Indoles. Part I. The Formylation of Indole and Some Reactions of 3-Formylindole.

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The yield of 3-formylindole by the formylation of indole by phosphorus oxychloride in excess of dimethylformamide has been raised to 95·5%, and the mechanism of this reaction studied. When pyrrole is formylated in this way an 83% yield of 2-formylpyrrole is obtained. A new method for the synthesis of urorosein salts is described.

Tyson and Shaw (*J. Amer. Chem. Soc.*, 1952, **74**, 2273) describe the conversion of indole into 3-formylindole in 72% yield, by use of a mixture of phosphorus oxychloride and dimethylformamide. By means of some simplifications in the procedure, a 95·5% yield of very pure product has now been obtained. The mechanism of this reaction is of interest, and has been studied in some detail.

Only one mol. of phosphorus oxychloride is essential for the reaction, but an excess of dimethylformamide is necessary simply to keep the reaction mixture reasonably fluid. In one experiment in which the ratio $POCl_3$: indole was 1 : 4, about 70% of the indole was recovered and 18% of pure 3-formyl derivative was isolated, the remaining 12% consisting of a mixture from which an unidentified product, m. p. 249—253°, was isolated. This experiment clearly indicates the necessity of a phosphorus oxychloride : indole ratio of 1 : 1; it is noteworthy that phosphorus oxychloride and dimethylformamide form a 1 : 1 complex, which begins to dissociate at about 100°/10 mm.

The clear viscous reaction mixture obtained by the addition of 1 mol. of indole to phosphorus oxychloride in excess of dimethylformamide, on being diluted with more solvent, shows two absorption maxima: 345 mμ, log ε 4·19; 276 mμ, log ε 3·96 (below 276 mμ absorption by solvent begins to interfere). Very similar absorption is shown by an aqueous solution of the reaction mixture: 337·5 mμ, log ε 4·21; 274 mμ, log ε 3·93; 268 mμ, log ε 3·95; 253 mμ, log ε 4·04; 244 mμ, log ε 4·03, and this is unchanged on careful neutralisation of the aqueous solution. The absorption changes, however, in alkaline solution to 324·5 mμ, log ε 4·09; 265 mμ, log ε 4·19, which is practically identical with that of an alkaline solution of 3-formylindole (Fig. 1, curve *b*).

The reaction intermediate is thus not decomposed by water; it is relatively stable in acid or neutral solution; in alkaline solution it is hydrolysed to 3-formylindole.

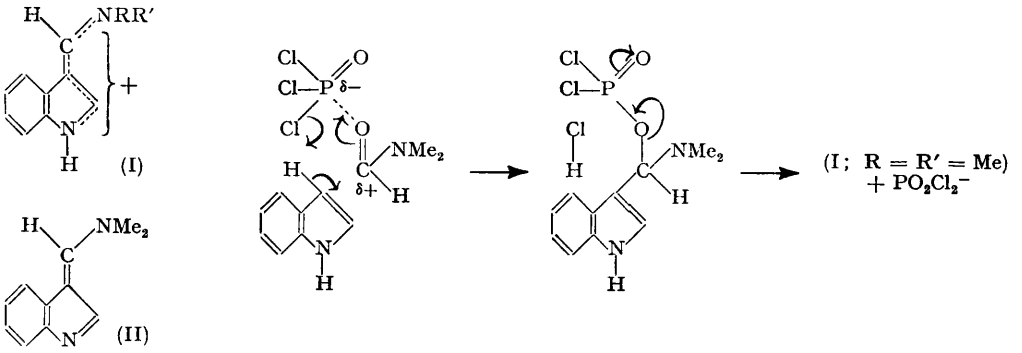
The hypothesis that the intermediate might be the mesomeric cation (I; R = R′ = Me) was soon confirmed. The aqueous neutralised solution was basified at −5° and rapidly extracted with chloroform: this yielded a crystalline base (absorption spectrum, Fig. 3, curve *a*), the absorption spectrum of the stable hydrochloride of which (Fig. 2, curve *a*) was identical with that of the reaction intermediate. Structure (II), 3-dimethylaminomethyleneindolenine, has been assigned to the base on the basis of its quantitative hydrolysis in boiling water to 3-formylindole and dimethylamine, its reduction to gramine by means of lithium aluminium hydride in ether, and the combustion analysis.

