132. *Preparation of Indole Trimethincyanines.*

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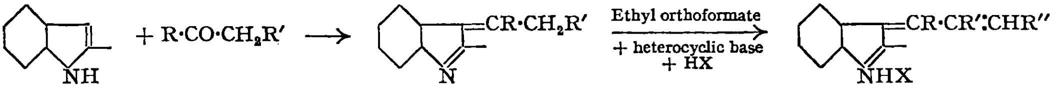
Representative indoles containing unsubstituted NH- and β-positions have been condensed with ketones and β-keto-esters to give indolylidene bases or salts thereof. Those bases or salts containing the groups $:C{\cdot}CH_2R$ (R = H, hydrocarbon residue, or CO_2Et) condense further with appropriate heterocyclic aldehydes to yield trimethincyanines.

In the preceding paper it was shown that pyrroles could, within certain limitations of substitution, be converted into polymethin dyes by reactions which involved condensation of the pyrrole with a ketone or aldehyde. It seemed that indoles capable of assuming an indolenine form might show similar reactions; the present paper records the reaction between a variety of indoles and carbonyl compounds, and the further condensation of the products to polymethin dyes.*

Aldehydes may react with two molecules of an indole containing a free β-position to give products of varied constitutions (see, for example, Freund and Lebach, *Ber.*, 1905, **38**, 2646; Fischer, *Annalen*, 1887, **242**, 372; Scholtz, *Ber.*, 1913, **46**, 1086, 2138; Burr and Gortner, *J. Amer. Chem. Soc.*, 1924, **46**, 1225), but there is apparently no record of aliphatic aldehydes reacting with indoles as in the first part of the following reaction scheme (R = H) :



(I.) (II.)

Similarly there appear to be no known reactions of ketones (R = hydrocarbon residue) of the desired type, although Scholtz (*loc. cit.*) described the condensation of 2-methylindole with ethyl acetoacetate to give the corresponding ethyl β-indolylidenebutyrate and other condensations between indoles and ketones. Consequently, although the formation of indomethenes from indoles and ethyl orthoformate is known (König, *J. pr. Chem.*, 1911, **84**, 217), it was not surprising that the method of the previous paper failed when applied to indoles in spite of the brilliant colours which were sometimes observed; the formation of indomethenes appeared to be so rapid that mixtures of dyes were formed and the isolation of the desired trimethin compounds was not accomplished.

However, it was shown that indoles carrying a free β-position condense regularly with β-keto-esters to give stable indolylidene esters or salts thereof to which constitutions of type (I) (R′ = CO_2Et) must be assigned. Crystalline salts were obtained from the following combinations : 2-methylindole and ethyl formylacetate; 7-methylindole and ethyl acetoacetate; 2-methylindole and ethyl benzoylacetate. There was good evidence that 2-phenylindole undergoes condensation but 2-phenyl-1-methylindole was unreactive. Under similar conditions indole or 2-methylindole failed to react with ethyl lævulate or ethyl acetonedicarboxylate.

Most of these condensation products gave polymethin dyes on reaction with appropriate heterocyclic aldehydes. Crystalline dyes were obtained, for example, from indolylidene esters, with limitations mentioned below, and 2-methylindole-3-aldehyde and 3-carbethoxy-4-phenyl-2-methylpyrrole-5-aldehyde. Intense colours were obtained with 1 : 3 : 3-trimethyl-2-methylindoline-ω-aldehyde, but no crystalline product was isolated. Attempted condensations with 1 : 3 : 3-trimethyl-2-anilinovinylindoline iodide and similar compounds were also unsuccessful. The constitution of the dyes so obtained is in no doubt for the following facts :

(*a*) Dye formation was independent of substitution in the 2-position of the indole nucleus and must have been due to reactivity of part of the substituent in the 3-position.

(*b*) Dye formation proceeded as easily with condensation products of ethyl benzoylacetate as with ethyl acetoacetate but failed when the indolylidene ester was derived from ethyl α-methylacetoacetate; elimination of water must take place, therefore, between the heterocyclic aldehyde and the methylene adjacent to the ester group as in (II) (R′ = CO_2Et). The deep colour and absorption measurements confirm the polymethin nature of the dyes.

These results suggested possible success by replacing the ketoesters by ketones or aldehydes. In presence of a large excess of carbonyl compound and mineral acid, β-free indoles afforded crystalline salts of bases undoubtedly of constitution (I; R = hydrocarbon residue, R′ = H or hydrocarbon residue). Compounds of this type were prepared in pure condition from 2-methylindole and acetone, methyl ethyl ketone, or *cyclo*pentanone. Where the original carbonyl compound contained the group $CO{\cdot}CH_2$, the condensation product reacted with heterocyclic aldehydes and from the deep colour of the resulting dyes it must be concluded that they also are of constitution (II) (R = a hydrocarbon residue, R′ = H or hydrocarbon residue). Paraldehyde

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* Patent protection pending.

was used with 2-methylindole, to provide a cyanine with an unsubstituted trimethin chain, though the intermediate indolenine was not isolated.

