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DYES CONTAINING THE INDOLE RING—II

TRINUCLEAR TRIMETHINCYANINES

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Abstract—Representative indoles containing a free β-position have been condensed with aliphatic acid chlorides or acid anhydrides and the products identified as substituted di-indolylmethenes. A substituted unsymmetrical di-indolylmethene has been synthesized by the condensation of 2-methyl-3-acetylindole with 2-phenylindole in the presence of phosphorus oxychloride. Some of these methenes have been shown to contain a reactive methylene group and have been condensed with both homocyclic and heterocyclic aldehydes to yield intensely coloured trinuclear dyes.

In view of the demonstration of the reactivity of the α-methyl group in α-methyl-trimethincyanines derived from the indole nucleus,[1] the possibility of preparing trinuclear indole trimethincyanines by the condensation of α-methyl-di-indolylmethenes (I) with heterocyclic aldehydes was investigated. Such di-indolylmethenes can be considered as cyanines but since the majority of them have already been described as methenes uniformity of nomenclature has been sacrificed in order to avoid confusion.

THE simplest route to α-methyl-di-indolylmethenes I appeared to be interaction of β-free indoles with 3-acetylindoles II. 2-Methylindole was refluxed with varying amounts of acetic anhydride and sodium acetate for periods up to 7 hr without noticeable conversion of the indole. In the search for a more vigorous reagent 2-methylindole was warmed with acetyl chloride. On raising the temperature of the mixture to 100°, a vigorous reaction occurred, there was a copious evolution of hydrogen chloride and the mixture became bright scarlet in colour. The dye was isolated by precipitation from glacial acetic acid solution with water, in the form of a brown solid soluble in polar solvents. The solutions faded to a yellow colour on addition of alkalies or ammonia but the original red colour was restored by the addition of acid. This behaviour resembled that of the di-indolylmethenes first named "Rosindoles" by Fischer.[2] The substituted di-indolylmethenes have been prepared by the oxidation of the analogous di-indolylmethanes (III) formed by the interaction of β-free indoles with aldehydes.[3] 2-Methylindole was condensed with acetaldehyde in alcohol solution to yield α,2,2′-trimethyl-di-indolylmethane. Upon oxidation with ferric chloride a red dye was produced identical with that formed by the interaction of 2-methylindole and acetyl chloride, which is identified as α,2,2′-trimethyl-di-indolylmethene hydrochloride. Since this constituted the desired intermediate it was refluxed with *p* dimethylaminobenzaldehyde in glacial acetic acid. The original red colour of the solution changed gradually to an intense blue and on addition of ether a black solid was precipitated having the characteristics of a dye of the "Ehrlich" type, being reversibly decolourized by both acids and alkalies. Other dyes were prepared from 2-methyl-3-carbethoxy-4-phenyl-5-pyrrole aldehyde and 2-methyl-3-indole aldehyde.

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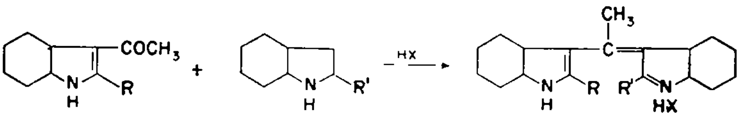
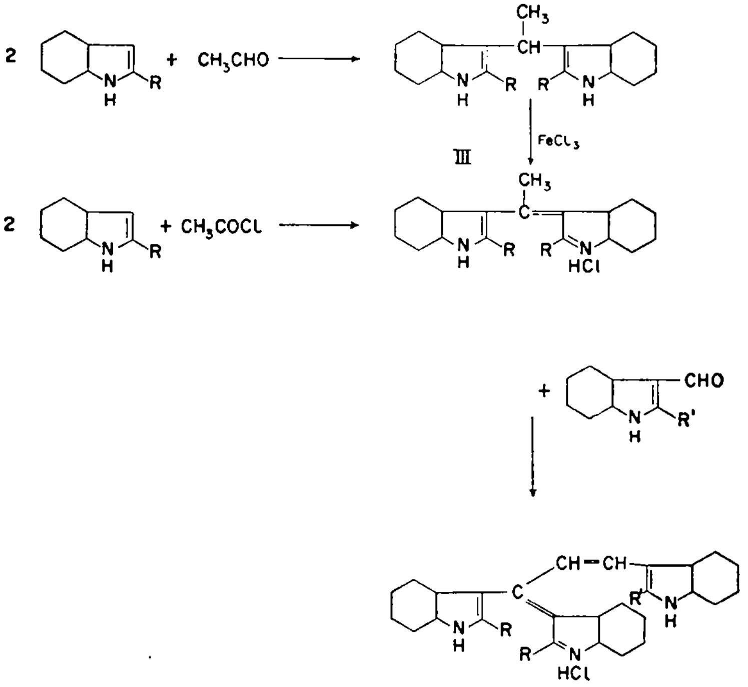
[1] Part 1: J. R. Majer, *Tetrahedron* **9**, 106 (1960).
[2] E. Fischer and P. Wagner, *Ber. Dtsch. Chem. Ges.* **20**, 815 (1887).
[3] M. Freund and G. Lebach, *Ber. Dtsch. Chem. Ges.* 36, 308 (1903).



