STUDIES IN THE HETEROCYCLIC SERIES.

By

George B. Dodds, B.Sc.

Thesis for the Degree of Doctor of Philosophy.

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G E N E R A L I N D E X.

STUDIES IN THE INDOLE SERIES. PART II. DERIVATIVES OF 2-PHENYLINDOLE

BY

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AND

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263. *Studies in the Indole Series. Part II. Derivatives of 2-Phenylindole.*

By E. B. Womack, Neil Campbell, and G. B. Dodds.

Nitrous acid is shown to form with 2-phenylindole, not only the 3-oximino-compound, but also 3-nitro-2-phenylindole and a dinitroindole identical with that formed by the direct nitration of 2-phenylindole; the second nitro-group is shown to be in the 5-position. Attempts to prepare a trinitro-2-phenylindole were unsuccessful.

The properties of 3-nitroso-2-phenyl-1-methylindole have been further investigated. An easy method for preparing 2′- and 4′-nitrodeoxybenzoins has been obtained, and the reduction of these compounds studied. An improved method for the preparation of *p*-nitrobenzil is given.

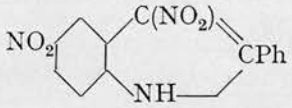
CAMPBELL and COOPER (J., 1935, 1208) suspected that, when an excess of nitrous acid acts upon 2-phenylindole, it not only forms the 3-oximino-compound but also oxidises the latter to the corresponding nitro-compound and effects nitration of the benzene ring. We have now shown that nitrous acid readily accomplishes the oxidation, and when in large excess it forms the dinitro-2-phenylindole first obtained by Angeli and Angelico (*Gazzetta*, 1900, **30**, 268), though their method of preparation is much superior. The m. p. of this dinitro-2-phenylindole was given as " above 280°," and no definite structure was assigned to it. We have obtained the compound in the pure state with a definite m. p. of 312°, and have proved it to be 3 : 5-dinitro-2-phenylindole (I) by oxidation with potassium permanganate in glacial acetic acid to 5-*nitro*-N-*benzoylanthranilic acid*. This nitration of the benzene ring in position 5 is paralleled by the nitration of 2 : 3-dimethylindole (Bauer and Strauss, *Ber.*, 1932, **65**, 308; Plant and Tomlinson, J., 1933, 955). By analogy, the dinitro-2-methylindole of Walther and Clemen (*J. pr. Chem.*, 1900, **61**, 249) is probably the 3 : 5-dinitro-compound.

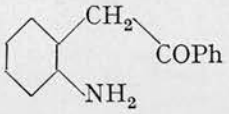
Since Mathur and Robinson (J., 1934, 1415) nitrated dinitro- to a trinitro-2-methylindole, we attempted to prepare trinitro-2-phenylindole by the same method. From the reaction mixture, however, only unchanged dinitro-2-phenylindole was obtained, whilst with stronger nitrating agents oxidation occurred, giving acidic compounds containing 5-nitro-*N*-benzoylanthranilic acid.

The properties of 3-nitroso-2-phenyl-1-methylindole have been further investigated. Although this is a true nitroso-compound, many of its properties are anomalous. All attempts to oxidise it to the corresponding nitro-compound failed. With alkaline permanganate, oxidation did occur, but the product was a colourless acid, and hence ring fission had taken place. It had been noted earlier that it did not condense with aniline (Campbell and Cooper, *loc. cit.*) : this work has been repeated with aniline, *p*-nitroaniline, and *p*-bromoaniline, but in all cases only the unchanged compound was obtained. Further, the nitroso-compound gave no colour with glacial acetic acid and diphenylamine (nitrosobenzene gives a pink coloration), formed no dye with hydroxylamine hydrochloride and α-naphthol, and liberated iodine from acidified aqueous-alcoholic potassium iodide much less readily than nitrosobenzene. Both in appearance and in some of its chemical properties, 3-nitroso-2-phenyl-1-methylindole resembles *p*-nitrosodimethylaniline rather than nitrosobenzene, for the former gives no colour with glacial acetic acid and diphenylamine, and liberates iodine from potassium iodide solution more slowly than does the latter.

With certain nitroso-compounds it is not possible to carry out the Liebermann reaction owing to sulphuric acid itself producing a coloration, and this also applies to the Angeli–Castellana reaction (*Atti R. Accad. Lincei*, 1905, **141**, 669), but the latter may be modified by using acetic acid instead of sulphuric acid. *C*-Nitroso-compounds such as nitrosobenzene give a pink coloration after a few minutes.

In the course of these investigations we have repeatedly attempted to prepare 2-phenylindole by the reduction of 2′-nitro- (so-called *o*-nitro-)deoxybenzoin with zinc dust and ammonia, as recorded by Pictet (*Ber.*, 1886, **19**, 1064) and List (*Ber.*, 1893, **26**, 2451), but no appreciable quantity of that compound could be isolated, the product being a crystalline compound of sharp m. p. which we believe to be 2′-*aminodeoxybenzoin* (II).

(I.) 



(II.)

The nitrodeoxybenzoin used by Pictet was a crude oily product (yield not quoted) which List showed to contain 25—30% of 2′-nitrodeoxybenzoin. We obtained the pure compound by nitrating deoxybenzoin with Menke's reagent (*Rec. Trav. chim.*, 1925, **44**, 141,

269), the resulting mixture of 2′- and 4′-isomers being easily separated into its constituents with ether. The reduction of both compounds yielded the corresponding aminodeoxybenzoins, though the 2′-compound afforded a trace of 2-phenylindole and in certain conditions larger quantities were obtained.

The formation of 2-phenylindole establishes the orientation of the 2′-amino-compound, and presumably the so-called *p*-isomer is the 4′-compound (Beilstein nomenclature). This was confirmed by the fact that 4′-nitrodeoxybenzoin, prepared as above, was identical with the nitrodeoxybenzoin prepared from *p*-nitrophenylacetyl chloride and benzene by the Friedel–Crafts reaction (Petrenko-Kritschenko, *Ber.*, 1892, **25**, 2242). The 4′-aminodeoxybenzoin was shown to be identical with that prepared by Golubew (*Ber.*, 1873, **6**, 1252) by reduction of *p*-nitrobenzil, though the mixed m. p. determination was not completely satisfactory, for the amino-compounds decompose on standing owing, possibly, to the condensation of the carbonyl group of one molecule with the amino-group of another.

We have improved Chattaway and Coulson's preparation of *p*-nitrobenzil (J., 1928, 1080).

Experimental.

The m. p.'s recorded were obtained with Kofler's micro-apparatus (" Mikroskopische Methoden in der Mikrochemie ") and calibrated thermometers. In agreement with his claims, the apparatus was found to be much more satisfactory than the ordinary capillary m. p. apparatus. Most of the analyses were done by Dr. Weiler, Oxford, and Mr. W. Brown, Edinburgh. 2-Phenylindole and 3-oximino-2-phenylindole were prepared by the procedure reported by Campbell and Cooper (*loc. cit.*).

Action of Nitrous Acid on 3-*Oximino- and* 3-*Nitro*-2-*phenylindole.*—The oximino-compound (1 g.) was suspended in boiling glacial acetic acid (15 c.c.) and treated with sodium nitrite (0·35 g.; 1 equiv.). The resulting precipitate crystallised from alcohol in yellow needles, and was shown by m. p. and mixed m. p. (236—238°, lit., 238°) to be 3-nitro-2-phenylindole; yield quantitative.

3-Nitro-2-phenylindole (2 g.), when treated in boiling glacial acetic acid with a large excess of sodium nitrite (5 g.), yielded a mixture of unchanged compound and a small amount (0·3 g.) of a yellow crystalline substance which was insoluble in alcohol and cold acetic acid and melted at 312° (decomp.). It was identified as 3 : 5-dinitro-2-phenylindole (I), and shown (mixed m. p.) to be identical with the dinitro-2-phenylindole prepared by Angeli and Angelico (*loc. cit.*). It was best prepared as follows. 2-Phenylindole (10 g.) was mixed with concentrated nitric acid (100 c.c.), and after a brisk reaction the dinitro-compound separated; it was purified by dissolution in dilute sodium hydroxide and precipitation with nitric acid, and crystallised in yellow plates (glacial acetic acid), m. p. 312°.

Oxidation of 3-*Oximino-*, 3-*Nitro-, and* 3 : 5-*Dinitro*-2-*phenylindole.*—Many oxidising agents were used, but the most satisfactory was potassium permanganate in glacial acetic acid. 3-Oximino- or 3-nitro-2-phenylindole (0·4 g.) was dissolved in glacial acetic acid and heated under reflux with powdered potassium permanganate (1 g.) for 3 hours, and the product poured into water. After decolorisation of the solution by sulphurous acid, a creamy precipitate of benzoylanthranilic acid was obtained, which was crystallised from alcohol, m. p. 179—181° (lit., 181°); yield 0·2 g. The compound was purified by dissolving it in dilute sodium hydroxide, removing any insoluble matter, and reprecipitating with dilute sulphuric acid. 3 : 5-Dinitro-2-phenylindole by the same treatment yielded 5-nitro-*N*-benzoylanthranilic acid, m. p. 257—258°, identical with an authentic specimen prepared as described below.

5-*Nitro*-N-*benzoylanthranilic Acid.*—5-Nitroanthranilic acid (Bogert and Scatchard, *J. Amer. Chem. Soc.*, 1919, **41**, 2066) could not be benzoylated in benzene by benzoyl chloride, but in pyridine 5-*nitro*-N-*benzoylanthranil* was easily obtained, m. p. 178—180° (Found : C, 62·8; H, 3·3; N, 10·4. $C_{14}H_8O_4N_2$ requires C, 62·7; H, 3·0; N, 10·4%). By hydrolysis with boiling hydrochloric acid, 5-*nitro*-N-*benzoylanthranilic acid* was obtained, m. p. 257—260° (Found : C, 59·3; H, 4·1; N, 9·6. $C_{14}H_{10}O_5N_2$ requires C, 58·8; H, 3·5; N, 9·8%).

Attempted Nitration of 3 : 5-*Dinitro*-2-*phenylindole.*—3 : 5-Dinitro-2-phenylindole (2 g.) was boiled with concentrated nitric acid (10 c.c.) for 15 minutes, and the solution cooled. The colourless solid so obtained was obviously a mixture, but after several crystallisations from aqueous alcohol a small amount of 5-nitro-*N*-benzoylanthranilic acid was obtained.

Nitration of Deoxybenzoin.—Deoxybenzoin (10 g.) was dissolved in acetic anhydride (50 c.c.), and cupric nitrate (15 g.) added slowly, the mixture being continuously stirred and the

temperature maintained at 25—30°. The mixture was then kept for an hour at room temperature, and poured into water (300 c.c.). The resulting solid (10 g.) was extracted with cold ether (100 c.c.), the 2′-compound dissolving and the 4′-isomer remaining. The nitro-compounds were purified by crystallisation first from benzene–light petroleum (b. p. 60—80°) (1 : 1), and then from alcohol: 2′-compound, m. p. 72—74° (lit., 73—74°), yield 6 g.; 4′-compound, m. p. 138—140° (lit., 141—142°), yield 2 g. Quantities up to 35 g. of deoxybenzoin have been nitrated by this method, but the temperature must be maintained between 25° and 30°: below 25° nitration does not occur, and above 30° oxidation to benzils takes place. Both compounds were identified by oxidation to the corresponding nitrobenzoic acids, and by their oximes and dinitrophenylhydrazones. 2′-*Nitrodeoxybenzoin*-2 : 4-*dinitrophenylhydrazone*, prepared by Brady's method (J., 1931, 756), was obtained in orange prisms (from tetralin), m. p. 219—221° (Found: N, 16·5. $C_{20}H_{15}O_6N_5$ requires N, 16·6%), and the 4′-*isomeride* was similarly obtained as orange-red prisms, m. p. 233—234° (Found: N, 17·0%). 4′-Nitrodeoxybenzoin was shown to be identical with the compound prepared as below.

Preparation of 4′-*Nitrodeoxybenzoin*.—Petrenko-Kritschenko's method (*loc. cit.*) was used with the following modifications. After the brisk reaction with aluminium chloride, the mixture was heated on the water-bath for an hour and then poured on ice and concentrated hydrochloric acid. The benzene layer was separated, more benzene being added if necessary to dissolve any remaining solid, and the solution was heated for an hour under reflux with good animal charcoal. The solution was filtered, an equal volume of light petroleum (b. p. 60—80°) added, and the mixture kept for 2 hours. The resulting precipitate was crystallised repeatedly from alcohol (charcoal); m. p. 141—142°, yield poor.

Reduction of 2′- *and* 4′-*Nitrodeoxybenzoins*.—In our hands the method of Pictet (*loc. cit.*) and List (*loc. cit.*) afforded a dark tarry product, which gave a definite pine-splint reaction but yielded only a very small amount of 2-phenylindole by tedious treatment with ligroin. A more satisfactory result was obtained when 2′-nitrodeoxybenzoin (5 g.) was treated with excess zinc dust in concentrated ammonia (25 c.c.). After reduction was complete, the mixture was filtered, and on neutralisation with dilute sulphuric acid yielded yellow crystalline 2′-*aminodeoxybenzoin* (II) (3 g.), which after crystallisation from alcohol melted at 170° (Found: C, 80·7; H, 5·2; N, 6·7. $C_{14}H_{13}ON$ requires C, 80·0; H, 6·2; N, 6·6%). The compound dissolved in hydrochloric acid, and decomposed on standing; a solution in acetic anhydride, after being kept at room temperature for several days, gave the pine-splint test, but no 2-phenylindole could be isolated. 4′-Nitrodeoxybenzoin, when reduced in a similar manner, gave 4′-aminodeoxybenzoin, m. p. 94—96° (lit., 95—96°), identical with the amine formed in very poor yields by reduction of *p*-nitrobenzil (Golubew, *loc. cit.*). Attempts to prepare picrates and acetyl and benzoyl derivatives of the amines were unsuccessful.

2-Phenylindole (1 g.) was obtained by reducing 2′-nitrodeoxybenzoin (6 g.) with zinc dust and glacial acetic acid, 4 g. of the nitro-compound being recovered unchanged.

Preparation of p-*Nitrobenzil*.—Pure benzoin (200 g.) was suspended in acetic anhydride (1000 c.c.), and the mixture cooled in ice. Concentrated sulphuric acid (200 c.c.) was added, and the mixture stirred and cooled to 0°. Potassium nitrate (110 g.) was added in small quantities, and the mixture then kept for 2 days at room temperature before being poured into water. The oil which separated was washed with water, extracted with ether, and the ether evaporated, leaving an oil which soon solidified and was crystallised twice from alcohol or acetone; m. p. 127—128° (lit., 125°), yield 60%. The compound was shown to be identical with the acetyl derivative of *p*-nitrobenzoin obtained by Francis and Keene (J., 1911, **99**, 344). *p*-Nitrobenzil was obtained by heating the acetyl compound (5 g.) with concentrated nitric acid (14 c.c.) on the water-bath for 1 hour and pouring the solution into water. The resulting precipitate was crystallised three times from glacial acetic acid; m. p. 142° (lit., 142°), yield 4 g.

Thanks are expressed to the Carnegie Trust for the Universities of Scotland for the award of a Teaching Fellowship to one of us (N. C.), to the Moray Fund for a grant, and to Dr. G. S. Learmonth for the method of preparation of *p*-nitrobenzil.

UNIVERSITY OF EDINBURGH. [*Received, July 20th*, 1938.]

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General Introduction

This thesis covers different fields in heterocyclic chemistry, and is divided for convenience into three main parts.

Part 1. Studies in the Indole Series.

Part 2. The Reactivity of Halogen Atoms in some Heterocyclic Molecules.

Part 3. A short Study of the Structure of 3-Benzeneazo-2-phenylindole.

For each part an introduction is given, outlining the work already covered on the subject; an experimental section giving the work done in the present investigations; and a discussion of the results obtained.

PART 1. STUDIES IN THE INDOLE SERIES.

A. The Mechanism of the Fischer Indole Synthesis.

B. Pictet's Method for the Preparation of 2-Phenylindole.

C. Nitration of 2-Phenylindole with Nitrous Acid and an Investigation of the Properties of 1-Methyl-2-phenyl-3-nitroso-indole.

I N T R O D U C T I O N

A. The Mechanism of the Fischer Indole Synthesis.

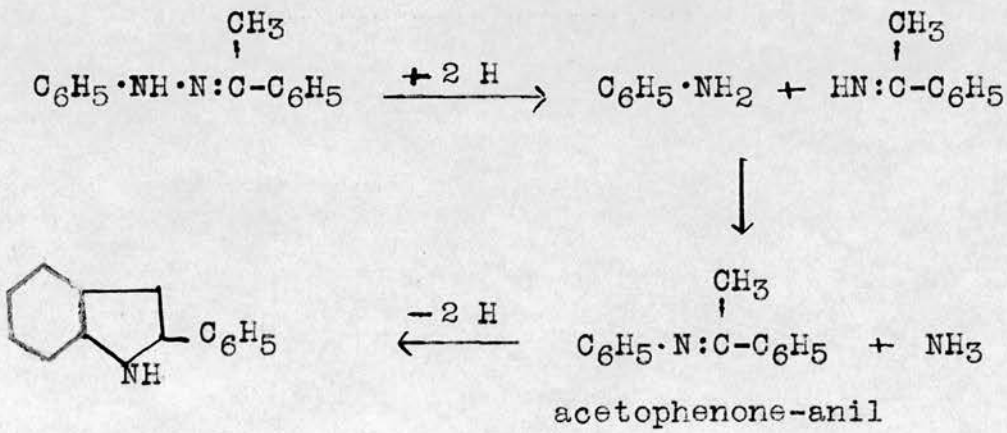
The mechanism of Emil Fischer's well known synthesis of indoles by the deamination of Aryl hydrazones, is a problem which has not yet been completely elucidated. Four theories have been put forward to explain the course of this reaction —— those of Brunner (1898), Reddelien (1912), Cohn (1919) and Bamberger and Landau (1919). Since Robinson and Robinson have taken the theory of Brunner, and brought forward evidence to support it, they may now, with good reason, claim it as their own.

The theories of Cohn (Die Carbazolegruppe,

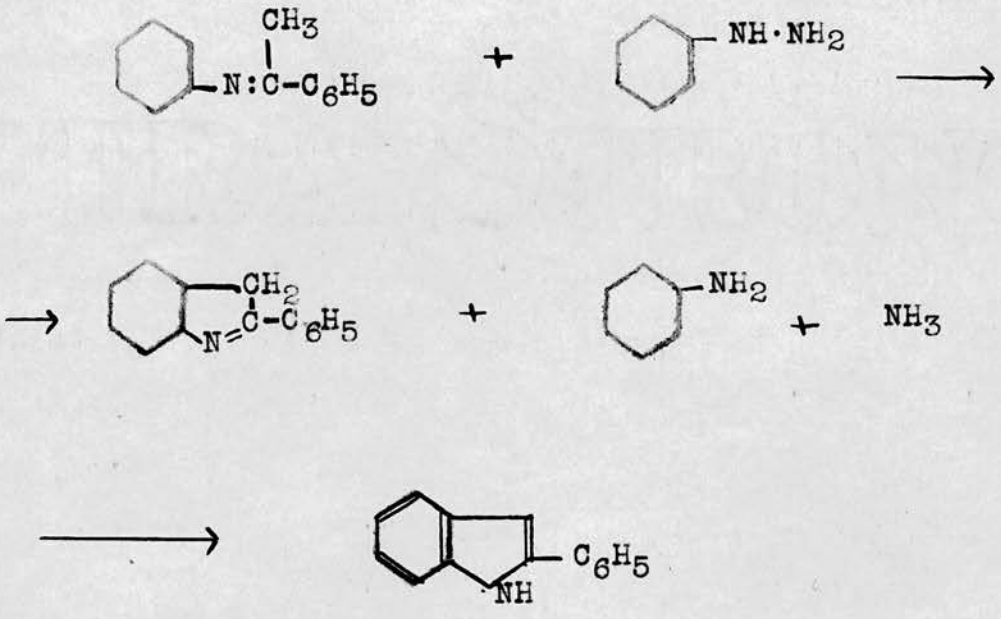
page 12) and Bamberger and Landau (Ber., 1919, 52, 1097) have been fully discussed in the literature, and vital objections have been brought against them by Hollins (J.A.C.S., 1922, 44, 1598) and by Robinson (J.C.S., 1924, 125, 827) so that these need not be further considered for the purpose of this thesis.

The theory of Reddelien (Ann., 1912, 388, 179) has been supported chiefly by Hollins (loc. cit.) who has brought forward a great deal of evidence in its favour, but on the other hand, it has been definitely criticised by Robinson. Final disproof of the theory has been shown by Bodforss (Ber., 1912, 45, 2150) , and by Cooper (Thesis 1934) who repeated the work of Bodforss in view of the uncertainty arising out of some of his results.

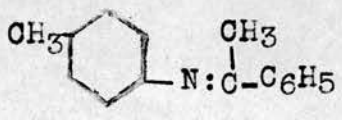
According to Reddelien the formation of 2-phenylindole from acetophenone-phenylhydrazone by the Fischer synthesis follows the course:-



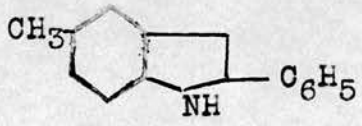
This view was based on the observation that 2-phenylindole was also formed by fusing together at 250° acetophenone-anil with phenylhydrazine zincichloride, a reaction which Reddelien interpreted as an oxidation of the anil by the phenylhydrazine- by the removal of two hydrogen atoms.



Thus fusion of acetophenone-p-tolil with phenylhydrazine-zincichloride should yield 2-phenyl-p-toluindole, and employment of the o-tolil instead of the p-tolil, should give 2-phenyl-o-toluindole.



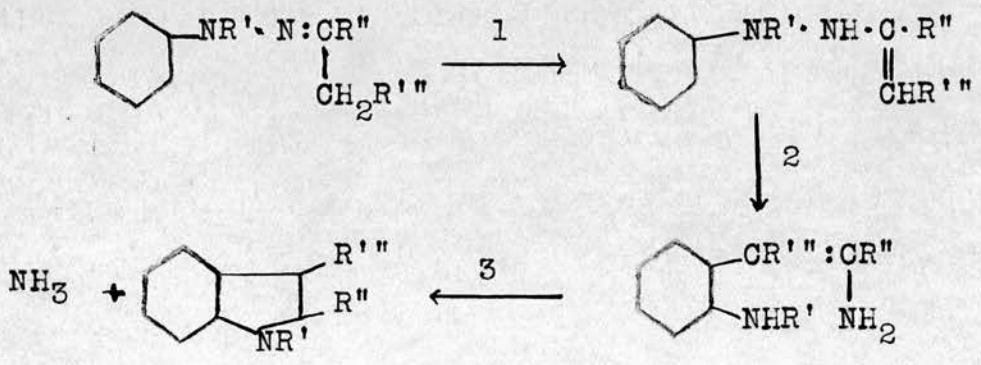
acetophenone-p-tolil



2-phenyl-p-toluindole

Cooper (thesis 1934) carried out these fusions and in each case isolated only 2-phenylindole. He explained the reaction as a double decomposition between the tolil (or anil) and the hydrazine with the production of a hydrazone, which under the influence of the zinc chloride was immediately converted into an indole derivative, as in a Fischer fusion. This work has rendered Reddelien's mechanism untenable, and Robinson's theory alone remains to explain the mechanism of the Fischer indole synthesis. Though not yet proved, the correctness of the theory is more than probable, as it gives an adequate explanation of all the observed phenomena, while no valid objection to it has yet been made. The intention of this thesis was to attempt to find proof for this theory.

Robinson's theory of the Fischer synthesis postulates an ortho-benzidine conversion thus:-

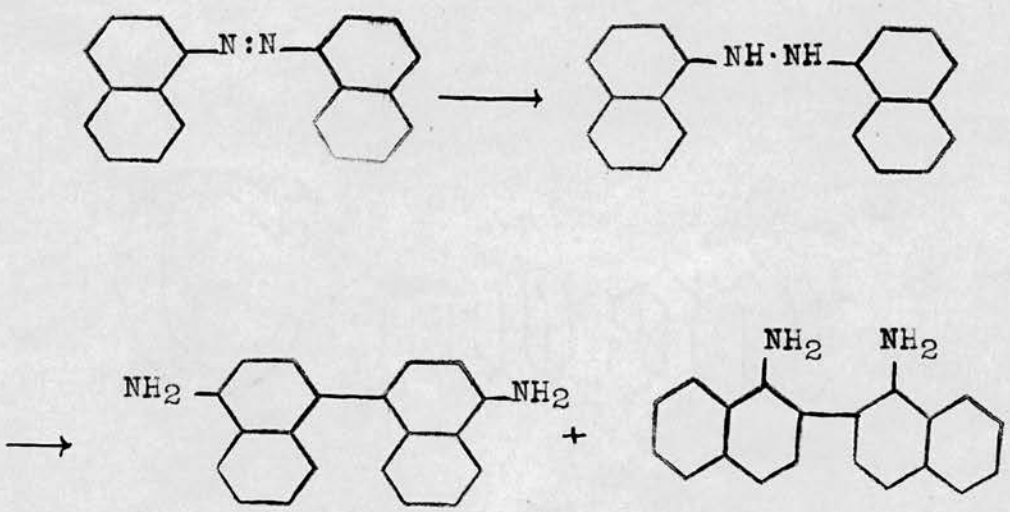


Considerable support for this theory may be adduced.

For each stage in the scheme well known analogies can be cited. Stage (1.), the transformation from enimic to enamic form is analogous to the ketone-enol isomerisation, and indeed involves such a change in the ketone part of the hydrazone. Therefore, if this theory is correct, it should be easier to form indoles from the hydrazones of easily enolisable ketones, than from the hydrazones of ketones enolised with difficulty. That this deduction is in accordance with experience is supported by the fact that phenyl-acetaldehyde-phenylhydrazone is easily converted into 3-phenylindole by boiling with alcoholic hydrochloric acid, (Fischer and Schmitt, Ber., 1888, 21, 1072), whereas acetophenone-phenylhydrazone is only converted into 2-phenylindole on fusing with zinc chloride at 180° (Fischer, Ann., 1886, 236, 133). This on Robinson's theory would be attributed to the fact that acetophenone is not easily enolisable, whereas phenylacetaldehyde is, a contention supported by the fact that only the latter gives an acetyl derivative on boiling with acetic anhydride (Semmler, Ber., 1909, 42, 584).

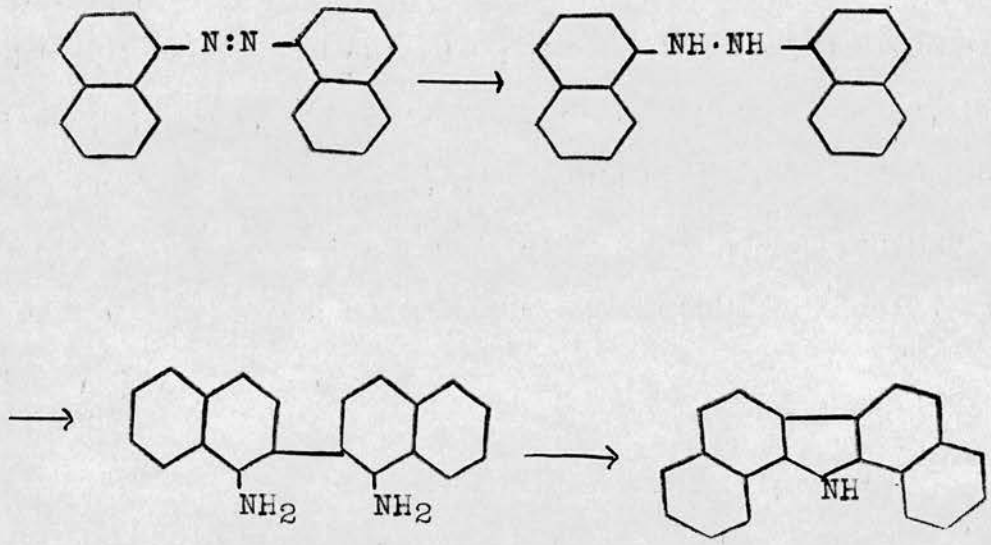
The ortho-benzidine conversion postulated in stage (2.), is a well known transformation, being

especially noted in the naphthalene series. For example, reduction of α-azonaphthalene with stannous chloride and hydrochloric acid yields naphthidine and dinaphthyline, those two substances being formed, under the action of the acid, by para-benzidine and ortho-benzidine conversions respectively from the primary product α-hydrazonaphthalene (Nietski and Goll, Ber., 1885, 18, 3252).

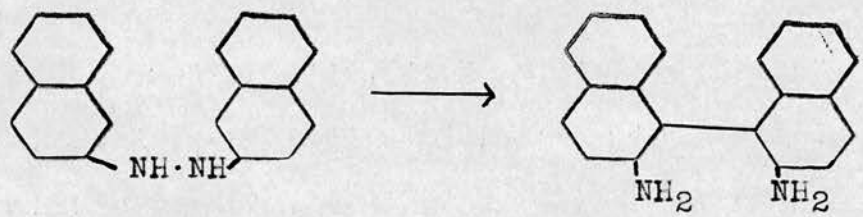


Naphthidine. Dinaphthyline.

Incidentally, it is to be noted that dinaphthyline on boiling with hydrochloric acid yields dinaphthacarbazole, so that the whole process of formation of this latter substance from α-azonaphthalene follows precisely the course postulated by Robinson as occuring in the Fischer indole synthesis.

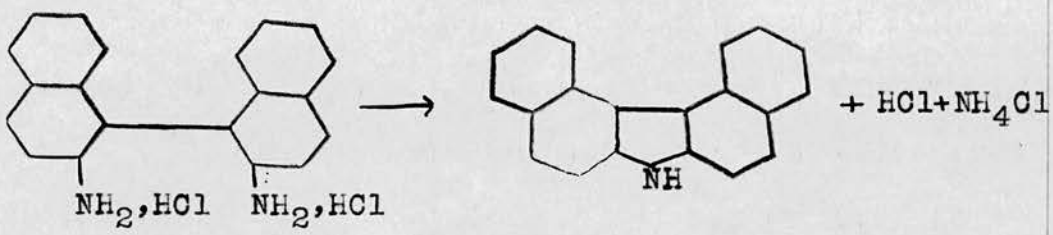


A second example of the ortho-benzidine conversion is the formation of 2:2'-diamino-1:1'-dinaphthyl from β-hydrazonaphthalene (Meisenheimer and Witte, Ber., 1903, 36, 4161).

