668. *The Structure and Properties of Certain Polycyclic Indolo- and Quinolino-derivatives. Part IX.* Derivatives of* 1 : 3 : 4 : 5-*Tetrahydro*-5-*oxobenz*[cd]*indole.*

By Frederick G. Mann and A. J. Tetlow.

1 : 3 : 4 : 5-Tetrahydro-6-methoxy-1 : 2-dimethyl-5-oxobenz[*cd*]indole (V; R = OMe) has been prepared by direct cyclisation of 3-2′-carboxyethyl-1 : 2-dimethyl-5-methoxyindole, followed by remethylation of the intermediate 6-hydroxy-derivative.

The phenyl- and the *as.*-methylphenyl-hydrazone of this 6-methoxy-5-oxobenz[*cd*]indole undergo indolisation, but the infrared evidence indicates that the products, which can be isolated only as salts, are indoline isomers of the expected indolo-derivatives.

By the Pfitzinger reaction the 6-methoxy-5-oxobenz[*cd*]indole gives 4 : 6-dihydro-1-methoxy-4 : 5-dimethylindolo[3,4-*bc*]acridine-7-carboxylic acid, which forms a coloured zwitterion, like previous compounds of this class. When heated with hydrochloric acid, it undergoes allylic transformation to the 4 : 7-dihydro-isomer.

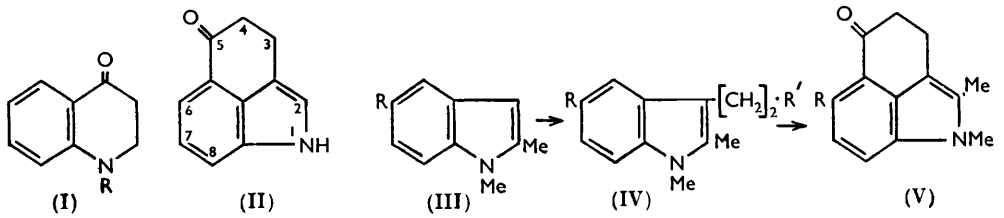
Decarboxylation of these two acids gives the corresponding isomeric 4 : 6-dihydro- and 4 : 7-dihydro-indolo-acridines. These differ from the isomeric pairs of such bases previously described, in that they are not interconvertible, and they give isomeric, instead of identical, oxidation products.

In previous papers in this series, the outstanding properties of the indolo-, quinolino-, and 4′-carboxyquinolino-derivatives obtained from various cyclic oxo-amines, such as

* Part VIII, preceding paper.

1 : 2 : 3 : 4-tetrahydro-4-oxo-1-phenyl(or methyl)quinoline (I; R = Ph or Me) [1,2] have been described and discussed. For a summary of these results see the preceding paper.[3]

In development of this work, we have investigated the preparation of suitable derivatives of 1 : 3 : 4 : 5-tetrahydro-5-oxobenz[*cd*]indole (II), a cyclic amino-ketone differing fundamentally in structure from all those previously studied in this series in that now the



amino- and the ketonic group are not in the same ring. The indole (II) has been prepared by Uhle,[4] and by Grob and Voltz,[5] in each case by a long route. To obtain a shorter synthesis, we initially (with the assistance of Dr. C. Y. Almond) converted 1 : 2-dimethylindole (III ; R = H) by the action of vinyl cyanide into 3-2′-cyanoethyl-1 : 2-dimethylindole (IV; R = H; R′ = ·CN), the structure of which was placed beyond doubt by the presence of the two methyl groups in the indole (III). All attempts, under various conditions, to induce the required cyclisation of this cyano-compound failed, and the 2′-carboxyethyl derivative (IV; R = H; R′ = CO_2H) gave only an insignificant yield of ketonic product. A similar failure to induce cyclisation of 3-1′ : 2′-dicarboxyethyl-2-methylindole was later recorded by Plieninger.[6]

In order, therefore, to activate the indole in the 4-position, we have converted 5-methoxy-1 : 2-dimethylindole (III; R = OMe) into the 3-2′-cyanoethyl derivative (IV; R = OMe, R′ = CN). Hydrolysis of this derivative gave 3-2′-carboxyethyl-5-methoxy-1 : 2-dimethylindole (IV; R = OMe, R′ = CO_2H); this acid was also obtained by the action of β-propiolactone [7] on the indole (III; R = OMe), but the former method was preferable for reasonably large-scale work.

All attempts to cyclise the 2′-cyanoethyl derivative failed, but the 2′-carboxyethyl derivative, when heated with a mixture of sulphuric and phosphoric acid,[8] underwent cyclisation and demethylation, giving 1 : 3 : 4 : 5-tetrahydro-6-hydroxy-1 : 2-dimethyl-5-oxobenz[*cd*]indole (V; R = OH); * the yield was 32% after allowance for the 3-2′-carboxyethyl-5-hydroxy-1 : 2-dimethylindole (IV; R = OH, R′ = CO_2H) which was recovered and could be similarly cyclised directly to (V; R = OH). This is the first recorded example of this cyclisation in a true indole, although Woodward and his co-workers [9] subsequently carried out a similar cyclisation of a 3-2′-carboxyethylindoline.

Although the 6-hydroxybenz[*cd*]indole (V; R = OH) gave acetoxy- and toluene-*p*-sulphonyloxy-derivatives, and also a phenylhydrazone, without difficulty, it showed marked hydrogen-bonding between the hydroxyl and the carbonyl group, and methylation of the hydroxy-group was ultimately achieved only by treatment with 30% aqueous sodium hydroxide and a large excess (*ca.* 10 mols.) of methyl sulphate in acetone. Infrared spectra clearly indicate this hydrogen-bonding : the spectrum of the 6-hydroxy-compound

* In a preliminary note (Mann and Tetlow, *Chem. and Ind.*, 1953, 823) this indole was named the 6-methoxy-derivative (V; R = OMe) in error.

[1] Mann, *J.*, 1949, 2816.
[2] Braunholtz and Mann, *J.*, 1955, 381.
[3] Mann and Wilkinson, preceding paper.
[4] Uhle, *J. Amer. Chem. Soc.*, 1949, **71**, 761.
[5] Grob and Voltz, *Helv. Chim. Acta*, 1950, **33**, 1796.
[6] Plieninger, *Chem. Ber.*, 1953, **86**, 404.
[7] Harley-Mason, *Chem. and Ind.*, 1951, 886; *J.*, 1952, 2433.
[8] Cf. Horning, Koo, and Walker, *J. Amer. Chem. Soc.*, 1951, **73**, 5827.
[9] Kornfeld, Fornefeld, Kline, Mann, Jones, and Woodward, *ibid* , 1954, **76**, 5256.

shows only an extremely weak band at 3·18 μ due to a hydroxyl group but a strong band at 6·08 μ due to the carbonyl group, whereas that of the 6-methoxy-compound shows a strong band at 6·00 μ.

The 6-hydroxy- and the 6-methoxy-benz[*cd*]indole (V; R = OH and OMe) form yellow and very pale yellow crystals respectively, but their ultraviolet spectra both closely resemble that of the unsubstituted compound (II) (Fig. 1).

It is noteworthy that solutions of the 6-methoxyindole (V; R = OMe) in carbon tetrachloride, ethanol, acetic acid, and concentrated hydrochloric acid are almost colourless, yellow, slightly deeper yellow and orange-red respectively, indicating strongly that, as the solvent becomes more acidic, the contribution of the polar form (VI) increases. The existence of a polar form similar to (VI) as a contributing canonical form of the unsubstituted 1 : 3 : 4 : 5-tetrahydro-5-oxobenz[*cd*]indole has been suggested by Grob and Payot.[10] We have obtained decisive evidence for the polar form (VI), for our compound (V; R = OMe) is markedly basic: its cold, almost colourless solution in benzene,

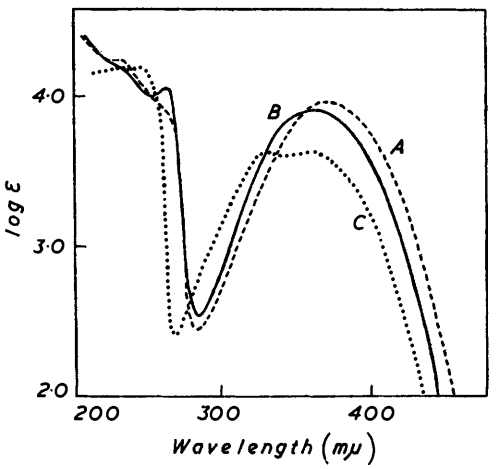
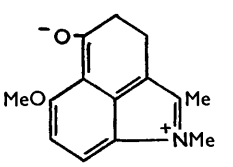


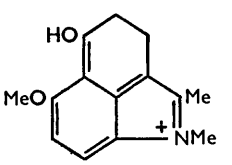
FIG. 1. *A*, 1 : 3 : 4 : 5-*Tetrahydro*-6-*hydroxy*-1 : 2-*dimethyl*-5-*oxobenz*[cd]*indole* (V; R = OH). *B*, 1 : 3 : 4 : 5-*Tetrahydro*-6-*methoxy*-1 : 2-*dimethyl*-5-*oxobenz*[cd]*indole* (V; R = OMe). *C*, 1 : 3 : 4 : 5-*Tetrahydro*-5-*oxobenz*[cd]*indole* (taken from ref. 5). All in ethanol.

when treated with dry hydrogen chloride, deposits deep garnet-red crystals of the unstable hydrochloride (VIA). The structure of this salt, and hence its formation by the protonation of the negative oxygen atom in (VI), are confirmed by the infrared spectrum, which gives strong evidence for the presence of an OH group, very feeble evidence for a CO group, and none for that of a $\equiv NH^+$ group (cf. p. 3363).