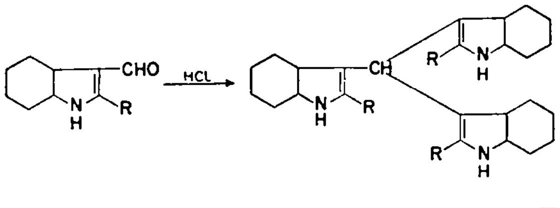
I

II



III

IV



V

Analysis showed all three to be trinuclear dyes formed by the elimination of water between the reactants. Despite the strong presumption that the reaction took place with the α-methyl group alone no direct evidence was available and therefore 2,2′-dimethyl-di-indolylmethene hydrochloride was prepared by the interaction of 2-methylindole, ethyl orthoformate and hydrochloric acid. It showed no reactivity whatever towards aldehydes. The trinuclear dye prepared by the reaction of 2-methyl-3-indole aldehyde and α,2,2′-trimethyl-di-indolylmethene hydrochloride (IV) has a certain formal resemblance to that prepared by Ellinger[4] from 2-methylindole and 2-methyl-3-indole aldehyde (V). Propionyl chloride and phenacetyl chloride were not

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[4] A. Ellinger, H., 1911, 71, 13.

as reactive as acetyl chloride and substantial yields were only obtained by prolonged refluxing in glacial acetic acid. Succinyl chloride on the other hand was more reactive and the condensation proceeded so vigorously that small particles of dye were carried up with the evolved hydrogen chloride which became tinged pink.

2-Phenylindole was less reactive than 2-methylindole and was refluxed for several hours with acetyl chloride in glacial acetic acid solution before reaction was complete.

α-Methyl-di-indolylmethene hydrochloride proved surprisingly difficult to synthesize; indole reacted vigorously at room temperature with acetyl chloride but the product was a pink glass which showed no further sign of reactivity and was probably polymeric in nature. Diluents such as acetic acid or acetic anhydride moderated the reaction but only unreactive tars were produced. König[5] has described the preparation of di-indolylmethenes by the interaction of indoles and ethyl orthoformate in ethanol solution in the presence of perchloric acid, but no crystalline products were isolated when ethyl orthoacetate was substituted or the perchloric acid replaced by other mineral acids. The methene was finally prepared by adding hydrobromic acid to a boiling solution of indole in acetic anhydride; it was precipitated from the resulting orange solution as a brown solid by the addition of ether. It was less reactive than any of the other methenes and the only trinuclear dye which could be isolated was prepared by heating it with *p* dimethylaminobenzaldehyde in acetic anhydride solution. There was a surprising variation in stability in the trinuclear dyes derived from *p* dimethylaminobenzaldehyde and the methenes. Those prepared from α-ethyl and α-benzyl 2,2′-dimethyl-di-indolylmethenes were rapidly destroyed in hot acetic anhydride, while those derived from α,2,2′-trimethyl-indolyl and α,α′-ethylene-bis-3-(2,2′-dimethyl-di-indolylmethene hydrochloride) were quite stable. When dyes were prepared from indole aldehydes as in the case of that obtained from 2-methyl-3-indole aldehyde and α-methyl-2,2′-diphenyl-di-indolylmethene hydrochloride it was important to free the methene from traces of uncombined hydrogen chloride for it has been shown that indole-3-aldehydes react in the presence of mineral acids to form the di-indolylmethenes (formerly called "uroroseins") by the elimination of formic acid.[6]

The synthesis of unsymmetrical di-indolylmethenes could only be achieved by the interaction of indole-3-methyl ketones and indoles unsubstituted in the 3-position. 2-Methyl-3-acetyl indole was prepared by the method of Salway.[7] A 30 per cent yield of 2-methyl-3-acetyl indole was obtained by treating 2-methylindole magnesium bromide with acetyl chloride in ether. The ketone was very unreactive and did not form methenes with indoles by treatment with mineral acids in acetic acid–acetic anhydride mixture. It condensed with 2-phenylindole in phosphorus oxychloride solution from which it was isolated as a red powder. The resulting unsymmetrical methene reacted readily in hot acetic acid–acetic anhydride mixture to yield trinuclear dyes with *p*-dimethylaminobenzaldehyde and 2-methyl-3-indole aldehyde.

