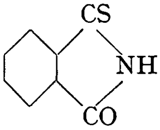
112. *Monothiophthalimide and Some Derivatives of Oxindole.*

By J. C. Porter, Sir Robert Robinson, and (the late) M. Wyler.

The work described in this communication was carried out in 1935 and its original objective was the synthesis of *dl*-eserethole essentially by the method published in the same year by Julian and Pikl. The opportunity was taken to make a series of new derivatives of *N*-methyloxindole, which is now readily accessible by the method of Stolle (1930). The paper includes a number of miscellaneous observations which are now brought together in view of the work of Drew and Kelly (following paper), of which we had cognisance a year or so later. The introduction which follows is a brief summary of the salient points.

The action of sodium hydrosulphide on phthalonitrile gives an excellent yield of o-*cyanothiobenzamide*, $CN{\cdot}C_6H_4{\cdot}CS{\cdot}NH_2$ (I), and this substance is converted by hydrochloric acid into the red *monothiophthalimide* (II), doubtless by the formation and hydrolysis of the imine (III), which was not isolated. Dithiophthalimide (Pratt and Brill, *Philippine J. Sci.*, 1914, **9**, *A*, 105) is also a red substance. The sulphur atom in thiophthalimide is reactive; for example, on heating with aniline, a *phenylimine* is produced. Condensation with *N*-methyloxindole in presence of piperidine gave (IV), and the quinophthaline of Ebner and Lange (*Annalen*, 1901, **315**, 351) was readily obtained by reaction with quinaldine. The expected condensation with α-naphthol did not occur, but instead bismetaindolone (β-*iso*indigo) (Liebermann and Bistrzycki, *Ber.*, 1893, **26**, 539) was produced. This substance is also obtained by heating thiophthalimide with copper bronze or, better, with oxindole. *N*-Methyloxindole reacts with ethyl oxalate in the presence of alcoholic sodium ethoxide to give *ethyl* N-*methyloxindole*-3-*oxalate* in almost theoretical yield. Extrusion of the oxalyl group occurs on coupling with diazonium salts.



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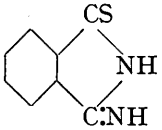

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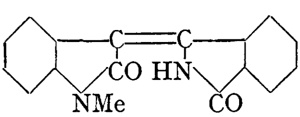

(IV.)

Vanillylidene, p-*dimethylaminobenzylidene*, and *anhydrocotarnine* derivatives of *N*-methyloxindole have been prepared. The 6-*aminopiperonylidene* derivative shows little tendency to undergo ring closure to a quinindoline, but the reaction was accomplished by heating with aminosulphonic acid in quinoline solution and this method may have more general application. *N*-Methyloxindole condenses readily with isatin-α-anil in acetic anhydride solution with the formation of *N*-methylindirubin.

According to Borsche, Weussmann, and Fritsche (*Ber.*, 1924, **57**, 1149) the nitration of oxindole gives the 6-nitro-derivative and not the expected 5-nitro-compound. We assume that the *nitro*-N-*methyloxindole* which we have prepared is similarly constituted but have no independent evidence of this orientation.

EXPERIMENTAL.

o-*Cyanothiobenzamide* (I).—Phthalonitrile (40 g.) was boiled with alcohol (200 c.c.), and the solution cooled. Aqueous sodium hydrosulphide, prepared by saturating a solution of sodium sulphide (100 g. cryst.) in water (100 c.c.) with hydrogen sulphide, was added to the resulting suspension and a slow stream of hydrogen sulphide was then passed through the stirred mixture for 6 hours. The yellowish-brown needles which separated were collected, washed with water, and dried at 90°. More of the product was obtained by diluting the dark red filtrate with water and adding hydrochloric acid to it until it was only faintly alkaline (total, 45 g.). This material may be employed for the preparation of thiophthalimide. The substance is sparingly soluble in the usual organic solvents; it dissolves freely in hot acetic acid, but is so transformed into monothiophthalimide. It gives deep red solutions in pyridine and quinoline, but could not be crystallised from these solvents.