The colour of an ethanolic solution of the indole (V; R = OMe) is unaffected by the addition of aqueous sodium hydroxide, but that of a similar solution of the 6-hydroxyindole (V; R = OH) becomes a much deeper yellow, undoubtedly by resonance between the anion provided by the hydroxyl group in (V; R = OH) and the anion (VII).

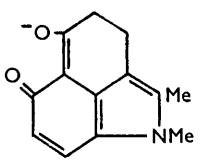


(VI)



(VIA)

Cl⁻



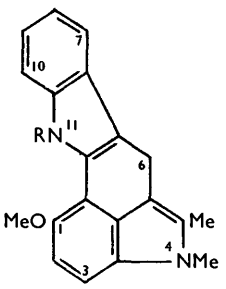
(VII)

An ethanolic solution of the 6-hydroxy-indole (V; R = OH) gives a green colour with ferric chloride, whereas that of the 6-methoxyindole is unaffected.

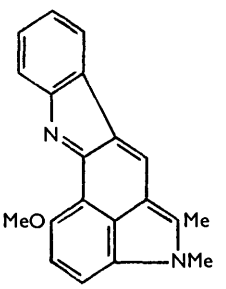
[10] Grob and Payot, *Helv. Chim. Acta*, 1953, **36**, 839.

The phenylhydrazone of the 6-methoxyindole (V; R = OMe) readily underwent indolisation in boiling ethanolic hydrogen chloride, giving an orange hydrochloride of composition $[C_{20}H_{17 \text{ or } 19}ON_2]Cl$, which was readily converted into the corresponding hydriodide, thiocyanate, and picrate. An aqueous solution of the hydrochloride, when made alkaline, deposited a reddish solid which darkened rapidly in the air or in a vacuum, decomposed more readily on attempted crystallisation, and gave a tar on attempted sublimation in a vacuum. Consequently structural identification was dependent on a study of the salts, the low solubility of which in hot solvents prevented recrystallisation.

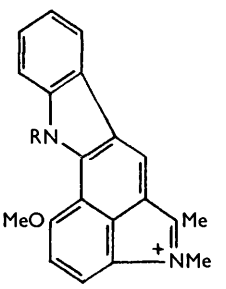
Now normal indolisation of the above phenylhydrazone would give 6 : 11-dihydro-1-methoxy-4 : 5-dimethyl-4*H*-indolo[4, 3-*ab*]carbazole (VIII; R = H) which, having two



(VIII)



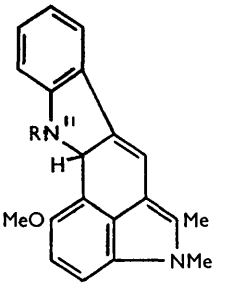
(IX)



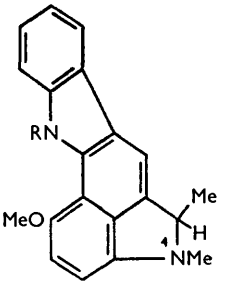
(X)

true indole groups, should be neutral. Several phenylhydrazones described in earlier papers in this series [1, 11, 12, 2] have, however, given yellow ψ-indoles, which have united readily with acids and with methyl iodide to give colourless salts. The phenylhydrazone of the 6-methoxyindole (V; R = OMe) could, therefore, have given 1-methoxy-4 : 5-dimethyl-4*H*-indolo[4, 3-*ab*]carbazole (IX) which with acids and with methyl iodide would have given the cations (X; R = H) and (X; R = Me) respectively. The analysis of the above hydrochloride and other salts did not differentiate sharply between a salt of the true indole (VIII) and that of the ψ-indole (IX).

The evidence against the ψ-indole structure (X; R = H) for the hydrochloride is twofold. (*a*) The infrared spectrum of this salt showed no band in the 2·95 μ region, indicating absence of an >NH group. (*b*) The methylphenylhydrazone of the 6-methoxyindole (V; R = OMe) underwent indolisation under similar conditions to give a crystalline orange hydrochloride having closely similar properties to those of the previous hydrochloride. The presence of the *N*-methyl group must now prevent ψ-indole formation of type (IX), but the normal indole (VIII; R = Me) should again be neutral.



(XI)



(XII)

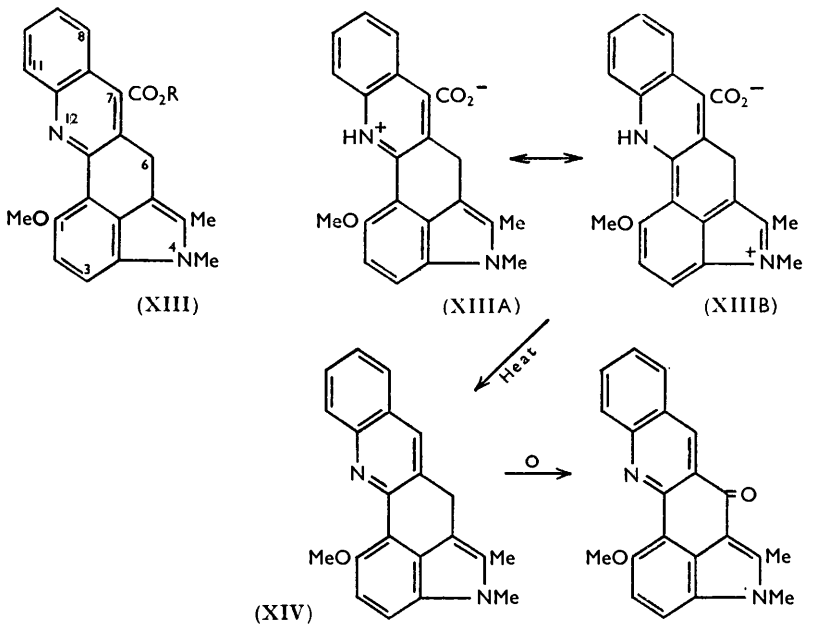
It is possible that the indole (VIII; R = H or Me) has undergone isomeric change, whereby the indole (XI) or (XII) might be formed: the fundamental difference between these two isomers is that in (XI) the upper, and in (XII) the lower, indole system has

[11] Mann and Smith, *J.*, 1951, 1898.
[12] Almond and Mann, *J.*, 1952, 1870.

adopted the indoline structure. Consequently salt formation would now occur by proton addition to the 11-nitrogen atom in (XI) and to the 4-nitrogen atom in (XII), giving in the hydrochlorides of the indoles (XI; R = H) and (XII; R = H), a $>NH_2^+$ and a $\equiv NH^+$ group respectively. The infrared spectrum of the hydrochloride again gives apparently decisive evidence, for it shows no absorption in the 3·85—3·90 μ region, where a $\equiv NH^+$ group usually gives broad absorption, but does show marked absorption in the 3·17—3·27 μ region, which would be expected if a $>NH_2^+$ group were present. (The absorption at 3·17—3·27 μ is quite distinct from a separate band at 3·4 μ due to CH groups.) The available evidence, therefore, strongly indicates that these indole derivatives have the structure (XI).