EXPERIMENTAL

Di-indolylmethenes

2-Methylindole (2·6 g) and ethyl orthoformate (1·6 g) were dissolved in hot glacial acetic acid (10 ml) and 50% hydrobromic acid in glacial acetic acid (1·6 ml) added. A vigorous reaction took

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[5] W. König, *J. Prakt. Chem.* **84**, 217 (1911).

[6] J. Harley-Mason and J. D. Bu'lock, *Biochem. J.* **51**, 430 (1952).

[7] A. H. Salway, *J. Chem. Soc.* 384 (1913).

place and the solution became bright orange. After 3 min the solution was cooled and diluted with water to precipitate the 2,2′-dimethyl-di-indolylmethene hydrobromide as a brown solid. On crystallization from methanol it was obtained as brown needles m.p. 236°.

A solution of indole (3·3 g) in acetic anhydride (5 ml) was boiled and hydrobromic acid (50%) in glacial acetic acid (1·6 ml) added dropwise. On cooling α-methyl-di-indolylmethene hydrobromide (2·1 g) was precipitated as a brown powder by addition of ether. It was obtained from acetic acid–ether as a brown powder m.p. 153° (Found: C, 63·5, H, 4·5, Br, 23·3; $C_{18}H_{15}N_2Br$ requires: C, 63·65, H, 4·42, Br, 23·6%).

2-Methylindole (13 g) and acetyl chloride (3·7 ml) were heated at 100° for 4 hr and the mixture poured into water. The precipitated solid was crystallized from acetic acid–ether to yield α,2,2′-trimethyl-di-indolylmethene hydrochloride (13 g) as a brown powder m.p. 118° (Found: C, 74·2, H, 5·8, Cl, 11·0; $C_{20}H_{19}N_2Cl$ requires: C, 74·3, H, 5·88, Cl, 11·0%).

2-Methylindole (10 g) paraldehyde (5 g) and zinc chloride (1·0 g) were heated at 100° for 3 hr. The product was crystallized from ethanol to yield α,2,2′-trimethyl-di-indolylmethane (5·0 g) as colourless prisms m.p. 191°.

Oxidation. The methane (5 g) was dissolved in hot glacial acetic acid (20 ml) and ferric chloride (2·0 g) added. After refluxing for 10 min the bright red solution was diluted with hydrochloric acid and the precipitated solid ground with ammonia and crystallized from benzene to yield α,2,2′-trimethyl -di-indolylmethene as light brown needles m.p. 202° (Angeli and Marchetti R.A.L. (5) 16, II, 794 give m.p. 203°). The methene was dissolved in dry benzene and dry hydrogen chloride passed through the solution. The solid precipitated was crystallized from acetic acid–ether to yield α,2,2′-trimethyl-di-indolylmethene hydrochloride as a brown powder m.p. 119°.

2-Methylindole (13 g) and succinyl chloride (4 ml) were heated at 100° for 3 hr. The red tarry residue was treated with acetone and water and crystallized from acetic acid–ether to yield α,α′-ethylene-bis-3-(2,2′-dimethyl-di-indolylmethene hydrochloride) (12 g) as a light red powder m.p. 106° (Found: C, 74·6, H, 5·4, Cl, 11·2; $C_{40}H_{36}N_4Cl_2$ requires: C, 74·65, H, 5·6, Cl, 11·05%).

2-Methylindole (13 g) and propionyl chloride (4.6 g) were heated at 100° for 7 hr, dissolved in glacial acetic acid (50 ml) and refluxed for 4 hr. Addition of ether precipitated a black oil which solidified on grinding with water. Crystallization from acetic acid–ether gave α-ethyl-2,2′-dimethyl-methene hydrochloride as a black powder (15·3 g) m.p. 134° (Found: C, 75·0, H, 6·3, Cl, 10·4; $C_{21}H_{21}N_2Cl$ requires: C, 74·77, H, 6·23, Cl, 10·55%).

