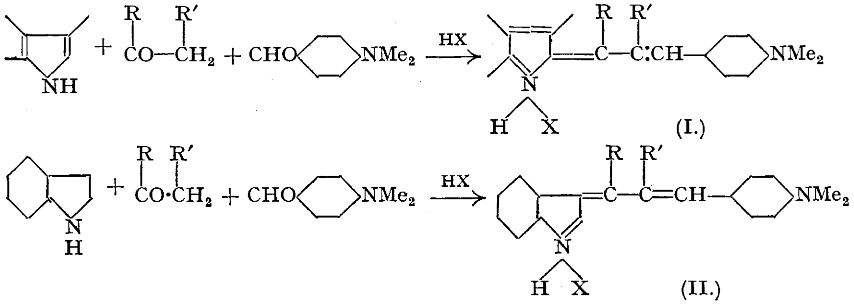
133. *An Extension of the Ehrlich Reaction.*

By A. H. Cook and J. R. Majer.

Pyrroles containing a free α-position and indoles with a free β-position have been condensed with ketones and *p*-dimethylaminobenzaldehyde to give blue dyes. The formulation of the products as trimethincyanines was confirmed by an alternative synthesis of a representative dye.

The Ehrlich reaction, *i.e.*, production of a deep red colour when pathological urine containing urobilinogen is treated with *p*-dimethylaminobenzaldehyde in acid solution in the cold, has long been known to be exhibited by all pyrrole compounds containing a free or potentially free α-position. The colour is due to equimolecular condensation of aldehyde with the pyrrolenine form of the pyrrole (Fischer-Orth, " Die Pyrrole," I, 66). Similar red colours form the basis of the Salkowski reaction (*Biochem. Z.*, 1919, **97**, 124) and its variants for the detection of indoles.

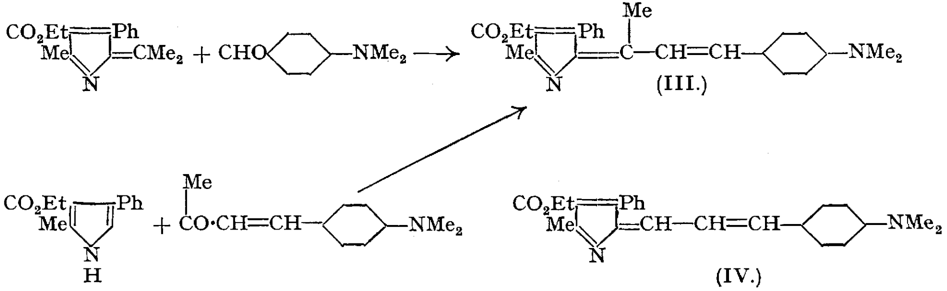
In a previous paper (this vol., p. 482) it was shown that unstable condensation products could be obtained between pyrroles containing at least one free α-position, as well as an imino-group, and ketones; with further appropriate reagents trimethincyanines could be prepared. In the preceding paper the similar behaviour of indoles was described, the intermediates in some cases being isolated in pure condition. In all these reactions the reactivity of the methylene in the original pyrrolenine or indolenine was transmitted through a double bond to a distant methyl or methylene group to provide a trimethin chain. It was therefore anticipated that these intermediates would condense with *p*-dimethylaminobenzaldehyde in the manner of the simpler Ehrlich and Salkowski reactions :



(I.)

(II.)

Employing either crystalline indolenine condensation products, or indolenines or pyrrolenines prepared *in situ*, we have obtained a range of dyes of types (I) and (II) by condensation with appropriate carbonyl compounds in warm acetic acid containing mineral acid; the dyes were isolated as the free bases or in the form of their salts. That the products have the suggested structures is confirmed by formation of the same base (III) in the following syntheses :

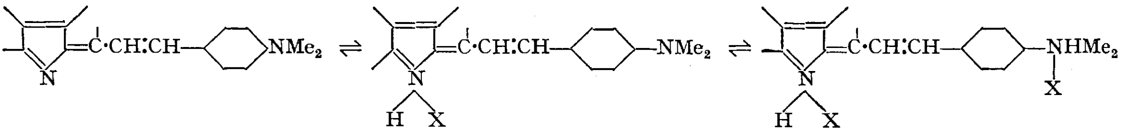


(III.)