By the Pfitzinger reaction the indole (V; R = OMe) gave a series of quinolino-derivatives having some clear similarities to, and some marked differences from, those obtained, for example, from the oxo-amine (I; R = Ph and Me).[1,2]

When an ethanolic solution of the indole, isatin, and potassium hydroxide was boiled, acidification subsequently gave the deep red 4 : 6-dihydro-1-methoxy-4 : 5-dimethylindolo[3, 4-*bc*]acridine-7-carboxylic acid (XIII; R = H). There is little doubt, however, that this acid exists as a zwitterion, which forms a resonance hybrid to which the forms (XIIIA) and (XIIIB) provide the chief contributions. The evidence of this can be summarised: (*a*) The formal structure (XIII; R = H) should not give rise to an intense colour. On the other hand, although the quinonoid character of (XIIIB) would impart some colour to the resonance hybrid, the chief source of colour arises from the fact that (XIIIA) and (XIIIB) are two canonical forms of a cyanine type of compound. The acid, moreover, forms a bright yellow sodium salt (XIII; R = Na), in which, although some charge separation undoubtedly occurs, this cyanine structure is absent. (*b*) The infrared spectrum of the acid shows a strong and a rather weaker band at 6·21 and 6·33 μ



respectively, due to the CO_2^- group (cf. Braunholtz and Mann [2,13]). (*c*) The ultraviolet spectra of the acid in ethanol, and in ethanol containing hydrochloric acid, are very similar, and differ markedly from that in ethanol containing sodium hydroxide (Fig. 2). This is to be expected, because the hydrochloride of the acid will give a cation having canonical

[13] Braunholtz and Mann, *J.*, 1955, 393.

forms identical with (XIIIA) and (XIIIB), apart from the conversion of the CO_2^- into the CO_2H group: the sodium salt (XIII; R = Na) will have a fundamentally different structure.

The acid (XIIIA–B) when heated in a vacuum underwent decarboxylation to form the orange-yellow amine (XIV), m. p. 156—158°, which gives red salts with acids. These colours are also to be expected, for the amine (XIV) has essentially the same structure as (XIII), with, however, the CO_2R group replaced by hydrogen, whereas the red salts of the amine will have a cation having contributing forms identical with (XIIIA–B) with the CO_2^- group replaced by hydrogen. The absorptions of solutions of the amine (XIV) in ethanol and hydrochloric acid are shown in Fig. 3.

The quinolino-amines similar in type to (XIV) but derived from the keto-amines (I; R = Ph and Me) [1,2] and from 1-oxojulolidine [11] underwent ready atmospheric oxidation, particularly in benzene solution, to give a cyclic amide. The amine (XIV) underwent this type of oxidation only when treated in cold acetone with potassium permanganate, furnishing the bright yellow 4 : 6-dihydro-1-methoxy-4 : 5-dimethyl-6-oxoindolo-[3, 4-*bc*]acridine (XV), m. p. 220—223°. The infrared spectrum of this compound showed bands at 6·09 and 6·17 μ, indicating a conjugated >CO group. The compound did not give a 2 : 4-dinitrophenylhydrazone, which accords with its structure as a vinylogue of an acid amide: it gave a crystalline dull orange hydriodide.

The above results are in general similar to those obtained with earlier analogous compounds. When, however, concentrated hydrochloric acid was added to the cold reddish-purple aqueous solution of the acid (XIIIA–B), the hydrochloride of the acid separated as a similarly coloured gel, which was very difficult to manipulate. On warming, the gel dissolved, the colour of the solution changed, and the orange-brown hydrochloride of the isomeric acid, 4 : 7-dihydro-1-methoxy-4 : 5-dimethylindolo[3, 4-*bc*]acridine-7-carboxylic acid (XVI) crystallised. It is unfortunate that the free acid (XVI), obtained in aqueous solution by treating the hydrochloride with alkali (1 equiv.), was too soluble to be isolated, and its low solubility in organic solvents prevented its satisfactory extraction: consequently its properties could not be studied directly. There is little doubt that the essential difference between the two acids is that the isomeric acid (XVI) has undergone the allylic transformation: this is supported by previous analogous examples,[2,11,13] and more strongly by the properties of the corresponding amine and its oxidation product described below.

It is uncertain, however, whether this acid exists as a zwitterion, although this structure in indicated by the low solubility in organic solvents. Furthermore, its hydrochloride should show resonance corresponding to (XVIA–B), but the addition of aqueous sodium hydroxide to the orange aqueous or ethanolic solutions produces only a deeper orange-brown colour, and the ultraviolet spectra of solutions of the hydrochloride in 0·1N-aqueous hydrochloric acid and 0·1N-aqueous sodium hydroxide are closely similar (Fig. 4) in strong contrast to the marked differences of the spectra of the acid (XIII; R = H) in these conditions. Consequently the relative contributions of the forms (XVIA and B) in the hydrochloride are also uncertain: the above evidence indicates strongly, however, that the form (XVIA) makes almost an exclusive contribution to the hydrochloride, and that, therefore, the hydrochloride and the sodium salt have fundamentally the same structure.

When, however, this hydrochloride was heated in a vacuum, hydrogen chloride and carbon dioxide were evolved with the formation of the yellow amine (XVII), m. p. 239—240°, isomeric with the amine (XIV). The amine (XVII) gave a deep red solution in hydrochloric acid, and formed a dark maroon-coloured crystalline hydriodide: it is clear, therefore, that the cation present in salts of the amine receives contributions from two canonical forms similar to (XVIA–B) with the CO_2H group replaced by a hydrogen atom, and thus shows the familiar cyanine-like resonance. The absorption of solutions of this amine (XVII) in ethanol and 0·1N-hydrochloric acid are shown in Fig. 5, for comparison with those of the isomeric amine (XIV) in Fig. 3.

Oxidation of the amine (XVII) with permanganate in acetone gave the yellow 4 : 7-dihydro-1-methoxy-4 : 5-dimethyl-7-oxoindolo[3, 4-*bc*]acridine (XVIII), m. p. 305—308°, isomeric with the 6-oxo-derivative (XV). The infrared spectrum of the compound (XVIII) showed a single band at 6·15 μ, again indicating a conjugated >CO group.

FIG. 2. 4 : 6-*Dihydro*-1-*methoxy*-4 : 5-*dimethylindolo*[3, 4-bc]*acridine*-7-*carboxylic acid* (XIII; R = H), (*A*) *in ethanol* (2·075 *mg.*/50 *c.c.*); (*B*) *in ethanol* (1·610 *mg.*/50 *c.c.*) *containing* 0·25 *c.c. of* 10% *aqueous* HCl; (*C*) *in* 10% *aqueous sodium hydroxide* (1·000 *mg.*/50 *c.c.*).

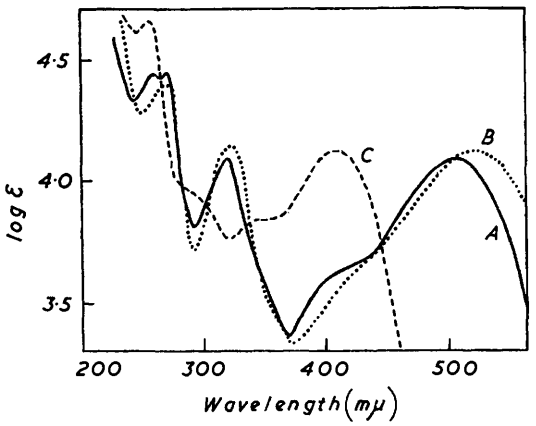
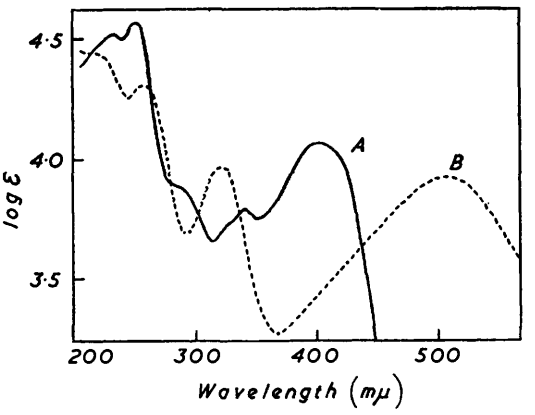


FIG. 3. 4 : 6-*Dihydro*-1-*methoxy*-4 : 5-*dimethylindolo*[3, 4-bc]*acridine* (XIV), (*A*) *in ethanol* (0·840 *mg.*/50 *c.c.*); (*B*) *in* 0·1N-*aqueous* HCl (0·930 *mg.*/50 *c.c.*).



