine, pyridine hydrobromide solution (page 62), practical results which are in agreement with theoretical deductions. As a matter of fact, the elimination of intramolecular rearrangement was the decisive feature in permitting the isolation of an intermediate product from this series, as any steric effect on

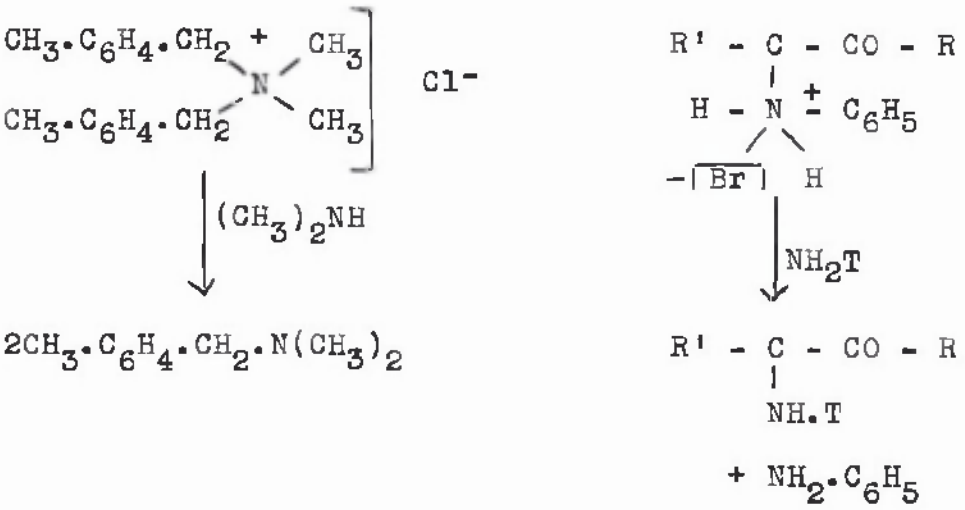
intramolecular rearrangement would promote the existence of the other.

Displacement.

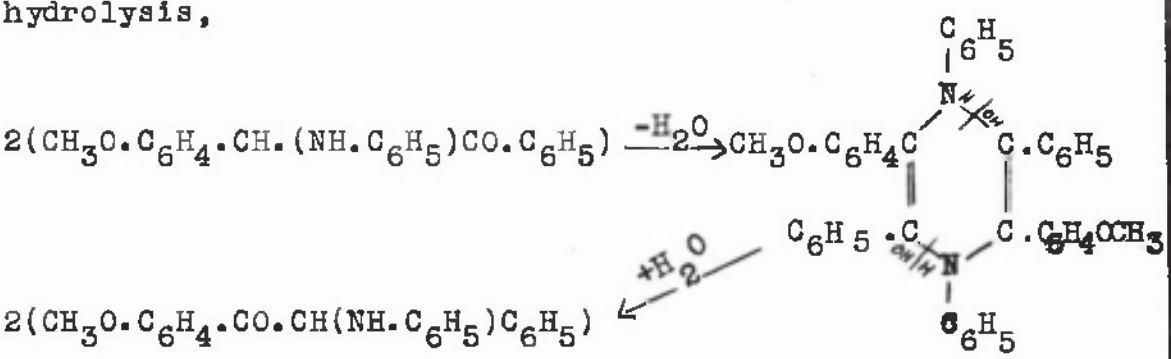
The discovery that displacement can be concurrent with and not dependent on rearrangement has helped to explain how the stable ∝ anilino p methoxy desoxybenzoin (IV) shows displacement of amine (Table II, b), but it has created difficulties which have not yet been explained. It will be observed that in most examples (Table VI) the displacement of amine from secondary bases by primary amine has been accomplished but no examples of displacement of amine using secondary amine media has occurred. In each example the production of a large amount of non-nitrogenous product could suggest fission in the molecule as has been observed with ∝ anilino camphor, etc. (page 63) when heated with pyridine, pyridine hydrobromide. The same results were obtained with ∝ anilino p methoxy desoxybenzoin (I) when heated in a sealed tube with pyridine, pyridine hydrobromide (page 43).

A close analogy to this phenomenon of displacement exists in the formation of p methyl benzyl dimethylamine from di-p methyl benzyl dimethylammonium chloride (72).