(IV.)

Similarly, condensation of 3-carbethoxy-4-phenyl-2-methylpyrrole with *p*-dimethylaminocinnamaldehyde afforded (IV), but attempts to condense the pyrrole and acetaldehyde, or paraldehyde, with *p*-dimethylaminobenzaldehyde were fruitless.

In view of the instability of the products of the Ehrlich reaction, the present dyes were surprisingly stable, and the salts as well as the bases could be purified by chromatography on alumina. The salts were all deep indigo-blue in solution, absorbing in the far red part of the visible spectrum. The behaviour of the dyes towards acids and alkalis, however, was similar to that of the Ehrlich dyes : *e.g.*, the colours faded reversibly in presence of excess acid or alkali; by analogy with the Erhlich dyes this must be attributed to the formation of base or acid salts :



Pale yellow. Blue. Pale yellow.

EXPERIMENTAL.

(For brevity, " aldehyde " throughout implies *p*-dimethylaminobenzaldehyde.)

Condensations between Pyrroles, Ketones, and Aldehyde.—Pyrrole (0·7 g.), acetone (0·7 c.c.), and acetic acid (30 c.c.) containing hydrobromic acid (0·8 g.) were mixed, and after 2—3 mins. aldehyde (1·5 g.) in a little acetic acid was added. After 2 hours on the steam-bath the purple solution was diluted with water and the dye crystallised from methanol–ether; *[2-pyrrole]-[4-dimethylaminobenzene]-α-methyltrimethincyanine bromide* (I; R = Me, R′ = H, X = Br) formed a dark brown powder decomposing above 300° (Found: C, 60·4; H, 6·3. $C_{16}H_{19}N_2Br$ requires C, 60·2; H, 6·0%). In similar manner 2 : 4-dimethylpyrrole (0·95 g.), acetone (0·7 c.c.), and aldehyde (1·5 g.) were condensed in acetic acid (24 c.c.) containing hydrobromic acid (0·8 g.), and reaction completed during 1 hour at 100°. Dilution of the deep blue solution and crystallisation of the precipitate from acetic acid–ether gave *[3 : 5-dimethyl-2-pyrrole]-[4-dimethylaminobenzene]-α-methyltrimethincyanine bromide*, m. p. 257° (decomp.) (Found: C, 62·6; H, 6·4. $C_{18}H_{23}N_2Br$ requires C, 62·3; H, 6·6%). By replacing acetone by the equivalent quantity of acetophenone, *[3 : 5-dimethyl-2-pyrrole]-[4-dimethylaminobenzene]-α-phenyltrimethincyanine bromide* (I; R = Ph, R′ = H, X = Br) was prepared (yield 90%); it crystallised from acetic acid–ether, and decomposed above 300° (Found: Br, 19·5. $C_{23}H_{25}N_2Br$ requires Br, 19·6%). 3-Carbethoxy-4-phenyl-2-methylpyrrole (2·3 g.) was condensed with acetone (0·7 c.c.) in acetic acid (16 c.c.) containing hydrobromic acid (0·8 g.) and then with aldehyde (1·5 g.) in acetic acid for 1 hour. On pouring the mixture into dilute ammonia *[4-carbethoxy-3-phenyl-5-methyl-2-pyrrole]-[4-dimethylaminobenzene]-α-methyltrimethincyanine bromide* (III) was precipitated; it crystallised from light petroleum and had m. p. 182° (Found: C, 82·7; H, 7·0; N, 7·2. $C_{26}H_{28}O_2N_2$ requires C, 83·0; H, 7·2; N, 7·0%). The same compound was obtained by heating 3-carbethoxy-4-phenyl-2-methylpyrrole (2·3 g.) with *p*-dimethylaminobenzylideneacetone (1·5 g.) in acetic acid (15 c.c.) containing hydrobromic acid (0·4 g.) to boiling for 1 hour and pouring the blue solution into ammonia. On similarly condensing the same pyrrole (2·3 g.) with *p*-dimethylaminocinnamaldehyde (1·3 g.) and pouring the solution in acetic acid into ether, *[4-carbethoxy-3-phenyl-5-methyl-2-pyrrole]-[4-dimethylaminobenzene]trimethincyanine bromide* (IV) was obtained. After purification by repeated precipitation from acetic acid with ether, it formed a black powder, decomposing above 300° (Found: Br, 17·0. $C_{25}H_{27}O_2N_2Br$ requires Br, 17·1%). On condensing 2-diphenylmethylpyrrole (2·3 g.) with acetone (0·7 c.c.) in acetic acid (20 c.c.), hydrobromic acid (0·8 g.), and aldehyde (1·5 g.) for 1 hour at 100° and pouring the deep blue solution into ammonia, *[5-diphenylmethyl-2-pyrrole]-[4-dimethylaminobenzene]-α-methyltrimethincyanine* was obtained; it crystallised from acetone–ether and decomposed above 300° without melting (Found: C, 85·95; H, 7·0. $C_{29}H_{28}N_2$ requires C, 86·1; H, 7·0%).