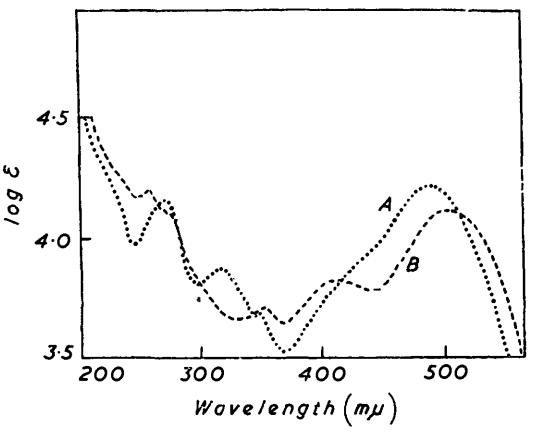


FIG. 4. *Hydrochloride of* 4 : 7-*dihydro*-1-*methoxy*-4 : 5-*dimethylindolo*[3, 4-bc]*acridine*-7-*carboxylic acid* (XVI), (*A*) *in* 0·1N-*aqueous* HCl (1·900 *mg.*/50 *c.c.*); (*B*) *in* 0·1N-*aqueous sodium hydroxide* (1·320 *mg.*/50 *c.c.*).

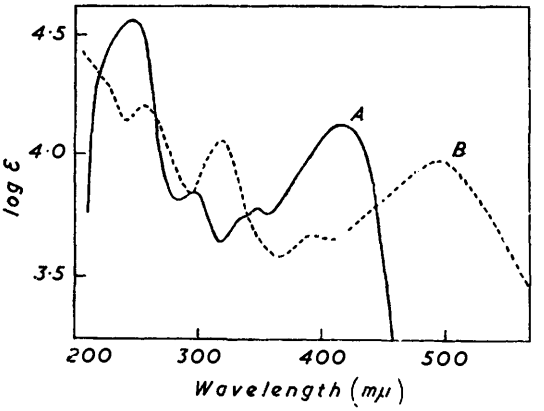


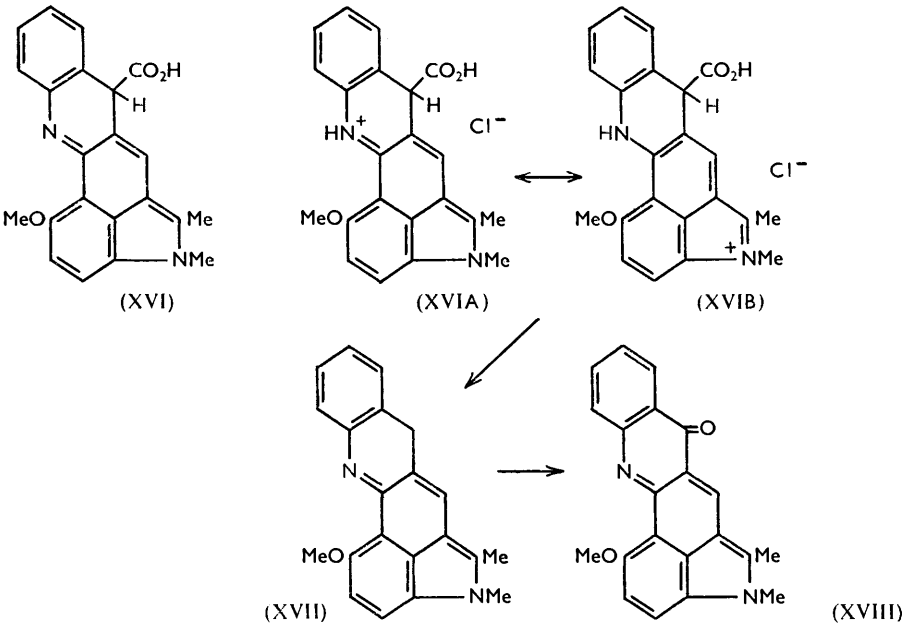
FIG. 5. 4 : 7-*Dihydro*-1-*methoxy*-4 : 5-*dimethylindolo*[3, 4-bc]*acridine* (XVII), (*A*) *in ethanol* (0·815 *mg.*/50 *c.c.*); (*B*) *in* 0·1N-*aqueous* HCl (0·985 *mg.*/50 *c.c.*).

The compound (XVIII), like the isomeric (XV), did not react with 2 : 4-dinitrophenylhydrazine, and gave a dark orange crystalline hydriodide.

The general structures of the isomeric bases (XIV) and (XVII), apart from the position of the " allylic " hydrogen, are so closely similar that their ultraviolet spectra in ethanol are also similar: the spectra in 0·1N-aqueous hydrochloric acid are correspondingly similar, although each is markedly different from that of the parent amine (Figs. 3, 5).

On the other hand, the spectra of the two isomeric oxidation compounds (XV) and (XVIII) in each of the above solvents are all closely alike (Figs. 6, 7), indicating that protonation leaves each compound essentially unchanged in structure.

In previous examples of bases similar to (XIV), namely, quinolino(2′ : 3′-1 : 2)-juloline,[11] 1 : 2-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline,[2] and diquinolino-(2′ : 3′-1 : 2)(3″ : 2″-5 : 6)juline,[13] the isomeric base, when heated in a vacuum, underwent conversion into the original base with sublimation. Our present bases (XIV) and (XVII) are exceptional in that each sublimes unchanged, and interconversion of the bases, by heating them with acids or by sublimation, has not been detected.



The absence of this interconversion of these two bases is not, however, unexpected. Braunholtz and Mann [2] have suggested that the mechanism of the acid-catalysed conversion of 1 : 2-dihydro- into 1 : 4′-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline consists essentially of two steps: (i) proton migration from the 1′- to the 1-nitrogen atom: the positive pole on the latter atom, being adjacent to the allylic methylene group, makes the hydrogen atom of this group more mobile, and catalyses step (ii), in which a proton migrates from position 2 to position 4′. This mechanism was supported by the fact that isomerisation of the corresponding 1-phenyl derivative was very sluggish, owing to the very weakly basic properties of the :NPh group.

In the base (XIV), however, the NMe group in position 4 is not only very feebly basic, but it is separated by a much longer chain from the 12-nitrogen atom. The comparable migration of the proton from the 12 to the 4-nitrogen atom would, therefore, be negligible, and the suggested mechanism of isomerisation could not apply to the base (XIV).

It is noteworthy that many attempts made to prepare 1 : 3 : 4 : 5-tetrahydro-6-methoxy-1 : 2-dimethyl-4 : 5-dioxobenz[*cd*]indole by the oxidation (direct or indirect) of the 4-methylene group in the 6-methoxyindole (V; R = OMe) group failed. Selenium dioxide under various conditions either left the indole unchanged or caused considerable decomposition: the application under the usual conditions of nitrous acid, pentyl nitrite, *p*-nitrosophenol, or *p*-nitrosodimethylaniline, in the hope of obtaining the oxime or anil in the 4-position for subsequent hydrolysis, gave intractable products. Further, the

ketone (V; R = OMe) did not appear to undergo condensation, with or without subsequent indolisation, with 1-amino-1 : 2 : 3 : 4-tetrahydroquinoline.

In view of the fact that our quinolinoindoles have a ring system approaching that of lysergic acid, the acid (XIIIA–B), the hydrochloride (XVIA–B), and the amines (XIV) and (XVII) were kindly tested by Imperial Chemical Industries Limited (Pharmaceuticals Division) for anti-inflammatory action against egg-albumin-induced œdema in mice. The first three compounds were inactive and the last showed slight activity.

FIG. 6. 4 : 6-*Dihydro*-1-*methoxy*-4 : 5-*dimethyl*-6-*oxoindolo*[3, 4-bc]*acridine* (XV), (*A*) *in ethanol* (1·170 *mg.*/50 *c.c.*); (*B*) *in* 0·1N-*aqueous* HCl (0·875 *mg.*/50 *c.c.*).

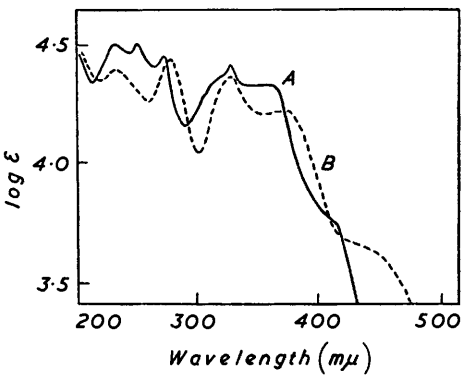
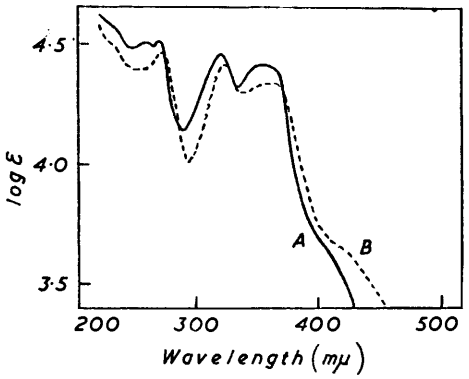


FIG. 7. 4 : 7-*Dihydro*-1-*methoxy*-4 : 5-*dimethyl*-7-*oxoindolo*[3, 4-bc]*acridine* (XVIII), (*A*) *in ethanol* (1·380 *mg.*/50 *c.c.*); (*B*) *in ethanol* (1·535 *mg.*/50 *c.c.*) *containing* 0·25 *c.c. of* 10% *aqueous* HCl.



