Reactions of 4,5-Dihydro-5-methylpyrano[4,3-*b*]indole-1,3-dione; a Synthesis of *N*-Methylisotryptophol

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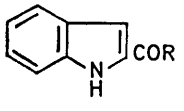
Boiling 4,5-dihydro-5-methylpyrano[4,3-*b*]indole-1,3-dione (7) with alcohols followed by decarboxylation of the half-esters so formed leads to esters of 1-methylindol-2-ylacetic acid; reduction of these esters then affords *N*-methylisotryptophol [2-(1-methylindol-2-yl)ethanol] (10). Reaction of 3-carboxy-1-methylindol-2-ylacetic acid (6; R = H) with acetic acid–sodium acetate gives 3,5-dimethylpyrano[4,3-*b*]indol-1(5*H*)-one (17); with dimethylformamide–phosphorus oxychloride, 4-(*NN*-dimethylaminomethylene)-4,5-dihydro-5-methylpyrano-[4,3-*b*]indole-1,3-dione (22) was obtained.

SEVERAL methods for the preparation of tryptophol, 2-(indol-3-yl)ethanol, have been described [1,2] and its reactions investigated; recently Humber [3] has described the preparation of tetrahydropyrano[3,4-*b*]indole derivatives by the condensation of tryptophol with carbonyl compounds. In contrast, little work has been reported on isotryptophol, 2-(indol-2-yl)ethanol, since it is difficult to obtain indoles substituted in the 2-position.[4] Lithiation of 1-substituted indoles occurs at position 2 and



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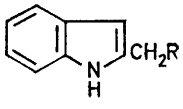

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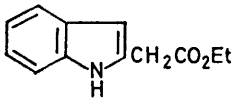

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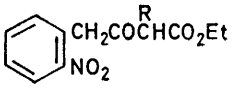
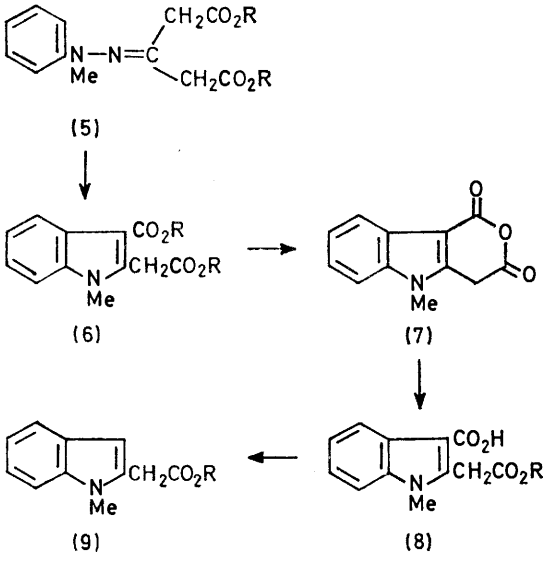


(4)

this reaction has been exploited [5,6] for the preparation of 2-substituted indoles. Isotryptophol has been prepared [7] by the reduction of (3) obtained from (1; R = OEt) *via* (1; R = NMe_2), (2; R = NMe_2), and (2; R = CN).[8] A second synthesis [9] utilised the reaction of *o*-nitrophenylacetyl chloride with acetoacetic ester to form (4; R = COMe) which was then ammonolysed to form (4; R = H), reduction of this compound then yielding (3). We have developed a synthesis of *N*-methylisotryptophol (10) starting from dimethyl 1,3-acetonedicarboxylate.†

Methylphenylhydrazine reacts with diethyl acetone-1,3-dicarboxylate in the presence of HCl to form the ester (6; R = Et).[11] We have prepared the hydrazone (5; R = Me) in high yield by the nitrosation of *N*-methylaniline, reduction of the nitroso-compound followed by the addition of the keto-ester, all without the isolation of the carcinogenic nitroso-compound or of the hydrazine. The ethyl ester (5; R = Et) [11] is lower-melting and less suitable than the methyl ester. Treatment of (5; R = Me) with methanolic HCl then gave (6; R = Me) in good yield. Hydrolysis then afforded the acid (6; R = H) which readily formed the anhydride (7).[11] Prolonged boiling of a suspension of the anhydride in ethanol yielded the half-ester (8; R = Et) which readily lost carbon dioxide to give (9; R = Et). Reduction of this ester then yielded *N*-methylisotryptophol. The anhydride dissolves very slowly in boiling ethanol, but using n-butyl alcohol the half-ester (8; R = Bu^n) was readily obtained. Decarboxylation of (8; R = Bu^n) followed by the reduction of (9; R = Bu^n) afforded (10).