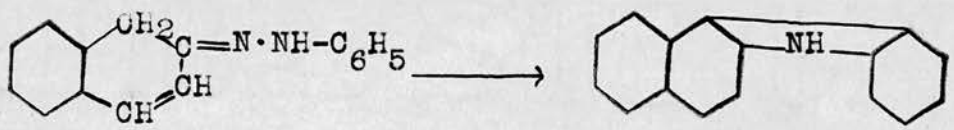


β-hydrazonaphthalene. 2:2'-diamino-1:1'-dinaphthyl,

This diamine can also be converted into a carbazole in the usual way by loss of ammonia on fusing the hydrochloride at 250° (ibid.).

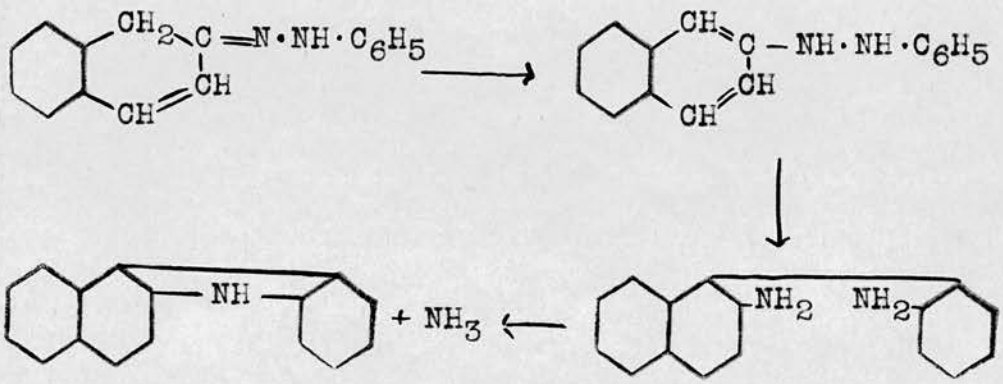


Japp and Maitland (J.C.S., 1903, 83, 267) prepared carbazoles by heating phenols with phenylhydrazine and phenylhydrazine-hydrochloride. The authors consider that the phenols react in tautomeric keto forms to give hydrazones which then undergo an ordinary Fischer reaction thus:-



In Robinson's opinion this habit of referring the reactions of phenols to their keto modifications is a retrograde step, and in any case even if such a hydrazone were formed, the next step would , according to his theory, be the production of a hydrazine, which would then undergo an ortho-benzidine

transformation followed by the loss of ammonia.

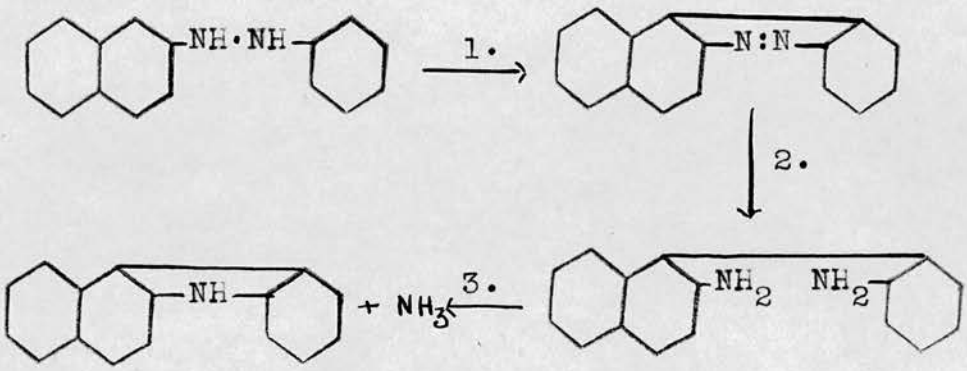


11. 1.

Evidence supporting this view of this reaction has been supplied since then by Fuchs and Niszel (Ber., 1927, 60, 209) who prepared the carbazole (11.) by the reaction of phenylhydrazine sodium bisulphite on β-naphthol, and isolated the diamine (1.) from the reaction mixture. They also showed that this diamine is converted, in excellent yield, into the carbazole (11.) by the action of sulphur dioxide.

Unfortunately the yield of the diamine was only 5% so that the experiment is open to the objection, actually made by Neber, Knoller, Herbst and Trissler (Ann., 1929, 471, 113) that this substance is not an intermediate product of the main reaction, but the product of some secondary reaction

such as the following:-



Stage (1.) is represented as being analogous to the formation of -azonaphthalene by reduction of -nitro-naphthalene (Meisenheimer and Witte, Ber., 1903, 36, 4153). Presumably, in Neber's scheme, the oxidation in stage (1.) is effected by the phenyl-hydrazone.

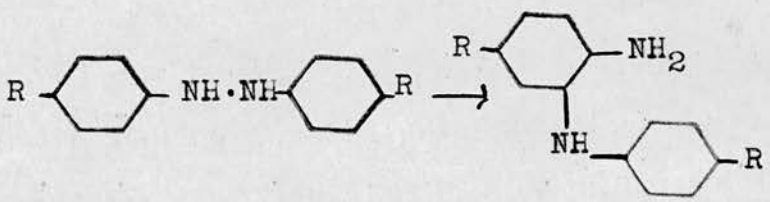
$$C_6H_5{\cdot}NH{\cdot}NH_2 + 2(H) \longrightarrow C_6H_5{\cdot}NH_2 + NH_3$$

or by the reaction involved in stage (2.)

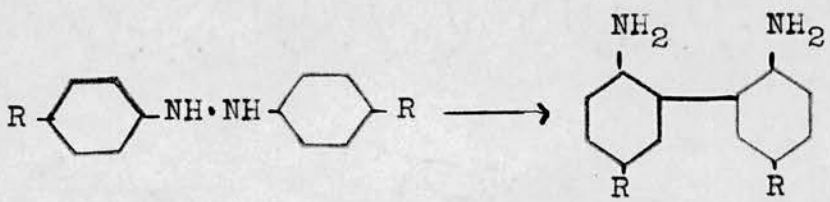
Stages (2.) and (3.) of course, represent well known general reactions —— disruptive hydrogenation of the azo-group, and carbazole formation from an o:o'-diamino-dinaphthyl.

The validity of Neber's objection, however, is open to question, and his alternative explanation of the production of the diamine (1.) does not seem

very probable. The chief criticism levelled at Robinson's theory is that all well established benzidine conversions take place in the para sense unless the para position is blocked by a substituent, which is not generally the case in a Fischer synthesis. Even in cases where such blocking does occur, and the blocking substituent is not eliminated to allow of a para-conversion, the usual transformation is an ortho-semidine one



rather than an ortho-benzidine one.



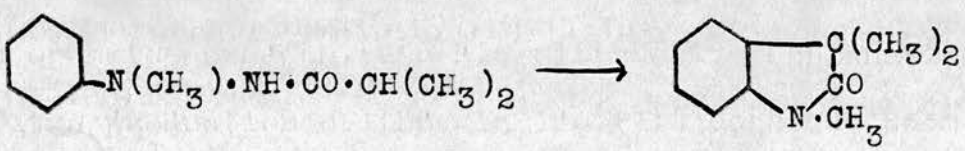
It should, however, be stressed, as Hollins pointed out, that if an ortho-benzidine conversion does take place, at least part of the hydrazone should undergo the more usual para-conversion. There is no evidence of this, although, as Robinson states, these products, even if formed, would, on account of their great reactivity, be obtained only as tars ____ and a certain amount of tarring always takes place in a

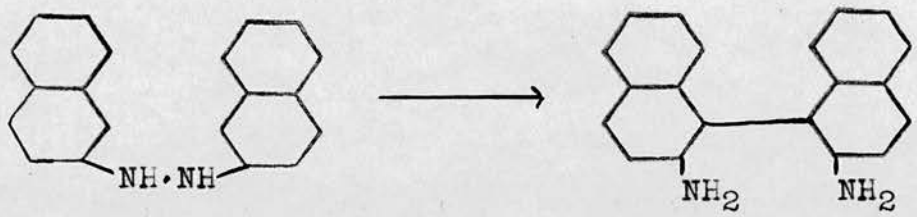
zinc chloride fusion.

A complete answer to this type of objection has, however, been put forward by Robinson in the shape of a general theory of the benzidine transformation (J.C.S., 1918, 113, 639). According to this theory only an ortho-benzidine change is possible.

It is further pointed by Robinson that "the necessary conditions for a Fischer synthesis, namely the acid reagent and a high temperature" are precisely the conditions which would favour each of his postulated stages if considered separately. Moreover each stage is more basic than its predecessor, a generally observed phenomenon in intramolecular transformations brought about by an acid reagent. The loss of basicity at the last stage is due to an accident, namely ring formation.

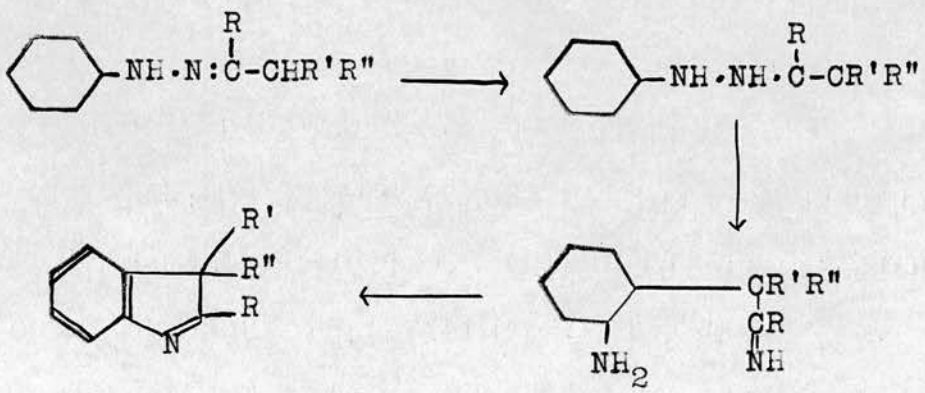
This statement, however, requires to be modified, as may be seen by reference to the two reactions actually mentioned by Robinson himself, namely, the Fischer synthesis of oxindoles from acid hydrazides, and the ortho-benzidine conversion of β-hydrazonaphthalene to 2:2'-diamino-1:1'-dinaphthyl.



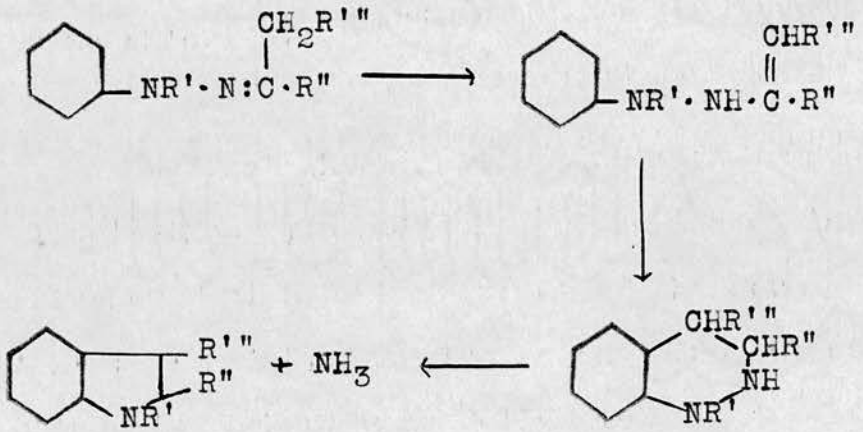


Both of these reactions are brought about by strong alkalis. Also the work of Korczynski , Brydowna and Kierzek (Gazz., 1925, 55, 361) shows that the Fischer synthesis is catalised quite readily by such neutral substances as powdered metals, the yields obtained (60% - 65%) being almost as good as with zinc chloride.

One fact which Hollins quoted in support of Reddelien's theory, namely the production of indolenines by a Fischer fusion of hydrazones of the form C_6H_5·NH·N:CR·CHR'R", can also be explained as easily by Robinson's mechanism as follows:-

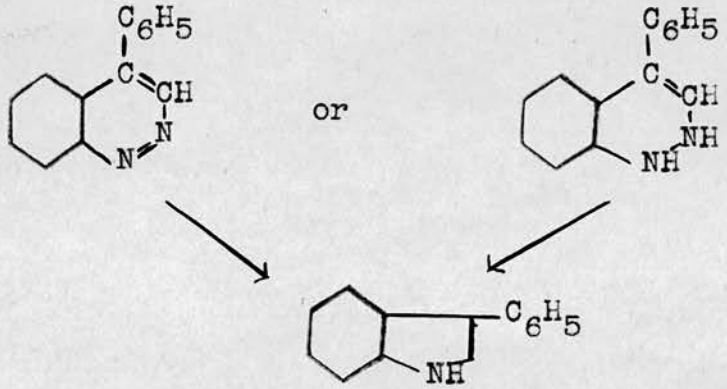


Neber (loc. cit.) advances another theory to replace the Robinson mechanism which he is unable to accept because of the above mentioned objection concerning the formation of ortho-benzidine instead of para-benzidine conversion products. This new theory postulates isomerisation of the hydrazone to an unsaturated hydrazine, as in Robinson's theory, followed by ring closure and the formation of a tetrahydro-cinnoline derivative, which then splits out ammonia to form the indole.

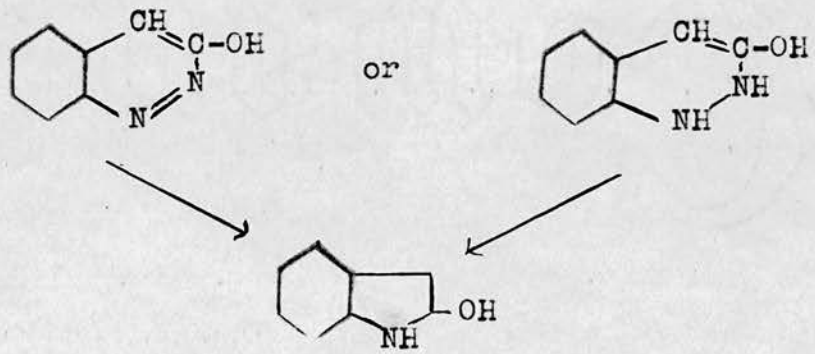


He produces evidence both for and against this mechanism, and finally concludes that neither his own theory nor that of Robinson satisfactorily explains the Fischer synthesis.

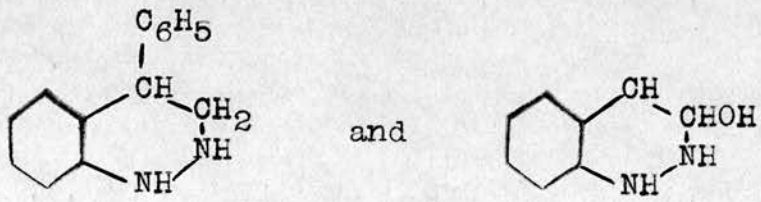
The basis of Neber's theory was the observation that 4-phenylcinnoline and its dihydro derivative both gave 3-phenylindole by reduction in acid solution.



Similarly acid reduction of 3-hydroxycinnoline and its dihydro derivative gave oxindole.



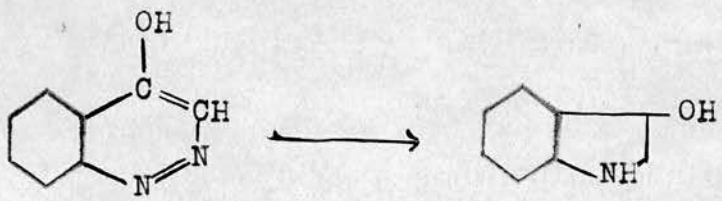
It seemed probable that these synthesis proceeded via the tetrahydrocinnoline derivatives.



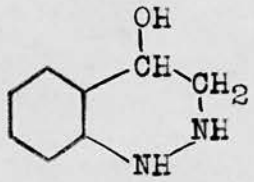
Since these derivatives, however, appeared to be converted immediately, in the presence of acid, into the corresponding indoles, it was found impossible to isolate them.

Some cases were therefore investigated in which it was considered probable, that in view of the heavily substituted nature of the tetrahydrocinnoline formed, the completion of the process of formation of an indole derivative would be impeded, and the intermediate compound found to be isolable. In no case was success attained as either the indole was formed at once, or else the reaction took an entirely different course yielding neither the intermediate product nor the indole expected.

It was then found that whereas reduction of 3-hydroxycinnoline by boiling hydriodic acid gave oxindole, a similar reduction of 4-hydroxycinnoline yielded chiefly a resin (which probably arose from the action of hydriodic acid on the indoxyl presumably formed).



From this resin, however, was isolated a substance which was identified as the hydroiodide of 4-hydroxy-tetrahydrocinnoline.



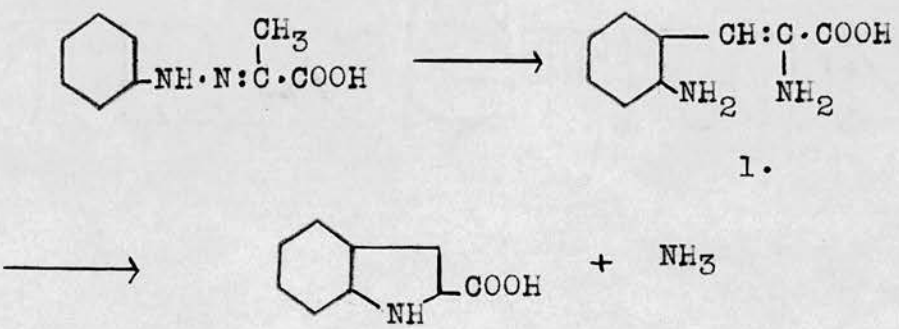
This substance was found to be quite stable to boiling hydriodic acid. Furthermore, 4-phenyl-tetrahydrocinnoline was prepared and shown to be quite stable to boiling hydrochloric acid, Only a trace of indole was formed after boiling for a whole day.

It was also found that 4-phenyl-tetrahydro-cinnoline and 4-phenylcinnoline were formed by heating 4-phenyldihydrocinnoline with hydrochloric acid in a sealed tube to 120°. This stability of the former product under conditions so favourable for indole formation made it almost certain that it could not be an intermediate compound in the formation of 3-phenyl-indole by the Fischer synthesis.

Object of Research.

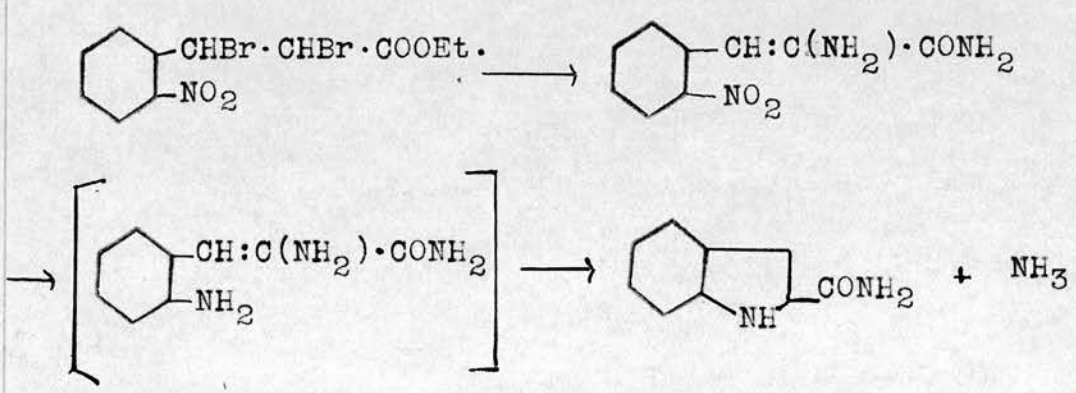
Attempts to test Robinson's Theory of Indole Formation.

In view of the doubt concerning the mechanism of the Fischer Indole synthesis, it was thought desirable to synthesise one of the intermediate compounds postulated by Robinson as being formed during the synthesis. Cooper (Thesis 1934) attempted to prepare the compound (1.) ——— the intermediate supposedly formed in the synthesis of indole-2-carboxylic acid.



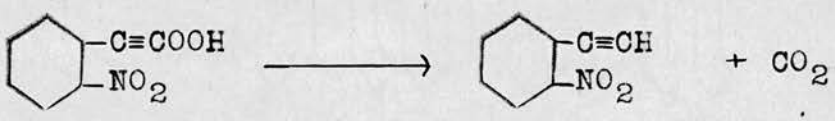
1.

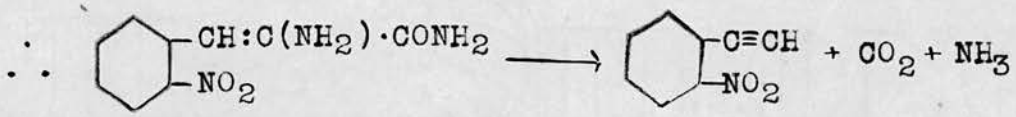
The following scheme was tried by Cooper:-



This synthesis was therefore repeated.

At the final stage, namely the reduction of ∝-amino-o-nitro-cinnamic acid amide with ferrous sulphate and ammonia, an ethereal extract was obtained which showed a slight fluorescence. This might have indicated the presence of an indole derivative, but none could be isolated. Nor did Ehrlich's reagent give the characteristic colouration. Cooper explained this reaction by the production of o-nitro-phenyl-acetylene, which was very volatile in steam and was therefore lost during the reduction.





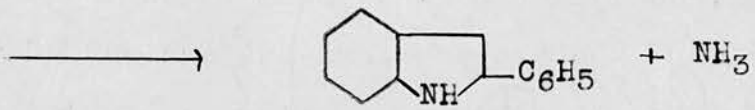
To avoid this difficulty a reduction was tried in the absence of water, and a saturated alcoholic solution of ammonia and ferrous sulphate was used as reducing agent. Again, no indole derivative could be isolated, and Ehrlich's reagent gave no positive characteristic colouration.

A new synthesis was then tried in which it was expected to cut out the possibility of losing the

final product of reduction by volatilising in steam

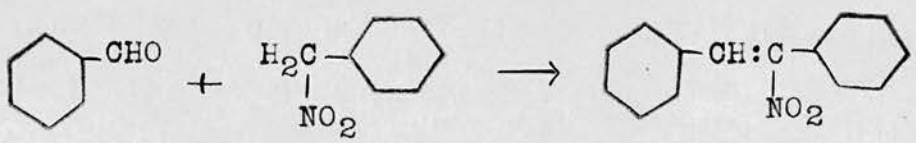
The formation of 2-phenylindole from acetophenonephenylhydrazone, according to the Robinson mechanism, proceeds as follows:-

1.



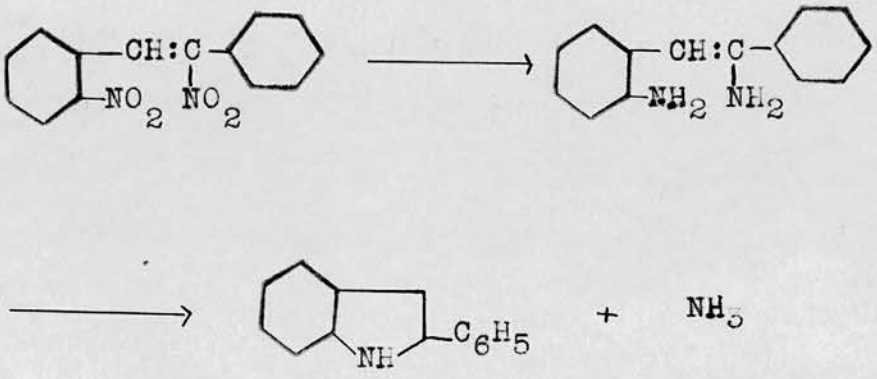
It was therefore attempted to synthesise the compound (1.) which probably would not be isolated but would pass immediately into the indole.

The following was the proposed scheme. Knoevenagel (Ber., 1904, 57, 4508) found that phenylnitromethane condensed with benzaldehyde in the presence of methylamine to give nitrostilbene.



The condensation of o-nitrobenzaldehyde and phenylnitromethane was therefore attempted. The product expected would then, on reduction, give the required intermediate, which would pass into the indole

with loss of ammonia.



Unfortunately this condensation gave an oil which only solidified after several weeks, during which it was repeatedly washed with methyl alcohol. From this solid both benzoic and o-nitrobenzoic acids were isolated. The condensation had, therefore, not taken place.

An examination of the literature disclosed that a similar condensation could be obtained with o-nitrobenzaldehyde and nitromethane. This was accomplished by heating the two compounds with zinc chloride in a sealed tube, (Posner, Ber., 1898, 31, 656).

A more satisfactoy method of obtaining the same compound was later found. Benzaldehyde and nitromethane readily condense in the presence of caustic soda at 0° to give α-nitrostyrene (Thiele, Ber.,1899, 32, 1293).

A similar condensation with o-nitrobenzaldehyde and nitromethane gave in very good yield a compound

which was identical with that obtained by Posner.

Priebs (Ann., 1884, 225, 350) obtained the same compound by nitrating ω-nitrostyrene with nitric acid. This nitration was found to give a good yield of the required dinitrostyrene when the temperature was maintained at 20° - 30°. As this is the range of temperature most suitable for nitrations using Menke's reagent (Rec. Trav. Chim., 1925, 44, 141 and 269), such a nitration of ω-nitrostyrene was carried out as a point of interest.

The reduction of this dinitrostyrene should give indole, as the diaminostyrene so obtained is the intermediate postulated by Robinson as being obtained in the formation of indole by fusing acetaldehyde-phenylhydrazone with zinc chloride.

B. Pictet's Method of Indole Formation.

There are four distinct methods known for the preparation of 2-phenylindole and its homologues, two of which embrace several quite different modifications.

1. Bischler's method consists of heating an anilide with an amine (Ber., 1892, 25, 2860) .

E.g. By boiling phenacylanilide with aniline 2-phenylindole is produced.

$$C_6H_5\cdot CO\cdot CH_2\cdot NH\cdot C_6H_5 + NH_2\cdot C_6H_5 \longrightarrow C_6H_5\cdot C(NH\cdot C_6H_5):CH\cdot NH\cdot C_6H_5 + H_2O$$

$$\longrightarrow \text{2-phenylindole} + C_6H_5\cdot NH_2$$

2. Madelung's method involves the dehydration of o-substituted acyl-amines by means of sodium ethoxide, sodium amyloxide or alkaline earth oxides at a high temperature (360°) , in the absence of air.

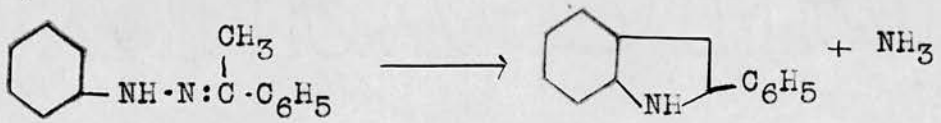
For example, 2-phenylindole is obtained from benzoyl-o-toluidine (Madelung, Ber., 1912, 45, 1131).

$$CH_3\text{-}C_6H_4\text{-}NH\cdot CO\cdot C_6H_5 \longrightarrow \text{2-phenylindole} + H_2O$$

Other workers have used different dehydrating agents. Verley (Bull. Soc. Chim., 1924, 35, 1039; 1925, 37, 189) used a fusion with sodamide, while the Imperial Chemical Industries have patented a process utilising the action of alkali metals on acylated amines suspended in inactive solvents such as diethylaniline and tetrahydronaphthalene (British Abstracts, B, 1930, 809).

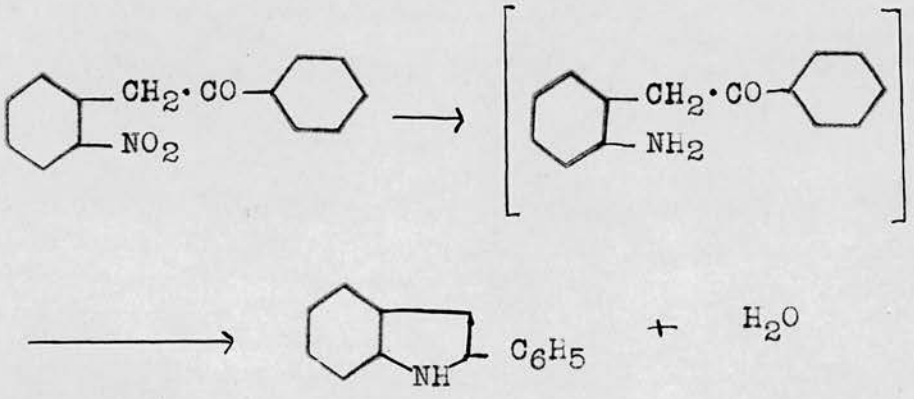
3. Fischer's method makes use of aryl hydrazones of aldehydes, ketones and keto-acids of the type $R{\cdot}CO{\cdot}CH_2{\cdot}R'$. These substances, under the influence of various catalysts, loose ammonia with the production of indole derivatives.

E.g. Acetophenonephenylhydrazone, when fused with zinc chloride at 180° , gives 2-phenylindole (loc. cit,)



4. The reduction of aromatic nitro compounds containing a suitable side chain in the ortho position frequently gives rise to indole derivatives by the elimination of water between the resultant amino group and the side chain, and subsequent ring closure.

E.g. The reduction of o-nitrodeoxybenzoin yields 2-phenylindole (Pictet, Ber., 1885, 19, 1064).



The first three methods have been fully examined and discussed by Campbell and Cooper (J.C.S., 1935, 1208) so that they need not be further discussed here. The method of Pictet, however, was found to be unsatisfactory as his method for preparing o-nitrodeoxybenzoin yielded an oily product which he failed to purify.

Pictet (Loc. cit.) nitrated deoxybenzoin, prepared by Graebe's method (Ber., 1879, 12, 1079), with concentrated nitric acid, whereby a heavy oil was obtained which was not purified before conversion into the indole by reduction with zinc dust and concentrated ammonia. Pictet made no mention of a yield obtained.