EXPERIMENTAL

The compounds prepared were colourless unless otherwise stated. Many compounds gave consistent m. p.s only if the latter were determined in sealed evacuated tubes (denoted by " E.T."), which in addition often had to be immersed just below the m. p. : the temperature of immersion is denoted as " T.I.".

3-2′-*Cyanoethyl*-1 : 2-*dimethylindole* (IV; R = H, R′ = CN).—A mixture of 1 : 2-dimethylindole (5 g.), vinyl cyanide (3·4 g.), powdered copper acetate (1·7 g.) and copper powder (1·7 g.) was heated in a sealed tube for 12 hr. at 120—130°. The cold solution was filtered, neutralised with aqueous potassium carbonate, and extracted with chloroform. After drying, removal of the chloroform left a residue which, recrystallised from aqueous ethanol, gave the crystalline *indole* (IV; R = H, R = CN), m. p. 108—109° (Found : C, 78·6; H, 7·4; N, 14·2. $C_{13}H_{14}N_2$ requires C, 78·7; H, 7·1; N, 14·1%) (3·5 g., 51%). Cyanoethylation was not achieved when a mixture of the indole and vinyl cyanide was (*a*) heated with sodium methoxide at 130—140° for 15 hr., (*b*) dissolved in glacial acetic acid and boiled under reflux for 6 hr., (*c*) dissolved in dioxan containing benzyltrimethylammonium hydroxide and similarly boiled.

3-2′-*Carboxyethyl*-1 : 2-*dimethylindole* (IV; R = H, R′ = CO_2H).—(*A*) A mixture of 1 : 2-dimethylindole (9·2 g.) and β-propiolactone (9·2 g.) was heated with stirring at 150° for 3 hr., cooled, and extracted with cold ether. Polymerised propiolactone solidified to a pink powder which was filtered from the ether solution. The latter was extracted with 10% aqueous potassium hydroxide (2 × 50 c.c.), which on acidification deposited the *acid* (IV; R = H, R′ = CO_2H), m. p. 153—154° (from aqueous ethanol) (Found : C, 72·0; H, 7·2; N, 6·6. $C_{13}H_{15}O_2N$ requires C, 71·8; H, 7·0; N, 6·5%) : 7 g., 51%. (*B*) The indole (IV; R = H, R′ = ·CN) was hydrolysed by boiling 10% aqueous potassium hydroxide, and the clear cold solution on acidification gave the above acid.

The following experiment is noteworthy among the many attempts to achieve cyclisation. A solution of the acid (IV; R = H, R′ = CO_2H) (3 g.) in acetic anhydride (125 c.c.) containing potassium cyanide (0·02 g.) was boiled under reflux for 20 hr., and the anhydride then distilled off. An ether extract of the residue, when washed with dilute alkali, dried and evaporated, left a crystalline product showing faint ketonic properties. Three recrystallisations from ethanol gave the *anhydride* of the above acid, needles, m. p. 117—118° (Found : C, 75·1;

H, 6·8; N, 6·8. $C_{26}H_{28}O_3N_2$ requires C, 75·0; H, 6·8; N, 6·7%) : it underwent ready hydrolysis to the acid.

The ethanolic mother-liquors on evaporation gave a residue, which was added to 5% aqueous sodium hydroxide, boiled for 15 min., cooled, and extracted with ether. This extract on evaporation gave a small quantity of an uncrystallisable ketonic oil. With ethanolic 2 : 4-dinitrophenylhydrazine, this deposited orange-red 1 : 3 : 4 : 5-*tetrahydro*-1 : 2-*dimethyl*-5-*oxobenz*[cd]*indole* 2 : 4-*dinitrophenylhydrazone monoethanolate*, m. p. 237—239° (decomp.) (E.T.) after washing with boiling ethanol (Found : C, 58·8; H, 5·1; N, 16·6. $C_{19}H_{17}O_4N_5,C_2H_6O$ requires C, 59·2; H, 5·45; N, 16·5%).

The following experiments (*A–C*) were directed to the preparation of 1-ethyl-2 : 5 : 7-trimethylindole, in which the 4-position should have marked activity.

(*A*) N-*Ethyl*-2 : 4-*dimethylaniline and its Hydrobromide*.—2 : 4-Dimethylaniline (121 g.) and ethyl bromide (109 g., 1 mol.) were set aside together for 3 days. The crystalline mass was then stirred with acetone and filtered, furnishing the *hydrobromide*, needles, m. p. 151—152° after crystallisation from acetone (1·5 l.) (Found : C, 52·2; H, 6·8; N, 6·1. $C_{10}H_{15}N,HBr$ requires C, 52·2; H, 7·0; N, 6·1%) : 131·5 g., 57%. Basification and ether-extraction then gave the *aniline*, b. p. 57·5°/0·4 mm. (Found : C, 80·4; H, 10·1; N, 9·45. $C_{10}H_{15}N$ requires C, 80·5; H, 10·1; N, 9·4%).

(*B*) N-*Ethyl*-2 : 4-*dimethyl*-N-*nitrosoaniline*.—A mixture of the aniline (110 c.c.), concentrated hydrochloric acid (110 c.c.), and crushed ice (300 g.) was stirred with external cooling whilst a solution of sodium nitrite (51·5 g., 1 mol.) in water (185 c.c.) was added during 10 min., stirring being continued for 1 hr. Extraction with ether and removal of solvent gave the nitrosamine as a yellow oil (112 g., 85%), which was not further purified.

(*C*) as.-*Ethyl*-2 : 4-*dimethylphenylhydrazine*.—Attempted reduction of the nitrosamine with zinc and acetic acid gave solely the original aniline. Consequently, lithium aluminium hydride (12 g.) in ether (400 c.c.) was placed in a 3-necked flask (2 l.) fitted with a stirrer, reflux condenser, and dropping-funnel. The ether was stirred whilst a solution of the nitrosamine (55 g., 1 mol.) in ether (100 c.c.) was slowly added, the reaction causing the mixture to boil. After 1 hour's stirring wet ether (200 c.c.) was added, and then, very cautiously, 30% aqueous sodium hydroxide (75 c.c.). The ethereal layer was separated, united with an ethereal extract of the aqueous layer, dried, and distilled. The *hydrazine* was obtained as an oil, b. p. 73°/0·4 mm. (Found : C, 73·5; H, 9·6; N, 16·8. $C_{10}H_{16}N_2$ requires C, 73·1; H, 9·8; N, 17·1%) (35 g., 69%). This procedure gave more satisfactory results than when conversely the ethereal hydride was added to the nitrosamine, which Poirier and Benington [14] recommend for such reductions.

Acetone (4·4 c.c.) was added to a solution of the hydrazine (10 g., 1 mol.) in 40% aqueous acetic acid (10 c.c.), which when shaken became warm as the hydrazone (12 g., 96%) separated as an upper layer. This was separated and dried, but attempts to convert it into the indole failed and its use was abandoned.

N-*Methyl*-N-*nitroso*-p-*anisidine*.—Methyl sulphate (1425 c.c.) was run into a stirred solution of *p*-anisidine (1845 g.) in methanol (1 l.) at such a rate that it boiled gently. The solution was heated at 100° for 2 hr., and the methanol then distilled off. The cold residue was treated with a solution of sodium hydroxide (750 g.) in water (1·5 l.), and the oil collected : a further quantity was obtained by ether-extraction of the aqueous layer. The crude *N*-methyl-*p*-anisidine was dissolved in concentrated hydrochloric acid (2·4 l.) containing ice (5 kg.) in a 27 l. earthenware vessel. A solution of sodium nitrite (1·2 kg.) in water (1·5 l.) was slowly run in below the surface of the stirred solution, with addition of ice to keep the temperature below 10°. After 1 hr., the yellow solid nitrosamine was collected, thoroughly washed with water, and dried; it had m. p. 42—44° (771 g., 31%). King and Robinson [15] give m. p. 45—46° for the recrystallised compound.