A portion was purified for analysis by solution in dilute aqueous sodium hydroxide and precipitation from the deep red solution with carbon dioxide. After washing with water and alcohol and drying at 100°, the product decomposed at about 218° (Found : C, 59·5; H, 4·0; N, 17·1; S, 20·1. $C_8H_6N_2S$ requires C, 59·3; H, 3·7; N, 17·3; S, 19·7%).

Monothiophthalimide (II).—*o*-Cyanothiobenzamide (20 g.) was boiled with water (500 c.c.), concentrated hydrochloric acid (70 c.c.) added, and the suspension boiled for 2—3 minutes. The needles that separated were collected and dried at 90° (yield, 85%). The *substance* crystallised from benzene in large, red needles, m. p. 175° (Found : C, 58·8; H, 3·2; N, 8·6; S, 19·9. C_8H_5ONS requires C, 58·9; H, 3·1; N, 8·6; S, 19·6%). It may be sublimed (needles) under diminished pressure without decomposition.

On treatment with cold concentrated aqueous sodium hydroxide a yellow sodium salt was formed. Hot alkaline solutions hydrolysed it to phthalamic acid.

Phenyliminophthalimidine.—Thiophthalimide (6 g.) and aniline (3·4 g.) were heated together at 170° for 30 minutes, a brisk evolution of hydrogen sulphide occurring. After cooling, the brown mass crystallised from alcohol in pale yellow needles (6·6 g.), m. p. 170° (Found : C, 75·7; H, 4·7; N, 12·7. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5; N, 12·6%).

On boiling the *anil* with hydrochloric acid or with acetic anhydride, phthalanil was produced. Boiling with 10% aqueous sodium hydroxide gave aniline, ammonia, and sodium phthalate.

Anhydrophthalimide-N-*methyloxindole* (IV).—A mixture of thiophthalimide (4 g.), *N*-methyloxindole (3·6 g.) (Stolle, *J. pr. Chem.*, 1930, **128**, 1), alcohol (40 c.c.), and piperidine (3 drops) was refluxed for 1 hour. The orange crystals that separated (6·3 g.) were recrystallised from acetic acid; m. p. 242° (Found : C, 74·0; H, 4·4; N, 10·2. $C_{17}H_{12}O_2N_2$ requires C, 73·9; H, 4·3; N, 10·1%).

β-*Quinophthaline.*—Thiophthalimide (4 g.) and quinaldine (3·5 g.) were heated at 170° for 30 minutes, hydrogen sulphide being rapidly evolved. The product crystallised from acetic acid in square, yellow prisms (5·4 g.), m. p. 213° (Ebner and Lange, *loc. cit.*, give m. p. 213°).

Bismetaindolone.—Thiophthalimide (4 g.) and α-naphthol (3·6 g.) were heated together for 2 hours at 180°; a little hydrogen sulphide was evolved and the melt gradually solidified. The product was boiled with hot alcohol, leaving small, yellowish-brown prisms (1·5 g.), practically insoluble in all organic solvents, and not melting below 350°. The substance is evidently the bismetaindolone of Liebermann and Bistrzycki (*loc. cit.*) (Found : C, 73·2; H, 4·2; N, 10·9. Calc. for $C_{16}H_{10}O_2N_2$: C, 73·2; H, 3·8; N, 10·7%). Subsequently the substance was obtained (*a*) in poor yield by heating thiophthalimide with copper bronze and (*b*) more satisfactorily by heating thiophthalimide with oxindole [Found : (*a*) C, 72·7; H, 4·1; N, 10·3%. (*b*) C, 73·0; H, 3·9%].

Phthalocyanine Pigment from Monothiophthalimide.—Monothiophthalimide (16 g.), ammonium aminosulphonate (32 g.), and anhydrous cupric chloride (4 g.) were mixed and heated for 1 hour at 220°. The cooled product was ground, extracted with hot water, dried, dissolved in 8 times its weight of 96% sulphuric acid, and poured into hot water (1 l.). The precipitated *phthalocyanine* was collected, washed until neutral, and dried (yield, 11 g.). It formed a blue, metallic powder, and was much greener and a little duller in shade than Monastral Fast Blue BR (Found : S, 4·0; Cl, 0·35. $C_{28}H_{16}N_4SCu$ requires S, 5·3%).