The reduction of (6; R = Et) by lithium aluminium hydride in boiling ether is said [11] to yield compound (11; R = H); however we found that the product was a mixture of (11; R = H) and (11; R = OH) (n.m.r. and mass spectra). In tetrahydrofuran (THF) solution at

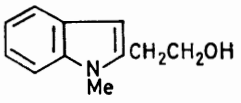


(5) (6) (7) (8) (9)

room temperature we found the main product to be the glycol (11; R = OH), a 2% yield of 1,3-dimethylisotryptophol (11; R = H) [12] being obtained. Leete [13] has reported that 3-hydroxymethylindoles readily lose formaldehyde and we attempted to prepare (10) from (11; R = OH). However in MeOH (30 °C) or in AcOH

† During the course of our work it was reported [10] that ethylene oxide reacts with 1-ethyl-2-lithio-indole to form 1-ethylisotryptophol.

at room temperature black tars were obtained. Heating (11; R = OH) *in vacuo* gave mainly tar and a small quantity of 1,2,3-trimethylindole; the pyran (12; $R^1 = R^2 = H$) [12] was not detected [(12; $R^1 = R^2 = H$) was shown to sublime unchanged]. However, when the glycol (11; R = OH) was treated with tosyl chloride in pyridine solution the tosyl derivative of *N*-methylisotryptophol (10) was isolated in moderate yield showing that loss of formaldehyde from (11; R = OH) had occurred.



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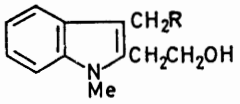

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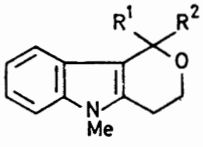

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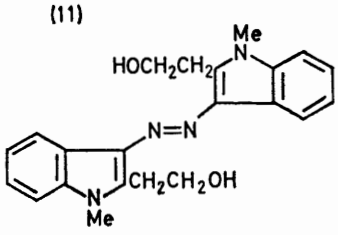

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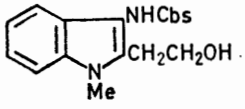
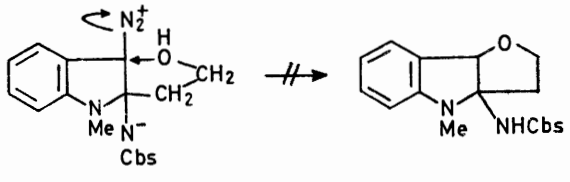


(14)

N-Methylisotryptophol condensed with aromatic aldehydes in acetic acid solution [14] forming 1-aryltetrahydropyrano[4,3-*b*]indoles (12; $R^1 = Ar$; $R^2 = H$). The compounds were rather unstable, decomposing slowly at 0 °C. With acetone containing BF_3–Et_2O [15] the dimethyl compound (12; $R^1 = R^2 = Me$) was obtained. Compound (10) reacted with *p*-chlorobenzenesulphonyl azide ($CbsN_3$) to give a mixture of the azo-compound (13) and the sulphonamide (14) (*cf.* the reaction of 1,2-dimethylindole [16]). There was no sign of compound (16) or of any product derived from (16) indicating that intramolecular displacement [17] of N_2 by OH in (15) did not occur. Treatment of the glycol (11; R = OH) with $CbsN_3$ gave polymeric materials.