Alkylation of the nitrogen atoms is clearly desirable, but so far this has proved impossible both in the case of the dyes themselves and of the intermediates. In the case of ethyl β-2-methylindolylidenebutyrate extended efforts were made to effect quaternisation, but the ester was surprisingly resistant. It failed to react even after prolonged treatment with methyl iodide at an elevated temperature; methyl sulphate had no action at room temperature and gave only oily, apparently decomposition, products on heating. In other ways also the ester was less reactive than might have been anticipated and failed to yield the expected anilide by the usual methods from aniline in xylene, or in presence of pyridine or phosphorus oxychloride; the anilide was not obtained on heating 2-methylindole with acetoacetanilide.

EXPERIMENTAL.

3-*Indolylidene Esters.*—2-Methylindole (2 g.) in ethanol (20 c.c.) was triturated with ethyl sodioformylacetate (2 g.) and treated dropwise with concentrated hydrochloric acid (5 c.c.) at 0°. After 3 days the solution was diluted with water, and the precipitate taken up in chloroform and chromatographed on alumina. *Ethyl β-2-methyl-3-indolylidenepropionate*, recovered from the filtrate, crystallised from benzene–light petroleum in pale yellow needles, m. p. 80° (Found: N, 6·0. $C_{14}H_{15}O_2N$ requires N, 6·1%).

7-Methylindole (2 g.) in ethanol (10 c.c.) was treated with ethyl acetoacetate (5 c.c.) and concentrated hydrochloric acid (5 c.c.). Heat was evolved and after 30 mins. the crystalline deposit was collected, treated with a little aqueous ammonia, and recrystallised from ethanol. *Ethyl β-7-methyl-3-indolylidenebutyrate* (yield, 1·5 g.) formed needles, m. p. 188°, which became red in the air (Found: C, 74·3; H, 6·8. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0%).

Ethyl β-phenyl-β-2-methyl-3-indolylidenepropionate was prepared similarly from 2-methylindole (2 g.), ethyl benzoylacetate (5 c.c.), ethanol (10 c.c.), and concentrated hydrochloric acid (5 c.c.). The crude product (2·5 g.) was collected after 3 days and repeatedly crystallised from ethanol to give pale yellow needles, m. p. 143° (Found: N, 4·7. $C_{20}H_{19}O_2N$ requires N, 4·6%).

Ethyl β-3-indolylidenebutyrate, prepared similarly, crystallised from ethanol in needles, m. p. 180° (decomp.) (Found: N, 6·2. $C_{14}H_{15}O_2N$ requires N, 6·1%).

3-*Alkylideneindoles.*—2-Methylindole (1·3 g.) in acetone (5 c.c.) was treated at 0° with concentrated sulphuric acid (0·55 c.c.) with vigorous shaking. Heat was evolved and, on cooling, the thick, bright yellow salt was collected and crystallised from acetic acid. 2-*Methyl*-3-iso*propylideneindolenine sulphate* was obtained as yellow needles, m. p. 165° (decomp.), which slowly darkened in moist air (Found: N, 5·2; S, 11·7. $C_{12}H_{15}O_4NS$ requires N, 5·3; S, 11·9%). Similarly prepared were: 2-*Methyl*-3-iso*butylideneindolenine sulphate*, separating in yellow needles, m. p. 89°, from acetic acid (Found: N, 4·9; S, 11·1. $C_{13}H_{17}O_4NS$ requires N, 5·0; S, 11·4%), and 2-*methyl*-3-cyclo*pentylideneindolenine sulphate*, yellow needles, m. p. 153° (decomp.) after previous darkening, from acetic acid (Found: N, 4·9; S, 11·0. $C_{14}H_{17}O_4NS$ requires N, 4·75; S, 10·85%).