Ethyl N-*Methyloxindole*-3-*oxalate*.—Hot solutions of *N*-methyloxindole (8 g.) in ethyl oxalate (12 g.) and of sodium (2 g.) in alcohol (28 c.c.) were mixed and the yellow semi-solid mass which formed very quickly was dissolved in water and acidified with hydrochloric acid. The flocculent, yellow precipitate was collected, m. p. 80°, and was pure enough for most purposes; the yield approached the theoretical. Some of the material, crystallised twice from alcohol, formed fine, yellow needles, m. p. 81° (Found : C, 63·2; H, 5·3; N, 5·7. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3; N, 5·7%), readily soluble in hot alcohol and in benzene, ether or carbon tetrachloride, moderately readily soluble in hot light petroleum.

The *phenylhydrazone*, prepared in acetic acid solution, crystallised from alcohol in irregular, pale yellow prisms, m. p. 158·2° (Found : C, 67·8; H, 5·7; N, 12·4. $C_{19}H_{19}O_3N_3$ requires C, 67·6; H, 5·6; N, 12·6%).

Condensation of Ethyl N-*Methyloxindole*-3-*oxalate with* p-*Toluidine*.—A solution of the above ester (2·3 g.) and *p*-toluidine (1 g.) in acetic acid (15 c.c.) was boiled for 10 minutes, and water (10 c.c.) then added. The product separated as an oil which solidified on keeping; it crystallised from alcohol in hard, yellow, rhombic prisms, m. p. 97° (yield, 75%) (Found : C, 71·6; H, 6·3; N, 8·4. $C_{20}H_{20}O_3N_2$ requires C, 71·4; H, 6·0; N, 8·3%).

p-*Nitrobenzeneazo*-N-*methyloxindole*.—A diazo-solution prepared from *p*-nitroaniline (0·9 g.) was added to a solution of ethyl methyloxindoleoxalate (1·4 g.) in cold aqueous sodium carbonate (10%). A flocculent, yellow precipitate formed and the filtrate contained sodium oxalate. The *azo*-compound, crystallised twice from acetic acid, formed long prisms, m. p. 272° (yield, almost quantitative) (Found : C, 60·5; H, 3·8; N, 19·0. $C_{15}H_{12}O_3N_4$ requires C, 60·8; H, 4·0; N, 18·9%).

A deep indigo-blue coloration is produced on addition of sodium hydroxide to an alcoholic solution. The substance is identical with the *p*-nitrophenylhydrazone of *N*-methylisatin and it was also obtained by the following method. A solution of methylisatin (1 g.) (Vanino, " Präparative Chemie," II, p. 756) and *p*-nitrophenylhydrazine (1 g.) in acetic acid (30 c.c.) was refluxed for 30 minutes. On keeping, yellowish-brown crystals separated, m. p. (after crystallisation from acetic acid) 272° alone or mixed with the above azo-compound.

When ethyl methyloxindoleoxalate was coupled with diazobenzenesulphonic acid, an azo-compound was obtained that gave moderately fast orange-yellow dyeings on wool.

3-*Vanillylidene*-N-*methyloxindole*.—A solution of *N*-methyloxindole (1 g.), vanillin (1 g.), and piperidine (3 drops) in alcohol (6 c.c.) was kept at 75° for 1½ hours and then overnight at room temperature. The bright orange crystals were collected, dried, and recrystallised from ethyl acetate, forming small, almost square, prisms, m. p. 180·5° (yield, 90%) (Found : C, 72·5; H, 5·5; N, 5·5. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·3; N, 5·1%).