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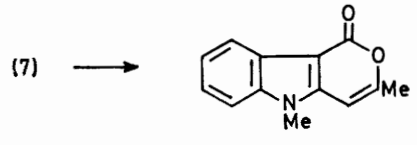
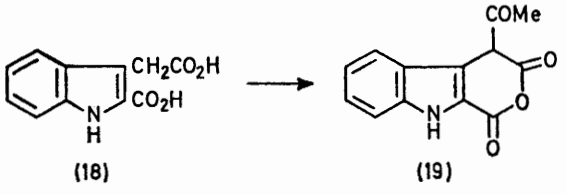


(17)

During one attempt to form the anhydride (7) by boiling the acid (6; R = H) with acetic anhydride a compound, m.p. 223—225 °C, was isolated, having a molecular weight of 213; and combustion analysis indicated a formula $C_{13}H_{11}NO_2$. The n.m.r. spectral data [τ 3.6 (CH=C) and 7.6 (CMe)] indicated structure (17) for the compound. The sample of acid (6) used in this preparation was found to contain small quantities of the corresponding potassium salt which was functioning as a base. It is possible to obtain (17) in 90% yield by boiling the pure acid (6; R = H) with acetic anhydride containing sodium acetate. This type of reaction is thought to involve acetylation of the anhydride followed by rearrangement and decarboxylation.[18] 2-Carboxyindol-3-ylacetic acid (18) reacts at room temperature with acetic anhydride in pyridine solution to form the acetylated derivative (19).[19] Under these conditions compound (6; R = H) gave (7) in high yield and no *C*-acetyl derivative was obtained; but treatment of the acid (6) at 0 °C with trifluoroacetic anhydride in pyridine solution gave the trifluoroacetylpyrone (20) which appears to be in the enolic form (20b) in dimethyl sulphoxide (DMSO) solution. The pyrone (17) was recovered (85%) after boiling for 5 h with ethanolic potash, and heating compound (17) with methylamine afforded the pyridine derivative (21). Treatment of compound (6; R = H) with phosphorus oxychloride in DMF gave the formylidene derivative (22) in high



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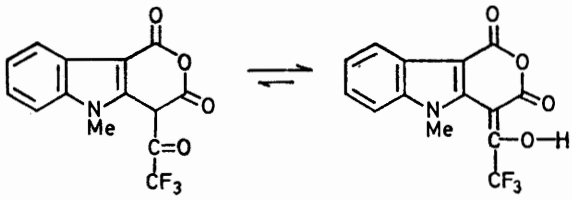
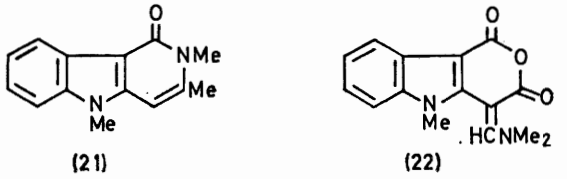


(20a) (20b)



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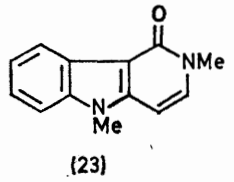

(23)

yield. This compound was stable in hot DMF–$POCl_3$ and did not form compound (23).[19]

EXPERIMENTAL

General details and instruments used have been reported.[20] U.v. spectra were recorded for solutions in ethanol and n.m.r. spectra for solutions in $CDCl_3$ unless otherwise stated; i.r. spectra were recorded for Nujol mulls. Column and thin layer chromatography were carried out on silica using ethyl acetate and ethyl acetate–benzene mixtures.