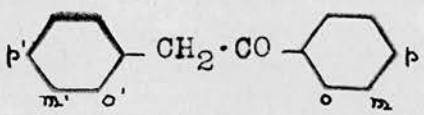
List (Ber., 1893, 28, 2451) repeated this work, and after obtaining the oily nitration product, separated it into the isomeric 2'- and 4'-nitrodeoxybenzoins. He found that the mixture contained only

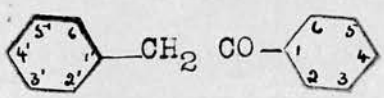
25% - 30% of the 2' compound, and he used this purified product to prepare the indole. Again no mention was made of a yield.

It was thus decided to modify Pictet's method in an attempt to obtain better results.

Nomenclature of Deoxybenzoins.

There are two distinct methods used to name these compounds. The one method affixes a substituent as being o-, m-, or p-, and o'-, m'-, or p'-, according to its position in either of the benzene rings. The other numbers the positions as 1,2,3,4,5,6, and 1',2',3',4',5',6', starting from the side chain.





The latter method is the one preferred by Beilstein and the British Chemical Journal, and is therefore the method used in this thesis.

Object of Research.

The pure isomeric nitro-compounds were obtained by nitrating deoxybenzoin with Menke's reagent (loc. cit.). The resulting mixture was easily separated into its constituents with ether, the 2'-compound dissolving while the 4'-compound remained. These compounds were identified by conversion to their oximes and by oxidation with chromic acid to the corresponding benzils and benzoic acids

The attempt to prepare 2-phenylindole by the reduction of the 2'-compound with zinc dust and concentrated ammonia proved unsuccessful, as in each case a tarry mass was obtained which yielded only a very small quantity of indole after repeated extraction with boiling ligroin. This reduction, however, with a slight modification yielded a yellow crystalline compound which was proved to be the 2'-aminodeoxybenzoin.

The isomeric 4'-nitrodeoxybenzoin was also subjected to reduction with zinc dust and ammonia, and the 4'-aminodeoxybenzoin shown to be identical with that prepared by Golebew (Ber., 1873, 6, 1252).

C. The Nitration of 2-Phenylindole with Nitrous Acid; and an Examination of the Properties of 1-Methyl-2-phenyl-3-nitroso-indole.

Campbell and Cooper (Loc. cit.) suspected that, when an excess of nitrous acid acted upon 2-phenylindole, it not only formed the 3-isonitroso-compound, but also oxidised the latter to the corresponding nitro-compound and effected further nitration of the benzene ring. This action has therefore been fully investigated, the resulting compounds isolated, and their structures proved.

1-Methyl-2-phenyl-3-nitroso-indole is a true nitroso-compound but many of its properties are anomalous. The effect of oxidising agents,and a complete study of its properties have been carried out. It had been noted earlier by Campbell and Cooper that it did not condense with aniline; this work was therefore repeated with aniline, p-nitraniline, and p- bromaniline, but in all cases only the unchanged compound was returned.

In each of the experimental sections, the melting points recorded were obtained with Kofler's micro-apparatus ("Mikroskopische Methoden in der Mikrochemie") and calibrated thermometers. In agreement with his claims, the apparatus was found to be much more satisfactory than the ordinary capillary melting point apparatus.

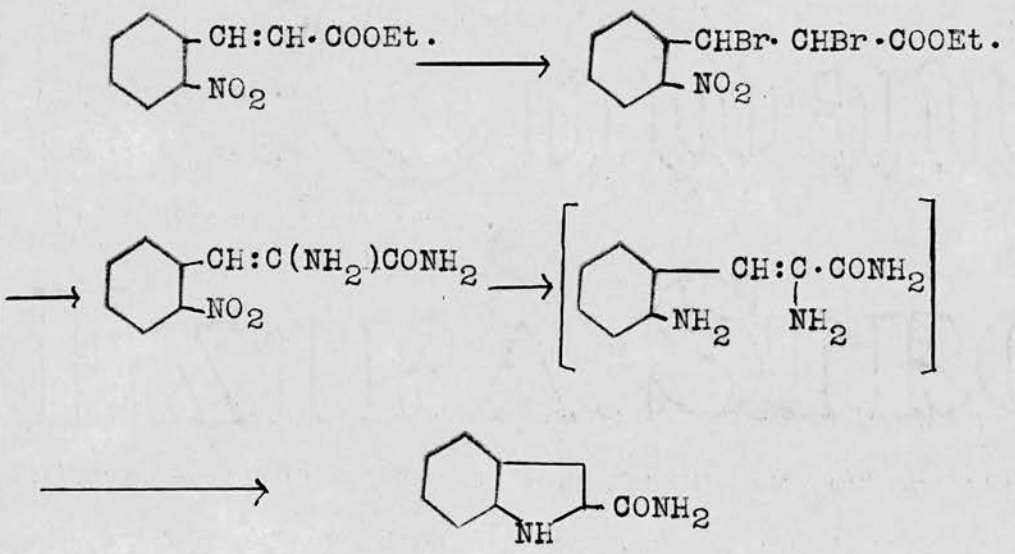
The yields obtained are expressed as percentages of the theoretical.

All new compounds obtained have been analysed by Dr. Weiler, Oxford, and Mr. W. Brown Edinburgh.

E X P E R I M E N T A L.

Synthesis of the intermediate compound 1. (page 20).

Scheme.



1. Preparation of o-nitrocinnamic acid

Perkin Reaction.

10 gms. o-nitrobenzaldehyde.

13 ccs. acetic anhydride.

10 gms. fused potassium acetate.

Yield 8.5 gms. (66% theory)

m.p. 240° (lit. 241° - 245°)

2. Esterification of o-nitrocinnamic acid

Fischer - Speier method.

50 gms. o-nitrocinnamic acid.
300 ccs. absolute alcohol saturated with dry hydrochloric acid.

The mixture was boiled under reflux for two hours and allowed to cool, when the ester separated as a yellow substance : melting point 38° - 40° : yield 21 gms.

The pure ester melts at 42°- 44°, but the product obtained was not purified further as this led to excessive loss. A second crop of 4 gms. was obtained, while the filtrate, on pouring into water gave a further yield of 14.5 gms. of fairly pure ester, so that the total yield of the crude product 39.5 gms. represented 69% of the theoretical.

3. α-β- Dibromo-β-(2-nitrophenyl)-propionic ester.

Muller, Ann., 1882, 212, 129.

26 gms. o-nitrocinnamic ester
400 ccs. dry carbon disulphide.
20 gms. bromine.

The ester was dissolved in the carbon

disulphide, and the solution boiled under reflux, while the bromine was added slowly from a dropping funnel over a period of from one to three hours. When all the bromine had been added the mixture was boiled until it was almost colourless. Part of the carbon disulphide was removed by distillation, and the residue allowed to crystallise when the dibromo-compound separated as yellow crystals.

yield 37 gms. (80% theory)
m.p. 70° (lit. 71°)

4. <u>α-amino-o-nitrocinnamic acid amide</u>.

Cooper, Thesis, Edinburgh 1934.

α-β-dibromo-β-(2-nitrophenyl)-propionic ester (20 gms.) was mixed with concentrated ammonia (100 ccs.) in a tightly stoppered lemonade bottle which was then placed in a thermostat at 50°. After two days a crystalline product deposited on the bottom of the bottle, but on the third day most of this had gone back into solution and the supernatant liquid became dark in colour.

The bottle was then opened, the excess of ammonia removed by distillation, and the solution

decolorised with animal charcoal and filtered. The filtrate deposited yellow crystals on cooling, which were soluble in alcohol.

Recrystallised from ligroin,

yield 3 gms. (18% theory).

m.p. 221° (Cooper, thesis 1934, 221°).

Reduction of α-Amino-o-nitrocinnamic acid amide.

The method adopted was that used for the analogous reduction of o-nitrocinnamic acid to o-amino-cinnamic acid (Gabriel, Ber., 1882, 15, 2294), in order to avoid the possibility of the double bond being reduced at the same time. It was not expected that the o-amino-compound would be isolated, as it was almost certain that this would pass, directly on formation, by the elimination of ammonia between the amino groups, into indole-2-carboxylic acid amide (assuming that Robinson's mechanism of the Fischer indole synthesis is correct).

α-Amino-o-nitrocinnamic acid amide (1 gm.) was dissolved in hot alcohol (30 ccs.) and added to a boiling mixture of ferrous sulphate (10 gms.) and

concentrated ammonia (100 ccs.). The whole was boiled under reflux for 30 minutes, cooled, and acidified with concentrated hydrochloric acid. After filtering from a small quantity of insoluble matter the mixture was extracted with ether. The resulting extract (reddish in colour), showed a strong purple fluorescence, characteristic of many indoles, but evaporation to dryness left only a minute residue, too small for thorough examination. This was therefore dissolved in 2 ccs. of alcohol and treated with Ehrlich's reagent, but no characteristic colouration was obtained.

A similar reduction was tried in alcoholic solution.

α-amino-o-nitrocinnamic acid amide (1 gm.) was dissolved in alcohol (100 ccs.) and powdered ferrous sulphate (10 gms.) added. The solution was then saturated with ammonia gas and refluxed for 30 minutes, after which most of the alcohol was removed by distillation and the remaining mass dissolved in hydrochloric acid. On extraction with ether a strong fluorescent solution was again obtained, from which no indole was isolated. Nor did Ehrlich's reagent give a positive characteristic colouration.

Attempted Condensation of o-Nitrobenzaldehyde and Phenylnitromethane.

The condensation attempted was similar to that of benzaldehyde and phenylnitromethane (Ber., 1904, 37, 4508).

o-Nitrobenzaldehyde (3 gms.) and phenylnitromethane (2.7 gms.) were dissolved in alcohol (25 ccs.), and after the addition of two drops of methylamine the mixture was refluxed for 24 hours. A dark brown viscid oil separated which crystallised in brown flakes, after repeated washing with methyl alcohol (the solvent was decanted off after each separation of an oil).

A few milligrams of this brown solid were sublimed and white flakes were obtained m.p. 120°. This was proved by a mixed melting point determination to be benzoic acid. As this could have been due to decomposition on subliming, the brown solid was then extracted with ligroin and from this solution two compounds were isolated. One m.p. 120° was again shown to be benzoic acid; the other m.p. 142° was proved by a mixed melting point determination to be o-nitrobenzoic acid (lit. m.p. 144°).

The expected condensation was not isolated

and these two compounds had been formed either by the oxidation of the original substances or by the oxidation of some intermediate condensation product.

Other condensing agents, namely, acetic anhydride, phthalic anhydride, and zinc chloride were used in the reaction, but all were equally unsuccessful as in each case the same brown product was obtained, from which only benzoic and o-nitrobenzoic acids could be isolated.

Condensation of o-Nitrobenzaldehyde and Nitromethane.

(Posner, Ber., 1898, 31, 656).

.5 gms. o-nitrobenzaldehyde.
2 gms. nitromethane.
0.2 gms. finely powdered anhydrous zinc chloride.

The mixture was heated in a sealed tube at 160° for two hours. The black tarry residue was then extracted with boiling alcohol. From this solution yellow needles of o-ω-dinitrostyrene separated.

yield 0.2 gms. (3% theory),
m.p. 106° (lit. 107°).

Condensation of Benzaldehyde and Nitromethane.

(Thiele, loc. cit.)

A solution of 25 gms. benzaldehyde and 15 gms. nitromethane in 100 ccs. of methyl alcohol was cooled in a freezing mixture and a solution of 10.5 gms. sodium hydroxide in 25 gms. of ice and water was slowly added with stirring so that the temperature of the mixture did not rise above 15°. As the condensation proceeded a bulky white precipitate formed and more alcohol had to be added to obtain mobility for stirring After standing for 15 minutes, water was added until solution was complete, and it was then neutralised by by running into a stirred solution of 50 ccs. concentrated hydrochloric acid and 75 ccs. water. A yellow solid was obtained which was recrystallised from alcohol.

yield 30 gms. (80% theory)

m.p. 57° - 58° (lit. 58°)

A similar condensation was attempted using o-nitrobenzaldehyde and nitromethane.

Condensation of o-Nitrobenzaldehyde and Nitromethane.

15 gms. o-nitrobenzaldehyde.
6 gms. nitromethane.
50 ccs. methyl alcohol.
4 gms. sodium hydroxide in
10 ccs. water.

The procedure was the same as that described above with some slight modifications. The temperature in this case was maintained below 0°. If it rose above this an oil was obtained which could not be crystallised. Again, on addition of the sodium hydroxide a greater time (30 minutes) elapsed before the white precipitate separated. On acidifying with hydrochloric acid a yellow solid was obtained which was recrystallised from alcohol.

yield 5 gms. (25% theory)
m.p. 107° (lit. 108°)

Nitration of ω-nitrostyrene.

(Priebs loc. cit.)

ω-nitrostyrene (5 gms.) was added in small portions to a nitrating mixture of 24 ccs. concentrated

sulphuric acid and 16 ccs. concentrated nitric acid, with vigorous stirring. After stirring for a further half hour the solution was poured into water, and the resulting yellow mass separated.

This was boiled with 20 ccs. alcohol and 10 ccs. water and filtered free from any insoluble material. The residue consisted of p-ω-dinitrostyrene. The filtrate on cooling deposited crystals of o-ω-dinitrostyrene.

p-ω-dinitrostyrene recrystallised from propyl alcohol.

yield 3 gms. (44% theory)
m.p. 197° (lit. 194°- 196°)

o-ω-dinitrostyrene recrystallised from alcohol.

yield 1 gm. (14.6% theory)
m.p. 52° (lit. 56°).

Nitration of ω-nitrostyrene with Menke's reagent.

(For details of this method see nitration of deoxybenzoin page 50).

15 gms. ω-nitrostyrene.
100 ccs. acetic anhydride.
30 gms. cupric nitrate.

On pouring into water, after the nitration was complete, a yellow oil was obtained which solidified on standing.

This yellow mass was then extracted with a mixture of 20 ccs. alcohol and 10 ccs. water, but the filtrate on cooling, deposited an oil which failed to crystallise. The mass was then shaken up with toluene, which succeeded in removing any unchanged ω-nitrostyrene and any o-ω-dinitrostyrene, while pure p-ω-dinitrostyrene remained. This was recrystallised from propyl alcohol.

yield 6 gms. (30% theory)
m.p. 197° (lit. 194°- 196°).

From the toluene yellow crystals separated which, when recrystallised from alcohol, melted at 52° and amounted to 5 gms. of the crude crystals. These were therefore unchanged ω-nitrostyrene m.p. 56°, proved by a mixed melting point determination.

No o-ω-dinitrostyrene was isolated from the nitration mixture.

When the toluene soluble residue was again extracted with ether a very minute residue was left which was proved by a mixed melting point determination (197°) to be p-ω-dinitrostyrene. On evaporation of the ether the ω-nitrostyrene obtained melted sharp at 56° (lit. 56°).

Attempted Condensation of o-Nitrobenzaldehyde and Phenylnitromethane.

The Thiele method was used in this attempt.

3 gms. o-nitrobenzaldehyde.

2.7 gms. phenylnitromethane.

0.8 gms. sodium hydroxide.

10 ccs. methyl alcohol.

The temperature was maintained under 0°, but after vigorous stirring for two hours no precipitate was obtained on addition of the sodium hydroxide. On acidifying with hydrochloric acid a colourless oil was obtained. This was dissolved in methyl alcohol and after several days, colourless crystals separated.

yield 0.5 gms. (10% theory)

m.p. 44° - 45°.

Analysis:

found C, 55.69%; H, 3.48%; N, 9.73%

$C_{14}H_{10}O_4N_2$, requires, C, 62.22%; H, 3.7% ; N, 10.3%.

These analysis figures do not agree, but if the empirical formula be worked out for the figures obtained, the best agreement is given with the formula for dinitrostilbene $C_{14}H_{10}O_4N_2$.

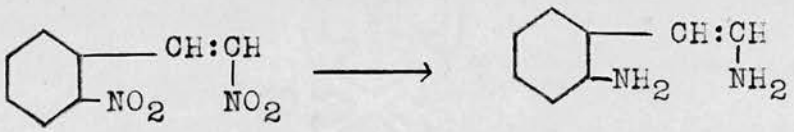
Attempted Reduction of the Condensation Product m.p. 44°- 45°.

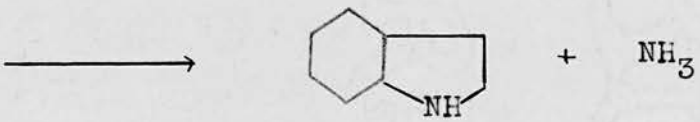
0.2 gms. of the compound were dissolved in 25 ccs. of glacial acetic acid, 2 gms. of zinc dust added, and the mixture heated on the steam bath for two hours. After cooling, the solution was filtered free from zinc, and solid sodium nitrite added, and the solution left overnight. Next day a yellow precipitate had settled. This was filtered and tested for 3-isonitroso-2-phenylindole (m.p. 280°). The compound melted about 250° with decomposition, but it could not be purified further, so that there existed considerable doubt as to its identity.

This condensation was, therefore, left over for a more detailed research.

Reduction of o-ω - dinitrostyrene.

If Robinson's theory of the mechanism of the Fischer indole synthesis is correct this compound on reduction should give indole.





1) Reduction with ferrous sulphate and ammonia.

o-ω-Dinitrostyrene (1 gm.) dissolved in alcohol was added to a mixture of ferrous sulphate (10 gms.) and concentrated ammonia (100 ccs.) and the whole refluxed for one hour. On cooling, the resulting solution was neutralised with concentrated hydrochloric acid and extracted with ether.

The ethereal extract, on evaporation, gave a dark red viscid oil which could not be purified, and which decomposed rapidly on standing, into a black charred residue.

For identification purposes the preparation

of derivatives was attempted on an alcoholic solution of the oil.

Picrate m.p. about 190° (decomp.)

This derivative was very impure as it was obtained as a black powder, and the melting point was not satisfactory.

With acetic anhydride the oil reacted extremely vigorously giving a dark brown compound which was purified by dissolving in alcohol, filtering free from any undissolved matter, and reprecipitating with water. m.p. above 280°.

This derivative was also unsatisfactory, and a pure speciman could not be made for analysis.

As the oil gave a red coloured solution in alcohol, Ehrlich's reagent could not be applied, since indole itself gave a red colouration with Ehrlich's reagent. Another colour test was however applied.

If, to a suspension of silicon dioxide, a little concentrated nitric acid is added and then indole, a very deep red solution is obtained which goes vivid purple on gently warming.

Applying this test to the oil, a slight red colour developed on addition of the nitric acid, and

this darkened a little on warming. This might have indicated a trace of indole but was very inconclusive.

(2) Reduction with granular zinc and a mixture of concentrated hydrochloric acid and water (1:1)

1 gm. of the compound , finely powdered, was suspended in 25 ccs. of the acid and zinc added. After 30 minutes the mixture was warmed to complete the solution. On cooling it was rendered alkaline (slightly) with ammonia and extracted with ether.

The ether extract gave a reddish oil, which solidified, on addition of a little alcohol, to give a dark brown substance, m.p. 67°- 70°.

Into a solution of this substance in alcohol hydrogen chloride gas was passed, and a brown solid was obtained, which when recrystallised from alcohol melted at 130°.

Quoted for dihydrocinnoline m.p. 80°,
hydrochloride m.p. 145°.

Therefore the product obtained was probably dihydrocinnoline.

In this case also a red colouration was obtained on warming with silicon dioxide and nitric acid.

3) A catalytic hydrogenation of the compound was attempted, and it was expected in this case to obtain the diamino-compound, which would then ring close with acid to give a cinnoline derivative as above, or an indole derivative.

1.94 gms. (0.01 moles) o-ω-dinitrostyrene was dissolved in 200 ccs. alcohol, 0.5 gms. platinum oxide (PtO_2) added and the solution then shaken up with hydrogen under pressure. The solution turned dark red and the pressure fell by 70 pounds. After two more days and the addition of some fresh catalyst the pressure did not drop any further.

The total pressure drop equivalent to the reduction to a diamino-compound was 102 pounds or 119 pounds if the double bond was also reduced. The reduction had therefore not proceeded as far as to yield the diamino-compound.

The solution smelt strongly of ammonia and on evaporation of the alcohol a dark brown solid was obtained. This was extracted with boiling ligroin

The dark brown solid obtained from the ligroin extract was further purified by sublimation.

m.p. 266°.

sublimed at 200°.

Analysis:

found N, 16.34%

An examination of the literature showed that this compound might be the following:

$$\begin{matrix} NHOH \cdot C_6H_4 \cdot CH \cdot CH:NOH \\ | \\ NHOH \cdot C_6H_4 \cdot CH \cdot CH:NOH \end{matrix}$$

$C_{16}H_{18}O_4N_4$, requires N, 16.8%.

The presence of the hydroxylamine groups, however, was very uncertain, and as only a small amount of the compound was obtained this compound could not be proved.

(c.f. Discussion).

Preparation of Deoxybenzoin.

(Org. Syn. 12, 16)

68 gms. phenylacetic acid.

30 gms. thionyl chloride.

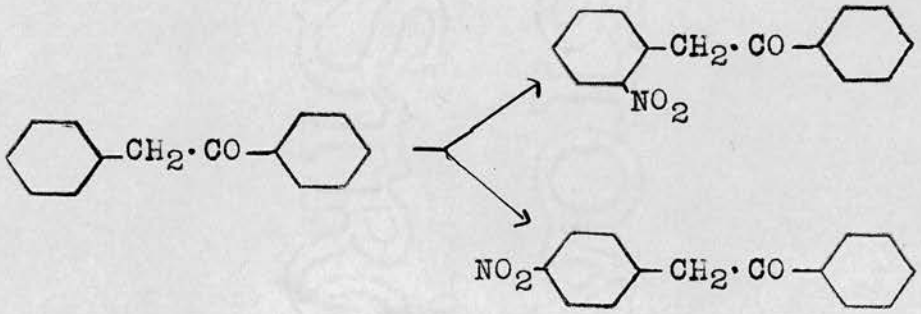
400 ccs. dry benzene.

75 gms. anhydrous aluminium chloride.

Yield obtained:- 82 gms. (80% theory)

m.p. 55° (lit. 56°)

Nitration of Deoxybenzoin.



10 gms. deoxybenzoin.

15 gms. cupric nitrate.

50 ccs. acetic anhydride.

The deoxybenzoin was dissolved in the acetic anhydride and the cupric nitrate added slowly with vigorous stirring, while the temperature was maintained

at 26° - 30°. The solution was allowed to stand for one hour, and then poured on to 300 gms. of ice and water. The yellow crystals, which separated, were filtered and triturated with hot water to remove the copper salts. The resulting product, consisting of a mixture of the 2'- and 4'-nitrodeoxybenzoins, was then separated with ether, the 2'-compound dissolving while the 4'-compound remained.

The nitro-compounds were purified by recrystallisation, first from benzene - light petroleum (b.p. 60°- 80°)(1:1), and then from alcohol.

2'-nitrodeoxybenzoin	m.p. 72°- 73°	(lit. 73°- 74°)
oxime	m.p. 118°	(lit. 118°)
yield	8 gms.	

4'-nitrodeoxybenzoin	m.p. 138°- 140°	(lit. 141°-142°)
oxime	m.p. 107°	(lit. 109°)
yield	2 gms.	
total yield	8 gms.	(80% theory).

Quantities up to 50 gms. of deoxybenzoin have been nitrated by this method, but the temperature must be maintained between 26°-- 30°; below 26° nitration does not occur, and above 30° oxidation to

benzils takes place.

Both compounds were identified by oxidation to their corresponding nitrobenzoic acids, and by their oximes and dinitrophenylhydrazones.

2'-Nitrodeoxybenzoin-2:4-dinitrophenylhydrazone.

Prepared by Brady's method (J., 1931, 756), this was obtained in orange prisms; recrystallised from tetralin m.p. 219° - 221°.

Analysis. Found N - 16.5%

$C_{14}H_{11}O_3N$ requires N - 16.6%

4'-Nitrodeoxybenzoin-2:4-dinitrophenylhydrazone.

Prepared in the same way this was obtained as orange-red prisms; recrystallised from glacial acetic acid m.p. 233°- 234°.

Analysis. Found N - 17%

$C_{14}H_{11}O_3N$ requires N - 16.6%

Reduction of 2'-Nitro and 4'-Nitrodeoxybenzoins.

Reduction of 2'-nitrodeoxybenzoin with zinc dust and concentrated ammonia (Pictet and List, loc. cit.) gave a dark tarry product, which gave a definite pine-splint reaction, but yielded only a very small amount of 2-phenylindole by prolonged extraction with boiling ligroin.

This method was then modified as follows and a more satisfactory result obtained.

2'-nitrodeoxybenzoin (5 gms.) was dissolved in alcohol (10 ccs.) and added to concentrated ammonia (25 ccs.). The whole was stirred vigorously and excess of zinc dust added in small quantities. After the reduction was complete, the mixture was filtered and neutralised with dilute sulphuric acid, when a yellow crystalline product was obtained. This was recrystallised from alcohol.

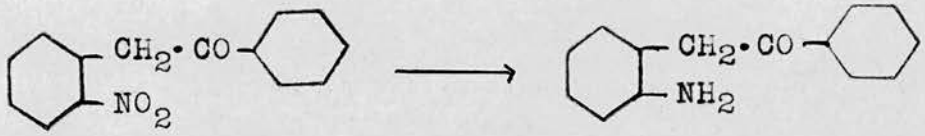
yield 3 gms.

m.p. 170°.

This compoumd was found to be 2'-aminodeoxybenzoin.

Analysis: found C, 80.7%; H, 5.2%; N, 6.7%.

$C_{14}H_{13}ON$ requires C, 80.0%; H, 6.2%; N, 6.6%.



The compound dissolved in hydrochloric acid, and decomposed on standing. A solution in acetic anhydride, after being kept for several days gave the pine-splint reaction, but no 2-phenylindole could be isolated.

4'-Nitrodeoxybenzoin, when reduced in a similar manner gave 4'-aminodeoxybenzoin, m.p. 94°- 96° (lit. 95°- 96°) and was proved to be identical with the amine formed in very poor yields by the reduction of p-nitrobenzil (Golubew, loc. cit.), by a mixed melting point determination.

Attempts to prepare picrates, acetyl and benzoyl derivatives, and dinitrophenylhydrazones of these amines proved unsuccessful.

Reduction with zinc dust and glacial acetic acid gave better results. In this way 6 gms. of the 2'-nitrodeoxybenzoin gave 1 gm. of 2-phenylindole, and 4 gms. of the original nitro-compound were recovered unchanged.

Acetophenone-phenylhydrazone.

(Cooper, Thesis, Edinburgh, 1934)

113 gms. phenylhydrazine.

126 gms. acetophenone.

These two substances were heated together on the water bath. The homogeneous mixture soon became turbid by the separation of water, and the whole solidified to a mass of crystals on cooling. This was recrystallised from alcohol, in which it is sparingly soluble in the cold, and extremely soluble in hot.

yield 199 gms. (90% theory)

m.p. 105° (lit. 105°)

2-Phenylindole.

(Fischer, Ann., 1886, 236, 116)

199 gms. acetophenone-phenylhydrazone.

626 gms. anhydrous zinc chloride.

The two substances were thoroughly mixed in a nickel crucible, which was then lowered into a metal bath preheated to a temperature of 190°. The mixture turned brown and the reaction took place

within two to three minutes. The molten mass frothed up vigorously but no ammonia was evolved. When the reaction mixture had cooled, the contents of the crucible were boiled with very dilute hydrochloric acid, and the aqueous extract decanted from the insoluble organic matter. The latter was then recrystallised repeatedly from alcohol until pure.

yield 76 gms. (42% theory)

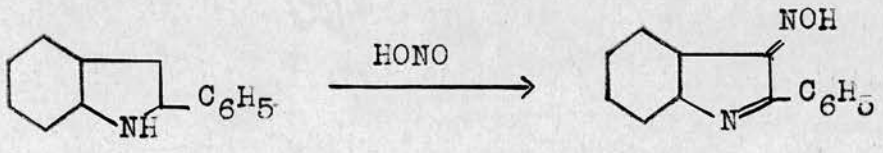
m.p. 189° (lit., Cooper and Campbell, 189°)

The filtrates from the recrystallisations, however, still contained some of the indole. These were therefore evaporated, redissolved in glacial acetic acid, and treated with sodium nitrite to form the isonitroso-compound.

yield 57 gms.

The total yield was thus 70% theory.

3-Isonitroso-2-phenylindole.



2-Phenylindole (20 gms.) was dissolved in glacial

acetic acid (enough to dissolve it in the cold), and powdered sodium nitrite (15 gms.) added. On further addition of water, the isonitroso-compound was obtained as a bright yellow substance, which was separated by filtration, washed with water, alcohol and ether, and then recrystallised.

When recrystallised from amyl acetate the compound was obtained in a pure condition. (Campbell and Cooper, loc. cit.).

m.p. 280° (quoted by Campbell and Cooper 280°)

yield 18 gms. (75% theory).

Action of Nitrous Acid on 3-Isonitroso-2-phenylindole.

The isonitroso-compound (1 gm.) was suspended in boiling glacial acetic acid (15 ccs.) and treated with sodium nitrite (0.35 gms.:1 equiv.). The resulting precipitate recrystallised from alcohol in yellow needles.

m.p. 236° - 238°.

yield quantitative.

This was proved to be 3-nitro-2-phenylindole by a mixed melting point determination with an authentic specimen (lit., m.p. 238°)

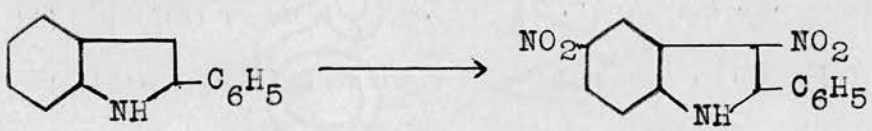
Action of Nitrous Acid on 3-Nitro-2-phenylindole.

3-Nitro-2-phenylindole (2 gms.) when treated with a large excess of sodium nitrite (5 gms.), yielded a mixture of unchanged compound and a small amount (0.3 gms.) of a yellow crystalline substance which was insoluble in alcohol and cold acetic acid, and melted at 312° (decomposition).