With (I; R = R′ = Me) as the structure of the reaction intermediate, the most plausible mechanism for the formylation seems to be that shown below. The $PO_2Cl_2^-$ ion is hydrolysed in water to orthophosphoric and hydrochloric acid.

The alkaline hydrolysis of (I; R = R′ = Me) almost certainly involves attack at the exocyclic carbon atom by hydroxyl ion to yield the unstable aldehyde ammonia, which then breaks down to dimethylamine and 3-formylindole.

That the hydrogen chloride formed in the formylation does not participate in the reaction was demonstrated when a 1 : 1 mixture of dry hydrogen chloride and indole in excess of dimethylformamide was kept at 70° for 15 min.; 83% of the indole was recovered and 3-formylindole was not detected. This also means that protonated solvent does not act as a formylating agent.

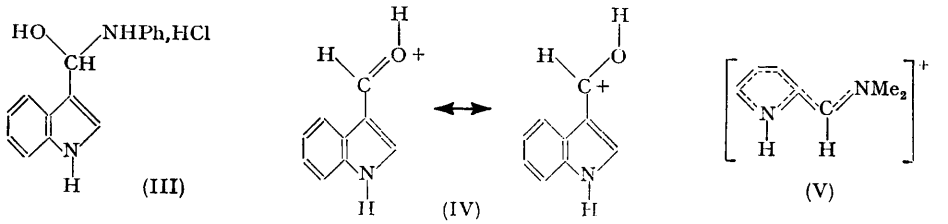
Thionyl chloride in excess of dimethylformamide also reacts very vigorously with indole, but the reaction is not clean even at 25—30°: the absorption spectrum of the filtered aqueous solution indicates only a 45—50% yield of (I; R = R′ = Me).



An attempted synthesis of the mesomeric cation (I; R = R′ = Me) by methylation of 3-methyliminomethylindole was unsuccesful. 3-Formylindole reacts very readily with aqueous methylamine, to give an amorphous base which does, however, yield a stable crystalline hydrochloride the absorption spectrum of which (Fig. 2, *b*) is very similar in type to that of (I; R = R′ = Me). Methylation of the base with methyl iodide or methyl sulphate, in the presence or absence of solvent, failed to yield a homogeneous crystalline product.

Majima and Kotake (*Ber.*, 1925, **58**, 2037) reported that interaction of 3-formylindole and aniline in the presence of hydrochloric acid gave a yellow compound, which they considered to be (III), converted by cold alkali into 3-phenyliminoindole. These two compounds have been prepared by a modified procedure, and there can be little doubt that the salt has the cation (I; R = H, R′ = Ph) (for absorption spectrum, measured in dioxan, see Fig. 2, *c*).

The salt is rapidly hydrolysed in water or alcohol to 3-formylindole and aniline hydrochloride, the aqueous solution becoming colourless in less than one minute. This ease of hydrolysis is to be contrasted with the stability of aqueous solutions of (I; R = R′ = Me) and (I; R = H, R′ = Me).



Majima and Kotake (*loc. cit.*) gave the red needles, formed when the yellow hydrochloride is warmed with hydrochloric acid, the molecular formula $C_{15}H_{17}O_2N_2Cl$, but no structure was proposed. This compound is obviously urorosein chloride, which is formed by the action of hydrochloric acid on 3-formylindole derived by hydrolysis of (I; R = H, R′ = Ph) (cf. Harley-Mason and Bu'Lock, *Biochem. J.*, 1952, **51**, 430); Majima and Kotake's analytical data are more in accord with this formulation (Found : N, 10·1; Cl, 12·3. Calc. for $C_{17}H_{13}N_2Cl$: N, 10·1; Cl, 12·6%).