A contrast is outlined below:-

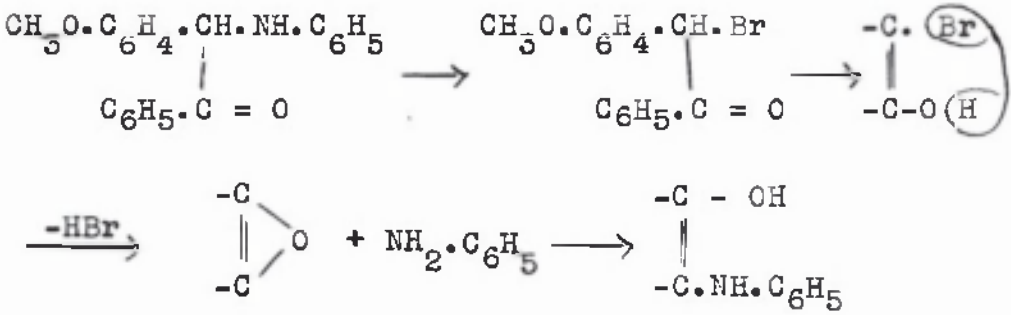


Attempts to explain rearrangement by the formation of a 1:4 dihydropyrazine ring system followed by hydrolysis,



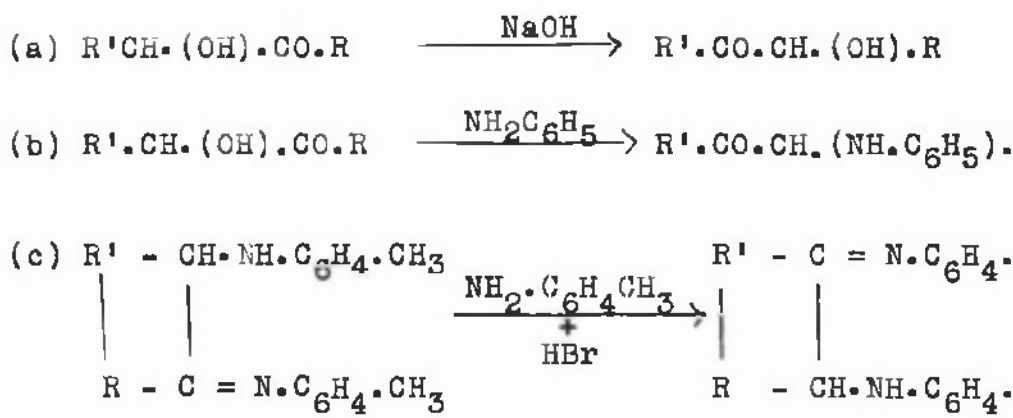
is contradicted by the failure of Mason & Winder (73) to hydrolyse an analogous system with dilute acids.

Moreover, the suggestion that the ∝ bromo compound is regenerated, followed by formation of an oxide ring as outlined below,



is disproved by the failure of ∝ bromo camphor to react with boiling aniline (page 56).

In conclusion it can be observed that a very close comparison of the benzoin series (a), ∝ anilino ketone series (b) and anil anilide series (c) can be drawn from the foregoing work; in each case the evidence of tautomerism has been proved.



(a) has been established experimentally by Buck & Ide (74), while evidence of the latter two is contained in this monograph (pages 18 ; 60).

ADDITIONAL PAPER.

Molecular Compounds of Certain Thio-derivatives.

Molecular Compounds of Certain Thio-derivatives.

Introduction.

On Pfeiffer's calculation (75) the number of instances of ternary (1:2*) type of crystalline complex formation is recorded as 1 - 2%.

Recently, however, Kent et al. (76, 77), by the choice of suitable compounds, both components (non-nitro and polynitro) and by minute modification of the structure of either or both, have prepared 75 new complexes, of which 44 (59%) were of ternary composition.

In the following paper a study of the effects of the replacement of oxygen by sulphur on the stability of complex formation of coumarin and various carbostyril derivatives is made, while an attempt to correlate the structure of the non-nitro component by its complex formation with s trinitro benzene is reviewed.

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*The nitro component is always mentioned first.

Experimental.

Preparation of Carbostyril.

Carbostyril was prepared by the treatment of quinoline with bleaching powder (78), (79).

A method of preparation by Tschitschibabin (80) and repeated by his co-workers for derivatives of carbostyril (81) gave no product even after repetition in minute detail.