This compound was identified as 3:5-dinitro-2-phenylindole by a mixed melting point determination with a specimen prepared by the method of Angeli and Angelico (loc. cit.).

3:5-Dinitro-2-phenylindole.

(Angeli and Angelico, Gazz., 1900, 30, 268).



2-Phenylindole (2 gms.) was suspended in hot glacial acetic acid and one equivalent of sodium nitrite (0.7 gms.) added slowly. At this point orange crystals of the nitro-compound separated. A large excess of concentrated nitric acid (10 ccs.) was then

added and the solution boiled. The mixture turned yellow and then cleared, while yellow plates of the 3:5-dinitro-2-phenylindole separated. These were washed with alcohol and dried.

m.p. 312° (lit., "above 280°").

yield quantitative.

Nitration of 2-Phenylindole with Nitric Acid.

(C.f. Mathur and Robinson, J., 1934, 1415).

Since these authors prepared a dinitro- and a trinitro-2-methylindole by treatment with nitric acid, the same procedure was carried out with 2-phenylindole, in an attempt to prepare a trinitro-2-phenylindole.

Dinitro-2-phenylindole.

2-Phenylindole (10 gms.) was mixed with concentrated nitric acid (100 ccs.) in the cold. A brisk reaction took place immediately and the dinitro-compound separated, (with 2-methylindole the mixture required to be heated on the water bath before the reaction began). It was purified by dissolution in dilute sodium hydroxide, and reprecipitation with dilute nitric acid. It was

then crystallised from glacial acetic acid, from which it separated in yellow plates, m.p. 312°. It was, therefore, the 3:5-dinitro-2-phenylindole prepared as above.

yield 12 gms. (85% theory),

A great deal of tarring occurs in this reaction, so that the product obtained was not so pure as that by the method of Angeli and Angelico; also the yield in the latter case was better. Thus the method of Angeli was preferred for the preparation of the dinitro-compound.

Attempted Preparation of Trinitro-2-phenylindole.

2-Phenylindole (10 gms.) was mixed with concentrated nitric acid (200 ccs.), and after the first brisk reaction had subsided, the mixture was heated on the steam bath for half an hour. On cooling, a colourless solid was obtained which was obviously a mixture, but after several recrystallisations from aqueous alcohol some 5-nitro-benzoylanthranilic acid was isolated. Thus, instead of further nitrating the 3:5-dinitro-2-phenylindole, obtained by the first brisk reaction, the nitric acid had acted as an oxidising agent.

Oxidation of 3-Isonitroso-, 3-Nitro-, and 3:5-Dinitro-2-phenylindole.

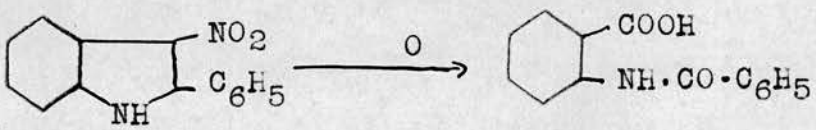
Many oxidising agents were used, but the most satisfactory was found to be potassium permanganate in glacial acetic acid.

The 3-isonitroso-, or 3-nitro-2-phenylindole (0.4 gms.) was dissolved in glacial acetic acid and heated under reflux with powdered potassium permanganate (1 gm.) for three hours, and the product poured into water. After decolorising the solution with sulphurous acid, a creamy precipitate of benzoylanthranilic acid was obtained, which was crystallised from alcohol.

yield 0.2 gms.

m.p. 179°- 181° (lit., 181°).

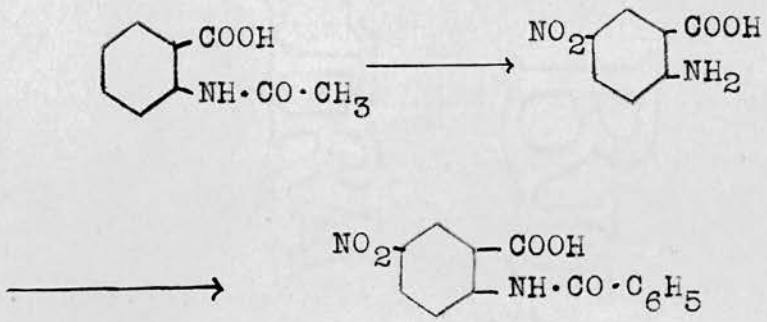
The compound was purified by dissolution in dilute sodium hydroxide, and reprecipitation after filtering from any insoluble matter, with dilute nitric acid.



3:5-Dinitro-2-phenylindole by the same treatment yielded 5-nitro-benzoylanthranilic acid m.p. 257°- 8°

which was proved identical with an authentic specimen prepared as described below.

Preparation of 5-Nitro-N-benzoylanthranilic Acid.



5-Nitroanthranilic acid.

(Bogert and Scatchard, J.A.C.S., 1919, 41, 2066).

Acetanthranilic acid (10 gms.) was added slowly to fuming nitric acid (20 ccs.) at a temperature below 5°. The mixture was then maintained at that temperature for four hours, followed by two hours at room temperature. A red colour then developed in the solution. The mixture was poured on to ice, separated and dried, and then crystallised from alcohol in the presence of animal charcoal.

m.p. 206°- 209° (lit., 214°- 215°).

yield 5 gms. (49% theory).

The 5-nitroanthranilic acid was then obtained by hydrolysing the above acetyl compound by boiling with concentrated hydrochloric acid for one hour.

m.p. 278° (lit. 278°)

yield 4 gms.

This compound could not be benzoylated in benzene with benzoyl chloride, but in pyridine 5-nitro-N-benzoylanthranil was easily obtained.

m.p. 178°- 180°

Analysis:

Found, C, 62.8; H, 3.3; N, 10.4:

$C_{14}H_8O_4N_2$ requires C,62.7; H, 3.0; N, 10.4.

The anil was then hydrolysed by boiling with hydrochloric acid to give the 5-nitro-N-benzoylanthranilic acid.

m.p. 257°-260°.

Analysis:

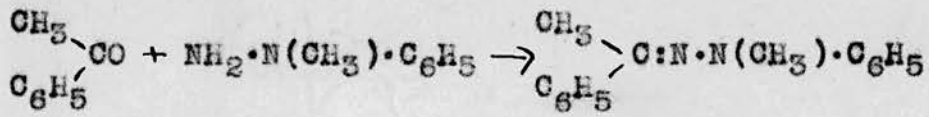
Found, C, 59.3; H, 4.1; N, 9.6:

$C_{14}H_{10}O_5N_2$ requires C, 58.8; H, 3.5; N, 9.8.

Preparation of 1-Methyl-2-phenyl-3-nitroso-indole.

(1). Acetophenone-methylphenylhydrazone.

(Degan, Ann., 1886, 236, 154).



25 gms. acetophenone.

25 gms. methylphenylhydrazine.

The two reactants were heated together on the steam bath for several days, and the oily mixture obtained distilled in vacuo, two fractions being collected. The first, distilling from 80° to 140° at 12 mms. pressure, consisted mainly of the unchanged reactants, and amounted to 7 gms. The second fraction boiling at 186° to 192° at 11 mms. pressure was the hydrazone, and was obtained as a thick viscid pale yellow syrup which crystallised with extreme slowness.

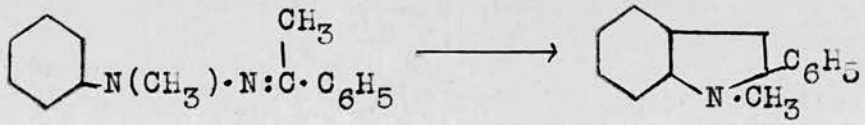
yield 24 gms. (52% theory)

On recrystallisation from ligroin the compound was obtained as crystals.

m.p. 49°- 50° (lit. 50°).

(11). 1-Methyl-2-phenylindole.

(Degan, loc. cit.)



A slight variation to the method of Degan was introduced by Campbell and Cooper (loc. cit.). Instead of heating the mixture for five hours at 130°, they carried out a fusion at a higher temperature. They considered that a short exposure to a higher temperature, of the sensitive hydrazone, would be more effective than a more prolonged exposure to a lower temperature, in the conversion into indole, and therefore a greater yield of the 1-methyl-2-phenylindole would be obtained. This prediction was borne out by experiment, and they found that an increase of 14% was obtained in their yield to that by Degan's method.

Acetophenone-methylphenylhydrazone (24 gms.) was mixed with powdered anhydrous zinc chloride (120 gms.) in a nickel crucible and immersed into a metal bath preheated to a temperature of 200°. Indole formation took place in two minutes. The

remaining zinc chloride was removed by boiling with dilute hydrochloric acid, and the residue filtered, and distilled in vacuo. The indole distilled at 214° at 32 mms. pressure.

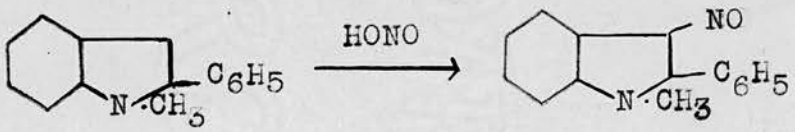
yield 12 gms. (54% theory).

m.p. 95°- 96° (lit. 100°- 101°).

The distillate was a clean, almost white, product and was not purified further, as this led to excessive loss.

(111). <u>1-Methyl-2-phenyl-3-nitroso-indole.</u>

(Campbell and Cooper, loc. cit.)



1-Methyl-2-phenylindole (10 gms.) was dissolved in cold glacial acetic acid and treated with a concentrated aqueous solution of sodium nitrite (5 gms. in 10 ccs. water). A red solution was formed at once, and this on pouring into water gave a pale yellowish-green precipitate. On filtering and washing the residue with water, an emerald green product was obtained, which was then crystallised

from ligroin.

yield 9 gms. (80% theory).

m.p. 144° (lit. 144.5°).

Picrate: m.p. 82°- 84°.

(easily decomposed with water.).

Attempted Oxidation of 1-Methyl-2-phenyl-3-nitroso--indole to the corresponding 3-Nitroindole.

Various oxidising agents were tried, but each was unsuccessful. With potassium permanganate in acetone, and with hydrogen peroxide, the nitroso-compound was recovered unchanged. With alkaline permanganate, and also with glacial acetic acid and permanganate, acidic residues were obtained, which showed that ring-rupture had occurred.

In each of the permanganate oxidations, the method adopted was as follows. 0.5 gms. of the nitroso-compound was mixed with 1 gm. of powdered potassium permanganate, the solvent - acetone, sodium hydroxide, or glacial acetic acid - added, and the mixture refluxed for three to four hours. The solution was then poured into water, decolorised with sulphurous acid, and the organic residue

separated.

In the case of the hydrogen peroxide, the two reactants were shaken up in a mechanical shaker for several days, and then the resulting product filtered off, and identified.

As these oxidations failed to give the 3-nitro-compound, other methods were tried.

Nitration of 1-methyl-2-phenylindole with concentrated nitric acid in the cold resulted in a green compound which did not melt and was therefore ~~was~~ not the required nitro-compound, but probably a polimer or di-indole, as such are known to be formed with 2-phenylindole by the action of mineral acids.

Angeli (Gazz., 1900, 30, 279) prepared the 1-ethyl-2-phenyl-3-nitroindole by ethylating 3-nitro-2-phenylindole. A similar reaction was then carried out to obtain the methyl compound.

Preparation of 1-Methyl-2-phenyl-3-nitroindole.

Metallic sodium (0.46 gms.) was dissolved in dry methyl alcohol (25 ccs.), and then methyl iodide (2.84 gms.) and 3-nitro-2-phenylindole (4.76 gms.) added. The whole was refluxed for one hour and then

poured into water. A yellow compound separated which was crystallised from alcohol.

yield 2.5 gms. (48% theory).

m.p. 122°.

Analysis:

Found N, 11.6%

$C_{15}H_{12}O_2N_2$ requires N, 11.2%.

Condensations of 1-methyl-2-phenyl-3-nitroso-indole with aniline, p-nitraniline, and p-bromoaniline were tried as follows. The nitroso-compound was dissolved in alcohol, and added to an equimolecular solution of the amine in alcohol. The mixture was heated on the steam bath for half an hour and then poured into water.

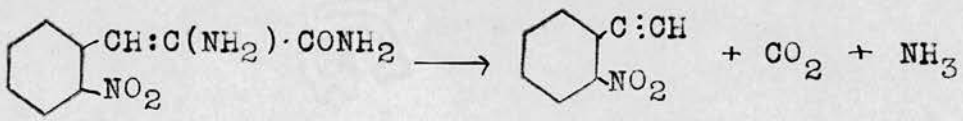
In each case the nitroso-compound was recovered unchanged and no combination had taken place.

D I S C U S S I O N .

Before giving a general discussion to the results obtained, it may be advantageous to consider each of the stages separately.

Reduction of α-Amino-o-nitrocinnamic Acid.

No further explanation can be given to that put forward by Cooper (Thesis, Edinburgh, 1934), namely the production of o-nitrophenylacetylene, resulting in the loss of the reaction products, due to the volatility of this substance. The fact that no product could be isolated both in aqueous and alcoholic solutions bears out this view of the reaction.

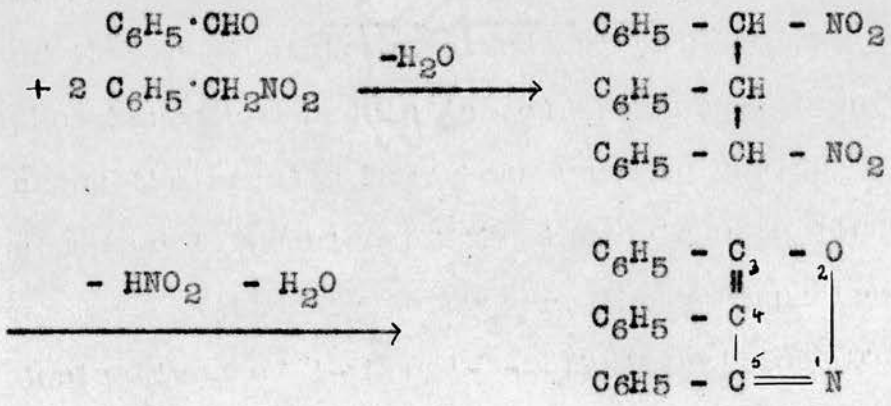


Condensation of o-Nitrobenzaldehyde and Phenylnitromethane.

Benzaldehyde and phenylnitromethane, in the

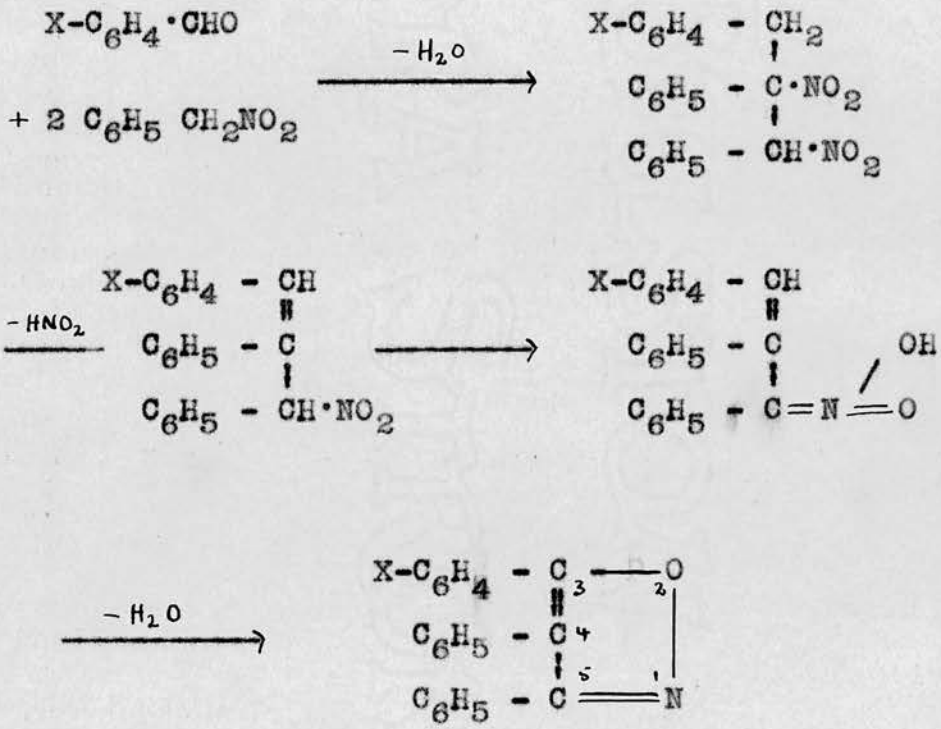
presence of methylamine condense very readily and the 7-nitrostilbene formed separates from the solution on cooling in a pure condition. It therefore seemed rather peculiar that a similar condensation of o-nitrobenzaldehyde and phenylnitromethane should not occur under similar conditions. In this particular case it would seem that the o-nitrobenzaldehyde was oxidised to o-nitrobenzoic acid and the phenylnitromethane to benzoic acid with the loss of nitrous acid.

Heim (Ber., 1911, 44, 2020) working on such condensations with phenylnitromethane and benzaldehyde and its substituted derivatives isolated isoxazoles from the reaction mixture. This is brought about by the condensation of two molecules of phenylnitromethane with one of the aldehyde and the subsequent loss of nitrous acid and water.



By this mechanism, using a substituted

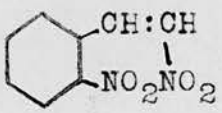
aldehyde, the resulting isoxazole contains the substituted phenyl group in the position 4. Ruggli and Hegedus (Helv. Chim. Acta., 1939, 22, 405) give a mechanism for the formation of a similar isoxazole whereby the resulting isoxazole contains the substituted phenyl group in the position 3.



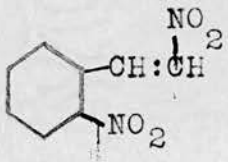
At present there is no chemical evidence to show which of these two mechanisms is the correct one, and both are equally probable, so that this mechanism raises a problem for future research.

Such a condensation would be expected to be more liable to take place with the o-nitrobenzaldehyde, as, due to the great polarity of the nitro group, the aldehyde group might be expected to be more reactive than in the unsubstituted aldehyde. This would then account for the tarry oil obtained from this particular condensation, and on this view, the oxidation of this product would give o-nitrobenzoic and benzoic acids.

When benzaldehyde condenses with nitromethane, only one ω-nitrostyrene results, but when o-nitrobenzaldehyde is used, two isomeric condensation products are possible: cis and trans forms.



cis.



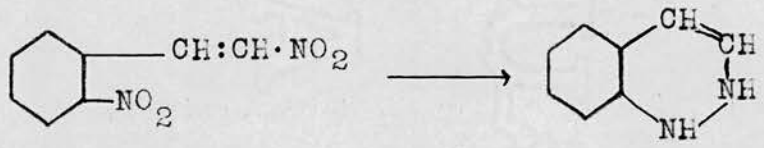
trans.

Reduction of o:ω-Dinitrostyrene.

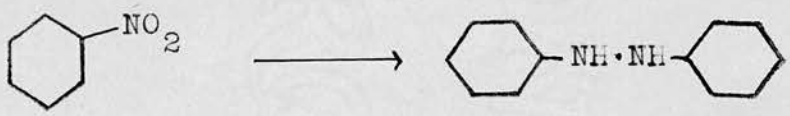
As the nitro group has a high polarity, the trans form would be expected to predominate in the condensation product. Reduction of the trans-o:ω-dinitrostyrene would then give trans-o:ω-diaminostyrene, which would not ring close very readily,

and therefore this is the compound that is most likely to have been obtained in the reduction of o:ω-dinitrostyrene with ferrous sulphate and ammonia. The compound was very unstable, as would be expected, and gave an acetyl derivative of very high melting point.

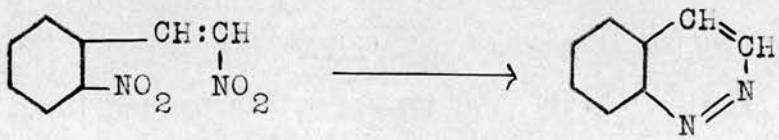
With zinc and hydrochloric acid a cinnoline derivative was obtained.



c.f. The alkaline reduction of nitrobenzene to hydrazobenzene.



With the cis-o:ω-dinitrostyrene, therefore, reduction to the cis-o:ω-diaminostyrene would be followed immediately by ring closure to give cinnoline.



The catalytic hydrogenation did not proceed so far as the diamino compound, but the fall in pressure denoted that the reduction had gone about half way, corresponding to a reduction of the nitro groups to oximino groups.

Drake and Kohler (J.A.C.S. 1923, 45, 1287) reduced ω-nitrostyrene with hydrogen and platinum catalyst, and they found that in the presence of acid (hydrochloric), phenylacetaldehyde oxime was formed.

$C_6H_5 \cdot CH_2 \cdot CH{:}NOH$ 1.

When there was no acid present, however, two molecules condensed to give the compound,

$$\begin{matrix} C_6H_5 \cdot CH \cdot CH{:}NOH \\ | \\ C_6H_5 \cdot CH \cdot CH{:}NOH \end{matrix}$$ 11.

and also further polimerisation occurred at the same time.

As there was no acid present in the catalytic hydrogenation attempted, compound 11, is the one expected to have been formed. In this way the nitro groups in the benzene nucleus would be reduced to hydroxylamino groups, though their presence could not be confirmed and was therefore very uncertain.

$$\begin{matrix} NHOH \cdot C_6H_4 \cdot CH \cdot CH{:}NOH \\ | \\ NHOH \cdot C_6H_4 \cdot CH \cdot CH{:}NOH \end{matrix}$$

The analysis figures obtained agree very well with this structure.

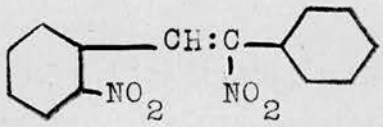
found N, 16.34%,

$C_{16}H_{18}O_4N_4$, requires N, 16.8%.

Also the melting point of the compound was very high, which is comparable to that of benzil dioxime.

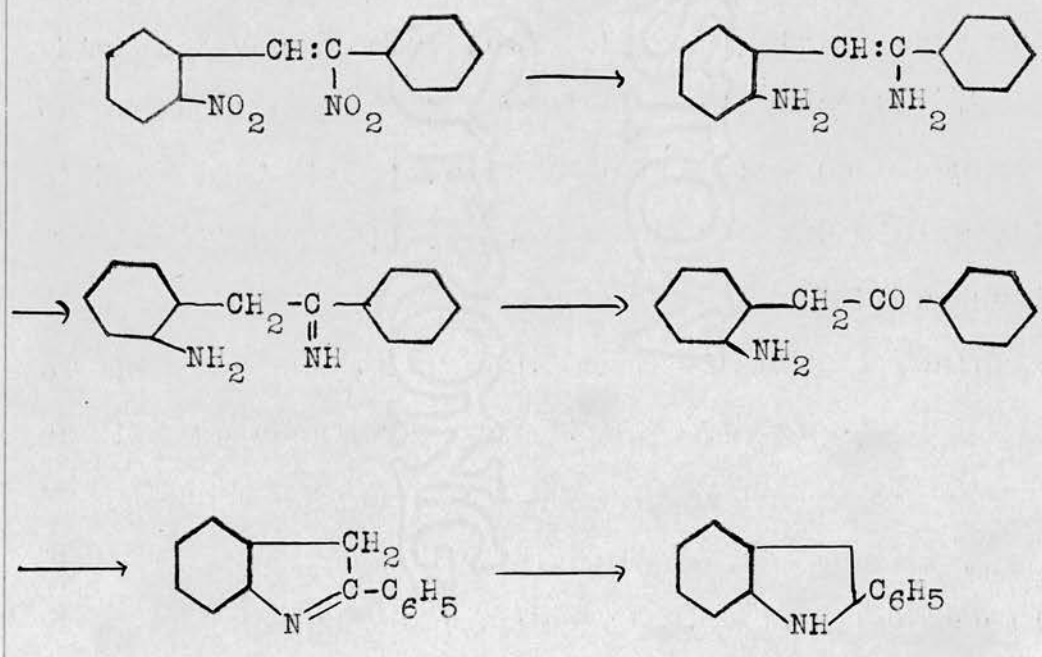
The condensation of o-nitrobenzaldehyde and phenylnitromethane by Thiele's method gave a product which was very uncertain. The analysis figures are not quite those of the required dinitrostilbene, although, if the structural formula be worked out for the figures obtained, the formula for dinitrostilbene ($C_{14}H_{10}O_4N_2$) is the only probable one. The reduction of this compound, however, was again unsatisfactory so that no conclusive result was obtained.

Ruggli and Hegedus (loc. cit.) have recently investigated the same condensation. By boiling a mixture of phenylnitromethane and o-nitrobenzaldehyde with methylamine, they isolated, among other products a compound m.p. 106°, which they showed to be dinitrostilbene.



It is possible that this compound and the one prepared in this thesis, are isomeric cis and trans forms, as they are prepared by different methods of condensation.

By reducing this dinitrostilbene with zinc dust and acetic acid, Ruggli isolated 2-phenylindole, and he interpreted this reaction as follows.



Thus he postulated 2'-aminodeoxybenzoin as an intermediate product in the reaction. He gives no adequate reasoning for his stages, and as in this

thesis, o-aminodeoxybenzoin has been isolated and found to be reasonably stable to such condensing agents as acetic anhydride, doubt arises as to the formation of this compound as an intermediate in the formation of 2-phenylindole by this method.

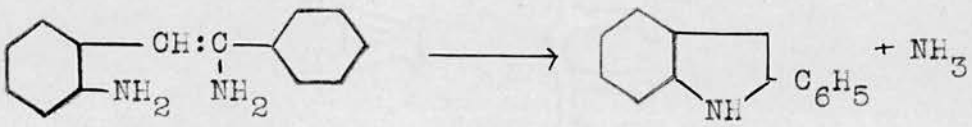
Robinson's theory gives an adequate explanation of all the observed phenomena in the synthesis of indoles by the Fischer method. As yet no valid objection has been made to it and the correctness of the theory is more than probable. It was unfortunate that the method of attack in this thesis bore no concrete result, as it was felt that the method was a promising one.

In fact the evidence obtained actually does not coincide with the theory, but rather supports Neber's theory, with ring closure to form a cinnoline derivative. As the cinnoline derivative obtained, however, was stable to boiling hydrochloric acid, and no indole was formed, this fact cannot be taken as favourable to Neber's theory.

The data put forward by Ruggli may actually be used to prove Robinson's theory, although this author does not mention his work in that respect. As his compound was the one expected from the work

in this thesis, that conclusion can be drawn here.

However, in view of the comparative stability of the o-aminodeoxybenzoin found in this work, a direct formation of 2-phenylindole, by the elimination of ammonia between the two amino groups, is put forward. This is actually what Robinson postulates in his theory for indole formation.



Pictet's Method of Indole Formation.

The nitration of deoxybenzoin with Menke's reagent, and the separation of the resulting 2'- and 4'-nitrodeoxybenzoins with ether, was much more satisfactory than the method employed by Pictet and List (loc. cit.). As the oil, obtained by Pictet, was shown by List to contain only 25% of the 2'-nitro-compound, the yield of indole obtained by the reduction with zinc dust and concentrated ammonia, could not have been very good. With the pure 2'-nitrodeoxybenzoin, the yield of 2-phenylindole, by reduction with zinc dust and ammonia was very small, but reduction with zinc dust and acetic acid proved much better. This can be explained as being due to the dehydrating action of the glacial acetic acid on the 2'-aminodeoxybenzoin.

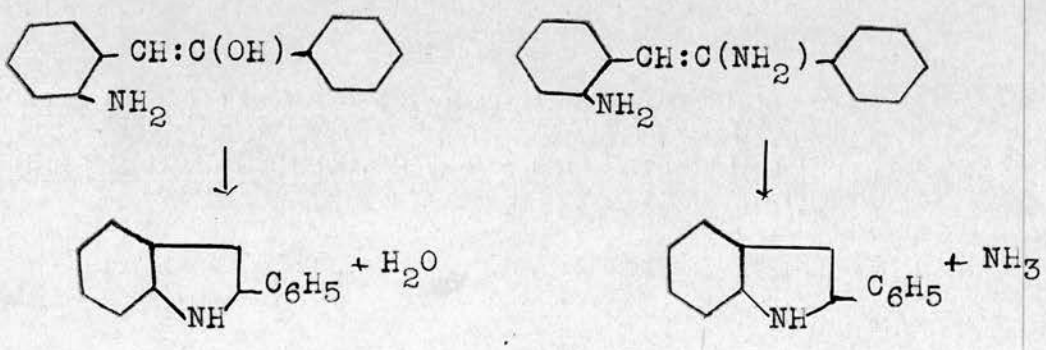
The isolation of 2'-aminodeoxybenzoin by acidification of the resulting solution in the reduction with zinc dust and ammonia, has proved very interesting, as it shows that the compound has a certain range of stability, and some kind of dehydrating agent must be present to convert it into 2-phenylindole. It was unfortunate that no derivatives could be made of this compound, but it was undoubtedly 2'-aminodeoxybenzoin as it gave

2-phenylindole on standing in acetic anhydride solution for several days at room temperature. Also the amino group was indicated by the solubility in mineral acids, and by the evolution of nitrogen by the action of nitrous acid.

The carbonyl group might have been reduced to an alcoholic group (-CHOH-) and the extra two hydrogen atoms would not make much difference to the analysis figures, but the results obtained do agree better with the carbonyl group (-CO-).

The failure to obtain any derivatives was taken as being due to the fact that the compound decomposed readily, probably the amino group of one atom with a carbonyl of the other, as decomposition in this manner did not give indole.

The formation of 2-phenylindole from 2'-aminodeoxybenzoin resembles Robinson's mechanism of the Fischer indole synthesis, though it takes place much less readily.



Derivatives of 2-Phenylindole.