Urorosein perchlorate can be very conveniently prepared in practically quantitative yield by the addition of perchloric acid to an equimolar mixture of 3-formylindole and indole in methanol. The mechanism of this reaction, which is catalysed by acid, must involve electrophilic substitution of the indole molecule at the reactive position 3 by protonated 3-formylindole (IV).

When pyrrole is treated with one mol. of $POCl_3$ in excess of dimethylformamide, an

83% yield of 2-formylpyrrole can be isolated. This represents a considerable improvement on the original method (Bamberger and Djierdjian, *Ber.*, 1900, **33**, 536) and on the reaction between pyrrylmagnesium halide and formic ester, which gave 35—40% yields (cf. Potokhin, *J. Russ. Phys. Chem. Soc.*, 1927, **59**, 76).

That the mechanism of this reaction is the same as that of the formylation of indole is demonstrated by the absorption spectrum of the reaction mixture in water (Fig. 4, curve *a*) which is very similar to that of 2-methyliminomethylpyrrole hydrochloride (Fig. 4, curve *b*) and therefore almost certainly contains the cation (V). 2-Methyliminoethylpyrrole

FIG. 1.

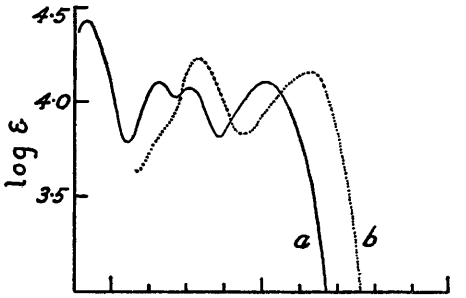
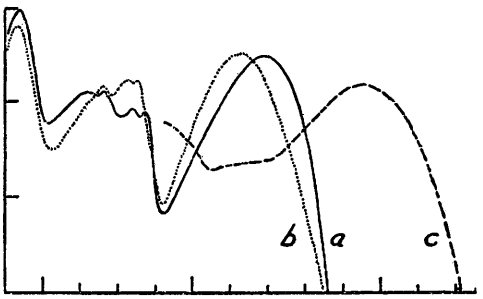


FIG. 2.



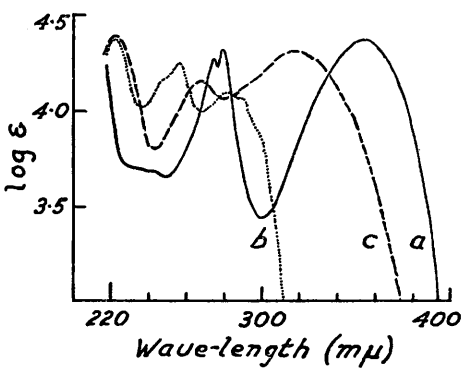


FIG. 3.

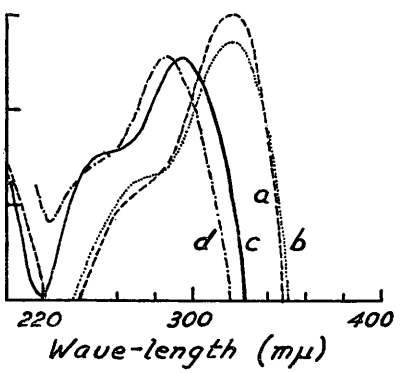


FIG. 4.

FIG. 1. *a*, 3-*Formylindole in water; b, in aqueous alkali.*

FIG. 2. *a*, 3-*Dimethylaminomethyleneindolenine* (II) *hydrochloride in water; b*, 3-*methyliminomethylindole hydrochloride in water; c*, (I; R = H, R′ = Ph) *hydrochloride in dioxan.*

FIG. 3. *a*, 3-*Dimethylaminomethyleneindolenine* (II) *in ether; b*, 3-*methyliminomethylindole in ether; c*, 3-*phenyliminomethylindole in ether.*

FIG. 4. *a*, 2-*Dimethylaminomethylene*iso*pyrrole hydrochloride in water; b*, 2-*methyliminomethylpyrrole hydrochloride in water; c*, 2-*formylpyrrole in water; d*, 2-*methyliminomethylpyrrole in* 95% *ethanol.*

was prepared by Emmert, Diehl, and Gollwitzer (*Ber.*, 1929, **62**, 1737) by the action of methylamine on 2-formylpyrrole. Attempts to isolate 2-dimethylaminomethylenepyrrolenine have so far failed. Methylation of 2-methyliminomethylpyrrole failed to yield a homogeneous product.