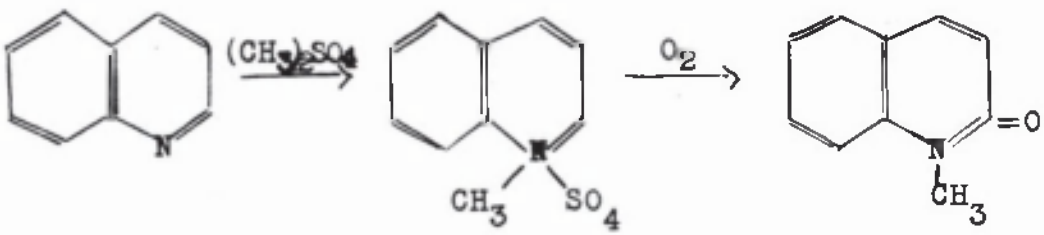
Henze's method (82) from quinoline, perbenzoic acid and benzoyl chloride gave a good yield, but the method was long and laborious.

Preparation of 2 thio carbostyril.

2 Thio carbostyril was obtained from carbostyril by heating with P_2S_5 (83).

N Methyl carbostyril.

N methyl carbostyril was easily prepared from quinoline by the method described by Spath (84)

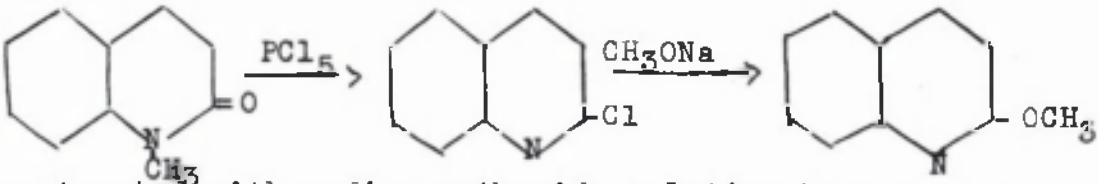


N methyl 2 thio carbostyril.

Thiolation (85) by fusing with P_2S_5 gave this product.

Carbostyril O methyl ether.

2 Chloro quinoline (84) prepared from N methyl carbostyril



was treated with sodium methoxide solution by a method analogous to that recorded by Friedlander & Ostermaier (86). The product distilled at 267 - 268°C. as a colourless liquid which readily darkened on standing.

2 Methyl thio quinoline (a methyl carbostyril) was prepared by two different methods, the second being the better preparation.

(a) Excess methyl mercaptan from the decomposition of methyl urea (87) by boiling with 5N caustic soda was bubbled into a methyl alcohol solution (10 c.cs.) containing sodium (17 gms.). To this solution was added 2 chloro quinoline (5 gms.) (vide supra), dissolved in methyl alcohol (5 ccs.) and refluxed for 2 hours. The solution after separation of sodium chloride was treated with successive quantities of picric acid (5 gms.). After separation of the sodium picrate 2 methyl thio

quinoline picrate separated. The crude product was crystallised from methyl alcohol, m.p., 182 - 184°C. Analysis gave 13.99% N; $(C_6H_3N_3O_7)C_{10}H_9NS_1$ requires 13.86% N.

Decomposition of this picrate with dilute sodium carbonate solution yielded a white product, which after drying, crystallised as white prisms, m.p., 57 - 59°C. from petrol ether (b.p., 40 - 60°C.). Analysis gave 8.15% N; $C_{10}H_9NS$ requires, 8.00% N. This product has not yet been described*. Its homologue, 2 ethyl thio quinoline, has been reported by Roos (88) as "A liquid which would not distil unchanged".

(b) By brief boiling of equimolecular proportions of 2 thio carbostyril with methyl picrate in methyl alcohol solution 2 methyl thio quinoline picrate was prepared. It crystallised as light yellow plates, m.p., 184 - 185°C. Admixture with the above product showed no depression. The yield was quantitative. Sodium bicarbonate solution decomposed this product to 2 methyl thio quinoline and sodium picrate.

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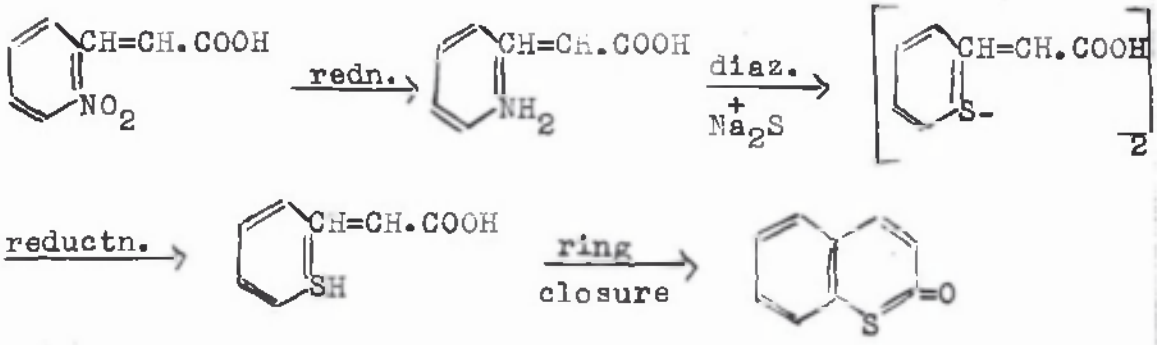
* Recently prepared by Beilenson, Hamer; J.C.S., 1939, 147.