Dyes derived from Indolenine Esters.—A solution of ethyl 2-methyl-3-indolylidenebutyrate (1·2 g.) and 3-carbethoxy-4-phenyl-2-methylpyrrole-5-aldehyde (1·3 g.) in acetic acid (15 c.c.) was heated to boiling, and 50% hydrobromic acid in acetic acid (0·8 c.c.) added. After the vigorous reaction had abated, the solution was poured into excess of dilute aqueous ammonia, and the pale brown solid collected. [2-*Methyl*-3-*indole*]-[4-*carbethoxy*-3-*phenyl*-5-*methyl*-2-*pyrrole*]-*β-carbethoxy-α-methyltrimethincyanine* separated from light petroleum as a yellow microcrystalline solid, m. p. 154° (Found: C, 75·1; H, 6·3. $C_{30}H_{30}O_4N_2$ requires C, 74·8; H, 6·2%). It was yellow in ethanol, becoming deep magenta on addition of acid. Light absorption (ethanol–hydrogen chloride): max. 5850 A.

The same indolylidene ester was condensed similarly with 2-methylindole-3-aldehyde. When the reaction mixture was kept overnight, *bis*-[2-*methyl*-3-*indole*]-*β-carbethoxy-α-methyltrimethincyanine bromide* separated in copper-coloured needles, m. p. 202° (decomp.) after recrystallisation from acetic acid (Found: N, 6·2; Br, 16·8. $C_{25}H_{25}O_2N_2Br$ requires N, 6·1; Br, 17·2%). The dye was deep purple in ethanol and the colour was reversibly discharged by alkali. Light absorption (ethanol): max. 5780 A. *Bis*-[2-*methyl*-3-*indole*]-*β-carbethoxy-α-phenyltrimethincyanine* was obtained similarly. It crystallised on cooling from the purple-red reaction medium and, recrystallised from acetic acid, formed steel-blue needles with a coppery reflex, m. p. 230° (Found: C, 67·9; H, 5·0. $C_{30}H_{17}O_2N_2Br$ requires C, 68·2; H, 5·1%). Light absorption, max. 5890 A.

Dyes derived from Alkylideneindolenines.—A mixture of 2-methylindole-3-aldehyde (0·8 g.), 2-methyl-3-*iso*propylideneindolenine sulphate (1·44 g.), and acetic acid (10 c.c) was refluxed for 30 mins. and cooled overnight. The long green needles were collected and recrystallised from acetic acid. *Bis*-[2-*methyl*-3-*indole*]-*α-methyltrimethincyanine sulphate* had m. p. 168° (decomp.) and gave a purple-red solution in ethanol (Found: N, 6·7; S, 7·8. $C_{22}H_{22}O_4N_2S$ requires N, 6·8; S, 7·8%). Light absorption (ethanol): max. 5790 A.

Indole (1·17 g.) in acetone (3 c.c.) was treated with concentrated sulphuric acid (0·55 c.c.). After the reaction, the excess of acetone was removed in a vacuum, 2-methylindole-3-aldehyde (1·6 g.) and acetic acid (10 c.c.) added, and the whole warmed on the water-bath for 30 mins. The solution was poured into aqueous potassium iodide, and the dye purified by repeated precipitation from acetic acid with ether. 3-*Indole*-3′-(2′-*methylindole*)-*α-methyltrimethincyanine iodide* formed a dark microcrystalline powder, m. p. 122° (decomp.), giving a deep red solution in ethanol (Found: I, 29·4. $C_{21}H_{19}N_{20}I$ requires I, 29·8%). Light absorption (ethanol): max. 5810 A.

2-Methylindole (1·3 g.) in paraldehyde (5 c.c.) was cooled with solid carbon dioxide until the paraldehyde was just solidifying, and concentrated sulphuric acid (0·55 c.c.) added slowly with shaking. The yellow solid was quickly collected, dissolved in acetic acid (15 c.c.), and treated with 2-methylindole-3-aldehyde (1·6 g.), and the whole boiled for 1 hr. On cooling, the crystals were collected and recrystallised from acetic acid. *Bis*-3-[2-*methylindole*]*trimethincyanine sulphate* decomposed above 300° (Found: N, 7·2; S, 7·9. $C_{21}H_{20}O_4N_2S$ requires N, 7·1; S, 8·1%). Light absorption (ethanol): max. 5550 A.

2-Methyl-3-*cyclo*pentylideneindolenine sulphate (1·5 g.) was heated on the water-bath for 30 mins. in acetic acid (10 c.c.) containing 3-carbethoxy-4-phenyl-2-methylpyrrole-5-aldehyde (1·3 g.). The purple-blue solution was diluted with ether, and the dye purified by precipitation with ether from acetic acid. [2-*Methyl*-3-*indole*]-[4-*carbethoxy*-3-*phenyl*-5-*methyl*-2-*pyrrole*]-*αβ-trimethylenetrimethincyanine sulphate* decomposed above 300° (Found: N, 5·6; S, 6·0. $C_{29}H_{30}O_6N_2S$ requires N, 5·3; S, 6·0%). Light absorption (ethanol): max. 6960 A.

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