As had been expected by Campbell and Cooper (loc. cit.), it has been found that nitrous acid readily accomplished the oxidation of 3-isonitroso-2-phenylindole to 3-nitro-2-phenylindole, and when in large excess, formed the 3:5-dinitro-2-phenylindole, first obtained by Angeli and Angelico (loc. cit.) though their method of preparation was much superior. The melting point of this dinitro-2-phenylindole was given as"above 280°" and no definite structure was assigned to it. The pure compound was obtained with a definite melting point of 312°, and was proved to be 3:5-dinitro-2-phenylindole, by oxidation with potassium permanganate in glacial acetic acid to 5-nitrobenzoyl-anthranilic acid. This nitration of the benzene ring in the position 5 is paralleled by the nitration of 2:3-dimethylindole (Bauer and Strauss, Ber., 1932, 65, 308; Plant and Tomlinson, J.C.S., 1933, 935). By analogy the dinitro-2-methylindole of Walther and Clemen (J.pr.Chem., 1900, 61, 249) is probably the 3:5-dinitro-compound.

The attempt to prepare a trinitro-2-phenylindole, by a similar method to that of Mathur and Robinson's preparation of trinitro-2-methylindole failed. The reactions in the case of 2-phenylindole

were more vigorous than in the case of 2-methylindole, but whereas the 3:5-dinitro-2-phenylindole was easily obtained, further heating with nitric acid led to oxidation with the formation of 5-nitrobenzoylanthranilic acid.

Properties of 1-Methyl-2-phenyl-3-nitroso-indole.

1-Methyl-2-phenyl-3-nitroso-indole is a true nitroso-compound but many of its properties are anomalous. The various attempts to oxidise this compound to the corresponding nitro-compound, with different reagents, were all equally unsuccessful. 3-Nitro-1-methyl-2-phenylindole is quite stable, and was easily prepared by methylation of 3-nitro-2-phenylindole with methyl iodide and methyl alcoholic potassium hydroxide.

Also the failure to obtain condensation products with aniline, p-nitraniline and p-bromo-aniline is contrary to the reactions expected of a nitroso-compound.

Further it gave no colour with glacial acetic acid and diphenylamine, (nitrosobenzene gives a pink colour), formed no dye with hydroxylamine hydrochloride and α-naphthol, and liberated iodine

from acidified aqueous alcoholic potassium iodide much less readily than did nitrosobenzene.

Thus both in appearance and in some of its chemical properties, 1-methyl-2-phenyl-3-nitroso-indole resembles p-nitrosodimethylaniline rather than nitrosobenzene, for the former gave no colour with glacial acetic acid and diphenylamine, and liberated iodine from potassium iodide more slowly than did the latter.

With certain nitroso-compounds it is not possible to carry out the Liebermann reaction owing to the sulphuric acid itself producing a colouration. This also applies to the Angeli Castellana reaction (Atti.R.Accad.,Lincei., 1905, 141, 669), but the latter case may be modified by using acetic acid instead of sulphuric acid. C-nitroso-compounds, such as nitrosobenzene give a pink colouration after a few minutes.

PART 2.

The Reactivity of Halogen Atoms in some Heterocyclic Molecules.

1. Indazole Series.
2. Benzimidazole Series.

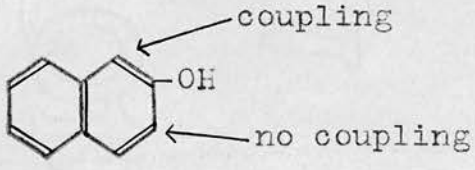
I N T R O D U C T I O N .

Bicyclic Compounds.

(Fries, Ann., 1927, 45, 121).

Fries has divided such compounds into two distinct groups: benzoid and naphthoid, certain chosen reactions being used as the criterion. It appears that for bicyclic compounds, very few are of genuine naphthoid character. The differentiation is not easy, in the same way that the difference between aromatic and aliphatic compounds is not always clearly marked.

Naphthoid compounds are taken as those in which the ortho positions are not equivalent, and also the two rings share a double bond: c.f. Naphthalene.



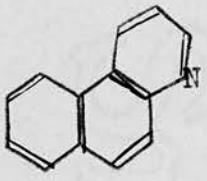
The reactions used for the differentiation are the following.

1. Coupling of primary amines with diazonium salts.

Diazoamino and aminoazo-compounds are obtained depending on the benzoid or naphthoid character of the compounds. This reaction is not entirely suitable since substituents in benzene also influence the course of the reaction, as does the nature of the diazonium compound.

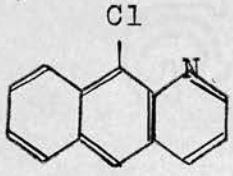
2. Quinoline formation according to Skraup. As pointed out by Campbell and McLeish (J.C.S. 1937, 1108) this also has certain limitations.
E.g. (Fries, Ann., 1935, 516, 285).

A Skraup synthesis on β-naphthylamine usually ring closes in the 1-position, resulting in the formation of the compound:



Thus indicating the existence of a double bond in the position 1-2.

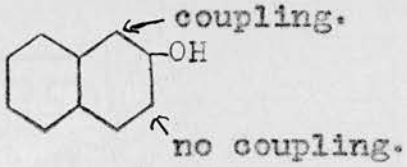
Fries, however, found that when the 1-position was blocked, he obtained some of the compound:



indicating a double bond in the position 2-3.

3. Coupling of phenolic compounds with diazonium salts. This is one of the most satisfactory methods. (c.f. Fieser, J.A.C.S., 1935, 57, 1459; and 1936, 58, 2050).

Naphthoid:

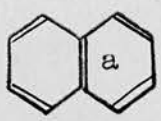


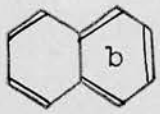
4. Nitration and halogenation, e.g. in naphthalene it is the 1-position which is mainly attacked.

5. Conversion of benzalamino-compounds into acridine derivatives. In the naphthalene series this occurs readily. In the benzene series more drastic conditions are necessary.

Fries has designated the following compounds to their respective groups.

Tetralin ---------- Benzoid.
Cumarin ---------- Benzoid.
Benzimidazole ---------- Mostly benzoid.
Benzthiazole ---------- Mostly benzoid.
Benzisothiazole ---------- Mostly benzoid.
Indazole ---------- Mostly naphthoid.

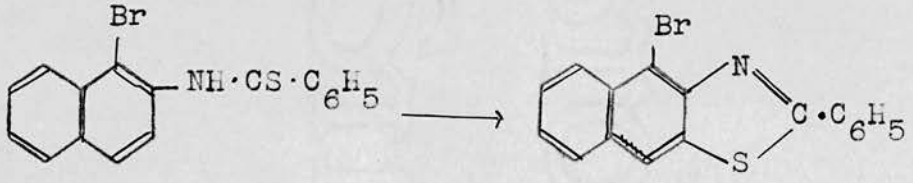




Fries is of the opinion that in naphthalene only one form (a) is present and that in the other compounds form (b) may also be present. There is probably equilibrium and naphthoid character is noted when form (b) is present only to a very small extent. (c.f. however, resonance).

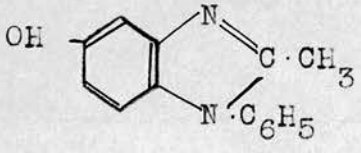
He considers in some detail, bromination from this point of view.

Under certain conditions "exceptional" reactions occur. Thus the following reaction takes place readily.



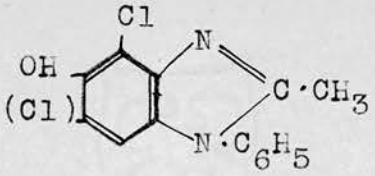
Benzimidazole Series.

Fries investigated the compound 1-phenyl-2-methyl-5-hydroxybenzimidazole.

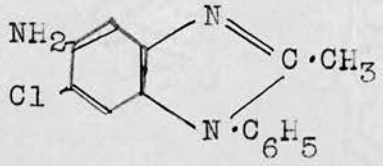


The substituents in the hetero-ring did not

affect reactions in the benzene ring. He found that chlorination gave (a)-compounds, while further chlorination gave only a small quantity of the c-o-dichloro-compound, a keto chloride being chiefly formed. c.f. naphthol.



Similarly with the amino-compound, but here also he found that small quantities of the 6-chloro-compound were obtained.

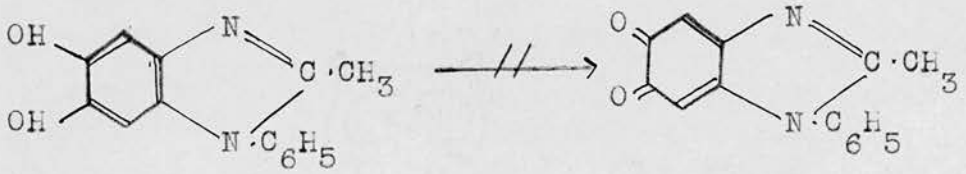


He found that both the 4- and 6-chloro-5-aminobenzimidazoles could not be diazotised to the corresponding hydroxy-compounds.

The bromination of the 5-hydroxy-compound gave first the 4-bromo-compound, and then a dibromo-compound. This is different from naphthalene. A further difference was noted in the case of diazotisation and nitration. Nitration of benzimidazole occurs at the 5-position and not at the 4 as in naphthalene. Fries showed that this was not due to the influence of the imino-group.

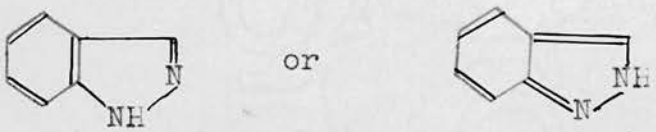
As in naphthalene, no quinone could be

formed from 5:6-compounds.



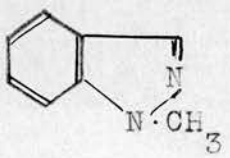
Indazole Series.

The structure of indazole has been given in the literature as;

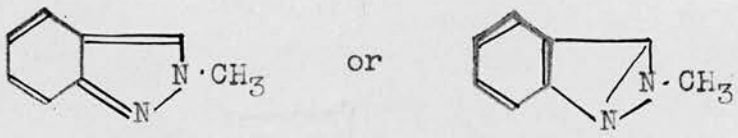


The hydrogen atom supposedly can be attached to either of the nitrogen atoms, so that indazole can be expressed as a tautomeric mixture of these two structural forms.

Auwers (Ann., 1937, 527, 291) prepared the isomeric 1-methyl and 2-methylindazoles and examined many of the physical properties of these compounds. He formulated the 1-methyl compound as:



and the 2-methyl compound as;



Noelting (Ber., 1904, 37, 2556) showed that the nitroindazoles were formed very easily by diazotisation of the various nitro-o-toluidines. In this work he showed that diazotisation in glacial acetic acid was more satisfactory than in mineral acids, as in the latter case a high percentage of nitrocresol was formed.

He found that methylation of these nitroindazoles resulted in a mixture of the isomeric methyl derivatives but did not separate the isomers.

Fries (Ann., 1927, 454, 307) later, isolated the 1-methyl and 2-methyl derivatives. He postulated "that the 1-methyl derivative has the lower melting point and occurs in prepondering amounts in the methylated mixture".

Theory of Activation by Unsaturated Groups.

In a molecule containing a system of conjugated double bonds, the influence exerted by any functional group may sometimes be propagated along the chain and make itself apparent by activating atoms at a remote point in the molecule. Fuson (Chem. Reviews, 1935, 16, 1) has shown that this effect has a wide application, and has called the phenomenon "vinylogy".

An illustration of this principle is the fact that the methyl group in ethyl crotonate behaves in some respects as it does when attached directly to the ester group in ethyl acetate.

$CH_3(CH{:}CH)\cdot C{:}O$ $\quad$ $CH_3\cdot C{:}O$

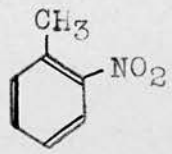
$\quad\quad\quad\quad\quad O\cdot C_2H_5$ $\quad\quad\quad\quad$ $O\cdot C_2H_5$

Ethyl crotonate. $\quad\quad$ Ethyl acetate.

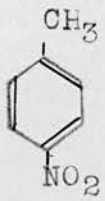
Fuson quotes further application of the principle to the case of the nitrotoluenes. It has been shown by the work of Angeli and others, that the methyl groups in the ortho and para nitrotoluenes are reactive and undergo similar reactions to those

of nitromethane. The benzene ring, according to the Kekule formula, consists of a system of double bonds, and the above observations are accordingly in agreement with Fuson's principle.

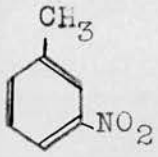
Furthermore, as would be expected, the methyl group in m-nitrotoluene is non-reactive.



Reactive

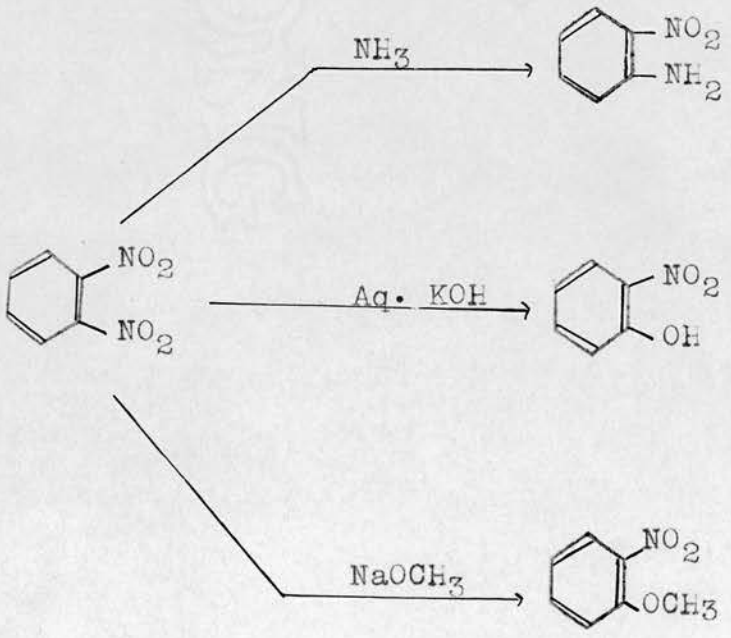


Reactive



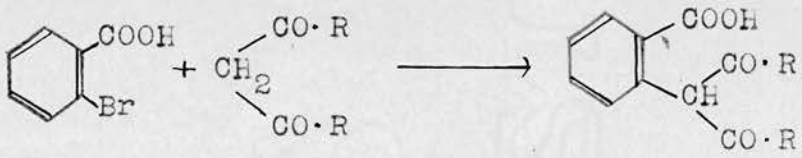
Non-reactive

In the case of o-dinitrobenzene, one of the nitro groups can be replaced by amino, hydroxyl, or methoxyl, by means of ammonia, aqueous alkali or sodium methoxide respectively.



In aromatic halogen substituted compounds, such as bromobenzene, the halogen atom is highly non reactive, but if the molecule is further substituted in the ortho or para positions by an unsaturated group, then the halogen atom becomes reactive.

Thus o-bromobenzoic acid reacts with active methylene compounds as follows:

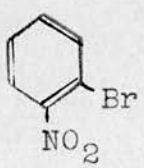


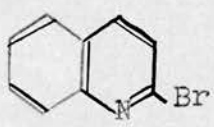
If this principle of activation be extended to the more complex aromatic compounds, then considerable evidence can be obtained with regard to the positions of the double bonds in these molecules, and as to whether the bonds are mobile or fixed.

Application of Fuson's Vinylogy Theory.

The theory of the reactivity of halogen atoms in an aromatic nucleus has been widely applied to the determination of the fine structures of many compounds, and was used for example by Campbell and Mc·Leish (J.C.S., 1937, 1103) to determine the structure of naphthalene. It has not, however, been very much applied to the heterocyclic series in which respect a modification of the usual method is required.

In a heterocyclic molecule, a halogen atom, rendered mobile due to its position relative to the unsaturated nitrogen atom, cannot be removed by boiling with piperidine as in the case of a halogen atom, rendered mobile by the presence of a nitro group. In such cases a more drastic effort is required (J.C.S. (Mills and Smith, 1922, 121, 2724)





Gabriel (Ber., 1886, 19, 1856) found that by heating the heterocyclic compound in a sealed

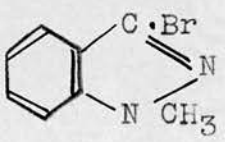
tube with red phosphorus and hydriodic acid "reactive" halogen was removed between 160°- 180°, while "non-reactive" halogen was not removed till over 180°. Below 160°, no halogen was removed and above 180° all halogen was removed.

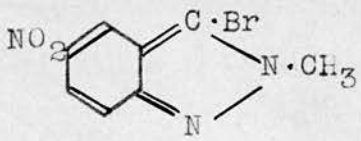
These determinations cannot be carried out quantitatively as in the piperidine method, but they enable us to distinguish between a"reactive"and a "non-reactive"halogen atom in a molecule.

Of course, nitro groups can also be introduced into the molecule to activate the halogen atoms.

E.g.

3-Bromo-1-methylindazole and 3-Bromo-2-methyl-5-nitroindazole.



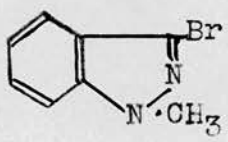


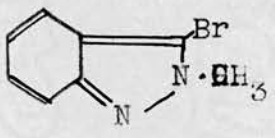
Only the nitro-compound is reactive to piperidine

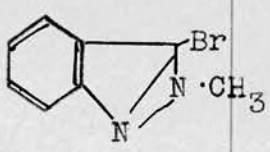
Object of Research.

Indazole Series.

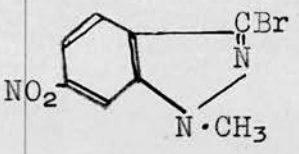
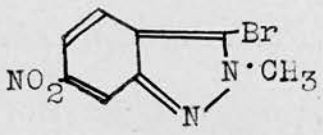
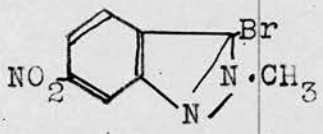
An attempt was first made to prepare the isomeric 1-methyl and 2-methyl-3-bromoindazoles, and test the reactivity of the bromine atoms in these molecules with red phosphorus and hydriodic acid. It was expected that the 1-methyl derivative would be found to be reactive, while the 2-methyl derivative would not.







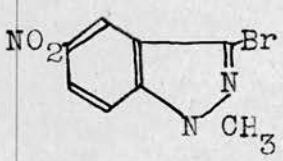
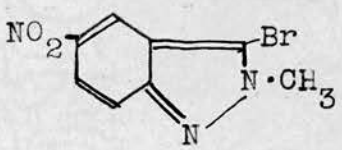
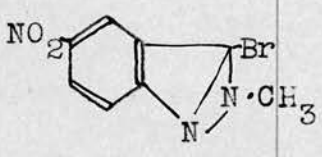
The isomeric 3-bromo-6-nitromethylindazoles were then prepared and the reactivity of the bromine atoms tested towards red phosphorus and hydriodic acid. Here again the 1-methyl-compound was expected to be reactive and the 2-methyl non-reactive.

(The nitro group in both of these molecules can have no effect on the bromine atom as no conjugated system is present between the two groups; thus any activity is due only to the unsaturated nitrogen atom.)

As these compounds also were new compounds, this reactivity was taken as a guide to the orientation of the 1-methyl and 2-methyl-6-nitroindazoles.

With the nitro group in the position 5, a conjugated system may occur between the nitro and bromo groups of the 2-methyl derivative.

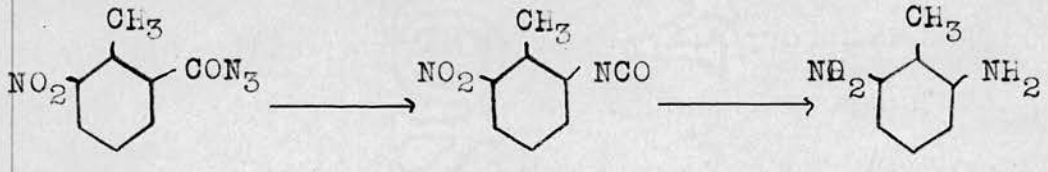




This compound, therefore, would be expected to possess a mobile halogen atom. The isomeric methyl-3-bromo-5-nitroindazoles were thus prepared and tested by the piperidine method.

The isomeric 3-bromo-6-nitro-methylindazoles were also tested by the piperidine method, and the 3-bromo-4-nitro-methylindazoles prepared and tested in the same way. Both of these series were not expected to show any reactivity, however, by this method.

During this research certain preparative difficulties were encountered, and in such cases efforts were made to improve the methods given in the literature.

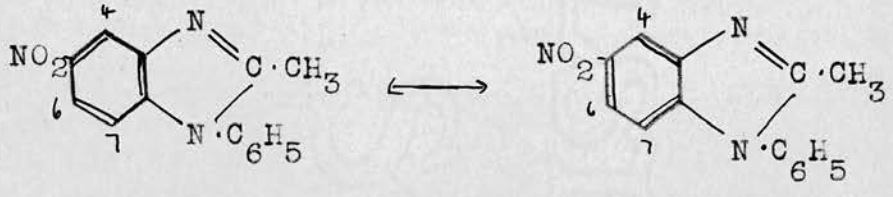
For example, difficulty was found in preparing 6-nitro-o-toluidine by the reduction of 2:4:6-trinitrotoluene, and another method was tried namely a Curtius reaction on 6-nitro-o-toluic-azide.



Benzimidazole Series.

Fries postulated that 1-phenyl-2-methyl-5-aminobenzimidazole was of a benzoid character - i.e. the ortho positions are equivalent - .

It was attempted to prove this by the preparation of isomeric halogeno-nitro compounds and testing the reactivity of the halogen atoms, towards piperidine.



The 4-compound was prepared by direct halogenation of the 5-acetamido-compound, and the 6-compound from 3-halogeno-4:6-dinitrodiphenylamine

It was expected that these amino-compounds would be converted into the corresponding nitro-compounds, by treatment of the diazonium salts with sodium nitrite and cupri-cupro sulphite (Hantzch and Blagden, Ber., 1900, 33, 2554). Unfortunately, however, success was not attained.

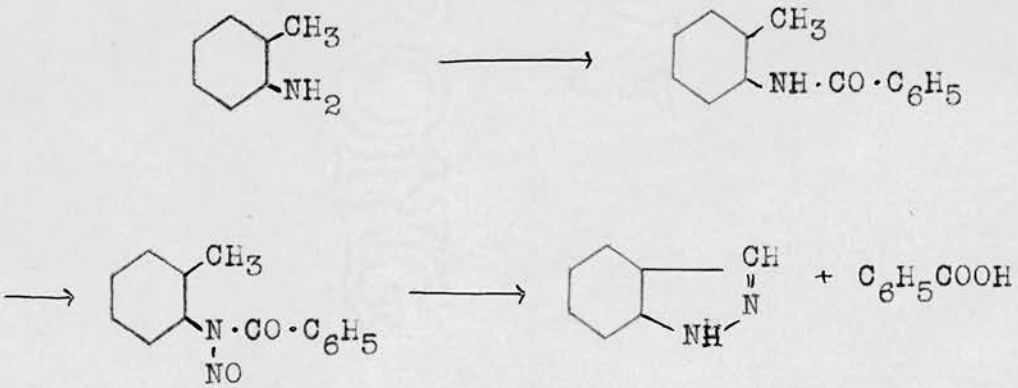
Direct halogenation of the 1-phenyl-2-methyl-5-nitrobenzimidazole was expected to give 1-phenyl-2-methyl-7-halogeno-5-nitrobenzimidazole, due to the meta-directive influence of the nitro group. The position of the halogen atom, however, is not certain and no proof could be found.

EXPERIMENTAL.

Preparation of Indazole.

(Ber., 1908, 41, 662.)

"A nitroso group cannot be introduced into o-aceto-toluidide very readily. The nitroso-acetyl compound thus obtained can be transformed into indazole by the action of benzene, but only in small quantities. Indazole formation is much easier when o-benzoyl-toluidide is used as the starting material."



o-Benzoyl-toluidide.

o-Toluidine (75 gms.) was dissolved in benzene (500 ccs.) and treated with benzoyl chloride (100 gms.)

The resulting benzoyl-compound was filtered, dried well by suction, and crystallised from alcohol.

method useless as toluidine HCl is formed.

yield almost quantitative.

m.p. 145°- 146° (lit. 146°).

N-nitroso-o-benzoyl-toluidide.

o-Benzoyl-toluidide (5 gms.) was dissolved by warming in glacial acetic acid (30 ccs.) and then allowed to cool with brisk stirring, so that fine crystals were obtained. This suspension was then cooled in ice-water, (care is necessary to avoid solidification of the acetic acid), and gaseous nitrous acid passed in until all the solid had gone into solution, which turned an intensive dark green colour. This solution was poured on to ice and the nitroso-compound first obtained as an oil, which on rubbing and standing became solid and filterable.

Several of these portions were collected and the solid filtered, washed with ice-water until the smell of nitrous acid had disappeared, and then dried by pressing on porous tile.

This crude product, yield almost theoretical, was not purified further before conversion into the indazole.

Indazole.

N-nitroso-benzoyl-toluidide (5 gms.) was covered with 55 ccs. of sodium dried benzene: the action soon began and the benzene boiled gently, the nitroso-compound going entirely into solution. Next day the contents of the flask were heated on the water bath for half an hour to complete the reaction. Most of the benzene was then removed by distillation and the remaining solution poured into a flat basin to evaporate completely. The residue was first triturated with dilute sodium carbonate solution to remove benzoic acid, and then submitted to distillation with superheated steam (the flask in an oil bath at 140°- 150°). The indazole distilled over and was extracted with ether (it is now no longer contaminated with o-benzoyl-toluidide or benzoic acid). It was further purified by dissolution in dilute hydrochloric acid and precipitation with sodium hydroxide. The indazole was filtered, washed with cold water, and crystallised from water.

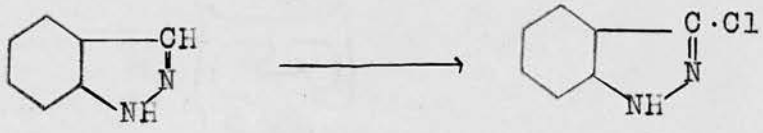
Yield 1 gm. (20% theory)

m.p. 146° (lit. 146.5°).

Several of these portions were collected.

3-Chlorindazole.

(Ann., 1937, 527, 291).



To obtain the indazole in a very finely divided form, it was dissolved in dilute hydrochloric acid and reprecipitated by adding sodium hydroxide and shaking.

Indazole (2 gms.) was suspended in 2N sodium hydroxide (50 ccs.) and a solution of sodium hypochlorite (30 ccs. of sodium hydroxide containing 1.2 gms. of chlorine) slowly added with shaking. The solution was neutralised with dilute hydrochloric acid, and a brown precipitate separated which melted at 195°- 205°. This was the 3:5-dichlorindazole. The filtrate on further acidification yielded 3-chlorindazole, which, when crystallised from water, was obtained as pure white needles.

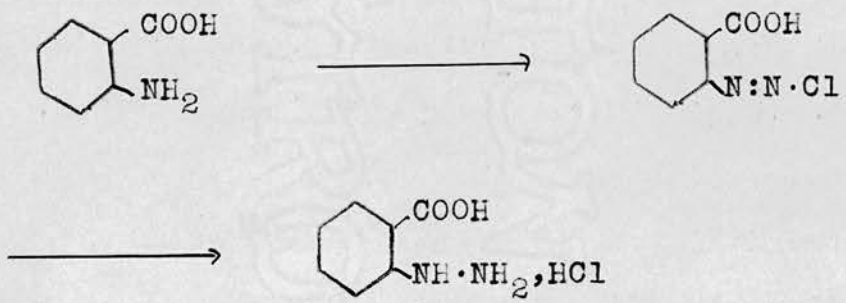
yield 1.8 gms. (72% theory)
m.p. 146°- 147° (lit. 148°).

Due to the poor yields of 3-chlorindazole

prepared by this method from N-nitroso-benzoyl-o-toluidide, another method was attempted. Emil Fischer gives a method whereby 3-chlorindazole is formed by heating in a sealed tube, a mixture of o-hydrazinobenzoic acid and phosphorus oxychloride. If so required, this 3-chlorindazole can then be reduced to give indazole, with zinc and hydrochloric acid (Ber., 34, 1901, 797).

Preparation of o-Hydrazinobenzoic acid.

(Ber., 1880, 13, 681 and 1901, 34, 796).



5 gms. anthranilic acid.
5 gms. sodium nitrite in 15 ccs. water.
5 ccs. concentrated hydrochloric acid in 15 ccs. water.
10 gms. sodium sulphite.

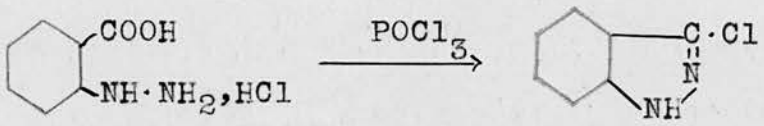
The anthranilic acid was dissolved in the mixture of hydrochloric acid and water, and after

cooling to 0° diazotised by running in slowly the solution of sodium nitrite. The resulting clear solution was then added to a concentrated slightly alkaline solution of sodium sulphite. The mixture was at first dark red, and later bright yellow, and finally was decolorised, after acidifying with acetic acid, by very gently heating with zinc dust. The solution now possesses strong reducing properties and contains the hydrazine sulphonic acid salt. To break this up the filtrate was saturated with hydrochloric acid whereby the resulting hydrazino-benzoic acid hydrochloride , on account of its lesser solubility in strong hydrochloric acid separated almost completely in the cold along with sodium chloride. From the admixed salt the hydrazine compound was easily separated by treating the filtered mass with small quantities of cold water.

yield 4.5 gms. (78% theory).

This compound was not purified further, as the next stage does not require it.

3-Chlorindazole.



