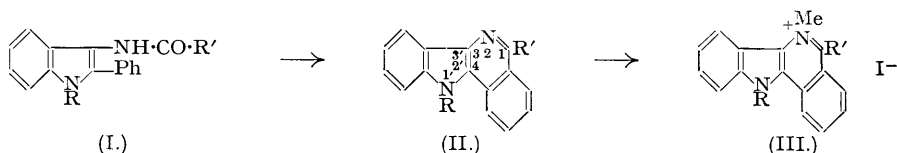


**615.** 1 : 2-Disubstituted 3-Aminoindoles. Part II. The Preparation of Indolo(3' : 2'-3 : 4)isoquinolines and of a New Type of Cyanine Dye derived therefrom.

By HUANG-HSINMIN and FREDERICK G. MANN.

The cyclisation of 3-acetamido-2-phenylindole and of 3-acetamido-2-phenyl-1-alkyl(or aryl)indoles to the 1-substituted and 1:1'-disubstituted indolo(3' : 2'-3 : 4)isoquinolines respectively is described. The methiodide of 1'-phenyl-1-methylindolo(3' : 2'-3 : 4)isoquinoline readily condenses with 1 : 2-disubstituted 3-nitrosoindoles, with *p*-nitrosodimethylaniline, and with *p*-dimethylaminobenzaldehyde, to give cyanine dyes of a new type. These cyanine dyes exist as a resonance hybrid of three canonical forms, since each of the three nitrogen atoms in the molecule can carry the formal positive charge.

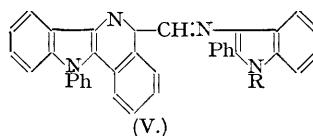
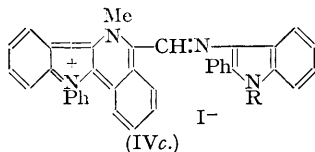
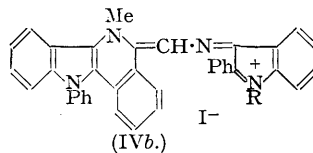
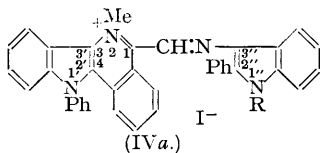
THE ready preparation of 3-acylamino-2-phenyl-1-alkyl(or aryl)indoles (I), described in the previous paper, has enabled us to investigate the cyclisation of such compounds to the corresponding 1'-R-1-R'-indolo(3' : 2'-3 : 4)isoquinolines (II). It appeared probable that this cyclisation would occur more readily in compounds of type (I) than in corresponding compounds



in which position 1 was unsubstituted, *i.e.*, in which R = H. Experiment has shown this to be true. Robinson and Thornley (*J.*, 1926, 3144) failed to cyclise 3-benzamido-2-phenylindole (I; R = H, R' = Ph) by heating it in ethereal solution with phosphorus trichloride for 15 minutes. We have, however, cyclised 3-acetamido-2-phenylindole (I; R = H, R' = Me) to 1-methylindolo(3' : 2'-3 : 4)isoquinoline (II; R = H, R' = Me) by heating it in boiling nitrobenzene with phosphoric anhydride for 2 hours, but the yield was low.

On the other hand, when 3-acetamido-1 : 2-diphenylindole (I; R = Ph, R' = Me) was heated in xylene solution with phosphoric anhydride, cyclisation readily occurred with the formation of 1'-phenyl-1-methylindolo(3' : 2'-3 : 4)isoquinoline (II; R = Ph, R' = Me) in 48% yield. This compound forms colourless crystals which give an ethanolic solution having a violet

fluorescence. Its *hydrochloride*, *picrate*, and *methiodide* (III; R = Ph, R' = Me) were readily obtained. The hydrochloride was also prepared directly by the cyclisation of 3-acetamido-1 : 2-diphenylindole (I; R = Ph, R' = Me) using phosphorus oxychloride instead of phosphoric anhydride. It is noteworthy that the hydrochloride and the methiodide (III) are yellow compounds : this yellow colour is presumably due to the fact that such salts will exist as a resonance hybrid of the canonical form corresponding to (III) and that in which the I'-N atom carries the positive charge. The *hydrochloride* of 1' : 1-diphenylindolo(3' : 2'-3 : 4)isoquinoline (II; R = R' = Ph) was similarly obtained by the action of phosphorus oxychloride on the benzamido-indole.