3-p-*Dimethylaminobenzylidene*-N-*methyloxindole*.—A mixture of *N*-methyloxindole (1 g.), *p*-dimethylaminobenzaldehyde (1 g.), alcohol (6 c.c.), and piperidine (3 drops) was refluxed for 1½ hours. A little water was added to the cooled solution and the precipitated product was collected and washed with alcohol (yield, 92%); it crystallised from alcohol in fine, brilliant yellowish-orange needles, m. p. 155° (Found : C, 77·8; H, 6·5; N, 10·2. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·5; N, 10·1%).

This compound was a fast yellow dye for wool, and it appeared to have considerable affinity for cotton. The method of application was to dissolve the substance in dilute hydrochloric acid, immerse the fibre, and dilute considerably; the dye was liberated as a colloid, which was readily adsorbed.

In an attempted alternative preparation of *p*-dimethylaminobenzylidenemethyloxindole, 3-formyl-*N*-methyloxindole (1 g.) (Julian and Pikl, *J. Amer. Chem. Soc.*, 1934, **56**, 1797) and dimethylaniline (0·7 g.) were dissolved in acetic acid (10 c.c.), concentrated hydrochloric acid (2 drops) added, and the solution boiled for 3 hours. The red *compound* (0·15 g.) that separated crystallised from alcohol in needles, m. p. 236° (Found : N, 9·2. $C_{19}H_{16}O_2N_2$ requires N, 9·2%). The compound has not yet been further investigated; it is possibly *N*-methyloxindolylmethyleneoxindole.

3-(6′-*Aminopiperonylidene*)-N-*methyloxindole*.—Aqueous potassium hydroxide (3 c.c. of 60%) was gradually added, with stirring, to a solution of 6-aminopiperonal (1·2 g.) and *N*-methyloxindole (1·3 g.) in methyl alcohol (15 c.c.). The orange-red precipitate was collected, washed with methyl alcohol, crystallised from aqueous acetic acid (50%), dried, and recrystallised from alcohol, forming fine, orange needles (0·8 g.), m. p. 186° (Found : N, 9·7. $C_{17}H_{14}O_3N_2$ requires N, 9·3%).

2 : 3-*Methylenedioxy*-10-*methylquinindoline*.—Excess of aminosulphonic acid was added to aminopiperonylidenemethyloxindole (0·55 g.) in quinoline (10 c.c.) and the solution was refluxed (metal bath) for 7 minutes. After cooling, aqueous sodium hydroxide was added, and the quinoline distilled in steam. The residue was extracted with chloroform, giving a pale yellow-violet, fluorescent solution. After removal of the solvent, the *base* crystallised from benzene in pale yellow leaflets, m. p. 225° (Found : C, 73·7; H, 4·2; N, 10·0. $C_{17}H_{12}O_2N_2$ requires C, 73·9; H, 4·3; N, 10·1%). The pure base is fluorescent in neutral solutions, but its pale yellow acid solutions do not exhibit this property.

6 (or 5)-*Nitro*-N-*methyloxindole*.—Potassium nitrate (2·75 g.) was added gradually, with stirring, to a solution of *N*-methyloxindole (4 g.) in concentrated sulphuric acid (40 g.), cooled in a freezing mixture. After ½ hour the solution was added to ice, and the white product collected and dried. It was crystallised expeditiously from boiling benzene, some decomposition always occurring, forming prisms, m. p. 196° (yield, 60%) (Found : C, 57·0; H, 4·2; N, 14·7. $C_9H_8O_3N_2$ requires C, 56·9; H, 4·2; N, 14·6%).

The amine obtained on reduction was diazotised and coupled with β-naphthol, giving a red azo-compound.

6 (or 5)-*Amino*-N-*methyloxindole*.—Reduction of the nitro-compound with iron in aqueous alcoholic solution in the presence of a trace of hydrochloric acid was unsuccessful owing to oxidation of the product by air.