The hydrazinobenzoic acid (2 gms.) was heated in a sealed tube at 120° for four hours with phosphorus oxychloride (14 gms.). The excess of the phosphorus oxychloride was then distilled off under reduced pressure and the residual 3-chlorindazole distilled in steam. The compound was filtered from the distillate on cooling, and crystallised from water, from which it separated in white needles.

yield 1 gm. (74% theory)

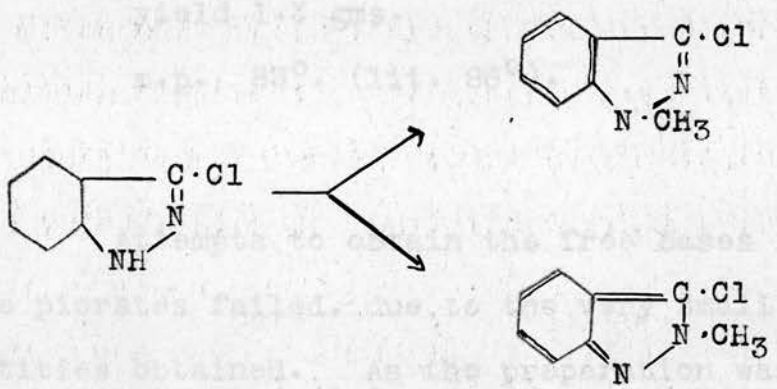
m.p. 148° (lit. 148°).

Methylation of 3-Chlorindazole.

(Auwers, Ann., 1937, 527, 291).

"By complete methylation, either with methyl iodide and sodium ethylate, dimethyl sulphate and caustic soda, or diazomethane, a resulting mixture of the two N-methyl derivatives can be formed in varying proportions. These are separated in the

customary manner with the aid of their picrates. From a very dilute ethereal solution the 2-derivative separates at once as bright yellow crystals melting at 129°- 131°. From the very concentrated solution the 1-derivative separates. The main portion is obtained by the complete evaporation of the solution. Golden yellow plates and prisms melting at 86°. From the salts, the bases are set free by treatment with ammonia.



Carrying out this procedure reported by Auwers, 3-chlorindazole (6 gms.) was dissolved in 10% sodium hydroxide (50 ccs.) and dimethyl sulphate (5.5 gms.) slowly added with shaking. The mixture was then warmed on the steam bath for half an hour and the dark brown oil, which separated, extracted with ether. To this extract was then added an ethereal solution of picric acid to form the picrates of the isomeric methyl-chlorindazoles.

From this solution the 2-methyl-3-chlorindazole picrate separated first, and was filtered and recrystallised from methyl alcohol.

yield 0.8 gms.

m.p. 128°- 131° (lit. 129°- 131°).

By complete evaporation of the ethereal extract the 1-methyl-3-chlorindazole picrate was obtained, and was crystallised from methyl alcohol.

yield 1.5 gms.

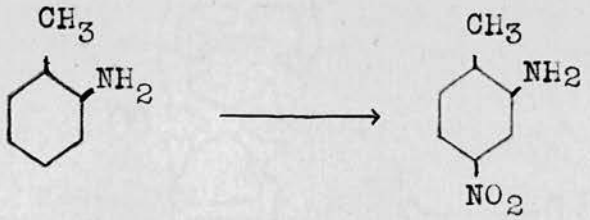
m.p. 83° (lit. 86°).

Attempts to obtain the free bases from these picrates failed, due to the very small quantities obtained. As the preparation was an extremely lengthy one, it was not repeated, but a series of nitroindazoles prepared instead. The presence of the nitro group in the benzene nucleus of the toluidine makes ring formation to the indazole much easier.

Preparation of 6-Nitroindazole.

1) 4-Nitro-o-toluidine.

(Ullman and Grether, Ber., 1902, 35, 337).



30 gms. o-toluidine.
450 gms. concentrated sulphuric acid.

28 gms. concentrated nitric acid.
100 gms. concentrated sulphuric acid.

The o-toluidine was dissolved in the sulphuric acid, forming the amine sulphate, the mixture cooled to 0° and the mixture of nitric and sulphuric acids added slowly with vigorous stirring. When all the nitration mixture had been added, the solution was kept at room temperature for two hours and then poured on to ice (600 gms.) and stirred. An almost clear solution resulted, which then deposited crystals of 4-nitro-o-toluidine sulphate. The filtered mass was stirred up with excess of sodium hydroxide, and the 4-nitro-o-toluidine separated, washed with water and recrystallised from alcohol.

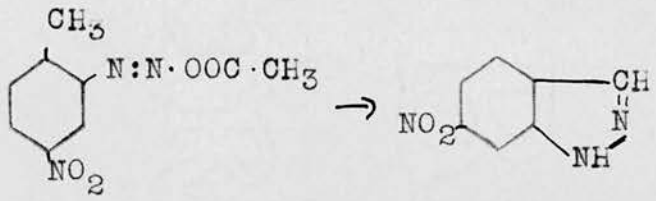
The 4-nitro-o-toluidine crystallised in yellow prisms.

yield 34 gms. (80% theory).

m.p. 107° (lit. 107°)

2) <u>6-Nitroindazole.</u>

(Noelting, Ber., 1890, <u>23</u>, 3635).



10 gms. 4-nitro-o-toluidine.

500 ccs. glacial acetic acid.

33 ccs. 2N sodium nitrite solution.

The 4-nitro-o-toluidine was dissolved in glacial acetic acid, ~~cooled to a temperature under 10°~~ and the sodium nitrite solution ~~slowly~~ added. When the diazo-reaction was finished, the brown reaction product was removed by filtration, and the solution distilled to one quarter of its original volume. On cooling, the indazole crystallised, and still more impure product was obtained by addition of water. Recrystallised from water the compound separated in brown needles.

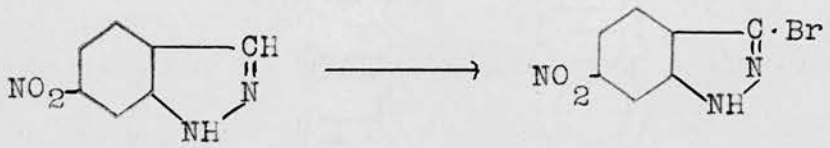
yield 10 gms. (90% theory).

m.p. 180° (lit. 181°).

As the method of diazotisation of nitro-amines given by Hodgson and Walker (J.C.S., 1933, 1620) has been very successful in so many cases, it was tried in the preparation of these indazoles. The resulting compound, however, underwent a great deal of charring due, in all probability to the heating with concentrated sulphuric acid. Also a much higher percentage of nitrocresol was formed. The method was therefore much inferior to that of Noelting.

Bromination of 6-Nitroindazole.

(Noelting, Ber., 1890, 23, 3639).

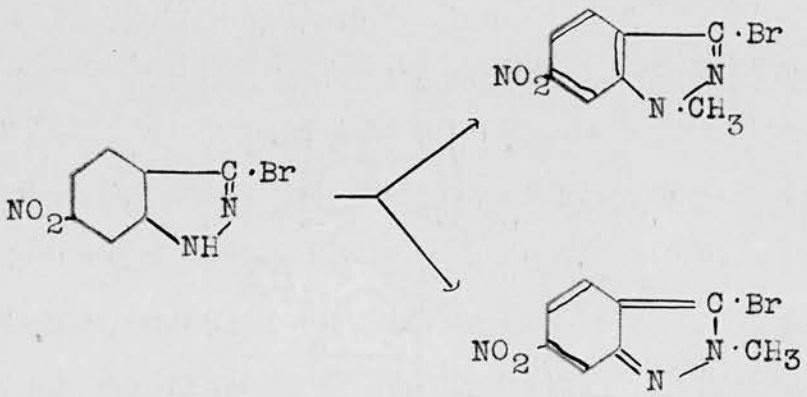


The 6-nitroindazole (3 gms.) was dissolved in a solution of 2N sodium hydroxide and reprecipitated by the addition of dilute sulphuric acid. Excess of bromine water was then added and the mixture well shaken up. After half an hour, the solid was filtered, triturated with hot water to remove any unchanged nitroindazole, and then recrystallised first from benzene, and then from 50% alcohol.

yield 2.5 gms. (68% theory)

m.p. 229° (lit. 230°).

Methylation of 3-Bromo-6-nitroindazole.



5 gms. 3-bromo-6-nitroindazole.

25 gms. methyl alcohol.

3 gms. potassium hydroxide.

9 gms. methyl iodide.

These were refluxed for four hours, after which the excess of methyl iodide was distilled off. The potassium iodide was washed out with water, and the remaining methyl derivatives allowed to crystallise from the solution.

A mixture of isomers was thus obtained and was separated with ether; one being soluble while the other was insoluble.

The soluble portion was recrystallised several times from methyl alcohol.

m.p. 140°- 145°. 130-146°!

yield 0.7 gms. (14% theory).

The portion insoluble in ether was recrystallised three times from absolute alcohol.

yield 2.5 gms. (50% theory).

m.p. 170°- 171°.

Analysis: compound m.p. 140°- 145°.

found Br, 31.52%,

$C_8H_6O_2N_3Br$. requires Br, 31.2%.

compound m.p. 170°- 171°.

found Br, 31.6%,

$C_8H_6O_2N_3Br$. requires Br, 31.2%.

According to the convention given by Fries (Ann., 1927, 454, 306), the 1-methyl derivative has the lower melting point, and occurs in the greater proportion of the mixture. He states, however, that this rule is not without exception.

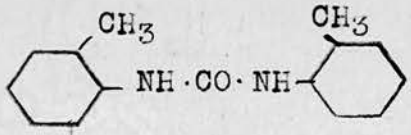
As in this case it is the higher melting fraction which is present in the greater proportion, no conclusion can be drawn from this convention, and some other method had to be used.

It was expected that the 1-methyl derivative would contain reactive bromine, while the 2-methyl derivative would not.

Preparation of 5-Nitroindazole.

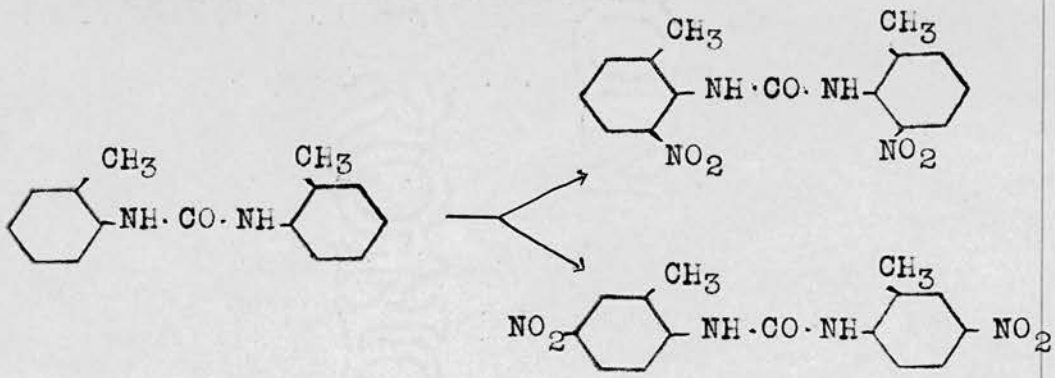
1). Preparation of 3-Nitro- and 5-Nitro-o-toluidine.

Bis-o-tolylurea.



This was prepared by passing a stream of carbonyl chloride through a solution of o-toluidine in alcohol. The resulting solid, which separated, was filtered, washed with water, and recrystallised from alcohol.

Nitration of Bis-o-tolylurea.



Bis-o-tolylurea (5 gms.) was added in small quantities to a mixture of fuming nitric acid (10 ccs.) and glacial acetic acid (10 ccs.) at a temperature of 0°, in the course of one hour. It first dissolved

giving a dark brown solution, but later a thick yellow paste was formed, which was then stirred for another one hour and finally poured into water (500 ccs.). The precipitate was separated, washed with cold water and thoroughly dried on tile.

yield 5.2 gms. (80% theory)

This crude product was then heated with pyridine (30 ccs.) for 14 hours, to liberate the base. The mixture of 3-nitro- and 5-nitro-o-toluidines was then extracted with carbon tetrachloride.

From the solution the 5-nitro-o-toluidine separated first as yellow leaflets.

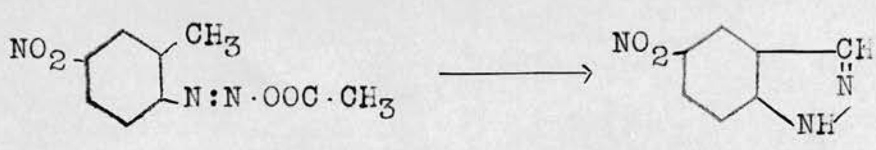
yield 3 gms. (50% theory),
m.p. 126° (lit. 126°).

By evaporating the solution to dryness the 3-nitro-o-toluidine was obtained in red leaflets.

yield 1.4 gms. (25% theory),
m.p. 96° (lit. 97°).

2). 5-Nitroindazole.

(Ber., 1920, 53, 1221). Auwers & Schwegler



10 gms. 5-Nitro-o-toluidine.

500 ccs. glacial acetic acid.

9.8 ccs. 50% sodium nitrite solution.

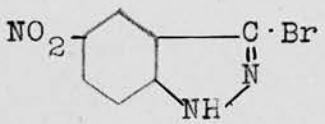
The 5-nitro-o-toluidine was dissolved in the acetic acid, cooled to a temperature under 10°, and diazotised by slowly adding the solution of sodium nitrite. The solution was allowed to stand at room temperature for three days, after which two thirds of the solvent was removed by distillation, and the remainder poured into water. To obtain the nitroindazole free from any nitrocresol formed in this reaction, the whole was dissolved in a little alcohol and caustic soda solution, filtered, ~~acidified~~ with acetic acid, added until the soln. is just alkaline and the nitroindazole precipitated with carbon dioxide.

The 5-nitroindazole was obtained as yellow crystals from alcohol. Ammon. sinks in soln.

yield 8 gms. (72% theory),

m.p. 208° (lit. 208°).

3-Bromo-5-Nitroindazole.



5-Nitroindazole(1 gm.) was suspended in dilute hydrochloric acid, excess of bromine water added and the mixture shaken for half an hour. The resulting product was filtered, washed with water, and crystallised from alcohol. After two recrystallisations the compound was obtained pure with a sharp melting point. appearance.

yield 1 gm. (72% theory),

m.p. 321° (sublimes at 180°).

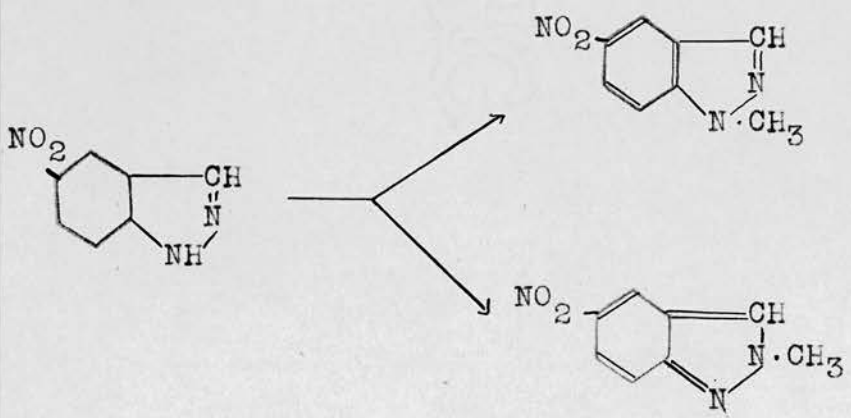
Analysis:

Found Br, 31.25%,

$C_7H_4O_2N_3Br$, requires Br, 33%.

Methylation of 5-Nitroindazole.

(Fries, 1927, 454, 307).



5 gms. 5-Nitroindazole.

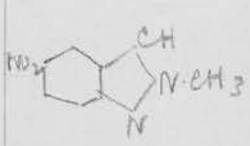
25 gms. methyl alcohol.

3 gms. potassium hydroxide.

9 gms. methyl iodide.

After refluxing for four hours, and removing the excess methyl iodide and potassium iodide, the mixture of methylated nitroindazoles was separated. To isolate the isomeric methyl-nitroindazoles, this mixture was suspended in twenty times its weight of water and warmed to 90°. The solution was then separated from any insoluble material.

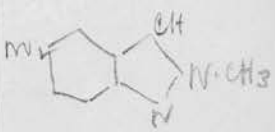
The insoluble portion was crystallised from alcohol and was obtained as red sandy crystals. This Fries takes to be 2-methyl-5-nitroindazole.



yield 0.5 gms. (9.2% theory),

m.p. 163° (lit. 163°)

From the hot aqueous filtrate, on cooling, there separated a yellow gelatinous precipitate which was crystallised first from water, and then from a benzene petrol-ether mixture (1:1), and was obtained in yellow needles.
This Fries takes to be 1-methyl-5-nitroindazole.



yield 3.2 gms. (60% theory),

m.p. 129° (lit. 129°)

Bromination of the Methyl-5-nitroindazoles.

Each of the above methyl-5-nitroindazoles was brominated, suspended in dilute hydrochloric acid, in a similar way to that already described for the bromination of 5-nitroindazole.

2-Methyl-3-bromo-5nitroindazole, crystallised from alcohol and glacial acetic acid in white sandy crystals.

m.p. 221° - 223°. from empd. mp. 163°.

Analysis:

found Br, 30.62%,

$C_8H_6O_2N_3Br$. requires Br, 31.2%.

1-Methyl-3-bromo-5-nitroindazole, crystallised from alcohol in yellow needles.

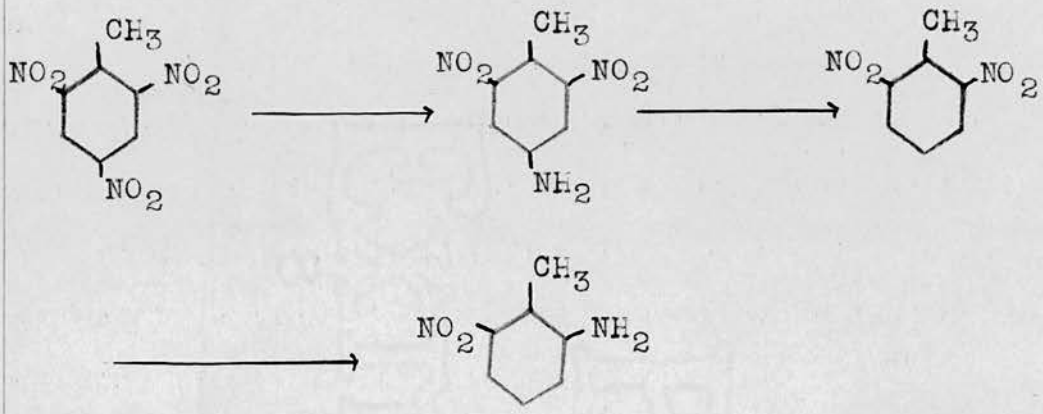
m.p. 183° - 185°. from empd. 129°.

Analysis:

found Br, 30.56%,

$C_8H_6O_2N_3Br$. requires Br, 31.2%.

Preparation of 6-Nitro-o-toluidine. (1 st. method)



2:6-Dinitro-4-aminotoluene.

(Ber., 1880, 13, 243).

150 gms. 2:4:6-Trinitrotoluene.
300 ccs. alcohol.
200 ccs. saturated solution of ammonium sulphide.

The trinitrotoluene was dissolved in the alcohol and cooled to below 10°, after which the ammonium sulphide was slowly added with stirring. When all was added, the solution was warmed on the steam bath for half an hour, and on cooling, the dinitro-aminotoluene was precipitated with water. The precipitate was then filtered and extracted repeatedly with dilute hydrochloric acid. The acid extract was neutralised with ammonia, and the precipitate after washing and thorough drying, dissolved in chloroform. When all the chloroform

had been removed the residue was crystallised from acetic acid.

yield 10 gms. (7% theory)

m.p. 166°- 168° (lit. 168°).

As the yield was not good, the reduction was repeated on a small scale, and sulphuretted hydrogen was passed in during the time of boiling. Again no satisfactory yield was obtained.

2:6-Dinitrotoluene.

(c.f. Ber., 1891, 24, 2773).

The method of Hodgson and Walker for the diazotisation of nitroamines was used in this case. (J.C.S., 1933, 1620).

10 gms. 2:6-dinitro-4-aminotoluene.

120 ccs. glacial acetic acid.

5 gms. sodium nitrite.

35 ccs. concentrated sulphuric acid.

The cooled solution of dinitroaminotoluene was added with vigorous stirring to the solution prepared by dissolving the finely powdered sodium nitrite in the sulphuric acid, the temperature being

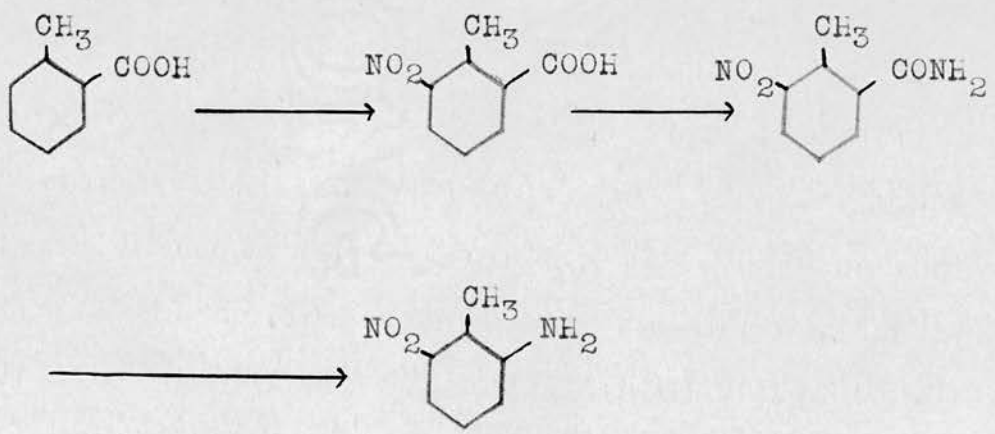
maintained under 10°. After the diazo-reaction was complete, the solution was cooled in ice, and 100 ccs. of alcohol added. The mixture was then gradually warmed to 80° and kept at that temperature for four hours. Next day the solution was poured into water and the precipitated dinitrotoluene filtered and dried.

yield 0.5 gms. (5.5% theory)

m.p. 60° (lit. 66°).

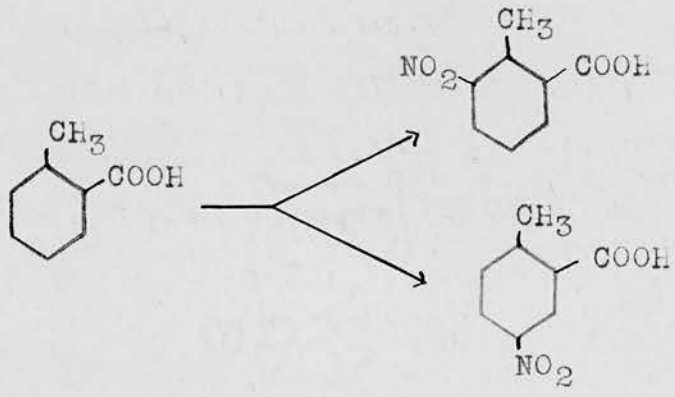
This method of preparation of 6-nitro-o-toluidine was therefore abandoned, the yields being so unsatisfactory.

Preparation of 6-Nitro-o-toluidine. (2nd. method).



1). 6-Nitro-o-toluic Acid.

(c.f. Rec. Trav. Chim., 1901, 20, 173).



125 ccs. concentrated sulphuric acid.

25 ccs. fuming nitric acid.

50 gms. o-toluic acid.

The o-toluic acid was gradually added to the mixture of acids and the temperature maintained under 5°. Vigorous stirring was necessary, and a thick pasty mass was obtained. After six hours this was poured into water and the resulting mixture of isomeric nitro-compounds separated by filtration, and dried on porous tile.

yield 75 gms.

This mixture was then separated into its constituent 6-nitro- and 4-nitro-acids by fractional crystallisation of their methyl esters.

Esterification of nitration mixture.

75 gms. Nitro-o-toluic acid.
300 ccs. dry methyl alcohol.
36 ccs. concentrated sulphuric acid.

The mixture was refluxed for six hours, and the admixed esters crystallised on cooling. The crystals were removed and the mother liquor precipitated with water, when more of the crude esters were obtained. The whole was then dissolved in 250 ccs. of methyl alcohol, by refluxing for quarter of an hour, and allowed to crystallise slowly.

Three separate fractions were isolated from the crystallisation: the first m.p. 69° was the pure 4-nitro-o-toluic ester, and the third m.p. 66°, was the pure 6-nitro-o-toluic ester. The second fraction was again submitted to fractional crystallisation and again three fractions were isolated. This procedure was carried out four times until complete separation had been effected.

(N.B. The second fraction in each case was taken as the largest: best results were obtained by allowing the hot solution to deposit crystals until it reached a temperature about 25°. The supernatant solution was then poured off and more crystals separated from this. The supernatant solution was again separated about

15°, and it was from this solution that the pure 6-nitro-o-toluic ester separated).

6-nitro-o-toluic ester,
yield 80 gms. (25% theory).

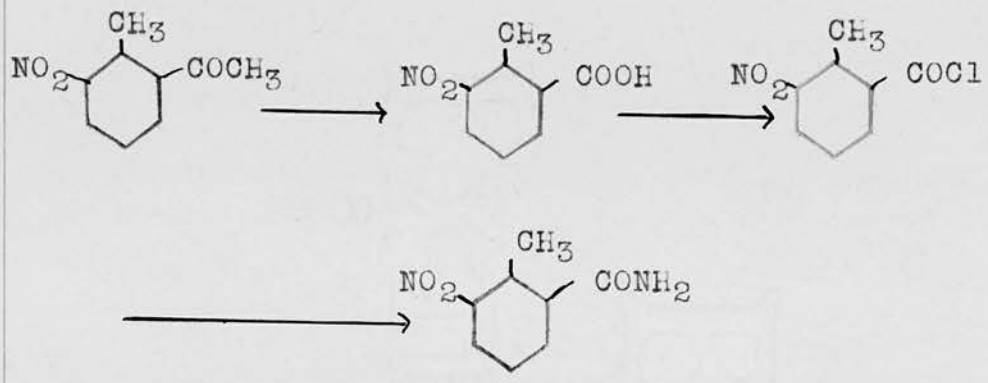
4-nitro-o-toluic ester,
yield 48 gms. (60% theory).

Some 4:6-dinitro-o-toluic ester was also isolated in the reaction. This was separated from the 4-nitro-compound by further fractional crystallisation. The 4:6-dinitro-o-toluic ester separated from the solution first. m.p. 72°

6-Nitro-o-toluic acid amide. (1st. method)

6-Nitro-o-toluic ester (5 gms.) was shaken with concentrated ammonia (50 ccs.) for 75 hours and the resulting compound separated, after removing most of the ammonia by distillation. The 5 gms. of the original ester were recovered unchanged and no amide had been formed.

6-Nitro-o-toluic acid amide (2nd. method)



Hydrolysis of the 6-nitro-o-toluic ester (10 gms.) to the acid was accomplished by boiling with concentrated hydrochloric acid (100 ccs.) and glacial acetic acid (20 ccs.) for 12 hours. The ester gradually went into solution, and the acid was formed, some of which separated from the solution. On cooling the acid was deposited in colourless needles.

yield 9.9 gms. (90% theory)

m.p. 184° (lit. 184°- 186°).

The acid chloride was formed by heating for three hours, the dry 6-nitro-o-toluic acid (5 gms.) with thionyl chloride (25 ccs.). The excess of the latter was then removed by distillation in vacuo, and the acid chloride was obtained as a dark brown solid.

This was dissolved in toluene and added to excess of ammonia, when the amide was formed immediately as a white substance which was filtered and crystallised from water. It separated in long colourless needles.

yield 5 gms. (quantitative)
m.p. 163° (lit. 163°).

Hofmann Degradation of 6-Nitro-o-toluic acid amide.

A solution of 5 gms. of potassium hydroxide and 5.5 gms. of bromine in 50 ccs. of water was added to the finely powdered 6-nitro-o-toluic acid amide (5 gms.) and the mixture added to a solution of 7 gms. of potassium hydroxide in 15 ccs. of water. The whole was then gradually warmed to 80° and kept at that temperature for one hour. The mixture was distilled with superheated steam, and the amine separated from the distillate in yellow needles.

yield 0.5 gms. (8% theory)
m.p. 90° (lit. 92°).

Degradation with Hydrazoic Acid

6-Nitro-o-toluic azide was prepared by the

acid chloride method.

Dry 6-nitro-o-toluic acid (10 gms.) was converted into the acid chloride by heating with thionyl chloride as above, and the excess of thionyl chloride removed in vacuo.

The acid chloride was dissolved in benzene (100 ccs.) and powdered sodium azide (3 gms.) slowly added with vigorous shaking. The benzene solution was then gently warmed and nitrogen was evolved, so that the remaining solution now contained 6-nitro-1-methyl-2-isocyanate which was converted into the amine by boiling with hydrochloric acid (concentrated acid:water, 1:1) for four hours. The benzene was distilled off, and the hydrochloride of 6-nitro-o-toluidine separated This was neutralised with ammonia to obtain the free amine and crystallised from alcohol.

yield 3.5 gms. (42% theory)

m.p. 91° (lit. 92°).

4-Nitroindazole.

(Noelting, Ber., 1904, 37, 2582).

5 gms. 6-Nitro-o-toluidine.
250 ccs. glacial acetic acid.
5 ccs. 50% sodium nitrite solution.

The toluidine was dissolved in acetic acid and when the temperature was below 5°, the sodium nitrite solution slowly run in until the diazotisation was complete. The solution was then allowed to stand at room temperature for five days, after which three quarters of the acetic acid was removed by distillation and the rest poured into water. The 4-nitroindazole separated and was filtered and crystallised from water.

yield 4 gms. (82% theory)
m.p. 203° (lit. 203°).

Methylation of 4-Nitroindazole.

(c.f. above ref., also Auwers, ~~Ann.~~ Ber., 1925, 58, 1374).

Noelting methylated with dimethyl sulphate and obtained a methylated mixture m.p. 82°- 86°. The methylation in our case was accomplished with methyl iodide and methyl alcoholic potassium hydroxide,

as success had been attained with that reagent in preparing previous methylindazoles.

4 gms. 4-nitroindazole.
25 gms. methyl alcohol.
3 gms. potassium hydroxide.
9 gms. methyl iodide.

The mixture was refluxed for four hours, and after the excess of methyl iodide had been removed by distillation, the resultant solution was poured into water. The precipitate obtained was then dried on porous tile and dissolved in ether. Hydrogen chloride gas was passed into the solution and the hydrochloride of 2-methyl-4-nitroindazole separated. This was removed by filtration. On evaporating the ethereal solution the hydrochloride of the 1-methyl-4-nitroindazole was obtained. These hydrochlorides were broken up with water and the nitromethylindazoles obtained.