N-p-*Methoxyphenyl*-N-*methylhydrazine*.—The nitrosamine, when reduced with lithium aluminium hydride as described above, gave the hydrazine, b. p. 139—142°/13 mm., in 30% yield. For large-scale work, a solution of the nitrosamine (166 g.) in glacial acetic acid (320 c.c.) was added during 3—4 hr. to a stirred mixture of zinc dust (480 g.) in 50% aqueous ethanol (600 c.c.) kept at 10—20°. After 1 hr. the mixture was warmed to 60°, filtered, made strongly alkaline with 30% aqueous sodium hydroxide, and extracted with ether. The dried extracts

[14] Poirier and Benington, *J. Amer. Chem. Soc.*, 1952, **74**, 3192.
[15] King and Robinson, *J.*, 1933, 271.

from two preparations were united, the ether removed, and the product, when distilled at 12 mm., gave the fractions: (*a*) b. p. 131—135°, 119 g.; (*b*) b. p. 137—141°, 13 g.; and (*c*) b. p. 143—146°, 133 g. The colourless fractions (*a*) and (*b*) were *N*-methyl-*p*-anisidine and crystallised when set aside. The brown fraction (*c*) was the required hydrazine (49%).

5-*Methoxy*-1 : 2-*dimethylindole* (III; R = OMe).—A mixture of the hydrazine (152 g.), acetone (80 c.c., 1·1 mols.), and acetic acid (5 c.c.) was heated for 2 hr., water separating as the hydrazone was formed. Without purification, the cold product was added to ethanol (1·5 l.) saturated with hydrogen chloride, which was boiled under reflux for 2 hr. and poured into water (10 l.). The dark tarry precipitate was collected, and the filtrate extracted with chloroform. The united solid and extract when distilled gave the *indole* (III; R = OMe) as a pale yellow oil, b. p. 134—137°/0·3 mm., m. p. 76·5—77·5° (from ethanol) (Found: C, 75·2; H, 7·45; N, 8·1. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·5; N, 8·0%) (64 g., 37%). The distillation left a considerable dark residue.

In an attempted alternative synthesis, monobromoacetone was added to *N*-methyl-*p*-anisidine in ethanol containing sodium hydrogen carbonate at 50°. Working up gave *p*-methoxyphenyl-*N*-methylaminopropanone, b. p. 175°/12 mm., which when heated with *N*-methyl-*p*-anisidine and a trace of hydrochloric acid gave 5-methoxy-1 : 3-dimethylindole, m. p. 59—60·5°, after crystallisation from ethanol (lit.,[16] m. p. 60—61°).

3 - 2′-*Cyanoethyl*-5-*methoxy*-1 : 2-*dimethylindole* (IV; R = OMe, R′ = CN).—This compound was prepared by Braunholtz and Mann's method,[17] a mixture of the indole (III; R = OMe) (87·5 g.), vinyl cyanide (36 c.c., 1·1 mols.), acetic acid (30 c.c.), and cuprous chloride (5 g.) being heated under reflux for 6 hr. and then poured into aqueous ammonia. The solid precipitate, when thoroughly washed with ammonia and water and crystallised from ethanol, afforded the *indole*, m. p. 124·5—125·5° (Found: C, 73·7; H, 6·85; N, 12·5. $C_{14}H_{16}ON_2$ requires C, 73·65; H, 7·05; N, 12·3%): 96 g., 84%.

3-2′-*Carboxyethyl*-5-*methoxy*-1 : 2-*dimethylindole* (IV; R = OMe, R′ = CO_2H).—(*A*) A mixture of the indole (III; R = OMe) (10 g.) and β-propiolactone (5 c.c., 1·4 mols.) was heated at 150° for 4 hr., cooled, and extracted with ether. The ethereal solution was filtered to remove polymerised lactone, and extracted with dilute aqueous sodium hydroxide. Evaporation of the ether gave unchanged indole (3·2 g.). Acidification of the alkaline extract gave an oil which solidified, and when recrystallised from 50% aqueous ethanol gave the *acid*, m. p. 119—120·5° (Found: C, 68·0; H, 6·7; N, 5·6. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7%) (6·7 g., 70% after allowance for recovered indole). (*B*) Solutions of the indole (IV; R = OMe, R′ = CN) (114 g.) in ethanol (500 c.c.) and of sodium hydroxide (120 g.) in water (1·2 l.) were mixed and boiled under reflux for 7 hr.; after the ethanol had been distilled off, acidification of the cold solution with concentrated hydrochloric acid precipitated the acid (119 g., 96%).

1 : 3 : 4 : 5-*Tetrahydro*-6-*hydroxy*-1 : 2-*dimethyl*-5-*oxobenz*[cd]*indole* (V; R = OH).—A mixture of the indole (IV; R = OMe, R′ = CO_2H) (20 g.), concentrated sulphuric acid (100 c.c.), and phosphoric acid (100 c.c.) was heated at 165° ± 5° for 30 min., allowed to cool slightly, and poured into water (1·5 l.). After 1 hr., the brown precipitate was collected and recrystallised from ethanol, giving the yellow *benzindole* (V; R = OH), m. p. 142—144° (Found: C, 72·2; H, 5·7; N, 6·55%; *M*, in boiling ethanol, 230. $C_{13}H_{13}O_2N$ requires C, 72·4; H, 6·0; N, 6·5%; *M*, 215) (4·3 g., 32% after allowance for recovered acid).

The aqueous solution was extracted with chloroform, which was then extracted with aqueous sodium carbonate. Acidification of the carbonate extract precipitated 3-2′-*carboxyethyl*-5-*hydroxy*-1 : 2-*dimethylindole* (IV; R = OH, R′ = CO_2H), m. p. 147—149° after recrystallisation from water (Found: C, 67·3; H, 6·6; N, 6·1. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·5; N, 6·0%) (4·3 g., 23%). This acid also underwent cyclisation to the benzindole (V; R = OH) under the above conditions.

The acid gave a transient purple colour with ferric chloride, and was readily converted into the indole (IV; R = OMe, R′ = CO_2H) by methyl sulphate and aqueous sodium hydroxide. The acid, when added to aqueous sodium hydroxide and treated with toluene-*p*-sulphonyl chloride in acetone, gave 3-2′-*carboxyethyl*-1 : 2-*dimethyl*-6-*toluene*-p-*sulphonyloxyindole* (IV; R = O·SO_2·C_7H_7, R′ = CO_2H), m. p. 199—200·5° (Found: C, 62·4; H, 5·6; N, 3·7. $C_{20}H_{21}O_5NS$ requires C, 62·0; H, 5·5; N, 3·6%).

Derivatives of the 6-*Hydroxy*-*benz*[cd]*indole* (V; R = OH).—(1) A solution of the indole

[16] Janetzky, Verkade, and Lieste, *Rec. Trav. chim.*, 1946, **65**, 199.
[17] Braunholtz and Mann, *J.*, 1953, 1817.

(0·5 g.), phenylhydrazine (0·5 c.c.), and acetic acid (0·2 c.c.) in ethanol (15 c.c.) was boiled for 1 hr., and on cooling deposited the crystalline *phenylhydrazone* (0·66 g., 95%), initially bright yellow, but separating from benzene as almost colourless crystals, m. p. 238—239° (E.T.; T.I. 232°) (Found: C, 74·5; H, 6·0; N, 13·6. $C_{19}H_{19}ON_3$ requires C, 74·7; H, 6·3; H, 13·75%). (2) A solution of the indole in acetic acid and acetic anhydride, when heated and poured into water, gave the yellow 6-*acetoxy-derivative* (V; R = OAc), m. p. 157·5—158·5° (from ethanol) (Found: C, 70·0; H, 5·8; N, 5·7. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·9; N, 5·45%). This gave a very pale cream *phenylhydrazone*, m. p. 224·5—225·5° (E.T.; T.I. 219°) (Found: C, 72·7; H, 6·2; N, 12·1. $C_{21}H_{21}O_2N_3$ requires C, 72·65; H, 6·1; N, 12·1%). (3) The indole gave a yellow 6-*toluene*-p-*sulphonyloxy-derivative* (V; R = $O{\cdot}SO_2{\cdot}C_7H_7$), m. p. 208—209°, after crystallisation from ethanol (Found: C, 65·4; H, 5·3; N, 3·6. $C_{20}H_{19}O_4NS$ requires C, 65·05; H, 5·2; N, 3·8%). This gave an orange 2 : 4-*dinitrophenylhydrazone*, m. p. 265° (E.T.; T.I. 255°) after crystallisation from much xylene (Found: C, 56·7; H, 3·95; N, 12·45. $C_{26}H_{23}O_7N_5S$ requires C, 56·8; H, 4·2; N, 12·75%). (4) A hot ethanolic solution of the indole, when treated with ethanol saturated with hydrogen chloride, became amber in colour and on cooling deposited green crystals, apparently of a very unstable hydrochloride. A sample recrystallised from ethanol regenerated the pure indole, m. p., mixed and unmixed, 142°. Another sample was collected and washed on the filter with ethanolic hydrogen chloride, but, in spite of being dried over calcium chloride at atmospheric pressure, it underwent very considerable dissociation although it retained the green colour and had m. p. 153—154° (Found: C, 71·0; H, 6·3. Calc. for $C_{13}H_{13}O_2N$,HCl: C, 62·3; H, 5·6. Calc. for $C_{13}H_{13}O_2N$: C, 72·4; H, 6·0%).