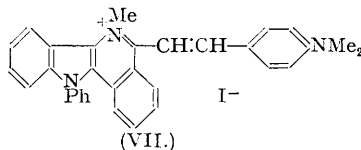
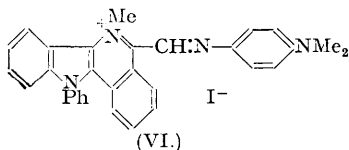


We have investigated in some detail the above methiodide, *i.e.*, 1'-phenyl-1 : 2-dimethyl-(3' : 2'-3 : 4)isoquinolinium iodide (III; R = Ph, R' = Me), because we expected the 1-methyl group in this compound to have a reactivity similar to that, for example, of the 2-methyl group of quinaldine methiodide, and condensation with suitable compounds should therefore give rise to a new type of cyanine dye. This has proved to be the case. The methiodide (III), when boiled in ethanol with 3-nitroso-2-phenyl-1-ethylindole and a trace of piperidine, readily condensed to give [1'-phenyl-2-methylindolo(3' : 2'-3 : 4)-1-isoquinoline][2''-phenyl-1''-ethyl-3''-indole]- $\beta$ -azadimethincyanine iodide (IVa-c; R = Et) as deep-red crystals.

Cyanine dyes of this novel type exhibit one unusual structural feature. Most cyanine dyes possess two heterocyclic nitrogen atoms, each of which can accept the positive charge of the cation, and hence the dye exists as a resonance hybrid of the two canonical forms. Our new cyanine dyes exist however as a hybrid of three canonical forms : there are the usual two forms (IVa) and (IVb), having the positive charge on the nitrogen atom of different heterocyclic systems, in which the alternation of double and single bonds in the methine chain is necessarily reversed ; and in addition there is the third form (IVc), in which the indolo-nitrogen atom of the indoloisoquinoline system carries the positive charge.

It is noteworthy that, when the original methiodide (III) was similarly condensed with 3-nitroso-1 : 2-diphenylindole, [1'-phenyl-2-methylindolo(3' : 2'-3 : 4)-1-isoquinoline][1'' : 2''-diphenyl-3''-indole]- $\beta$ -azadimethincyanine iodide (IVa-c; R = Ph) was obtained as red crystals, but loss of methyl iodide also occurred with the formation of the greenish-yellow crystalline  $\beta$ -azadimethin-1-[1'-phenylindolo(3' : 2'-3 : 4)isoquinoline]-3''-[1'' : 2''-diphenylindole] (V; R = Ph). This loss of methyl iodide must have occurred after the cyanine-dye formation, because quaternary salt formation is known to be necessary in order to activate the methyl group in compounds of the same general type as 1'-phenyl-1-methylindolo(3' : 2'-3 : 4)isoquinoline (II; R = Ph, R' = Me) for cyanine-dye formation, and experiment showed that this base would not condense with the nitroso-indole under precisely those conditions which readily led to condensation of the methiodide.

It is clear that our work on this new type of cyanine dye could be considerably extended. For example, the methiodide (III) also readily condensed with *p*-nitrosodimethylaniline to



give [1'-phenyl-2-methylindolo(3' : 2'-3 : 4)-1-isoquinoline][*p*-dimethylaminobenzene]- $\beta$ -azadimethincyanine iodide (VI) as red crystals, but again a portion of this salt lost methyl iodide to

give  $\beta$ -azadimethin-1-[1'-phenylindolo(3' : 2'-3 : 4)isoquinoline][p-dimethylaminobenzene] as green crystals. On the other hand, the methiodide condensed with *p*-dimethylaminobenzaldehyde to give [1'-phenyl-2-methylindolo(3' : 2'-3 : 4)-1-isoquinoline][p-dimethylaminobenzene]dimethincyanine iodide (VII) as deep-red crystals, and in this case no indication of subsequent loss of methyl iodide was obtained. Both the cyanine dyes (VI and VII) can exist as resonance hybrids of three canonical forms similar in type to (IVa, b, and c).

Further examples of cyanine dyes obtained from the methiodide are now being investigated.