1-Methyl-4-nitroindazole crystallised from petrol-ether.

yield 0.8 gms.
m.p. 136° (lit. 138°- 139°).

2-Methyl-4-nitroindazole crystallised from water.

yield 0.3 gms.

m.p. 98° (lit. 101°- 103°).

Total yield 1.1 gms. represents 26% theory.

Each of these compounds was then brominated with bromine water in a suspension in dilute hydrochloric acid, and the resultant compounds crystallised from alcohol.

2-Methyl-3-bromo-4-nitroindazole, m.p. 195° 199°.

1-Methyl-3-bromo-4-nitroindazole, m.p. 216°- 220°.

Analysis:

Found Br, 29.4%,

$C_8H_6O_2N_3Br$, requires Br, 31.2%.

The nomenclature of these compounds are as they are given in the literature.

Preparation of 8-Chloroquinoline.

(J.pr.Chem., 1893, 48, 141.)

(J.A.C.S., 1930, 5085.)

The boric acid modification of the Skraup synthesis.

14 gms. ferrous sulphate.

50 gms. o-chloraniline.

50 gms. nitrobenzene.

These were mixed in the order given and a cooled solution of 25 gms. of boric acid in 150 gms. of glycerol added, and the whole thoroughly mixed. Finally 70 ccs. of concentrated sulphuric acid was added and the mixture refluxed for 8 hours. It was then distilled in steam until the distillate was clear, when the contents of the flask were cooled and made alkaline with 250 ccs. of 60% sodium hydroxide. The mixture was again distilled in steam, and the oily distillate separated from the water, dissolved in sulphuric acid, and heated on the water bath for one hour with powdered potassium dichromate. The contents of the flask were then made alkaline and distilled in steam. The distillate was extracted with ether, and the 8-chloroquinoline, after evaporation of the ether was purified by distillation under reduced

pressure.

yield 50 gms. (47% theory)

b.p. 288° (lit. 288°).

8-Chloroquinoline-dichromate.

This derivative was prepared by dissolving the chloroquinoline in dilute hydrochloric acid and adding a calculated amount of potassium dichromate in a concentrated aqueous solution. The dichromate was then recrystallised from water.

m.p. 160° (lit. 160°- 161°).

8-Chloroquinoline-picrate.

m.p. 164°- 166°.

Analysis:

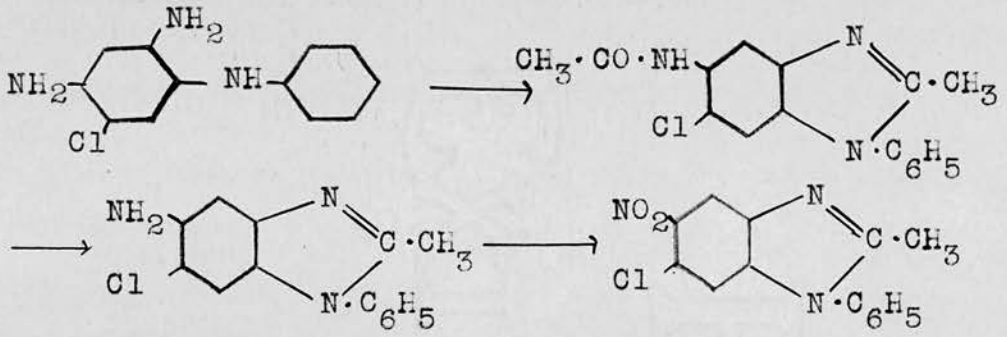
found N, 14.15%,

$C_{15}H_9N_4O_6Cl$, requires N, 14.28%.

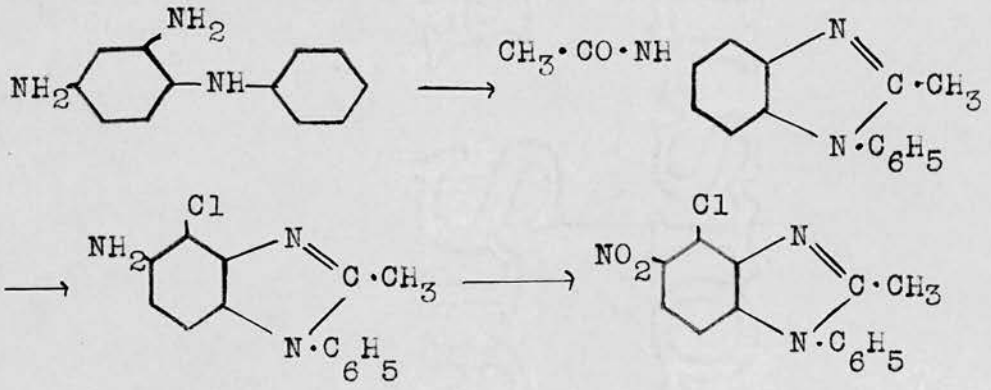
Benzimidazole Series.

It was expected to prepare the following compounds.

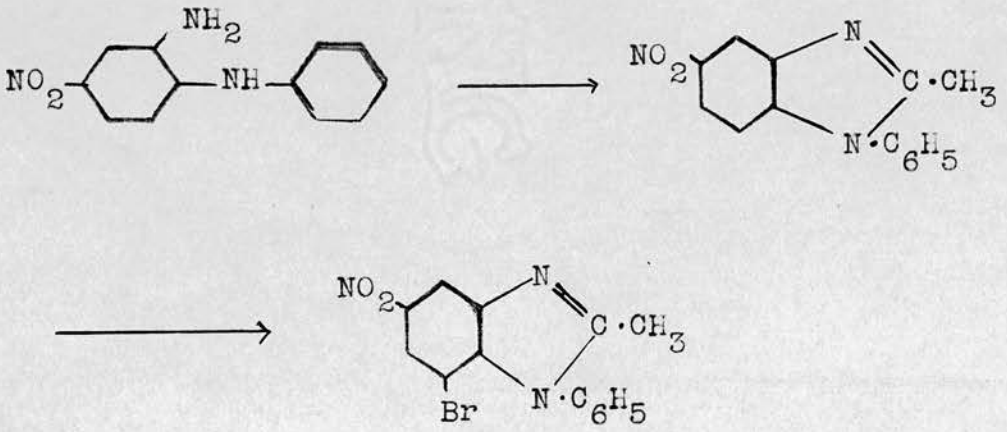
1-Phenyl-2-methyl-6-chloro-5-nitrobenzimidazole.



1-Phenyl-2-methyl-4-chloro-5-nitrobenzimidazole.



1-Phenyl-2-methyl-7-bromo-5-nitrobenzimidazole.



Benzimidazole Series.

Preparation of m-Bromonitrobenzene.

(Org. Synthesis, 14, 67).

90 gms. freshly distilled nitrobenzene.
60 ccs. dry bromine.
9 gms. iron powder (ferrum reductum).

yield 90 gms. (60% theory)
m.p. 50° (lit. 51.5° - 52°).

m-Bromoaniline.

(Rec. trav. Chim., 1909, 28, 107).

90 gms, Bromonitrobenzene.
2700 ccs. alcohol.
130 gms. sodium sulphide.
18 gms. sulphur.

The mixture was refluxed for eight hours and the precipitated sodium thiosulphate filtered. Most of the alcohol was removed by distillation and the remaining m-bromoaniline distilled in steam. The distillate was extracted with ether and the m-bromoaniline purified by further distillation.

yield 65 gms. (84% theory)
b.p. 219° (lit. 219°).

m-Dibromobenzene.

A
60 gms. m-bromoaniline.
90 ccs. concentrated hydrochloric acid, in 20 ccs. of water.
30 gms. sodium nitrite in 20 ccs. of water.

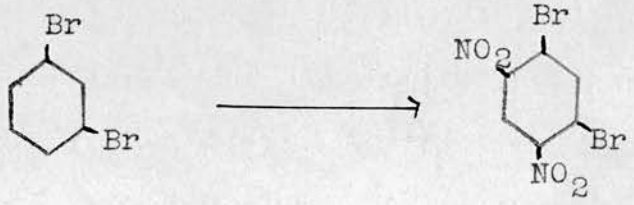
B
90 gms. copper sulphate in 300 ccs. water.
45 gms. potassium bromide.
150 ccs. hydrobromic acid.

The diazo-solution (A) was poured into the solution of cuprous bromide in hydrobromic acid (B). After standing for two hours, the m-dibromobenzene was distilled in steam, extracted with ether and purified by further distillation.

yield 50 gms. (62.5% theory)
b.p. 217° (lit. 217°).

1:3-Dibromo-4:6-dinitrobenzene.

(c.f. Nietski, Ber., 1897, 30, 1666).



40 gms. m-Dibromobenzene.

160 gms. fuming nitric acid.

320 gms. concentrated sulphuric acid.

250 ccs. glacial acetic acid.

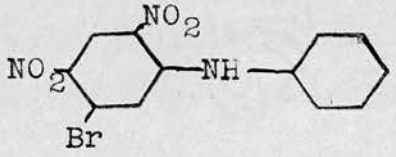
The m-dibromobenzene was dissolved in the acetic acid and the solution boiled under reflux. The mixture of fuming nitric and sulphuric acids was then slowly run in. When the nitration started heating was no longer necessary.

On cooling the 1:3-dibromo-4:6-dinitrobenzene crystallised in long yellow needles. These were filtered, washed with water, and crystallised from glacial acetic acid.

yield 50 gms. (83% theory)

m.p. 117° (lit. 117°).

<u>3-Bromo-4:6-dinitrodiphenylamine</u>.



40 gms. 1:3-Dibromo-4:6-dinitrobenzene.

11.5 gms. aniline.

250 ccs. alcohol.

Molecular quantities of dibromodinitro-

benzene and aniline were refluxed in alcoholic solution for half an hour. The 3-bromo-4:6-dinitrodiphenylamine crystallised from the hot solution and after separation, was recrystallised from glacial acetic acid.

yield 38 gms. (quantitative)
m.p. 157° (lit. 157°).

3-Chloro-4:6-dinitrodiphenylamine was prepared in exactly the same way as that described above for the 3-bromo-compound.

m-Dichlorobenzene b.p. 172° (lit. 172°).
1:3-Dichloro-4:6-dinitrobenzene. m.p. 102° (lit. 103°).
3-Chloro-4:6-dinitrodiphenylamine. m.p. 120° (lit. 120°).

Attempted reduction of 3-Bromo-4:6-dinitrodiphenylamine.

10 gms. 3-Bromo-4:6-dinitrodiphenylamine.
50 ccs. glacial acetic acid.
25 gms. zinc dust.

The mixture was refluxed for three hours and the resulting solution poured into water. An oil separated, which soon solidified and was filtered, and crystallised from glacial acetic acid.

m.p. 157°.

A mixed melting point determination with the original substance showed no depression. Therefore no reduction had taken place.

Reduction of 3-Bromo-4:6-dinitrodiphenylamine.

30 gms. sodium sulphide.
4 gms. sulphur.
600 ccs. alcohol.
10 gms. bromodinitrodiphenylamine.

The mixture was refluxed for six hours, cooled and separated from sodium thiosulphate. Alcohol was removed by distillation and the remaining mass crystallised from alcohol. Red needles separated from the solution.

m.p. 82° - 86°.

This compound contained no bromine and was shown to be 2-amino-4-nitrodiphenylamine m.p. 90° by further purification and a mixed melting point determination.

The two nitro groups being in the ortho and para positions to the bromo group, had activated this atom so that it was removed by the alkaline solution.

1-Phenyl-2-methyl-6-chloro-5-acetamidobenzimidazole.

(Fries, Ann., 1927, 454, 200).

20 gms. 3-Chloro-4:6-dinitrodiphenylamine.
34 ccs. glacial acetic acid.
169 gms. stannous chloride.
134 ccs. concentrated hydrochloric acid.

A solution of the chlorodinitrodiphenylamine was added to the mixture of stannous chloride and hydrochloric acid and the whole gently warmed. After a short time the reaction began and no more heating was required. The stannous chloride-diamino-double compound was precipitated from the cold solution by saturating with hydrochloric acid.

The double compound was filtered, dried thoroughly on porous tile, and added to 150 ccs. of acetic anhydride. The mixture was warmed until the reaction began, and it then proceeded spontaneously. On cooling the hydrochloride of the 1-phenyl-2-methyl-6-chloro-5-acetamidobenzimidazole separated. This was filtered, dissolved in water, and any tin in solution removed with hydrogen sulphide.

The solution, free from tin, was then evaporated to dryness and the hydrochloride obtained, hydrolysed to the free amine by boiling with a saturated solution of alcoholic potassium hydroxide

(150 ccs.) for two hours.
The amine separated from the solution and was recrystallised from benzene.

yield 2 gms. (12% theory)
m.p. 206° (lit. 208°).

This compound decomposed very readily on standing.

A similar reduction of the 3-bromo-4:6-dinitrodiphenylamine was also attempted, but the stannous chloride-diamino-double compound was not precipitated even when the solution was saturated for two days with hydrochloric acid. The solution was therefore poured into 50% potassium hydroxide and extracted with ether. The ethereal extract gave a very small amount of oil, which was too small for examination.

Preparation of 2:4-Dinitrodiphenylamine.

50 gms. 1-Chloro-2:4-dinitrobenzene.
23 gms. aniline.
200 ccs. alcohol.

The mixture was refluxed for half an hour,

the dinitrodiphenylamine separating from the hot solution in bright red needles, which were recrystallised from glacial acetic acid.

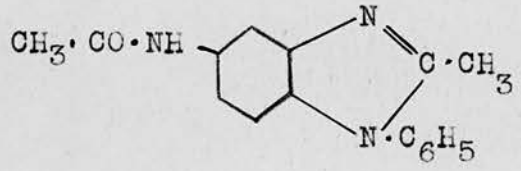
yield 60 gms. (quantitative)
m.p. 154° (lit. 157°).

2:4-Diaminodiphenylamine.
(Ber., 1895, 28, 2970).

Iron filings (50 gms.) were mixed to a paste with 2% hydrochloric acid (1000 ccs.) and the red nitro compound (50 gms.) added in small quantities. The nitro compound went into solution, which then became dark brown in colour. The solution was filtered and neutralised with solid sodium carbonate. The diaminodiphenylamine was obtained by extracting with boiling water. It separated from the filtered solution in dark brown needles.

yield 10 gms. (25% theory)
m.p. 130° (lit. 130°).

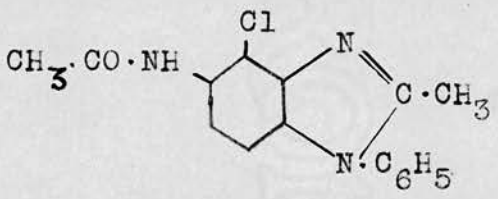
1-Phenyl-2-methyl-5-acetamidobenzimidazole.



2:4-Diaminodiphenylamine (10 gms.) was added slowly to acetic anhydride (20 ccs.). The solution was then boiled for quarter of an hour, poured into water and neutralised with sodium carbonate. The 1-phenyl-2-methyl-5-acetamidobenzimidazole was filtered and recrystallised from aqueous alcohol.

yield 4 gms. (30% theory)
m.p. 225° (lit. 233°).

1-Phenyl-2-methyl-4-chloro-5-acetamidobenzimidazole.



1-Phenyl-2-methyl-5-acetamidobenzimidazole (4 gms.) was dissolved in alcohol (10 ccs.) and chlorine gas passed into the solution cooled in a freezing mixture. (The chlorine was formed by adding concentrated hydrochloric acid to 1 gm. of potassium permanganate, and thus obtaining the calculated amount of chlorine required for monochlorination.)

After 15 minutes the solution was poured into water and sodium acetate (20 gms.) added. The chloro compound separated, was filtered, dried and crystallised from alcohol.

yield 2.5 gms. (55% theory)

m.p. 228° (lit. 228°).

1-Phenyl-2-methyl-4-chloro-5-aminobenzimidazole.

The free amine was obtained by hydrolysing the acetamido-compound by boiling with 10 ccs. of concentrated hydrochloric acid and 40 ccs. of alcohol for two hours, pouring into water, and precipitating the amino-compound with ammonia. The compound was crystallised from benzene.

yield 1.5 gms. (70% theory)

m.p. 250° (lit. 257°).

The compound decomposed readily on standing.

Attempted Preparation of 1-Phenyl-2-methyl-6-chloro-5-nitrobenzimidazole.

(c.f. Hantzch, Ber., 1900, 33, 2554).

1). Preparation of the Cupri-cupro Sulphite.

(Abegg Anorganishe Chemie, vol. 11, page 556).

Copper sulphate crystals (10 gms.) were dissolved in water (100 ccs.) and 2N sodium hydroxide was added until all the copper had been precipitated as hydroxide. Sulphur dioxide was then passed into the suspension, cooled in ice water, and a red precipitate of the cupri-cupro sulphite was obtained weighing 5 gms.

2). Conversion of Amino-compound to Nitro-compound.

1-Phenyl-2-methyl-6-chloro-5-aminobenzimidazole (2 gms.) was converted into the sulphate with the addition of concentrated sulphuric acid (5 ccs.). This was dissolved in water, cooled, and diazotised with solid sodium nitrite.

10 gms. cupri-cupro sulphite.
30 gms. sodium nitrite.
120 ccs. water.

This mixture was stirred vigorously in a

flask, and the diazo solution above added slowly. A brisk evolution of gas occurred and when this had moderated, the flask was heated on the steam bath to complete the reaction.

The solution was then submitted to distillation with steam to isolate the required nitro compound, but nothing was obtained from the distillate.

The attempt to form the nitro-compound was thus unsuccessful, and the reaction was not attempted with the 1-phenyl-2-methyl-4-chloro-5-aminobenzimidazole.

2-Amino-4-nitrodiphenylamine.

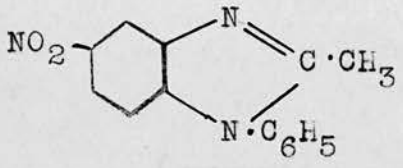
(J. pr. Chem., 1904, 69, 41).

30 gms. sodium sulphide.
4 gms. sulphur.
600 ccs. alcohol.
12 gms. 2:4-dinitrodiphenylamine.

The mixture was refluxed for six hours, cooled and filtered free from sodium thiosulphate. Most of the alcohol was removed by distillation and the 2-amino-4-nitrodiphenylamine allowed to crystallise It was recrystallised from alcohol.

yield 8 gms. (76% theory)
m.p. 85° - 90° (lit. 90°).

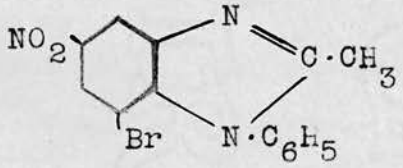
1-Phenyl-2-methyl-5-nitrobenzimidazole.



2-Amino-4-nitrodiphenylamine (5 gms.) was added to acetic anhydride (10 ccs.) and the mixture boiled. On pouring into water a yellow oil separated, which solidified, and was filtered, washed with water and crystallised from alcohol.

yield 2 gms. (36% theory)
m.p. 168°- 170° (lit. 170°).

Bromination of 1-Phenyl-2-methyl-5-nitrobenzimidazole.



1-Phenyl-2-methyl-5-nitrobenzimidazole (1 gm.) was dissolved in glacial acetic acid (10 ccs.) and bromine (0.6 gms.) in 5 ccs. of glacial acetic acid added. The solution was shaken for 30 minutes and yellow needles separated. These were recrystallised from alcohol.

yield 0.6 gms. (46% theory)
m.p. 201°- 202°

The position of this bromine atom in the molecule was not known, but it was expected to be in the position 7, as it was thought that the nitro group would direct the substitution there.

As the three compounds which were aimed at, had not been successfully prepared, no reactivity measurements were carried out in the benzimidazole series.

Semi-quantitative Experiments.

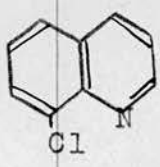
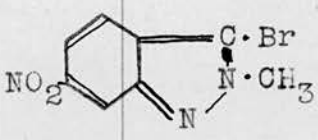
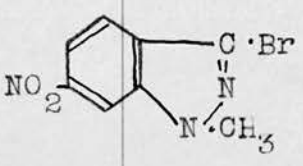
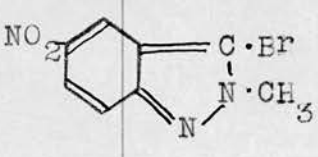
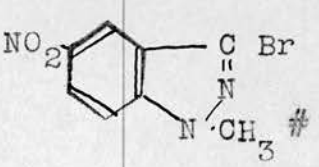
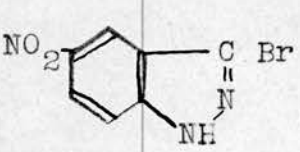
(J. Salkind, Ber., 1931, 64, 289).

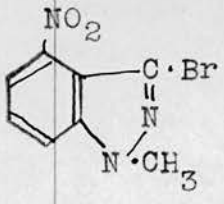
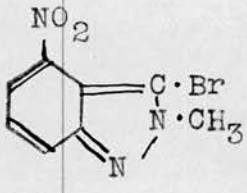
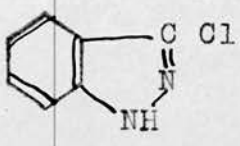
Approximately 0.15 gms. of halogeno-nitro compound was weighed accurately in a test-tube provided with a ground glass stopper, 1 cc. of piperidine added, and the tube immersed in a thermostat at 40° to 50°C. After a definite interval, the contents of the tube were washed into a separating funnel with distilled water (50 ccs.) and shaken up with pure benzene. The benzene removed organic material from the aqueous layer, while the halogen was left behind. In most cases a good separation was obtained and the aqueous layer was left practically colourless. The halogen in the solution was determined by Volhard's method, by titration with silver nitrate and potassium thiocyanate, ferric alum being used as indicator.

In reactive halogeno-nitro compounds, the halogen was removed by the piperidine giving piperidine hydrochloride or hydrobromide. When mixed with water the piperidine halogen compound decomposed into piperidine and the free halogen acid while the other organic material present was removed with benzene, thus leaving a clear solution for the titration.

Solutions of silver nitrate and potassium thiocyanate approximately N/50 were prepared and standardised accurately; the silver nitrate by titration against weighed quantities of potassium bromide, and the potassium thiocyanate against the silver nitrate with ferric alum as indicator.

(One of the determinations was carried out by refluxing the solution of methyl-bromo-nitroindazole in piperidine for one hour. #)

Compound	Weight (gms.)	Volume (pip.)	Time (hrs)	Temp.	% Bromine removed
	0.1548	1	24	50°	0
	0.1246	2	24	50°	0
	0.1534	2	48	50°	0
	0.1389	1	24	50°	0
	0.1852	1	48	50°	0
	0.1506	1	1	50°	0
	0.1827	1	48	50°	0
	0.1365	1	1	50°	2
	0.1528	1	48	50°	30
	0.1823	1	1	reflux	30
	0.1065	1	48	50°	0
	0.1432	1	48	50°	4

Compound	Weight (gms.)	Volume (pip.)	Time (hrs)	Temp.	% Bromine removed
	0.1452	1	48	50°	0
	0.1036	1	48	50°	0
	0.1837	1	48	50°	0
	0.2312	2	48	50°	0

* The structural formulae used here are as they are given in the literature. The results obtained do not agree with these structures, however, so that they have to be reversed. (See discussion).

Reactivity Measurements with Hydriodic Acid and Red Phosphorus.

Treatment with hydriodic acid and red phosphorus was carried out in the following manner.

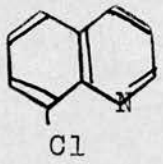
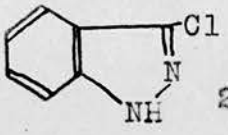
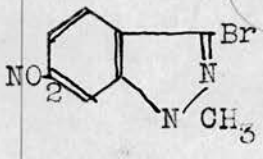
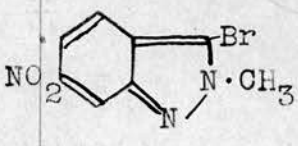
0.5 gms. of the heterocyclic compound was mixed with 0.2 gms. of red phosphorus and 5 ccs. of hydriodic acid in a sealed tube and heated in a small furnace at a fixed temperature for a definite interval of time. After cooling the contents of the tube were poured into water and extracted with ether. The contents of the ether extract were then isolated and identified wherever possible. The method is cruder than the piperidine method and it is only possible to tell whether the halogen is completely removed or not removed at all.

With the nitrobromoindazoles, a great difficulty was incurred due to the reduction of the nitro group. The resulting amino-compound, when isolated, was tested with copper wire. A positive test showed that bromine was still present in the amino-compound and therefore had not been reactive, while a negative test showed that bromine was absent and so had been reactive in the original compound.

As some compounds containing nitrogen sometimes give a positive test with copper wire, due

to the formation of cyanide, a blank test was carried out with nitroindazole itself, but no positive result was obtained, so that the tests when obtained actually showed the presence of bromine.

With the nitro compounds, the contents of the tube were poured into water, excess of sodium hydroxide added to destroy the hydriodic acid, and the amino-compound extracted with ether, its melting point taken, and then tested with copper wire for the presence of bromine.

Compound.	Temp.	Time. (hrs)	Compound isolated	Bromine reactive?
	170°	2	8-chloroquinoline picrate m.p. 164°	
	190°	2	quinoline picrate m.p. 200°	No.
	170°	2	Indazole m.p. 140° neg. brom. test.	
	200°	2	Indazole m.p. 140° neg. brom. test	Yes.
	170°	2	Amino-compound m.p. 150° neg. brom. test.	Yes
	170°	2	Amino-compound m.p. 100° pos. brom. test.	No

D I S C U S S I O N .

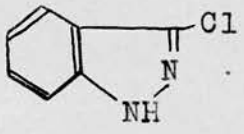
Since Gabriel (loc. cit.) found in the quinoline series, that a reactive halogen was removed by heating with red phosphorus and hydriodic acid between 160° and 180°, whereas an inactive halogen was not removed until the temperature was about 200°, it was assumed that this range would hold for other series. With the halogeno-nitro compounds, a reactive halogen atom towards piperidine was taken to denote the presence of a double bond or a conjugated system, between the nitro and halogen groups.

Indazole.

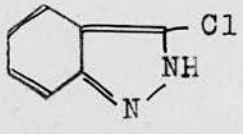
It was unfortunate that the isomeric 1-methyl and 2-methyl-3-chlorindazoles could not be isolated from the methylated mixture, but in view of the difficult preparation of these compounds, it was thought justifiable to work with the series of nitroindazoles, which were usually prepared very easily.

The reactivity measurement on 3-chlorindazole

was undertaken to find out whether form 1, or 2, existed in that compound.



1



2

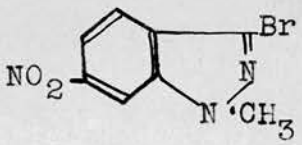
The fact that indazole was isolated both at 170° and 200° showed that form 1, predominated, but this method does not give any indication to what extent the form 2, existed.

6-Nitroindazole.

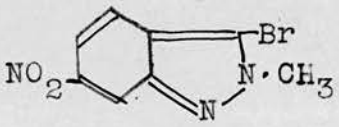
The 1-methyl and 2-methyl-3-bromo-6-nitro-indazoles were easily prepared by methylating 3-bromo-6-nitroindazole with dimethyl sulphate, and separating the mixture into its constituents with ether.

Of the two compounds obtained, the one m.p. 170° existed in the greater proportion to that m.p. 140°. According to Fries (loc. cit.), the 1-methyl-derivative has the lower melting point and occurs to the greater extent in the methylated mixture. The results obtained by the reactivity measurements with hydriodic acid showed that the compound m.p. 170° contained reactive bromine, while the compound m.p. 140° did not. Thus it can be concluded that the compound

m.p. 170°, is the 1-methyl and the compound, m.p. 140°, the 2-methyl-3-bromo-6-nitroindazole.

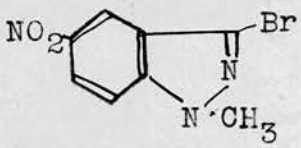


m.p. 170°

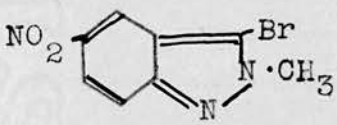


m.p. 140°

5-Nitroindazole.



1.



2.

These isomeric methylbromonitroindazoles presented a different field of work. Form 2, due to the conjugated system of bonds connecting the nitro and bromo groups would be expected to show reactivity towards piperidine, so that this was the method used in this case.

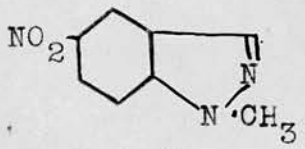
The isomeric 1-methyl and 2-methyl-5-nitroindazoles were known (Fries, loc. cit.), and were easily prepared. They were then brominated and the resulting bromo-compounds termed the 1-methyl and the 2-methyl, according to the nomenclature of the

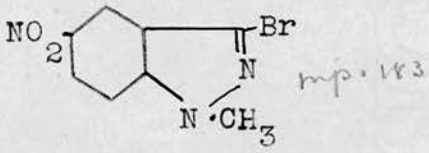
original 1-methyl (1) and 2-methyl (2) nitroindazoles given in the literature (Fries).

These compounds were then submitted to reactivity measurements with piperidine and the results showed that the compound (1) exhibited activity and the compound (2) did not.

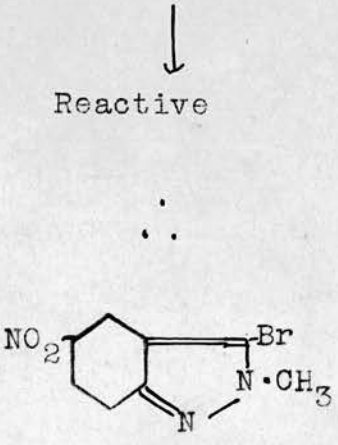
Fries, in naming the 1-methyl and 2-methyl-5-nitroindazoles, assumed that the 1-methyl-derivative had the lower melting point, but he stressed that this rule is not without exception. From the results here obtained, the compound (1) is the 2-methyl derivative (structure 2) and the compound (2) the 1-methyl-derivative (structure 1).