2-Methylindole (13 g) and phenacetyl chloride (7·7 g) were heated at 100° for 7 hr, dissolved in glacial acetic acid and refluxed for 4 hr. Addition of water precipitated a red oil which solidified on treatment with acetone and ether. Repeated crystallization from acetone–ether gave α-benzyl-2 2′-dimethyl-di-indolylmethene hydrochloride (6·2 g) as a brown powder m.p. 150° (Found: C, 78·1, H, 5·6, Cl, 9·0; $C_{26}H_{23}N_2Cl$ requires: C, 78·2, H, 5·76, Cl, 8·91%).

2-Phenylindole (4 g) and acetyl chloride (1 ml) were refluxed in glacial acetic acid (15 ml) for 4 hr and diluted with ether. The precipitate was repeatedly recrystallized from acetic acid–ether to yield α-methyl-2,2′-diphenyl-di-indolylmethene hydrochloride (4·2 g) as a black powder m.p. 192° (Found: Cl, 7·8, $C_{30}H_{23}N_2Cl$ requires: Cl, 7·95%).

2-Methyl-3-acetyl indole (3·66 g) and 2-phenylindole (3·86 g) were added in portions to phosphorus oxychloride (10 ml). The mixture became hot, evolving hydrogen chloride and assuming a cherry red colour. The mixture was left for 24 hr and poured onto cracked ice. The precipitate was crystallized from acetic acid–ether to yield α,2-dimethyl-2′-phenyl-di-indolylmethene hydrochloride (7 g) as pinkish needles m.p. 112° (Found: C, 77·8, H, 5·3, Cl, 9·1; $C_{25}H_{21}N_2Cl$ requires: C, 77·7, H, 5·4, Cl, 9·23%).

Polynuclear dyes

Indole (1·15 g) was dissolved in hot acetic anhydride (5 ml) and 50% hydrobromic acid in glacial acetic acid (0.81 ml) added. After the reaction had subsided the solution was refluxed for 2 min and *p*-dimethylaminobenzaldehyde (0·75 g) added. As the solution was refluxed for a further 3 min the orange colour gradually changed to a deep green. Addition of ether precipitated a green solid which was crystallized from methanol–ether to yield 3-indole-(4-dimethylaminobenzene)-3′-indole trimethincyanine bromide (1·5 g) as green needles m.p. 108° (Found: C, 69·0, H, 5·0, Br, 17.0; $C_{27}H_{24}N_3Br$ requires: C, 68·9, N, 5·1, Br, 17·0%).

α,2,2′-Trimethyl-di-indolylmethene hydrochloride (1·5 g) and 2-methyl-3-carbethoxy-4-phenyl-5-pyrrole aldehyde (1·3 g) were refluxed in glacial acetic acid (15 ml) for 1 hr when crystals deposited out of the purple solution. On crystallization from glacial acetic acid 3-(2-methylindole)-2′-(3-phenyl-4-carbethoxy-5-methylpyrrole)-α-3″-(2-methylindole) trimethincyanine chloride (1·1 g) was obtained as brassy octahedra m.p. 294° (Found: C, 75, H, 5·7, Cl, 6·5, $C_{35}H_{32}O_2N_3Cl$ requires: C, 74·73, H, 5·65, Cl, 6·3%).

α,2,2′-Trimethyl-di-indolylmethene hydrochloride (1·5 g) and 2-methyl-3-indole aldehyde (0·8 g) were refluxed in glacial acetic acid (15 ml) for 1 hr and the solution diluted with ether when a black solid was precipitated. On crystallization from acetic acid–ether, bis-3-(2-methylindole)-α-3′-(2-methylindole) trimethincyanine chloride (1·9 g) was obtained as black needles m.p. 247° (Found: C, 77·2, H, 5·7, Cl, 7·5; $C_{30}H_{26}N_3Cl$ requires: C, 77·11, N, 5·6, Cl, 7·66%).

α-Ethyl-2,2′-dimethyl-di-indolylmethene hydrochloride (1·8 g) and *p*-dimethylaminobenzaldehyde (0·75 g) were refluxed in glacial acetic acid–acetic anhydride mixture (15 ml) with vigorous stirring for 5 min and diluted with ether. The precipitate was crystallized from acetic acid–ether to give 3-(2-methylindole)-1′-(4-dimethylaminobenzene)-α-3″-(2-methylindole)-β-methyl-trimethincyanine chloride (2·2 g) as dark blue needles. m.p. 300° (Found: C, 76·7, H, 6·2, Cl, 7·6, $C_{30}H_{30}N_3Cl$ requires C, 76·92, H, 6·41, Cl, 7·6%).