A mixture of nitromethyloxindole (2·5 g.), stannous chloride (10·5 g.), and concentrated hydrochloric acid (17 c.c.) was heated on the steam-bath for 30 minutes. The solution was diluted to 300 c.c. with water, excess of zinc added, and the mixture heated; a precipitate of the zincichloride of the amine then separated. This was dissolved by dilution with water and boiling, and the solution was filtered from tin and zinc. On cooling, the crystalline zincichloride was obtained. This salt was treated with aqueous sodium hydroxide (15%) in a coal-gas atmosphere and the liberated *amine* was collected in an atmosphere of carbon dioxide. The product, after being washed with a little water and dried, crystallised from light petroleum (b. p. 60—80°) in white needles, m. p. 112·5° (Found: N, 16·8. $C_9H_{10}ON_2$ requires N, 17·3%).

Anhydrocotarnine-N-*methyloxindole*.—*N*-Methyloxindole (0·5 g.) and cotarnine (0·75 g.) were dissolved in the minimum quantity of cold alcohol. After 4 hours the product was deposited in pale yellow cubes (1·1 g.), which were almost pure. The *base* crystallised from benzene in pale yellowish cubes, m. p. 154·5° (decomp.) (Found : C, 68·7; H, 6·2; N, 7·7. $C_{21}H_{22}O_4N_2$ requires C, 68·8; H, 6·0; N, 7·75%).

The hydrochloride was prepared by passing hydrogen chloride into a benzene solution of the base; it was readily soluble in water.

The base was treated with methyl sulphate in warm benzene and a pale yellow compound, crystallising in fine needles, was obtained; and recrystallised from acetone, this had m. p. 183°. Analysis showed, however, that it was a mixture of a mono- and a di-methosulphate, and it was not found possible to separate the constituents.

N-*Methylindirubin*.—A solution of *N*-methyloxindole (1 g.) and isatin-α-anil (1·4 g.) in acetic anhydride (20 c.c.) was refluxed for 30 minutes; the product separated on cooling. It crystallised from acetic acid in fine, deep copper-coloured needles (1·5 g.), m. p. 283°, very sparingly soluble in most organic solvents, giving pale violet solutions. It corresponds in every way to the substance described by Wahl and Bagard (*Compt. rend.*, 1913, **156**, 900; cf. Martinet, *ibid.*, 1919, **169**, 183) except that no m. p. has been previously recorded. This derivative is very similar to indirubin itself, but is more readily soluble in most solvents. Like its homologue, it gives a yellow vat with alkaline hydrosulphite solution, from which it may be regenerated by aerial oxidation. The solution of the leuco-compound is unstable, however, and indigo or methylindigo is gradually produced in it.

5-*Hydroxy*-N-*methyloxindole*.—Acet-*p*-anisidide (60 g.) was dissolved in xylene (140 c.c.) in which sodium powder (7 g.) was suspended; the mixture was refluxed for 1 hour with stirring. Methyl sulphate (31 g.) was then added, and the whole heated on the steam-bath for 30 minutes. The xylene was removed under diminished pressure, and the residue heated on the steam-bath for 36 hours with a solution of potassium hydroxide (52 g.) in alcohol (180 c.c.) and water (20 c.c.). The alcohol was removed under diminished pressure, and water added; the product (36 g.), isolated by means of ether, had b. p. 120—122°/14 mm. It was dissolved in dry benzene, and chloroacetyl chloride (15 g.) in benzene solution added slowly with cooling. The mixture was heated for 30 minutes on the steam-bath, water added, and the benzene layer separated, washed with water and dilute acid, and dried. The benzene was evaporated, and powdered aluminium chloride (20 g.) added to the residue; the mixture was kept at 50° until evolution of hydrogen chloride ceased. More aluminium chloride (20 g.) was then added, and the flask heated with stirring for 1 hour (oil-bath at 180°). Before it was cold the paste was poured on ice; the brown powder that separated was collected, washed, and dried. The *substance* crystallised from alcohol in irregular, pale brown plates, m. p. 186·5° (yield, almost theoretical) (Found: C, 66·3; H, 5·5; N, 8·6. $C_9H_9O_2N$ requires C, 66·3; H, 5·5; N, 8·6%).