Methyl 3-Methoxycarbonyl-1-methylindol-2-ylacetate (6; R = Me).—A solution of *N*-methylaniline (21.5 g) in AcOH (80 ml) containing concentrated hydrochloric acid (10 ml) and water (16 ml) was cooled (ice–salt) to 0 °C. A solution of $NaNO_2$ (14 g) in water (25 ml) was added to the stirred solution during 5 min; the mixture was then stirred at room temperature for 15 min. Meanwhile, a stirred suspension of zinc dust (50 g) in water (80 ml) was cooled (ice–salt) to 5 °C. The acid solution was then added slowly (45 min) to the zinc suspension. Stirring was continued at room temperature for 1 h; the mixture was then heated rapidly to 80 °C, Celite (2—3 g) added, and the mixture filtered. The residue was washed with a mixture of water (20 ml) and AcOH (20 ml) and to the filtrate was added dimethyl acetone-1,3-dicarboxylate (dimethyl 2-oxopropane-1,3-dicarboxylate) (25 ml). The mixture was shaken vigorously (5 min), cooled, and water (150 ml) added. The solid was collected and washed with aqueous AcOH (50%; 20 ml) and aqueous methanol (50%; 20 ml). The *N-methylphenylhydrazone* (5; R = Me) (52 g) formed needles, m.p. 93—94 °C (from MeOH) (Found: C, 60.5; H, 6.6; N, 10.1. $C_{14}H_{18}N_2O_4$ requires C, 60.4; H, 6.5; N, 10.1%); $\nu_{max.}$ 1 600, 1 660, 1 730, and 3 190—3 240 cm^{-1}; *m/e* 278 (M^+, 57%), 246 (49), and 77 (100). Acetyl chloride (8.5 ml) was added slowly to ice-cold MeOH (40 ml). This mixture was then added to a solution of the phenylhydrazone (5; R = Me) (20 g) in MeOH (100 ml) and the mixture boiled under reflux for 1.5 h. The mixture was filtered and water (100 ml) added to the filtrate. The *methyl ester* (6; R = Me) was collected and recrystallised (MeOH) (13.1 g), m.p. 100—101 °C (Found: C, 64.4; H, 5.8; N, 5.4. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.8; N, 5.4%); $\lambda_{max.}$ 206, 231sh, and 290 nm (ε 29 700, 19 000, and 11 700); $\nu_{max.}$ 1 620, 1 690, and 1 730 cm^{-1}; τ 2.4—3.0 (4 H, m), 5.62 (2 H, s), and 6.10, 6.30, and 6.33 (each 3 H, s); *m/e* 261 (M^+, 46%), and 228 (100).

3-Carboxy-1-methylindol-2-ylacetic acid (6; R = H).—The ester (6; R = Me) (19 g) was dissolved in EtOH (40 ml) and boiled (30 min) with a solution of KOH (17 g) in H_2O (40 ml) and EtOH (40 ml). Water (50 ml) was added followed by a large excess of hydrochloric acid, yielding (6; R = H) (16.1 g), m.p. 261 °C (lit.,[11] 262 °C); $\nu_{max.}$ 1 650, 1 700, and 2 150—3 400 cm^{-1}; *m/e* 233 (M^+, 3%), 189 (42), and 144 (100). The acid (15.3 g) was suspended in acetic anhydride (100 ml); the mixture was boiled under reflux (30 min) and cooled, and the anhydride (7) was collected and washed with acetone (yield 13.7 g), m.p. 252—253 °C (lit.,[11] 253—254 °C); $\nu_{max.}$ 1 745 and 1 755 cm^{-1}; τ(CF_3CO_2H) 1.9—2.0 (1 H, m), 2.4—2.6 (3 H, m), 5.64 (2 H, s), and 6.15 (3 H, s); *m/e* 215 (M^+, 90%), 271 (100), 143 (95), and 128 (26).

N-Methylisotryptophol (10).—The anhydride (7) (15.2 g) was suspended in EtOH (500 ml) and the mixture boiled under reflux (4 h). The undissolved material was then allowed to settle, and the ethanol decanted and replaced by fresh EtOH (500 ml). This boiling and decanting was continued until most of the solid had dissolved (total 2.5 l of EtOH). The ethanolic solution was concentrated to *ca.* 40 ml and the solid (17.4 g) collected.