1 : 3 : 4 : 5-*Tetrahydro*-6-*methoxy*-1 : 2-*dimethyl*-5-*oxobenz*[cd]*indole* (V; R = OMe).—The following were the only conditions discovered under which the 6-hydroxy-compound could be methylated. The 6-hydroxybenzindole (V; R = OH) (23·6 g.) was dissolved in warm acetone (600 c.c.), and alternate additions of 30% aqueous sodium hydroxide (10 c.c.) and methyl sulphate (7 c.c.) were made with vigorous shaking until precipitation no longer occurred and a clear solution was obtained. (In a typical experiment, 15 such additions of each reagent, *i.e.*, *ca.* 10 mols. of sulphate, were required.) The solution was diluted with water (1 l.), the acetone distilled off, and the dull yellow product recrystallised from ethanol, giving the very pale yellow 6-*methoxybenz*[cd]*indole* (V; R = OMe), m. p. 144—145° (Found: C, 73·25; H, 6·8; N, 6·3%; *M*, in boiling ethanol, 239. $C_{14}H_{15}O_2N$ requires C, 73·35; H, 6·6; N, 6·1%; *M*, 229).

Hydrochloride. A cold benzene solution of the indole (V; R = OMe), when treated with a stream of dry hydrogen chloride, became red and deposited well-formed deep red crystals of the hydrochloride. These crystals, when collected with a minimum of exposure to damp air and placed in an atmospheric or evacuated desiccator, slowly faded in colour, and when exposed to the air became sticky and reddish-black at the edges. A fresh sample was collected, washed on the filter with benzene–hydrogen chloride, pressed between filter-paper to absorb excess of benzene, and subjected at once to infrared absorptiometry and elementary analysis. The latter (Found: C, 12·15. Calc. for $C_{14}H_{15}O_2N$,HCl: Cl, 13·4%) does not differentiate between contamination with benzene or slight dissociation. The infrared spectrum, determined in a film pressed between sodium chloride plates, showed a broad OH band centred about 3308—3360 cm.$^{-1}$ (2·98—3·02 μ), but only a very feeble $>$CO band at 6·0 μ, and no indication of a $\equiv NH^+$ band in the 3·8—3·9 μ region. A small amount of Nujol was then rubbed in the film, which was again compressed. The spectrum still showed the broad OH band, but a moderately strong $>$CO band had now developed at 6·0 μ, and the film had become paler. A portion of the initial red crystals, when stirred with 5% aqueous sodium hydroxide, lost their red colour and deposited yellowish crystals, m. p. 138—140°, which after recrystallisation from ethanol gave the pale yellow 6-methoxyindole (V; R = OMe), m. p. and mixed m. p. 140—142°.

A warm ethanolic solution of this indole, when treated with ethanolic hydrogen chloride, became deep red but did not deposit crystals when chilled. It was taken to dryness in a vacuum desiccator, and the brittle deep red resin recrystallised from hot acetone to which just sufficient ethanolic hydrogen chloride was added to give a complete solution, which when cooled and stirred slowly deposited a fine brown microcrystalline powder, m. p. 207° (decomp.) (T.I. 200°) when dried over calcium chloride in an atmospheric desiccator (Found: C, 63·1; H, 6·2; N, 5·5; Cl, 13·5. $C_{14}H_{15}O_2N$,HCl requires C, 63·3; H, 6·0; N, 5·3; Cl, 13·4%). Although this compound appeared to be a *hydrochloride*, it differed from the authentic red salt in that (*a*) when exposed to the air it decomposed much more slowly, without becoming sticky, (*b*) when treated with 5% aqueous sodium hydroxide it gave only a dark sticky intractable gum. The

indole appeared, therefore, to have undergone some fundamental change during this treatment, and the nature of this brown salt was not further investigated.

The 6-methoxybenz[*cd*]indole (V; R = OMe) readily gave a *phenylhydrazone*, almost colourless plates, m. p. 150—150·5° (from ethanol) (Found: C, 75·4; H, 6·3; N, 13·2. $C_{20}H_{21}ON_3$ requires C, 75·2; H, 6·6; N, 13·15%), and a yellow *methylphenylhydrazone*, m. p. 131—132° (E.T.; T.I. 127°) (from ethanol) (Found: C, 75·9; H, 7·1; N, 12·55. $C_{21}H_{23}ON_3$ requires C, 75·65; H, 6·95; N, 12·6%). The phenylhydrazone had high stability and was unchanged in appearance and m. p. after 2 years, whereas the methylphenylhydrazone had darkened considerably after 4 months.

Indolo-derivatives.—Since these compounds were isolated only as salts, in which the position of the tautomeric hydrogen atom, although very probably that shown in (XI), is not quite certain, they will be considered for simplicity of reference and nomenclature to have the normal indolo-structure (VIII).

6 : 11-*Dihydro*-1-*methoxy*-4 : 5-*dimethyl*-4H-*indolo*[4, 3-ab]*carbazole* (VIII; R = H). The hydrazone (2 g.) of the benz(*cd*)indole (V; R = OMe) in ethanol (15 c.c.) was mixed with saturated ethanolic hydrogen chloride (15 c.c.), and heated under reflux for 3 hr., an orange solid separating meanwhile. The mixture was set aside overnight at 0°, and the solid, m. p. 296° (E.T.; T.I. 285°) (1·0 g.) collected. It dissolved readily in hot methanol, which on cooling deposited the orange yellow *hydrochloride* (Found, in two preparations: C, 70·7, 71·6; H, 5·4, 5·0; N, 8·7, 8·1. $C_{20}H_{18}ON_2,HCl$ requires C, 70·9; H, 5·65; N, 8·25%).

A methanolic solution of the hydrochloride, treated with aqueous sodium iodide, deposited the *hydriodide*, orange-yellow needles, m. p. 304° (decomp.) (E.T.; T.I. 300°) (Found: C, 56·2; H, 4·1; N, 6·65. $C_{20}H_{18}ON_2,HI$ requires C, 55·8; H, 4·45; N, 6·5%). The *thiocyanate*, similarly prepared, formed yellow needles, m. p. 279° (E.T.; T.I. 275°) (Found: C, 69·8; H, 4·75; N, 11·4. $C_{20}H_{18}ON_2,HCNS$ requires C, 69·8; H, 5·3; N, 11·6%). The *picrate* formed yellow needles, m. p. 240—241° (E.T.; T.I. 230°) (Found: C, 58·6; H, 3·85. $C_{20}H_{18}ON_2,C_6H_3O_7N_3$ requires C, 58·7; H, 4·0%).

6 : 11-*Dihydro*-1-*methoxy*-4 : 5 : 11-*trimethyl*-4H-*indolo*[4, 3-ab]*carbazole* (VIII; R = Me) A mixture of the methylphenylhydrazone (1 g.), ethanol (7·5 c.c.) and saturated ethanolic hydrogen chloride (7·5 c.c.) was boiled under reflux for 5 hr., and the orange-coloured solution was concentrated, cooled, and diluted with acetone, the orange-yellow hydrochloride (0·45 g.), m. p. 343° (E.T.; T.I. 340°), slowly separating.

This salt was soluble in water, methanol and ethanol, and no suitable solvent for recrystallisation was found. The addition of alkali to its aqueous solution precipitated a reddish solid which rapidly darkened in air, and could not be sublimed in a vacuum. An aqueous solution of the hydrochloride, when treated with aqueous sodium iodide, deposited the orange *hydriodide hemihydrate*, m. p. 341° (E.T.; T.I. 339°) (Found: C, 55·75; H, 5·15. $C_{21}H_{20}ON_2,HI,0{\cdot}5H_2O$ requires C, 55·7; H, 4·9%). The orange *perchlorate*, similarly prepared, had m. p. 314° (E.T.; T.I. 310°) (Found: C, 61·2; H, 5·1; N, 6·8. $C_{21}H_{20}ON_2,HClO_4$ requires C, 60·5; H, 5·1; N, 6·7%).