*5-Methoxy-*N*-methyloxindole.*—The crude hydroxy-compound (70 g.) was dissolved in aqueous sodium hydroxide (270 c.c. of 7·5%), and methyl sulphate (50 c.c.) added slowly to the cooled, stirred solution. The mixture was heated on the steam-bath for 30 minutes, with addition of aqueous sodium hydroxide from time to time to keep the solution alkaline. After cooling, the product was isolated by means of ether and distilled as a yellow oil (45 g.), b. p. 149—151°/1 mm. It rapidly solidified, and crystallised from ether in colourless, irregular prisms, m. p. 92° (Found: C, 68·0; H, 6·5; N, 8·2. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9%).

*Attempted Preparation of 5-Methoxy-3-β-phenoxyethyl-*N*-methyloxindole.*—A solution of methoxymethyloxindole (20 g.) in absolute ether (150 c.c.) was refluxed with sodium powder (2·6 g.) for 14 hours. β-Phenoxyethyl bromide (22·7 g.) together with a little ether was added, and the mixture refluxed for 12 hours. Water was added and the ethereal and aqueous layers filtered from a white solid (5 g.). The ethereal layer afforded an oil, which was steam-distilled; the residue in the flask was worked up and unchanged methoxymethyloxindole (5 g.) was recovered together with an intractable residue. The white solid was very sparingly soluble in ether and sparingly soluble in most other organic solvents; it was, however, freely soluble in acetic acid. It crystallised from alcohol in irregular prisms, m. p. 233° (Found: C, 67·3; H, 6·6; N, 7·9; OMe, 17·55. $C_{20}H_{24}O_4N_2$ requires C, 67·4; H, 6·7; N, 7·9; OMe, 17·42%). The analysis indicates that the compound is derived from two molecules of the oxindole by the addition of two hydrogen atoms. It corresponds in fact to the pinacol of the cyclic amide, but we consider this formulation a highly improbable one and suggest that some further intramolecular change must be postulated. The substance was neutral and gave no ferric reaction; after boiling with concentrated hydrochloric acid, a trace of a base of pleasant odour was isolated. This gave a deep greenish-blue coloration with ferric chloride.

5-Methoxy-1 : 3-dimethyl-3-β-phenoxyethyl-2-indolinone.—For the preparation of 5-hydroxy-*N* : 3-dimethyloxindole the method used was the same as that of Julian and Pikl (*J. Amer. Chem. Soc.*, 1935, **57**, 565), *N*-methyl-*p*-anisidine being used in place of *N*-methyl-*p*-phenetidine. The dried product from the Friedel–Crafts reaction (140 g.) was dissolved in aqueous potassium hydroxide (1000 c.c. of 5%), and methyl sulphate (90 c.c.) added slowly with stirring at room temperature. The mixture was heated on the steam-bath for 30 minutes, with addition of aqueous potassium hydroxide from time to time so as to keep the solution alkaline. The product, isolated by the use of ether, was a straw-coloured oil (45 g.), b. p. 147—151°/2—3 mm., which soon solidified.

A solution of methoxydimethyloxindole (42 g.) in absolute ether (150 c.c.) was added to sodium powder (5·1 g.) under absolute ether (50 c.c.). A vigorous reaction, with rapid evolution of hydrogen, ensued. The mixture was heated on the steam-bath for a few hours; β-phenoxyethyl bromide (50 g.) was then added, the solution refluxed for 12 hours, and water added. The product, isolated by means of ether, was a viscous oil (36·5 g.), b. p. 230—243°/1 mm., mostly b. p. 237—240°/1 mm. (King and Robinson, J., 1932, 332, give b. p. 238—243°/1 mm.). The identity of the compound was confirmed by the preparation of the trinitro-derivative (*loc. cit.*), m. p. 192—193° alone or mixed with an authentic specimen. In view of the anticipations of our intended work in other laboratories we abandoned this investigation.

Attempted Synthesis of 3 : 3-Dimethyloxindole.—Aniline was treated with α-bromo*iso*butyryl bromide, and the α-bromo*iso*butyranilide isolated in the usual way. The reaction with aluminium chloride appeared to proceed normally, but no oxindole derivative could be isolated. The conditions were varied considerably without any positive result being obtained.

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