#### EXPERIMENTAL.

**3-Acetamido-2-phenylindole** (I; R = H, R' = Me).—3-Oximino-2-phenylindole was obtained by the nitrosation of 2-phenylindole (cf. Fischer, *Annalen*, 1886, **236**, 116; *Ber.*, 1888, **21**, 1073; Angeli and Angelico, *Gazzetta*, 1900, ii, **30**, 268; Campbell and Cooper, *J.*, 1935, 1208). A suspension of the oximinoindole (1.4 g.) in acetic anhydride (25 c.c.) containing Adams's platinum catalyst (0.02 g.) was hydrogenated at room temperature and pressure. In 4 hours hydrogen (570 c.c.) had been absorbed and a clear solution obtained. This was added to much cold water, and, after hydrolysis of the anhydride, the precipitated 3-acetamido-2-phenylindole was collected, dried, and recrystallised from benzene; the colourless crystals (0.91 g.) had m. p. 202—203° (Found: C, 76.3; H, 5.4; N, 11.4.  $C_{16}H_{14}ON_2$  requires C, 76.8; H, 5.6; N, 11.2%). This material, when recrystallised from dilute acetic acid, had m. p. 203.5—204.5°, but when recrystallised from ethanol gave crystals of m. p. 189—190° and of unchanged composition (Found: C, 76.8; H, 5.9; N, 11.8%). Crystallisation from benzene regenerated material of m. p. 202—203°, changed to 189—190° when crystallised once more from ethanol; these m. p.s appear characteristic of this compound when it separates from these two solvents.

**1-Methylindolo(3' : 2'-3 : 4)isoquinoline** (II; R = H, R' = Me).—A solution of the above acetamidoindole (1.5 g.) in nitrobenzene (10 c.c.) was heated under reflux with phosphoric anhydride (4 g.) for 2 hours with occasional vigorous shaking. After the nitrobenzene had been removed by steam-distillation, the residual solution was treated with an excess of sodium carbonate and extracted with ether. The extract, when dried, filtered, and evaporated, gave a solid residue (0.25 g.) which when crystallised from ethanol, then sublimed under reduced pressure, and finally again recrystallised, afforded the pure base (II; R = H, R' = Me) as colourless crystals, m. p. 244—245° (Found: C, 82.2; H, 5.6; N, 12.1.  $C_{16}H_{12}N_2$  requires C, 82.7; H, 5.2; N, 12.1%). Its ethanolic solution possessed a violet fluorescence.

When a methanolic solution of this base containing an excess of methyl iodide was heated under reflux for 2 hours and then cooled, large yellow needles of 1 : 2-dimethylindolo(3' : 2'-3 : 4)isoquinolinium iodide (III; R = H, R' = Me) readily separated on cooling. On recrystallisation from methanol, a monohydrate was apparently formed; it decomposed above 320° (Found: C, 51.9; H, 4.7; N, 7.45.  $C_{17}H_{15}N_2I \cdot H_2O$  requires C, 52.1; H, 4.35; N, 7.15%).

**1'-Phenyl-1-methylindolo(3' : 2'-3 : 4)isoquinoline** (II; R = Ph, R' = Me).—Phosphoric anhydride (20 g.) was added to a solution of 3-acetamido-1 : 2-diphenylindole (I; R = Ph, R' = Me) (6 g.) in boiling dry xylene (70 c.c.), and the mixture heated under reflux for 1 hour with occasional vigorous shaking. The boiling xylene was decanted and the dark gummy residue extracted twice with hot xylene (50 c.c.  $\times$  2) and then, when cool, thrice with ether (40 c.c.  $\times$  3). (The xylene solution and the washings when evaporated gave a negligible residue.) The main residue was then thoroughly stirred with dilute ammonia; the insoluble gum when stirred with ethanol (10 c.c.) crystallised and, after being washed in turn with ethanol (5 c.c.) and water (50 c.c.), gave the above base (II; R = Ph, R' = Me), m. p. 191—192° (2.7 g., 48%). Recrystallisation from ethanol furnished colourless crystals, m. p. 192—193°, which after sublimation at 0.4 mm. pressure had m. p. 193.5° (Found: C, 85.6; H, 5.3; N, 9.4.  $C_{22}H_{18}N_2$  requires C, 85.7; H, 5.35; N, 9.1%).

Solutions of this base in ethanol, ether, acetone, and other organic solvents showed a beautiful violet fluorescence. The base is insoluble in aqueous caustic alkali solution, slightly soluble in dilute hydrochloric or sulphuric acid, and freely soluble in acetic acid; its solutions in all acids were pale yellow.