Quinolino-derivatives.—4 : 6-*Dihydro*-1-*methoxy*-4 : 5-*dimethylindolo*[3, 4-bc]*acridine*-7-*carboxylic acid* (XIIIA–B). The 6-methoxy-indole (V; R = OMe) (4·5 g.), isatin (3·3 g.), and 40% aqueous potassium hydroxide (10 c.c.) were added to ethanol (40 c.c.), which was then boiled under reflux for 30 hr. The cold solution was filtered and diluted with water (80 c.c.) and acetic acid (10 c.c.), the yellow colour changing to a deep red. The solution was extracted with chloroform (3 × 30 c.c.), acetic acid (10 c.c.) being added after each extraction. The combined extracts were concentrated and diluted with light petroleum (b. p. 60—80°) (50 c.c.), a red solid, m. p. 160—163° (effervescence, E.T.; T.I. 150°) (5·8 g.), being precipitated. Recrystallisation from ethanol–acetone gave the *acid* (XIIIA–B), dull red crystals, m. p. 190° (effervescence, E.T.; T.I. 185°) (Found: C, 73·5; H, 4·95; N, 7·5. $C_{22}H_{18}O_3N_2$ requires C, 73·7; H, 5·05; N, 7·8%). The acid is readily soluble in water, but insoluble in chloroform and petroleum. It can, however, be extracted from its solution in dilute acetic acid by chloroform, almost certainly as its acetate, *i.e.*, the material of m. p. 160—163°, which then readily dissociates on recrystallisation: hence the above method of isolating the free acid.

The acid dissolved readily in 10% aqueous sodium hydroxide to give a yellow solution, which when set aside deposited bright yellow crystals of the *sodium salt* (XIII; R = Na) (Found: N, 7·1. $C_{22}H_{17}O_3N_2Na$ requires N, 7·35%).

4 : 6-*Dihydro*-1-*methoxy*-4 : 5-*dimethylindolo*[3, 4-bc]*acridine* (XIV). The above acid (1 g.)

when cautiously heated at 0·001 mm., the bath temperature rising finally to 300°, melted, effervesced, and then gave a sublimate of the orange-yellow *indoloacridine* (XIV), m. p. 156—158° (E.T.; T.I. 150°) (from ethanol) (Found: C, 80·15; H, 5·8; N, 8·95. $C_{21}H_{18}ON_2$ requires C, 80·25; H, 5·75; N, 8·9%) (0·4 g., 44%). When this decarboxylation was carried out with the initial precipitate, m. p. 160—163°, a gentle heating at 15 mm., during which acetic acid was liberated, preceded the stronger heating: the liberation of acetic acid confirms the identity of the precipitate as an unstable acetate.

The amine dissolves in dilute hydrochloric acid to give a red solution from which the hydrochloride could not be isolated: addition of ethanolic hydrogen chloride to an ethanolic solution of the base deposited the very hygroscopic red hydrochloride. Addition of dilute sulphuric acid to the ethanolic base deposited the dull red *hydrogen sulphate*, m. p. 232° (E.T.; T.I. 230°) (from aqueous ethanol) (Found: C, 61·0; H, 4·6. $C_{21}H_{18}ON_2,H_2SO_4$ requires C, 61·15; H, 4·9%). Hydriodic acid similarly gave the maroon *hydriodide*, m. p. 196—197° (decomp.) (T.I. 194°) (from aqueous ethanol) (Found: C, 57·05; H, 4·55; N, 6·3. $C_{21}H_{18}ON_2,HI$ requires C, 57·05; H, 4·35; N, 6·35%).

Oxidation. (*A*) The pale yellow solution of the base (XIV) in cold benzene was exposed to the air for 7 days, evaporation losses being made good from time to time. The reddish-brown solution was then evaporated, but the rust-coloured solid residue could not be crystallised, or sublimed in a vacuum.

(*B*) An acetone solution of potassium permanganate was added to a solution of the base (XIV) in acetone until, even when gently warmed, it retained a faint pink colour. The solid residue obtained by evaporation was then extracted with benzene (Soxhlet), the extract affording bright yellow 4 : 6-*dihydro*-1-*methoxy*-4 : 5-*dimethyl*-6-*oxoindolo*[3, 4-bc]*acridine* (XV) (50%), m. p. 220—223° (E.T.; T.I. 215°) after recrystallisation from benzene (Found: C, 76·5; H, 4·7; N, 8·8. $C_{21}H_{16}O_2N_2$ requires C, 76·8; H, 4·9; N, 8·55%). This compound did not give a 2 : 4-dinitrophenylhydrazone. Its solution in dilute hydrochloric acid, when treated with aqueous sodium iodide, deposited the dull orange *hydriodide*, m. p. 296—299° (E.T.; T.I. 290°) (from aqueous ethanol) (Found: C, 55·3; H, 4·0; N, 6·4. $C_{21}H_{16}O_2N_2,HI$ requires C, 55·25; H, 3·75; N, 6·15%).

Isomerisation of the acid (XIIIA–B). The deep reddish-purple solution of this acid (3·8 g.) in warm water (130 c.c.), when stirred and treated with concentrated hydrochloric acid (30 c.c.), set to a gel, which on further warming gave a clear deep purple solution. When heated for a further 20 min., the solution became deep orange-brown, and when scratched deposited the orange-brown 4 : 7-*dihydro*-1-*methoxy*-4 : 5-*dimethylindolo*[3, 4-bc]*acridine*-7-*carboxylic acid hydrochloride* (XVIA–B) (3·0 g., 78%), which, after recrystallisation from dilute hydrochloric acid, softens or melts at 160—170° (E.T.), resolidifies, and remelts at 235° (Found: C, 67·1; H, 5·2; N, 7·3. $C_{22}H_{18}O_3N_2,HCl$ requires C, 66·9; H, 4·9; N, 7·1%). This salt gave orange solutions in water or ethanol, the colour becoming a deeper orange on the addition of alkali: this behaviour is in marked contrast to that of the acid (XIIIA–B).

4 : 7-*Dihydro*-1-*methoxy*-4 : 5-*dimethylindolo*[3, 4-bc]*acridine* (XVII). The above hydrochloride (1 g.), when heated in a short-path sublimation apparatus at 0·001 mm., the bath-temperature rising to 280—300°, gave a sublimate of the yellow *base* (XVII) (0·6 g., 78%), m. p. 239—240° (E.T.; T.I. 238°) (from benzene) (Found: C, 80·0; H, 5·6; N, 9·1. $C_{21}H_{18}ON_2$ requires C, 80·25; H, 5·75; N, 8·9%). This base is very similar in appearance to the isomeric base (XIV), but is less soluble in ethanol and benzene: a mixture of the bases had m. p. 145—205°. The base (XVII) gave a deep red solution in dilute hydrochloric acid: addition of aqueous sodium iodide gave the dark maroon *hydriodide monohydrate*, m. p. 310—311° (E.T.; T.I. 305°) (from ethanol) (Found: C, 55·1; H, 4·3; N, 6·2. $C_{21}H_{18}ON_2,HI,H_2O$ requires C, 54·8; H, 4·6; N, 6·1%).

Attempts to obtain this base by boiling solutions of the base (XIV) in dilute hydrochloric acid, with subsequent basification, failed: no evidence that isomerisation occurred in these or similar conditions was obtained.

Oxidation. (*A*) The yellow solution of the base (XVII) in benzene was unchanged in colour after 5 days' exposure to the atmosphere, unchanged base being recovered.

(*B*) The base in acetone was oxidised with permanganate as described above. Extraction (Soxhlet) of the solid residue with benzene afforded 4 : 7-*dihydro*-1-*methoxy*-4 : 5-*dimethyl*-7-*oxoindolo*[3, 4-bc]*acridine* (XVIII) (10%), which after vacuum-sublimation and recrystallisation from 2-methoxyethanol formed yellow crystals, m. p. 305—308° (E.T.; T.I. 280°)

(Found : C, 76·8; H, 5·0; N, 8·65. $C_{21}H_{16}O_2N_2$ requires C, 76·8; H, 4·9; N, 8·55%). It did not form a 2 : 4-dinitrophenylhydrazone. Addition of sodium iodide to its solution in hot dilute hydrochloric acid deposited the hygroscopic dull orange *hydriodide hemihydrate*, m. p. 336—338° (E.T.; T.I. 330°) (Found : C, 54·1; H, 3·9; N, 6·4. $C_{21}H_{16}O_2N_2,HI,0{\cdot}5H_2O$ requires C, 54·3; H, 3·9; N, 6·05%).

We are greatly indebted to Dr. C. Y. Almond for assistance in the preliminary stages of this work, to Imperial Chemical Industries Limited, Dyestuffs Division, for materials, and to Imperial Chemical Industries Limited (Pharmaceuticals Division) for therapeutic tests.

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