2-Ethoxycarbonylmethyl-1-methylindole-3-carboxylic acid (8; R = Et) formed needles, m.p. 202—203 °C (Found: C, 64.2; H, 5.9; N, 5.5. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.8; N, 5.4%); $\lambda_{max.}$ 216, 230sh, 250sh, and 288 nm (ε 20 100, 15 700, 5 200, and 9 000); $\nu_{max.}$ 1 660, 1 730, and 3 300—3 650 cm^{-1}; τ 1.6—1.8 (1 H, m), 2.6—2.75 (3 H, m), 5.54 (2 H, s), 5.75 (2 H, q, *J* 7.5 Hz), 6.23, (3 H, s), and 8.7 (3 H, t, *J* 7.5 Hz); *m/e* 261 (M^+, 48%), 217 (15), 188 (100), and 144 (42). The half-ester (16.5 g) was melted *in vacuo* (3 min) and the liquid distilled (b.p. 195—205 °C at 0.2 mmHg). *Ethyl 1-methylindol-2-ylacetate* (9; R = Et) had m.p. 46—48 °C (yield 9.9 g) (Found: C, 72.3; H, 7.0; N, 6.6. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 6.9; N, 6.5%); $\lambda_{max.}$ 221, 273sh, 280, and 292sh nm (ε 50 000, 11 000, 11 500, and 9 500); $\nu_{max.}$ 1 745 cm^{-1}; τ 2.3—2.5 (1 H, m), 2.7—3.0 (3 H, m), 3.58 [1 H, s, 3-H], 5.88 (2 H, q, *J* 7.5 Hz), 6.27 (2 H, s), 6.34 (3 H, s), and 8.8 (3 H, t, *J* 7.5 Hz); *m/e* 217 (M^+, 22%) and 144 (100%). The anhydride (7) (11.1 g) was suspended in Bu^nOH (500 ml) and the mixture boiled until all the anhydride had dissolved (2 h). The solution was then concentrated to small volume, cooled and *2-n-butoxycarbonylmethyl-1-methylindole-3-carboxylic acid* (8; R = Bu^n) collected, (13.9 g), m.p. 189—190 °C (Found: C, 66.5; H, 6.4; N, 4.9. $C_{16}H_{19}NO_4$ requires C, 66.4; H, 6.5; N, 4.9%); $\nu_{max.}$ 1 660, 1 725, and 3 300—3 650 cm^{-1}; τ[$(CD_3)_2SO$] —2 (1 H, br, OH), 1.9—2.0 (1 H, m), 2.4—2.9 (3 H, m), 5.58 (2 H, s), 5.9 (2 H, t, *J* 6 Hz), 6.30 (3 H, s), 8.4—8.9 (4 H, m), and 9.15 (3 H, t, *J* 6 Hz); *m/e* 289 (M^+, 40%), 245 (7), 215 (100), 188 (73), and 144 (20). Heating the acid *in vacuo* followed by distillation afforded *n-butyl 1-methylindol-2-ylacetate* (9; R = Bu^n), m.p. 33—34 °C (Found: C, 73.1; H, 7.7; N, 5.8. $C_{15}H_{19}NO_2$ requires C, 73.3; H, 7.7; N, 5.7%); $\nu_{max.}$ 1 730 cm^{-1}; τ 2.4—3.0 (4 H, m), 3.62 (1 H, s), 5.9 (2 H, t, *J* 6 Hz), 6.23 (2 H, s), 6.35 (3 H, s), 8.4—8.9 (4 H, m), and 9.12 (3 H, t, *J* 6 Hz); *m/e* 245 (M^+, 15%), and 144 (100). Reduction ($LiAlH_4$) of (9; R = Et) and of (9; R = Bu) in Et_2O (room temperature, 1 h) gave *2-(1-methylindol-2-yl)ethanol* (10) (88% yield), sublimed (0.1 mmHg), m.p. 60—61 °C (Found: C, 75.5; H, 7.4; N, 7.9. $C_{11}H_{13}NO$ requires C, 75.4; H, 7.4; N, 8.0%); $\lambda_{max.}$ 223, 283, and 292 nm (ε 23 900, 5 900, and 4 100); $\nu_{max.}$ 3 100—3 500 cm^{-1}; τ 2.55—2.7 (1 H, m), 2.8—3.2 (3 H, m), 3.9 (1 H, s), 6.3 (2 H, t, *J* 7 Hz), 6.50 (3 H, s), 7.22 (2 H, t, *J* 7 Hz), and 7.8—8.0 (1 H, s, exchanged with D_2O); *m/e* 175 (M^+, 28%), 144 (100, m* 118.5), 158 (8), and 130 (3, m* 95.1). The *tosyl derivative* (prepared in pyridine, 0 °C, and recrystallised from dichloromethane) had m.p. 134—135 °C (Found: C, 65.7; H, 5.7; N, 4.3; S, 9.6. $C_{18}H_{19}NO_3S$ requires C, 65.7; H, 5.8; N, 4.3; S, 9.7%).