The following derivatives of this base were prepared.

**Hydrochloride.** (a) When hydrogen chloride was passed into an ethanolic solution of the base, the pale yellow crystalline hydrochloride was precipitated, m. p. 270—273°, unchanged by admixture with the sample prepared below.

(b) A mixture of the 3-acetamidoindole (0.44 g.), xylene (10 c.c.), and phosphorus oxychloride (7 c.c.) was heated under reflux for 3.5 hours. Distillation of the solvent under reduced pressure gave a yellowish-brown residue (0.57 g.) which was digested with 10% hydrochloric acid (30 c.c.) for 10 minutes. The filtered extract on cooling deposited the crystalline hydrochloride, which on recrystallisation from acetone and then ethanol gave beautiful yellow crystals, m. p. 268—273° (Found: C, 75.5; H, 5.1; N, 8.35.  $C_{22}H_{18}N_2 \cdot HCl$  requires C, 76.5; H, 5.0; N, 8.1%). Low values for carbon were obtained with a number of such salts). Method (a) gives the purer product.

Prepared in cold concentrated ethanolic solution, the *picrate* separated as bright yellow crystals, m. p. 210° (decomp.) (Found: C, 61.5; H, 3.7; N, 12.8.  $C_{22}H_{16}N_2 \cdot C_6H_3O_7N_3$  requires C, 62.7; H, 3.6; N, 13.0%).

**Methiodide.** A solution of the base in an excess of methyl iodide was heated under reflux for 10 hours, and the yellow crystals of 1'-phenyl-1 : 2-dimethylindolo(3' : 2'-3 : 4)isoquinolinium iodide (III; R = Ph, R' = Me) which had separated were then collected and recrystallised from methanol. They had m. p. 238—239° (Found: C, 61.4; H, 4.45; N, 6.0.  $C_{23}H_{19}N_2I$  requires C, 61.35; H, 4.25; N, 6.2%).

The base (II; R = Ph, R' = Me), unlike its methiodide (see below), would not react with 3-nitroso-1 : 2-diphenylindole or with *p*-nitrosodimethylaniline in boiling ethanolic solution containing a trace of piperidine.

**Hydrochloride of 1 : 1'-Diphenylindolo(3' : 2'-3 : 4)isoquinoline** (II, R = R' = Ph).—This was prepared essentially as the above hydrochloride, a mixture of 3-benzamido-1 : 2-diphenylindole and phosphorus

oxychloride (without xylene) being boiled for 2 hours. Digestion of the residue with hot 5% hydrochloric acid then gave the almost insoluble *hydrochloride*, which after recrystallisation from acetone formed colourless leaflets, m. p. 310—311° (Found : C, 78.4; H, 4.8.  $C_{27}H_{18}N_2 \cdot HCl$  requires C, 79.4; H, 4.7%).

[1'-Phenyl-2-methylindolo(3' : 2'-3 : 4)-1-isoquinoline][2''-phenyl-1''-ethyl-3''-indole]- $\beta$ -azadimethincyanine Iodide (IVa-c; R = Et).—A solution of the methiodide (III; R = Ph, R' = Me) (0.450 g.) and pure 3-nitroso-2-phenyl-1-ethylindole (0.25 g.) in boiling methanol (10 c.c.) containing a few drops of piperidine was heated under reflux for 20 hours. A deep-red colour appeared after 20 minutes' heating and masked the green colour of the nitroso-indole. The solvent was removed under reduced pressure, and the powdered residue extracted with dry ether (Soxhlet) for 6 hours. The residual red gum was dissolved in methanol (5 c.c.). The solution when carefully diluted with ether (30 c.c.) deposited the *cyanine iodide* as red crystals, m. p. 171—175° (decomp.) unaffected by recrystallisation from ethanol-ethyl acetate or from ethanol-ether; before analysis it was dried at 80°/0.4 mm. (Found : C, 68.9; H, 4.75; 7.85.  $C_{39}H_{31}N_4I$  requires C, 68.6; H, 4.6; N, 8.2%).