EXPERIMENTAL

3-*Formylindole*.—Phosphorus oxychloride (5·0 c.c., 0·055 mol.; freshly distilled) was added dropwise with stirring to dimethylformamide (16 g., 0·22 mol.) in a flask protected from atmospheric moisture, the temperature being kept at 10—20°. Indole (5·85 g., 0·050 mol.) in dimethylformamide (4 g.) was then slowly added with stirring, the temperature of the mixture being kept at 20—30°. The mixture was kept at 35° for 45 min., then poured on crushed ice, and the clear solution treated at 20—30° with sodium hydroxide (9·5 g., 0·24 mol.) in water (50 c.c.), at such a rate that the solution was always acidic, until about three-

quarters of the alkali had been added. The last quarter was added all at once, and the solution quickly boiled for 1 min. The white crystals were filtered off, carefully washed with water (5 × 25 c.c.), and dried to a constant weight at 100°/10 mm. The off-white product (6·93 g., 95·5%) had m. p. 197—199°.

3-*Dimethylaminomethyleneindolenine*.—The pale red aqueous reaction mixture, obtained as above (half quantities), was cooled to −5° and very slowly, with efficient stirring, treated with aqueous sodium hydroxide (1·3 equiv.) at −5°. The still acidic solution was left at about 10° for 1 hr., then more alkali (1·6 equiv.) slowly added with stirring at −5°. The weakly acidic solution was well shaken with pre-cooled chloroform (75 c.c.), rapidly treated with pre-cooled aqueous sodium hydroxide (1·15 equiv.), and the whole shaken for 20 sec. The chloroform layer was run on to anhydrous sodium sulphate and then filtered and the chloroform evaporated under reduced pressure. The residue deposited the crystalline *base*, which was filtered off, washed with a little dimethylformamide, and immediately dried at 37°/0·01 mm. The pale yellow plates (2·74 g., 63%) had m. p. 152—154° (Found: C, 76·45; H, 6·3; N, 16·7. $C_{11}H_{12}N_2$ requires C, 76·75; H, 6·95; N, 16·25%).

The *hydrochloride*, prepared by the addition of dry ethereal hydrogen chloride to a solution of the base in chloroform, formed thick prisms, m. p. 224—226° (from ethanol) (Found: Cl, 16·85. $C_{11}H_{12}N_2$,HCl requires Cl, 17·0%).

Hydrolysis. (*a*) The absorption spectrum of the base in water was identical with that of 3-formylindole (Fig. 1, curve *a*). (*b*) The base (133 mg.) was suspended in water (150 c.c.), and 60 c.c. of the water distilled off during 1 hr. The distillate required 7·60 c.c of 0·1N-hydrochloric acid for neutralisation (to pH ~6·5) (Calc. for 3-dimethylaminomethyleneindolenine: 7·74 c.c.). The cooled distillation residue yielded 3-formylindole (109 mg., 97%).

Reduction. The base (340 mg.) was dissolved in boiling ether (100 c.c.) and excess of an ether solution of lithium aluminium hydride added. After 10 min. the mixture was extracted with dilute sulphuric acid, and the aqueous phase filtered, basified, and extracted with ether. The ether extract yielded impure gramine (210 mg.), m. p. 120—127°. A further partition between ether and acid, followed by several crystallisations from aqueous alcohol, yielded a purer product as characteristic leaflets, m. p. 125—130° undepressed by authentic gramine, m. p. 128—132°.