2-(3-Hydroxymethyl-1-methylindol-2-yl)ethanol (11; R = OH).—To a cold (5 °C) stirred suspension of $LiAlH_4$ (1.5 g) in dry THF (15 ml) was added (5 min) a solution of (6; R = Me) (4 g) in THF (20 ml). After 15 min at room temperature the usual work-up gave a solid which was recrystallised from benzene. The *glycol* (11; R = OH) (65% yield) had m.p. 106—107 °C (Found: C, 70.1; H, 7.2; N, 6.7. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.3; N, 6.8%); $\lambda_{max.}$ 225, 283, and 292sh nm (ε 38 100, 9 000, and 7 800); $\nu_{max.}$ 3 060—3 550 cm^{-1}; τ 2.3—2.55 (1 H, m), 2.7—3.1 (3 H, m), 5.3 (2 H, s), 6.25—6.55 (5 H, m, NMe +

$ArCH_2$), and 7.07, (2 H, t, *J* 5.5 Hz); *m/e* 205 (M^+, 77%), 187 (35), 157 (100), and 130 (34). Chromatography of the mother-liquors afforded 1,3-dimethylisotryptophol (11; R = H) (30 mg), identical (i.r.) with an authentic sample,[12] and (11; R = OH) (0.12 g). Attempted tosylation of the glycol (11; R = OH) gave the tosyl derivative of (10) (35%). Sublimation of the glycol gave an oil (39%), b.p. 155—163 °C at 10 mmHg, shown (u.v. and i.r.) to be 1,2,3-trimethylindole.

N-Methylisotryptophol (1 g) and benzaldehyde (0.66 g) were dissolved in AcOH (10 ml) under nitrogen. After 24 h the solution was neutralised ($NaHCO_3$ aq) and extracted with ether. The dried solution was evaporated and the residue recrystallised from cyclohexane (0.48 g). 1,3,4,5-*Tetrahydro-5-methyl-1-phenylpyrano*[4,3-b]*indole* (12; R^1 = Ph, R^2 = H) formed fine needles, m.p. 97—99 °C (Found: C, 82.1; H, 6.5; N, 5.4. $C_{18}H_{17}NO$ requires C, 82.1; H, 6.5; N, 5.3%); $\lambda_{max.}$ 228 and 292 nm (ε 31 000 and 7 500); τ 2.5—3.4 (9 H, m), 3.85 (1 H, s), 6.35 (3 H, s), 6.65 (2 H, t, *J* 7 Hz), and 7.10 (2 H, t, *J* 7 Hz); *m/e* 263 (M^+, 87%), 186 (100), and 144 (97). The p-*methoxyphenyl* compound (12; R^1 = *p*-methoxyphenyl, R^2 = H) formed needles, m.p. 123—124 °C (Found: C, 77.7; H, 6.5; N, 4.8. $C_{19}H_{19}NO_2$ requires C, 77.8; H, 6.5; N, 4.8%); $\lambda_{max.}$ 228 and 287 nm (ε 29 400 and 7 100); τ 2.7—3.2 (8 H, m), 3.9 (1 H, s), 6.25 (3 H, s), 6.33 (3 H, s), 6.64 (2 H, t, *J* 7 Hz), and 7.1 (2 H, t, *J* 7 Hz).