2 Thio coumarin was prepared from coumarin by heating with P_2S_5 (89).

1 Thio coumarin was obtained by the following series of reactions:



6 Nitro cinnamic acid (90) was reduced with ammoniacal ferrous sulphate solution (91) to o amino cinnamic acid. The dithio acid (92) was reduced quantitatively by the method of Claaz (93). The dithio cinnamic acid (1 gm.) and anhydrous sodium acetate (.7 g.) were dissolved in water (3 ccs.) and glucose (.6 g.) was added. The mixture was heated on the water bath for 10 minutes and immediately acidified on cooling. The product was quickly dried before crystallisation from absolute alcohol.

Formation of Molecular Compounds.

It will be observed that absolute alcohol has been used generally as a solvent for the formation of molecular compounds from their components. This is dependent partly on the suggestion of authors (94) that the solubility of the components in the solvent media is a factor determining complex formation, partly to the view that it possesses widely different solubilities at its boiling point and at the temperature of crystallisation (room temperature). Moreover, for logical comparison of stability a common medium must, as far as possible, be employed. If no complex formation was observed, however, other solvents were tried.

A general method of preparation of the different complexes was used throughout the experimental section: ($\frac{1}{1000}$th gm. mol.) of the aromatic component and an equimolecular weight of nitro compound were accurately weighed and dissolved in absolute alcohol (6 - 8 ccs.). The solution was boiled for 5 - 10 minutes under reflux and allowed to cool, when crystals were deposited. These were filtered and examined practically. By reduction of the filtrate "solution evidence" as to the composition of the complex was obtained.

The specimen after purification was analysed.

(A) With s trinitro benzene (T.N.B.).

2 Thio carbostyril formed a 1:1 molecular compound crystallising from alcohol as light brown plates, m.p., 164 - 165°C. Analysis gave 15.3% N; calculated 15.0% N. Attempted crystallisation from benzene produced decomposition to its components.

Carbostyril O methyl ether formed a binary (1:1) compound in methyl alcohol solution. Stable to boiling with charcoal. Light yellow plates, m.p., 89 - 90°C. were obtained. Analysis gave 15.01% N; calculated 15.05% N.

N methyl 2 thio carbostyril yielded an unstable ternary complex, crystallising from concentrated solution of alcohol as orange red needles, m.p., 98 - 99°C. Analysis gave 12.53% N; $C_6H_3(NO_2)_3:2C_{10}H_9NS$ requires 12.43% N.

2 Methyl thio quinoline gave a stable (1:1) complex, crystallising from methyl alcohol as long light brown needles, m.p., 99 - 101°C. "Solution evidence" confirmed its composition, while analysis gave 14.51% N; $C_6H_3(NO_2)_3:C_{10}H_9NS$ requires 14.43% N.

2 Thio coumarin formed a stable (1:1) complex, crystallising from absolute alcohol as chocolate brown plates, m.p., 87 - 88°C. Analysis gave 11.2% N;

calculated 11.2% N. "Solution analysis" was in agreement with this composition.

1 Thio coumarin failed to give a complex either from alcohol, benzene or chloroform. No colouration was perceptible on solution of the components.

TABLE VII.

	Aromatic Component	Nitro Component	Complex			Page No.
			Comp.	M.P.	Colour	
a	Carbostyril	T.N.B.	1:2	178°C.	yellow	Ref.95
b	O Me Carbostyril	T.N.B.	1:1	89-90°C.	pale yellow	p. 88
c	6 Me Carbostyril	"	(1:2)*	-	-	Ref.77
d	4 Me Carbostyril	"	1:2	226-227°C	canary yellow	Ref.77
e	N Methyl C.	"	(1:1)*	-	-	Ref.77
f	Coumarin	"	(1:2)*	-	-	Ref.96
a'	2 Thio Carbostyril	T.N.B.	1:1	165°C.	light brown	p. 88
b'	s Me thio C.	T.N.B.	1:1	99-101°C	light brown	p. 88
c'	6 Me 2 thio Carbostyril	"	1:2	159-161°C	orange	Ref.77
d'	4 Me 2 thio Carbostyril	"	1:2	190-192°C	light brown	Ref.77
e'	N Me 2 thio Carbostyril	"	1:2**	98-99°C	orange	p. 88
f'	2 Thio Coumarin	"	1:1	86-87°C	chocolate brown	p. 88
g'	1 Thio Coumarin	"	-	-	-	p. 88a

* These have been determined by a melting point curve, and show no stable or coloured crystalline derivatives.