(Fries, m.p. 129°)



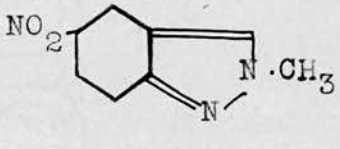


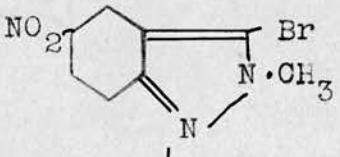
mp. 183



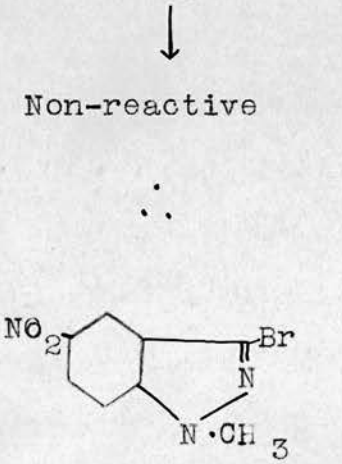
Reactive

(Fries, m.p. 163°)



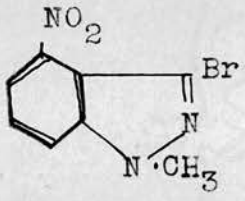
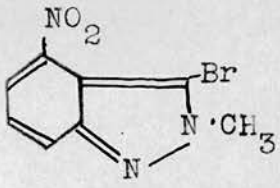
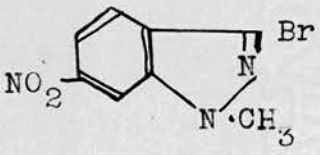
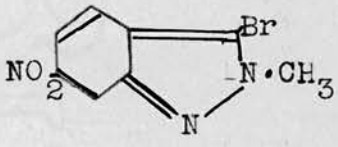


mp. 220°

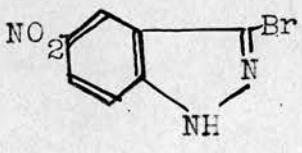


Non-reactive

The 6-nitroindazole and 4-nitroindazole series were also submitted to reactivity measurements with piperidine, but as was expected, neither showed activity.

The 3-bromo-5-nitroindazole also showed no activity towards piperidine, so that this compound exists mainly in the form 1. This result compares with that of 3-chlorindazole towards red phosphorus and hydriodic acid.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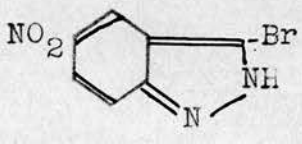

2

6-Nitro-o-toluidine.

The method given in the literature for the preparation of this compound utilises the reduction of 2:4:6-trinitrotoluene to 2:6-dinitro-4-aminotoluene.

Tiemann (Ber., 1870, 3, 218) reduced 2:4:6-trinitrotoluene by passing hydrogen sulphide into a boiling alcoholic solution, but did not mention any yield. Later Beilstein (Ber., 1880, 13, 243) showed that the method of Tiemann did not give satisfactory results, and he put forward another method using a saturated solution of ammonium sulphide for the reduction. This method was used in our work but again no satisfactory yield was obtained.

Cohen and Dakin (J.C.S. 1902, 81, 26) found that reduction with ammonium sulphide gave mostly the 4-hydroxylamino-compound, which could then be converted into the 4-amino-compound by heating with potassium iodide and concentrated sulphuric acid.

Körner and Cortardi (Atti. R, Accad. Lincei., 1916, 25, 339) stated that they received a 60% yield with the same reduction and promised to give experimental details in a later paper, which, however, has not yet been published.

The method tried in this thesis has been quite successful, the main loss in the synthesis being in the nitration of o-toluic acid, when the greater

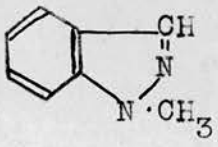
portion of the nitration mixture is the 4-nitro-compound.

Degradation to the amine with hydrazoic acid proved a much better method, in this case, than did the degradation of the amide by Hofmann's method.

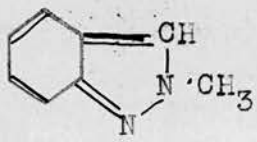
4-Nitroindazole.

The isomeric 1-methyl and 2-methyl-3-bromo-4-nitroindazoles were easily prepared from 6-nitro-o-toluidine. The reactivity of the bromine atoms was measured towards piperidine, and, as was expected, both were inactive. The reactivity towards red phosphorus and hydriodic acid was not measured, as the main object of this compound was to show that the nitro group in position 4 had no influence towards the reactivity of the halogen atom to piperidine, while the nitro group in the position 5 had an activating effect on the 2-methyl-derivative.

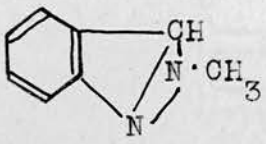
The formulae advanced for the indazole methyl ethers are as follows:



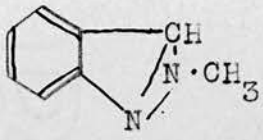
1



11



111a



111b

The 1-methyl-compound is represented without ambiguity by the formula 1. The structure of the 2-methyl-compound, however is less certain. Auwers rejects form 111, and accepts form 11, though in support for this he compares 11, with the unsymmetrical formula for naphthalene which is not now generally accepted (Campbell and McLeish).

Fries, however objects to form 11, on the grounds that 2-methylindazole shows no quinonoid properties and has definite aromatic properties. In the light of the work of this thesis, it can scarcely be doubted that 2-methylindazole is a resonance hybrid of the forms 11, 111a, and 111b, with form 11, as a preferred structure. This is shown by the fact that 2-methyl-3bromo-5-nitroindazole is reactive to piperidine.

In view of the great physical evidence in its favour, the extreme view of bond fixation must be modified in terms of the Resonance theory, and we may conclude that polycyclic aromatic compounds are resonance hybrids with one structure making a greater contribution than the others. (c.f. Pauling, J, Chem. Phys., 1933, 1, 280). This results in the bonds not being equivalent, some having greater double bond character than others. It is also clear from the chemical evidence that the reactivity of certain positions in contrast to others is due to this difference in bond strength (see, for example the results of Campbell and McLeish, loc. cit.).

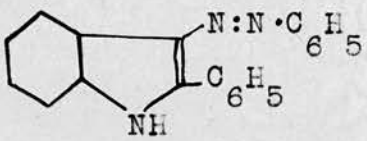
Instead of using the usual symbols for double bonds in aromatic compounds it may be preferable to use the formulae suggested by Brockway (Annual Reports, 1937, 201).

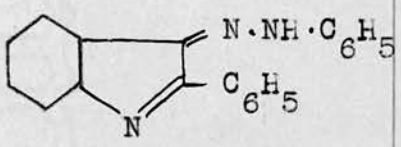
PART 3.

A short Study of the Structure of 3-Benzeneazo-2-phenylindole.

I N T R O D U C T I O N .

Plancher and Soncini (Gazz. Chim. Italia, 1902, 32, 452, and 462) prepared 3-benzeneazo-2-phenylindole by treating an alcoholic solution of 2-phenylindole with benzenediazonium chloride. They assigned two possible structures to this compound, 3-benzeneazo-2-phenylindole (1) or 3-hydrazono-2-phenylindolenine (11).



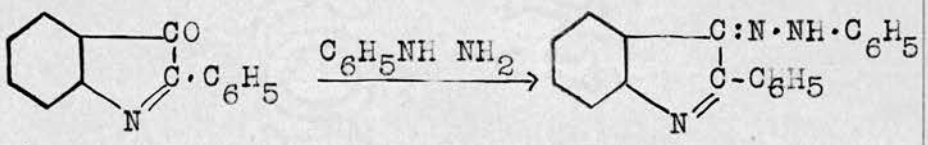


The only chemical evidence hitherto advanced for the structure of this compound is the fact, noted by Plancher and Soncini, that it does not react with phenylisocyanate. A compound of structure (1) would be expected to react.

Object of Research.

An attempt was made to find some clue to the possible structure of the compound in the following manner.

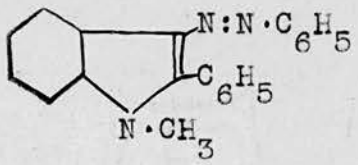
3-Benzeneazo-2-phenylindole was first prepared by the method of Plancher and Soncini, and an attempt made to form the acetyl derivative of the compound. The phenylhydrazone of 2-phenylindolone was then prepared and shown to be identical with the original 3-benzeneazo-2-phenylindole, so that it seemed that these two compounds formed a tautomeric mixture



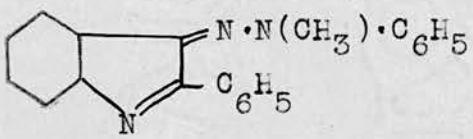
It was then decided to try a physical method of comparing this compound with two others of known structure.

The following three compounds were prepared as pure as possible and their absorption spectra determined.

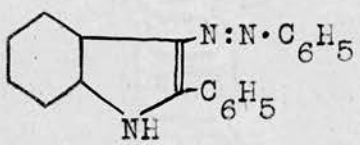
1. 3-Benzeneazo-1-methyl-2-phenylindole.



2. 2-Phenylindolone-methylphenylhydrazone.



3. 3-Benzeneazo-2-phenylindole.

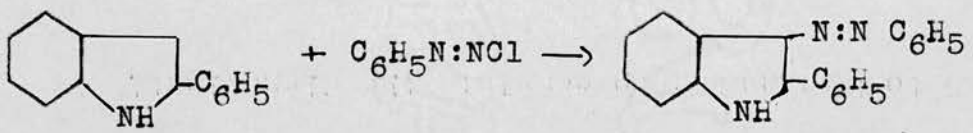


Compound (1) has a true benzeneazo structure, while compound (2) has a true hydrazono structure. Comparison of the absorption spectra of these three compounds should then show whether compound (3) has a benzeneazo structure, hydrazono structure, or is a mixture of both.

An attempt was made to obtain compound (1) by methylating 3-benzeneazo-2- phenylindole with methyl iodide and methyl alcoholic potassium hydroxide.

EXPERIMENTAL.

Preparation of 3-Benzeneazo-2-phenylindole.



Aniline (3 gms.) was dissolved in concentrated hydrochloric acid (15 ccs.) and water (3 ccs.) added. The solution was cooled under the tap, and excess of solid sodium nitrite added, after which the mixture was allowed to stand at 10° for 5 to 30 minutes to complete the diazotisation. The excess nitrous acid was then destroyed with urea, until the evolution of gas ceased or until the mixture no longer turned starch-potassium iodide paper blue. A solution of sodium acetate (12 gms.) in a little water was then added, and if a yellow precipitate appeared at this stage (diazoaminobenzene $C_6H_5 \cdot N{:}N \cdot NH \cdot C_6H_5$), incomplete diazotisation of the aniline was thereby indicated, and the whole

preparation had to be repeated.

To the resultant clear, pale yellow solution was added a suspension of 2-phenylindole (3 gms.) in alcohol, and the mixture shaken. After standing a few minutes, it was poured into water and the precipitate filtered, dried on tile, and recrystallised repeatedly from ligroin, from which it separated in red cubes, giving a yellow powder on being ground up.

yield 3.5 gms. (80% theory)

m.p. 156°.

On another recrystallisation, this time from benzene, the compound was obtained as a yellow powder.

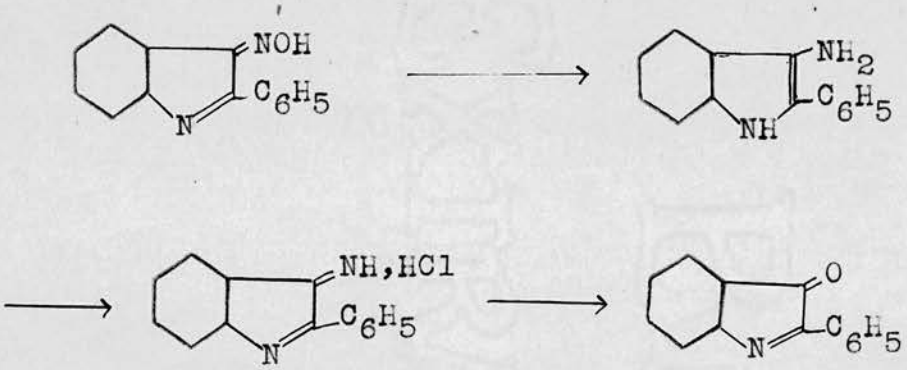
m.p. 163°- 165° (lit. 165°).

Attempted acetylation of 3-Benzeneazo-2-phenylindole.

3-Benzeneazo-2-phenylindole (0.5 gms.) was added to acetic anhydride (10 ccs.) and the solution boiled for one hour. A red solution was obtained which, on cooling, deposited red flakes (m.p. 160°). A mixed melting point determination with the original benzeneazo-compound showed no depression. No acetylation had, therefore, taken place.

Preparation of 2-Phenylindolone.

(Kalb and Baeyer, Ber., 1912, 45, 2150).



1). 3-Amino-2-phenylindole.

3-Isonitroso-2-phenylindole (7 gms.) was dissolved by heating, in a mixture of 2N sodium hydroxide (40 ccs.) and alcohol (20 ccs.). Sodium hydrosulphite ($Na_2S_2O_4$; 15 gms.) was added gradually with shaking. The mixture was then cooled rapidly and filtered; the residue washed with water and alcohol, and dried rapidly.

The yield obtained was almost theoretical (6.5 gms.).

2). 3-Imino-2-phenylindole.

The finely powdered 3-amino-2-phenylindole (6.5 gms.) was suspended in benzene (100 ccs.), and lead peroxide (25 gms.) added. The mixture was

heated on the water bath, with frequent shaking, until a test portion showed no green colour on filtering, and warming the filtrate with acetic acid.

The mixture was then filtered and the residue washed with hot benzene. The deep yellow filtrate was evaporated under reduced pressure, until crystallation commenced, when the imino-compound was obtained as gleaming yellow leaflets.

yield 4.5 gms. (69% theory).

3). 2-Phenyl-3-indolone.

The imino-compound above (4.5 gms.) was ground up in a porcelain basin with just sufficient concentrated hydrochloric acid to convert the whole of the orange yellow compound into a deep brown mush (a few drops of acid only were required). This was immediately pressed on a porous saucer until powdery, and then dried more completely in a vacuum desiccator over soda-lime. The finely powdered substance was then boiled with 230 ccs. of benzene, and 1 gm. of finely powdered chalk added to complete the removal of hydrochloric acid. After evaporation of the benzene solution to a small volume (in vacuo), it was treated with twice its volume of petrol ether. A

yellow precipitate of the ketone hydrate separated and was removed by filtration. The filtrate was then evaporated to a small bulk and allowed to crystallise, when 2-phenylindolone separated as bright scarlet crystals.

yield 4 gms. (90% theory)
m.p. 100°- 101° (lit. 102°).

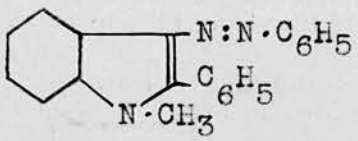
Action of Phenylhydrazine on 2-Phenylindolone.

Pure phenylhydrazine was added to an alcoholic solution of 2-phenylindolone, and the mixture refluxed for one hour. A very dark solution resulted which gradually became lighter in colour. On pouring into water a yellow compound separated, which was crystallised from benzene. After the first crystallisation it melted at 140°, but on a second, a yellow powder was obtained.

m.p. 159°- 162°.

A mixed melting point determination of this hydrazone of 2-phenylindolone with 3-benzeneazo-2-phenylindole showed no depression.
It was therefore evident that these two compounds are identical, or form a tautomeric mixture.

1-Methyl-3-benzeneazo-2-phenylindole.



This was prepared in exactly the same way as 3-benzeneazo-2-phenylindole, from 1-methyl-2-phenylindole and diazotised aniline. The compound was obtained as a yellowish red powder, which crystallised from alcohol in gleaming flakes.

m.p. 149°.

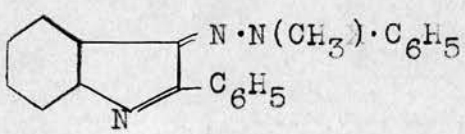
Analysis:

found N, 13.56%,

$C_{21}H_{17}N_3$, requires N, 13.5%.

This compound must have the pure benzeneazo structure, since the methyl group is stable and is not susceptible to migration like a hydrogen atom.

2-Phenylindolone-methylphenylhydrazone.



Methylphenylhydrazine (0.05 gms.) was added

to an alcoholic solution of 2-phenylindolone (1 gm.); a dark red solution resulted, which on boiling, became green in colour. After standing over night nothing had separated, so the solution was poured into water, and the yellow compound, which separated, removed by filtration and crystallised from aqueous alcohol.

The compound crystallised in yellow needles (forming a green solution in alcohol).

yield 0.2 gms. (18% theory)

m.p. 138°- 140°.

Analysis:

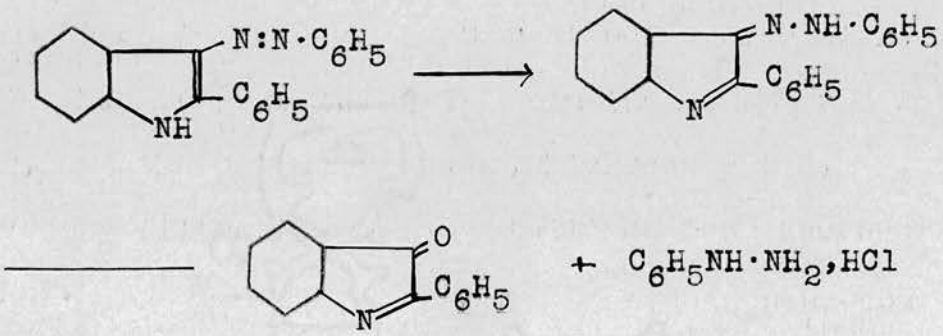
found, N, 13.76%,

$C_{21}H_{17}N_3$, requires N, 13.5%.

The compound turned brown on standing, due to decomposition, and an alcoholic solution gradually became yellow after standing for several days.

As the methyl group in this case also is stable, this compound must have a true hydrazono-structure.

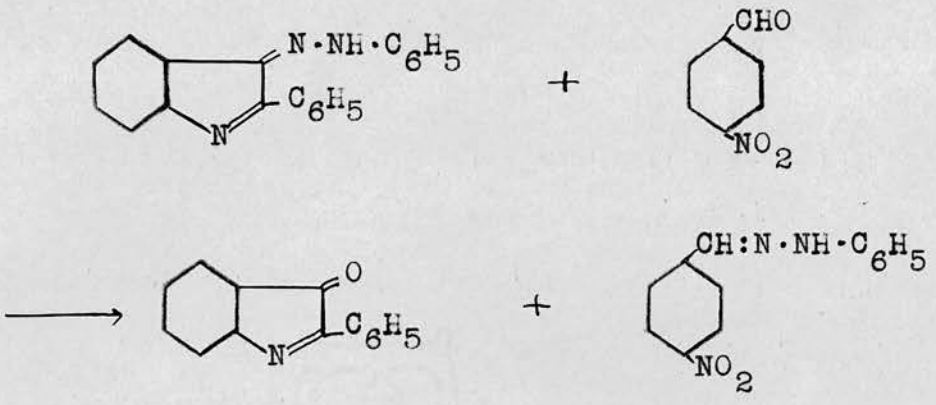
Attempted Hydrolysis of 3-Benzeneazo-2-phenylindole.



It was expected that, if the compound existed to any great extent as the hydrazone form, 2-phenylindolone would be isolated on hydrolysis.

After boiling with concentrated hydrochloric acid for three days, a red compound was obtained, m.p. 140°, which was neither 2-phenylindolone, nor the original 3-benzeneazo-2-phenylindole, but was expected to be an addition product with the hydrochloric acid, as indoles in general are known to give red coloured compounds with hydrochloric acid.

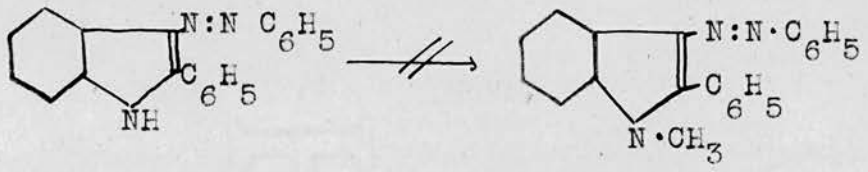
A second attempt was made using a very reactive aldehyde. It was expected that this aldehyde would form the hydrazone and liberate 2-phenylindolone.



3-Benzeneazo-2-phenylindole (0.5 gms.) was dissolved in alcohol and p-nitrobenzaldehyde (0.3 gms.) added and the solution boiled for three hours. It was then poured into water and the resulting mixture separated by filtration.

This mixture was crystallised from alcohol and white needles were obtained, m.p. 98°. This was, therefore, p-nitrobenzaldehyde, m.p. 106°, and no hydrazone was obtained, so that the hydrolysis did not take place.

Attempted Methylation of 3-Benzeneazo-2-phenylindole.



Potassium hydroxide (1 gm.) was dissolved in methyl alcohol (10 ccs.) and methyl iodide (4 gms.) added. 3-Benzeneazo-2-phenylindole (2 gms.) was then added and the mixture refluxed for two hours. The excess of methyl iodide was then removed by distillation and the remaining solution poured into water. A yellowish brown precipitate settled, which was filtered, washed with water, dried on porous tile, and crystallised from benzene.

m.p. 160° - 163°.

This, therefore, was the unchanged 3-benzeneazo-2-phenylindole (lit. m.p. 165°) and no methylation had taken place.

The absorption curves in the visible region of the spectrum for the compounds

1. 3-Benzeneazo-1-methyl-2-phenylindole.
2. 2-Phenylindolone-methylphenylhydrazone.
3. 3-Benzeneazo-2-phenylindole.

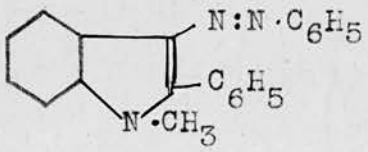
were determined using a Hilger wavelength Spectraphotometer. Tables 1, 11, 111, indicate the results obtained. Column (1) gives the wavelength in A° units; column (2) the density reading giving a measure of the amount of absorption; and column (3) is the extinction coefficient (ε), calculated from the relation

$$\varepsilon = \frac{C\ D}{L}$$

where C is the concentration, and L the length of the cell.

Graphs 1, 11, and 111, show the absorption curves obtained by plotting ε against λ.

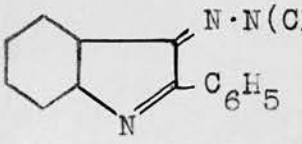
Table 1.



Concentration 0.0000852 M.

λ	d	ε
4100	1.91	0.000430
4200	1.39	0.000313
4300	1.22	0.000275
4400	1.015	0.000228
4500	0.75	0.000169
4600	0.57	0.000128
4700	0.40	0.000090
4800	0.31	0.000070
4900	0.19	0.000043
5000	0.16	0.000036
5100	0.06	0.000014
5500	0.04	0.000009

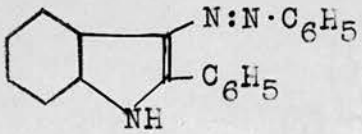
Table 11.



Concentration 0.00023 M.

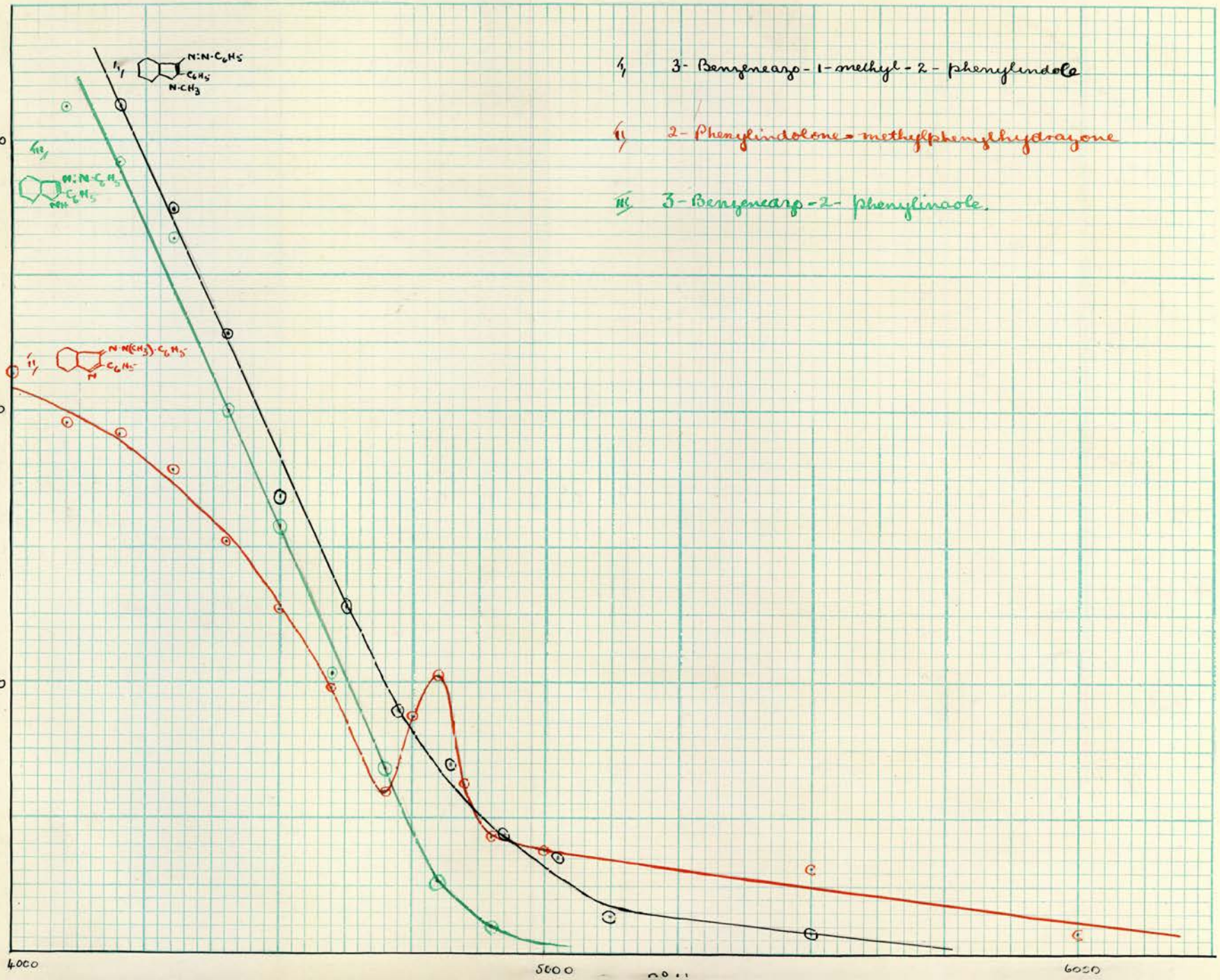
λ	d	ε
4000	0.93	0.000214
4100	0.85	0.000196
4200	0.83	0.000191
4300	0.78	0.000179
4400	0.66	0.000152
4500	0.55	0.000126
4600	0.43	0.000099
4700	0.26	0.000060
4750	0.38	0.000087
4800	0.44	0.000101
4850	0.27	0.000062
4900	0.19	0.000044
5000	0.17	0.000039
5500	0.14	0.000032
6000	0.03	0.000007

Table 111.



Concentration 0.0002 M.

λ	d	ε
4100	1.56	0.000312
4200	1.38	0.000276
4300	1.32	0.000264
4400	1.00	0.000200
4500	0.79	0.000158
4600	0.52	0.000104
4700	0.34	0.000068
4800	0.13	0.000026
4900	0.05	0.000010
5000	0.00	0
5100	0.00	0
5500	0.00	0
5700	0.00	0
6000	0.00	0


I 3- Benzeneazo-1-methyl-2-phenylindole
II 2-Phenylindolone-methylphenylhydrazone
III 3-Benzeneazo-2-phenylindole.
ε.
.000300
.000200
.000100
4000
5000
6000

D I S C U S S I O N .

The chemical evidence obtained in this work is rather contradictory.

The fact, noted by Plancher and Soncini, that the compound did not react with phenyliscocyanate, and the failure in this thesis to obtain an acetyl derivative tend to show that the hydrazono structure is present, while the failure to hydrolyse the compound does not agree with this view. The attempted methylation of 3-benzeneazo-2-phenylindole to the 3-benzeneazo-1-methyl-2-phenylindole with methyl iodide and methyl alcoholic potassium hydroxide proved unsuccessful. The methylation would be expected to go readily if the benzeneazo structure was present.

The absorption curves of the three compounds show that 3-benzeneazo-2-phenylindole has a benzeneazo structure as the curve resembles that of 3-benzeneazo-1-methyl-2-phenylindole rather than that of 2-phenylindolone-methylphenylhydrazone.

S U M M A R Y .

Robinson's mechanism of the Fischer Indole Synthesis has been studied in detail, and final proof been brought forward in its favour.

The method of Pictet and List for the preparation of 2-phenylindole has been repeated and criticised, the intermediate compound, postulated by these authors, being isolated and shown to possess a certain range of stability. At the same time derivatives of 2-phenylindole have been prepared, and a complete study of the chemical properties of 1-methyl-2-phenyl-3-nitrosoindole has been carried out.

Various bromonitroindazoles, and bromonitro-methylindazoles have been prepared and the reactivities of the bromine atoms towards piperidine and red phosphorus and hydriodic acid measured. In some cases the results have been used to verify the structural formulae of the isomeric methylindazoles.

Attempts to prepare the various bromonitro derivatives of 1-phenyl-2-methylbenzimidazole, with a view to obtain some insight to the fine structure of that compound, failed.

A short study of the properties of 3-benzeneazo-2-phenylindole has been carried out, and the absorption spectrum of this compound compared with those of 1-methyl-3-benzeneazo-2-phenylindole and 2-phenylindolone-methylphenylhydrazone, resulting in the formulation of the compound with a true benzeneazo structure.

In conclusion, the author wishes to express his gratitude to Dr. Neil Campbell for valuable advice and helpful encouragement throughout the course of this research.