Compound (10) (0.87 g) and acetone (0.6 g) were dissolved in THF (10 ml) and BF_3–Et_2O (1.2 g) was added. The mixture was boiled (2 h) under N_2, cooled, and ice added followed by aqueous NaOH (2M). Ether extraction followed by recrystallisation (cyclohexane) of the residue afforded 1,3,4,5-*tetrahydro-1,1,5-trimethylpyrano*[4,3-b]*indole* (12; R^1 = R^2 = Me) (0.91 g), m.p. 127—129 °C (Found: C, 78.1; H, 8.0; N, 6.5. $C_{14}H_{17}NO$ requires C, 78.1; H, 7.9; N, 6.5%); $\lambda_{max.}$ 217, 286, and 292 nm (ε 24 900, 7 300, and 7 000); τ 2.4—3.0 (4 H, m), 6.0 (2 H, t, *J* 6 Hz), 6.5 (3 H, s), 7.32 (2 H, t, *J* 6 Hz), and 8.4 (6 H, s); *m/e* 215 (M^+, 20%), 200 (100), and 158 (27).

To a solution of (10) (1 g) in DMSO (1 ml) was added $CbsN_3$ (2.5 g) in DMSO (2 ml). After 2 d, water (20 ml) was added and the mixture stirred. The aqueous layer was decanted and acetonitrile (5 ml) added to the solid residue. Next day the orange solid (0.35 g) was collected and washed with EtOH (30 ml); the *azo-compound* (13) had m.p. 240—246 °C (decomp) (Found: C, 69.3; H, 6.5; N, 14.3. $C_{22}H_{24}N_4O_2$ requires C, 70.2; H, 6.4; N, 14.9%); $\lambda_{max.}$ ($CHCl_3$) 255sh, 280, 300sh, 383, 402, and 425 nm (ε 16 000, 13 000, 10 000, 24 000, 24 500, and 24 300); $\nu_{max.}$ 3 100—3 600 cm^{-1}; τ[$(CD_3)_2SO$] 1.5—1.8 (2 H, m), 2.4—2.6 (2 H, m), 2.6—3.0 (4 H, m), 5.1 (2 H, t, *J* 6 Hz, exchanged with D_2O), 6.15 (6 H, s), and 6.0—6.7 (8 H, m); *m/e* 376 (M^+, 60%), 346 (10), and 159 (100). From the mother-liquors a second crop (0.35 g) was obtained on standing. The combined mother-liquors and washings were concentrated and kept at 0 °C yielding 3-p-*chlorophenylsulphonylamino*-2-(2-*hydroxyethyl*)-1-*methylindole* (14) (0.4 g), prisms, m.p. 188—189 °C (Found: C, 56.5; H, 4.7; N, 7.7; S, 8.9. $C_{17}H_{17}ClN_2O_3S$ requires C, 56.2; H, 4.4; N, 7.7; S, 8.8%); $\lambda_{max.}$ 230, 288, and 300sh nm (ε 42 000, 9 300, and 6 700); $\nu_{max.}$ 3 240 (NH) and 3 570 (OH) cm^{-1}; τ[$(CD_3)_2SO$] 2.32 (2 H, d, *J* 9 Hz), 2.5 (2 H, d, *J* 9 Hz), 2.6—3.3 (4 H, m), 6.35 (3 H, s), 6.5 (2 H, t, *J* 8 Hz), and 7.2 (2 H, t, *J* 8 Hz); *m/e* 364 (M^+, 5%), 189 (44), and 159 (100).

3,5-*Dimethylpyrano*[4,3-b]*indol*-1(5H)-*one* (17).—(*a*) The acid (6; R = H) (2.9 g) was added to a solution of AcONa (0.9 g, anhydrous) in Ac_2O (100 ml). The mixture was boiled (20 min), cooled, and the solid collected (2.3 g). The *pyran* (17) formed needles (from MeCN), m.p. 223—224 °C (Found: C, 73.2; H, 5.2; N, 6.5. $C_{13}H_{11}NO_2$ requires C, 73.2; H, 5.2; N, 6.6%); $\lambda_{max.}$ 243, 247, and 313 nm (ε 41 300, 59 600, and 14 000); $\nu_{max.}$ 1 640 and 1 720 cm^{-1}; τ 1.8—2.0 (1 H, m), 2.6—2.8 (3 H, m), 3.72 (1 H, s), 6.32 (3 H, s), and 7.65 (3 H, s); *m/e* 213 (M^+, 100%), 198 (81), 170 (10), and 142 (21). (*b*) The acid (3.1 g) was boiled (30 min) with Ac_2O (100 ml) containing pyridine (0.8 g); yield of (17) 2.46 g. At room temperature the acid (6; R = H) gave the anhydride (7) and not (17).