Condensations between Indoles, Ketones, and Aldehyde.—Ethyl 2-methylindolylidenebutyrate (1·0 g.) and aldehyde (0·65 g.) were dissolved in boiling acetic acid (10 c.c.) containing hydrobromic acid (0·25 g.), and the mixture allowed to cool. The deep blue solution was poured into dilute ice-cold ammonia, and the precipitate (yield quantitative) collected. Several crystallisations from a mixture of benzene and light petroleum gave *[2-methyl-3-indole]-[4-dimethylaminobenzene]-β-carbethoxy-α-methyltrimethincyanine* in yellow feathery needles, m. p. 141° (Found: C, 77·0; H, 7·1. $C_{24}H_{26}O_2N_2$ requires C, 77·0; H, 7·0%). It was yellow in ethanol, becoming intense blue with a trace of acid. 2-Methylindole (1·3 g.) and acetophenone (3 c.c.) were treated with concentrated sulphuric acid (0·6 c.c.) with shaking. After 20 mins., excess of acetophenone was removed in a high vacuum, and the residue heated with acetic acid (15 c.c.) and aldehyde (1·5 g.) for 1 hour on the steam-bath. *[2-Methyl-3-indole]-[4-dimethylaminobenzene]-α-phenyltrimethincyanine sulphate* was purified by repeated precipitation with ether from acetic acid; it had m. p. 211° (decomp.) and gave an intense blue solution in ethanol (Found: N, 6·1; S, 7·1. $C_{26}H_{26}O_4N_2S$ requires N, 6·3; S, 6·9%). 2-Phenylindole (2 g.) and acetone (5 c.c.) were treated dropwise at 0° with concentrated sulphuric acid (0·55 c.c.). Excess of acetone was decanted, and the oily product boiled for 30 mins. with acetic acid (10 c.c.) and aldehyde (1·5 g.). The green solution was poured into dilute ammonia and the precipitate taken up in chloroform and chromatographed on alumina. *[2-Phenyl-3-indole]-[4-dimethylaminobenzene]-α-methyltrimethincyanine* was crystallised several times from chloroform–light petroleum and then had m. p. 219° (Found: C, 85·5; H, 6·3; N, 7·5. $C_{26}H_{24}N_2$ requires C, 85·7; H, 6·6; N, 7·7%). It was yellow in ethanol, becoming green in presence of acid.

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