α,2,2′-Trimethyl-di-indolylmethene hydrochloride (1·5 g) and *p*-dimethylaminobenzaldehyde (0·75 g) were refluxed in glacial acetic acid (15 ml) for 30 min and the blue solution diluted with ether. The precipitate was crystallized from acetic acid–ether to yield 3-(2-methylindole)-1′-(4-dimethylaminobenzene)-α-3″-(2-methylindole) trimethincyanine chloride (2·0 g) as copper needles m.p. 221° (Found: C, 76·5, H, 6·0, Cl, 7·7; $C_{29}H_{28}N_3Cl$ requires: C, 76·65, H, 6·15, Cl, 7·83%).

α-Methyl-2,2′-diphenyl-di-indolylmethene hydrochloride (1·1 g) and 2-methyl-3-indole aldehyde (0·4 g) were refluxed in glacial acetic acid (15 ml) for 2 hr. On cooling solid was precipitated from the blue solution. On crystallization from glacial acetic acid 3-(2 methylindole)-3′-(2-phenylindole)-α-3″-(2-phenylindole) trimethincyanine chloride (0·5 g) was obtained as blue needles m.p. 258°. (Found: C, 81·4, H, 5·0, Cl, 6·0; $C_{40}H_{30}N_3Cl$ requires: C, 81·63, H, 5·1, Cl, 6·04%).

2,2′-Dimethyl-α-benzyl-di-indolylmethene hydrochloride (3·77 g) and *p*-dimethylaminobenzaldehyde (1·5 g) were refluxed in glacial acetic acid (30 ml) for 30 min and the blue solution diluted with ether. The precipitate was crystallized from acetic acid–ether to yield 3-(2-methylindole)-1′-(4-dimethylaminobenzene)-α-3″-(2-methylindole)-β-phenyl-trimethincyanine chloride (4·2 g) as black crystals m.p. 226°. (Found: C, 79·5, H, 6·3, Cl, 6·6; $C_{35}H_{32}N_3Cl$ requires: C, 79·24, H, 6.04, Cl, 6.7%).

α,α′-ethylene-bis-(2,2′-dimethyl-di-indolylmethene hydrochloride) (3·2 g) and *p*-dimethylaminobenzaldehyde (1·5 g) were refluxed in 1 : 1 glacial acetic acid–acetic anhydride mixtuie (30 ml) for 5 min and the ink-blue solution diluted with ether. The precipitate was crystallized from acetic acid–ether to yield β,β′-bis-[3-(2-methylindole)-1′-(4-dimethylaminobenzene)-α-3″-(2-methylindole) trimethincyanine chloride] (3·5 g) as a dark blue powder m.p. 300°. (Found: C, 76·6, H, 6.3, Cl, 7·7; $C_{58}H_{54}N_6Cl_2$ requires: C, 76·9, H, 5·96, Cl, 7·83%).

α,2-Dimethyl-2′-phenyl-di-indolylmethene hydrochloride (2·4 g) and 2-methyl-3-indole aldehyde (1·0 g) were refluxed in glacial acetic acid–acetic anhydride mixture (20 ml) for 5 min and cooled. The brown solid which separated was crystallized from glacial acetic acid to yield bis-3-(2-methylindole)-α-3′-(2-phenylindole) trimethincyanine hydrochloride (0·5 g) as copper octahedra m.p. 198°. (Found: C, 79·6, H, 5·1, Cl, 6·6, $C_{35}H_{28}N_3Cl$ requires: C, 79·85, H, 5·32, Cl, 6·75%).

α,2-Dimethyl-2′-phenyl-di-indolylmethene hydrochloride (1·9 g) and *p*-dimethylaminobenzaldehyde (0·75 g) were refluxed in 1 : 1 glacial acetic acid–acetic anhydride mixture (20 ml) for 3 min and cooled. The solid which separated was crystallized from glacial acetic acid to yield 3-(2-phenylindole)-1′-(4-dimethylaminobenzene)-α-3″-(2-methylindole) trimethincyanine chloride as copper brown needles, m.p. 238°. (Found: C, 79·2, H, 5·9, Cl, 6·7, $C_{34}H_{30}N_3Cl$ requires: C, 79·07, H, 5·81, Cl, 6·88%).