4,5-*Dihydro-5-methyl-4-trifluoroacetylpyrano*[4,3-b]*indole-1,3-dione* (20).—TFAA (3 ml) was added dropwise to a stirred solution of (6; R = H) (0.5 g) in dry pyridine (5 ml) at 0 °C. After 30 min, ice (20 g) was added and the mixture neutralised (aqueous $NaHCO_3$). The *ketone* (20) was collected (0.6 g) and washed with MeOH, m.p. 217—218 °C (Found: C, 54.1; H, 2.6; N, 4.6. $C_{14}H_8F_3NO_4$ requires C, 54.0; H, 2.6; N, 4.5%); $\lambda_{max.}$ 225, 249, and 318 nm (ε 15 900 24 300 and 10 900); $\nu_{max.}$ 1 680, 1 740, and 2 700—3 200 cm^{-1}; τ 1.9—2.6 (4 H, m), 3.3—3.8 (1 H, br s, exchanged with D_2O), and 6.05 (3 H, s); δ_F − 10.5 p.p.m. (from TFA); *m/e* 267 ($M - CO_2$, 100%), 250 (20), and 198 (267 − CF_3, 78).

2,5-*Dihydro-2,3,5-trimethylpyrido*[4,3-b]*indol*-1-*one* (21).—The pyran (17) (0.98 g) was mixed with aqueous methylamine (75 ml; 25%) and EtOH (25 ml). The mixture was heated (70 °C, 2 d), cooled, and neutralised (HCl; 2M). The precipitate was collected and recrystallised from dichloromethane (yield 0.66 g), m.p. 197—199 °C (Found: C, 74.3; H, 6.1; N, 12.4. $C_{14}H_{14}N_2O$ requires C, 74.3; H, 6.2; N, 12.4%); $\lambda_{max.}$ 243, 249, 311, and 325 nm (ε 52 900, 61 200, 17 000, and 20 100); $\nu_{max.}$ 1 670 cm^{-1}; τ 1.6—1.8 (1 H, m), 2.6—2.9 (3 H, m), 4.00 (1 H, s), 6.49 (3 H, s), 6.51 (3 H, s), and 7.70 (3 H, s); *m/e* 226 (M^+, 100%), 211 (30), and 196 (20).

4-(NN-*Dimethylaminomethylene*)-4,5-*dihydro-5-methylpyrano*[4,3-b]*indole-1,3-dione* (22).—Phosphorus oxychloride (1.54 g) was added dropwise to a stirred (0 °C) solution of (6; R = H) (2.3 g) in DMF (7.3 ml). The mixture was stirred at 0 °C for 45 min and then for 1 h at room temperature. Ice was then added, and the solid was collected, washed with water, and recrystallised (MeCN). The *compound* (22) formed yellow needles (2.48 g), m.p. 238—240 °C (Found: C, 66.7; H, 5.3; N, 10.3. $C_{15}H_{14}N_2O_3$ requires C, 66.7; H, 5.2; N, 10.4%); $\lambda_{max.}$ 218, 237, 291, and 365 nm (ε 29 100, 29 000, 13 800, and 8 600); $\nu_{max.}$ 1 685 and 1 730 cm^{-1}; τ[$(CD_3)_2SO$] 1.58 (1 H, s), 2.1—2.3 (1 H, m), 2.5—2.9 (3 H, m), 6.2 (3 H, s, 5-Me), 6.5 (3 H, s), and 6.8 (3 H, s); *m/e* 270 (M^+, 73%), 227 (29), 187 (100), and 155 (68). Heating the $POCl_3$–DMF mixture on a steam-bath (8 h) gave compound (22) (yield 82%) and not (23).

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