Reaction of 3-Formylindole with Aqueous Methylamine.—3-Formylindole (1·45 g.) was treated with 33% aqueous methylamine (10 c.c.; excess), and the mixture warmed with swirling to 30—35°. After 3 hr. at room temperature, the mixture was extracted with benzene (30 c.c.), the extract dried as far as possible over anhydrous sodium sulphate, and the solvent and the last traces of methylamine and water removed under reduced pressure. The residue (1·60 g.) was a pale brown gum, very soluble in all organic solvents except light petroleum. The *hydrochloride* was prepared by passing dry hydrogen chloride into a dry ether solution of the base. It crystallised from ethanol as pale yellow platelets, m. p. 240—242° (with sublimation), and was extremely soluble in water (Found: Cl, 17·9. $C_{10}H_{10}N_2$,HCl requires Cl, 18·2%).

Ururosein Perchlorate.—A solution of 3-formylindole (1·45 g., 0·01 mole) and indole (1·17 g., 0·01 mole) in hot methanol (15 c.c.) was treated with 60% aqueous perchloric acid (1·7 g., 0·01 mole). Immediate crystallisation occurred giving deep red crystals with a greenish metallic lustre (3·05 g.), which carbonise when heated. The mother-liquor yielded more product (0·22 g.); total yield, 94·5% of theory. The absorption spectrum of the product in alcoholic perchloric acid agreed with that observed for ururosein perchlorate by Harley-Mason and Bu'Lock (*loc. cit.*).

2-*Formylpyrrole*.—Pyrrole (3·38 g., 0·05 mole) was added slowly with stirring and exclusion of moisture to a mixture of dimethylformamide (15 g., 0·2 mole) and phosphorus oxychloride (5·0 c.c., 0·055 mole), the temperature being kept between 10° and 15°. After 30 min. at 35°, the reddish viscous mixture was poured on ice (30 g.), and the clear solution extracted with ether (100 c.c.). This removed a colourless liquid (0·1 g.) having a strong pyrrole odour. The aqueous phase was treated with sodium hydroxide (10 g., 0·25 mole) in water (20 c.c.), and the alkaline solution left at 15° for 20 min., just acidified with dilute hydrochloric acid and extracted with ether (3 × 75 c.c.). The extracted material was distilled at 8 mm., three fractions being collected: (*a*) b. p. 40—91° (0·81 g.), a mobile liquid; (*b*) b. p. 91—98° (1·79 g.), partially crystalline; and (*c*) b. p. 98—100° (2·62 g.), m. p. 42—44°. Fraction (*b*) was partitioned between water and benzene, and the benzene layer then yielded a product (1·32 g.), m. p. 41—44°. The total yield of 2-formylpyrrole is thus 3·94 g. (83% of theory).

The absorption spectrum of 2-formylpyrrole in water (Fig. 4, curve *c*) is not changed by

the addition of three drops of dilute sodium hydroxide. This is in marked contrast with 3-formylindole, which is thus much more strongly acidic in character.

Reaction of 3-Formylindole with Aniline.—A solution of 3-formylindole (1·45 g.) in pure aniline (5 c.c.; excess) was boiled for 1 min.; water soon began to separate and was removed by reducing the pressure to 10 mm. for a short time. The residual clear solution was kept at 100° for 2 hr. After as much as possible of the excess of aniline had boiled off under reduced pressure, the viscous residue was dissolved in dry ether (10 c.c.), carbon tetrachloride (10 c.c.) was added, and the solid which crystallised out was filtered off; it (1·51 g.) had m. p. 127—129°. The mother liquor was freed from ether and the further crop (0·45 g.) of product filtered off; the total yield of the anil is thus 89%. One crystallisation from dry benzene gave thick prisms, m. p. 128·5—130°.

The hydrochloride was formed in quantitative yield when a dry ethereal solution of the base was treated with a slight excess of dry ethereal hydrogen chloride. The bright yellow salt had m. p. 235—241° (decomp.) (Found: Cl, 13·55. Calc. for $C_{15}H_{12}N_2$,HCl: Cl, 13·8%). This represents an improvement on the material obtained by Majima and Kotake's method (Found: Cl, 13·25, 13·1. Found by Majima and Kotake: Cl, 12·75, 13·1%), which was obviously contaminated with 3-formylindole formed by hydrolysis.

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