** Denotes unstable compounds in dilute alcohol solution.

(B) With picric acid.

2 Thio carbostyril gave a stable molecular picrate crystallising from absolute alcohol as crimson needles, m.p., 144 - 145°C. Analysis showed its composition to be (1:1): found 14.1% N; calculated 14.4% N. Confirmed by "solution evidence".

N methyl 2 thio carbostyril formed a molecular picrate of the ternary variety, unstable in dilute absolute alcohol solutions. Crystallises from concentrated solution as bright orange prisms, m.p., 104 - 105°C. Analysis gave 12.34% N; calculated 12.08% N.

N methyl carbostyril yielded a salt picrate crystallising from alcohol as long yellow needles, m.p., 128 - 129°C. Analysis gave 14.53% N; calculated 14.43% N. Solution evidence confirmed its (1:1) composition.

2 Methyl thio quinoline picrate (see page 84).

2 Thio coumarin picrate (97) crystallised as a yellow "salt like" picrate from alcohol, m.p., -118°C.

1 Thio coumarin picrate formed a yellow (1:1) picrate, m.p., -148°C. It crystallised from alcohol as yellow needles. Analysis gave 10.8% N; calculated 10.7% N.

TABLE VIII.

	Aromatic Component	Nitro Component	Complex			Page No.
			Comp.	M.P.	Colour	
a	Carbostyril	P.A.	1:1	132°	greenish yellow	Ref.98
b	O Methyl C	"	1:1	170-171°	greenish yellow	Ref.99
c	6 Methyl C	"	-	-	-	-
d	4 Methyl C	"	1:1	165-167°	yellow needles	Ref.100
e	1 Methyl C	"	1:1	129°	greenish yellow	Ref.77
f	Coumarin	"	1:1	112°	greenish yellow	Ref.101
a'	2 Thio Carbostyril	"	1:1	145°	crimson	p. 90
b'	s Methyl Thio C	"	1:1	173-175°	greenish yellow	p. 84
c'	6 Methyl 2 Thio C	"	1:2	140-142°	scarlet	Ref.77
d'	4 Methyl 2 Thio C	"	1:2	193-195°	orange red	Ref.77
e'	1 Methyl 2 Thio C	"	1:2*	104-105°	orange	p. 90
f'	2 Thio Coumarin	"	1:1	118°	greenish yellow	Ref.101
g'	1 Thio Coumarin	"	1:1	148-149°	greenish yellow	p. 90

*Unstable in dilute alcohol.

Discussion.

Trinitro benzene derivatives.

From the above table a contrast of the effect of the replacement of oxygen by sulphur on the stability is apparent.

In 3 well defined examples, c, e and f, no crystalline derivatives have been isolated, while with c', e' and f', their thio counterpart, markedly stable crystalline compounds have been obtained. There is, however, with the latter two substances a change in composition, e showing binary formation, while e' is ternary and vice versa with f and f'.

This latter phenomenon, in this limited field of study, might be interpreted as a change in structure of the non-nitro component. For example, c and c', d and d', e and e' being 1:2 as formed by the 3, 4, 5 and 7 methyl homologues (77) could suggest the amide formation $\diagdown_{NH}\diagup C = O$ for carbostyril, while the hydroxy quinoline form is supported by b and b' (97). It is difficult, however, to explain the positions of a' and e in this scheme.

O methyl carbostyril, b, is an interesting contradiction to the hypothesis that complex formation is a factor of solubility of the components (94), as this compound is a mobile liquid very soluble in alcohol.

The replacement of "oxonium oxygen" in coumarin has no influence on complex formation, whereas the replacement of ketonic oxygen increases the stability of its complexes.

Picrates.

Three different types of picrates have been observed among these compounds (Table VII). Carbostyril picrate (98), although apparently "salt-like", is extremely soluble in ether. N methyl quinolonium picrate (77) is a true salt picrate, while 6 methyl 2 thio carbostyril and N methyl thio carbostyril picrates are unstable ternary "molecular" compounds.

The formation of methyl picrates and their decomposition have been discussed (page 84).

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