[1'-Phenyl-2-methylindolo(3' : 2'-3 : 4)-1-isoquinoline][1'' : 2''-diphenyl-3''-indole]- $\beta$ -azadimethincyanine Iodide (IVa-c; R = Ph).—A solution of the methiodide (III; R = Ph, R' = Me) (0.44 g.) and 3-nitroso-1 : 2-diphenylindole (0.292 g., 1 mol.) in ethanol (15 c.c.) containing a trace of piperidine, when boiled under reflux for 5 hours, developed a deep red colour and when then cooled deposited permanganate-coloured crystals (0.035 g.). These when collected and recrystallised from ethanol gave greenish-yellow crystals of  $\beta$ -azadimethin-1-[1'-phenylindolo(3' : 2'-3 : 4)isoquinoline]-3''-[1'' : 2''-diphenylindole] (V; R = Ph), m. p. 315—317° (Found : N, 9.5.  $C_{42}H_{28}N_4$  requires N, 9.5%).

The original mother-liquor, when concentrated to ca. 5 c.c. and cooled, gave the above *iodide*, which after recrystallisation from methanol had m. p. 270—271° (decomp.) after softening at 180° (Found : C, 70.35; H, 4.5; N, 7.9.  $C_{43}H_{31}N_4I$  requires C, 70.6; H, 4.3; N, 7.7%).

When equimolecular quantities of the base (II; R = Ph, R' = Me) and the nitroso-indole were heated under reflux in methyl iodide solution, a mixture of products difficult to separate satisfactorily was obtained.

[1'-Phenyl-2-methylindolo(3' : 2'-3 : 4)-1-isoquinoline][p-dimethylaminobenzene]- $\beta$ -azadimethincyanine Iodide (VI).—A solution of the methiodide (III; R = Ph, R' = Me) (0.350 g.) and p-nitrosodimethylaniline (0.130 g., 1.1 mols.) in ethanol (10 c.c.) containing a trace of piperidine was heated under reflux for 10 hours and then thoroughly cooled. The deep-green crystals (0.115 g.) which separated consisted of the above cyanine iodide and the iodide-free by-product. They were collected, mixed with acetone (5 c.c.), boiled for a few minutes, and cooled. The acetone extract, which contained the cyanine iodide, was filtered off, and the insoluble residue, when recrystallised from ethanol (15 c.c.), furnished green crystals of  $\beta$ -azadimethin-1-[1'-phenylindolo(3' : 2'-3 : 4)isoquinoline][p-dimethylaminobenzene], m. p. 218—220° after drying at 80°/0.4 mm. (Found : C, 81.5; H, 5.9; N, 12.5.  $C_{30}H_{24}N_4$  requires C, 81.8; H, 5.5; N, 12.7%).

The original ethanolic mother-liquor, when concentrated to ca. 5 c.c., gave a dark gum. When this was vigorously stirred with a small quantity of acetone, the cyanine iodide was extracted and a second crop (0.01 g.) of the above by-product remained undissolved. The two filtered acetone extracts were united and evaporated to dryness, and the residue stirred with ether. The residual red crystalline *cyanine iodide* was collected and recrystallised from ethanol. It formed a *monoethanolate*, which was unaffected by heating at 60°/0.4 mm. for 2 hours and then had m. p. 197° (decomp.) (Found : C, 63.1; H, 5.3; N, 9.2.  $C_{31}H_{27}N_4I \cdot C_2H_5O$  requires C, 63.1; H, 5.3; N, 8.9%).

[1'-Phenyl-2-methylindolo(3' : 2'-3 : 4)-1-isoquinoline][p-dimethylaminobenzene]dimethincyanine Iodide (VII).—This was prepared as the compound (VI), from the methiodide (0.51 g.), p-dimethylaminobenzaldehyde (0.27 g., 1.5 mols.), and ethanol (20 c.c.) with heating for 33 hours, during which the colour changed from orange to red. The solution, when concentrated in a vacuum to small bulk, deposited deep-red crystals of the *cyanine iodide*, which when twice recrystallised from methanol separated as the *dimethanolate*, which was unaffected by being heated at 80°/0.4 mm. for 6 hours and then had m. p. 183° (decomp.) after softening at 172° (Found : C, 62.8; H, 5.6; N, 6.9.  $C_{32}H_{28}N_4I \cdot 2CH_4O$  requires C, 63.2; H, 5.6; N, 6.5%). The tenacious retention of alcohol of crystallisation by certain of the above cyanine dyes is of course frequently shown by other types of cyanine dye.

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