Fluorination of Benzofuran and of *N*-Acylindoles with Trifluorofluoro-oxymethane

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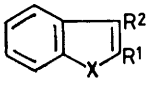
The reactions of certain heteroaromatic substrates with trifluorofluoro-oxymethane gave $CF_3O(F)$ and F(F) adducts. Subsequent reactions with base regenerated the heteroaromatic system substituted by fluoro or trifluoromethoxy. Under these conditions methyl 1-acetylindol-3-ylacetate gave 1-acetyl-2-hydroxy-3-methoxycarbonylmethylene-indoline.

REACTION of trifluorofluoro-oxymethane with olefins gives the expected electrophilic addition product but with *cis*-stereochemistry.[1] Heteroaromatic substrates should permit further study of regio- and stereo-selectivity. The reactions of benzofuran (1a) and of substituted indoles with trifluorofluoro-oxymethane are described here.

Benzofuran (1a) gave three products with trifluoro-fluoro-oxymethane at −78 °C. Two were $CF_3O(F)$ adducts. Their constitution as 2-fluoro-3-trifluoro-methoxy-derivatives followed from the n.m.r. spectra, showing a low-field signal in each case for the proton geminal to fluorine. Analysis of coupling constants suggested the identification of the *trans*-isomer (2a) ($J_{H,H}$ 0, $J_{H,F}$ 60 and 15, J_{F,CF_3O} 0 Hz), which was less polar than the major product, the *cis*-isomer (3a) ($J_{H,H}$ 4, $J_{H,F}$ 62 and 17, J_{F,CF_3O} 3.5 Hz). The third compound was the difluoro-adduct (3b), for which satisfactory microanalytical data were not obtained.

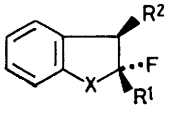
The corresponding reaction of benzofuran (1a) in methanol gave, in addition to the adducts (2a) (44%), (3a) (2%), and (3b) (9%), 2-fluoro-3-methoxy-2,3-dihydrobenzofuran (2b). The configuration assigned to (2b) was based on coupling constants [2] (see Experimental section).

Both *trans*- (2a) and *cis*- (3a) 2-fluoro-3-trifluoro-methoxy-2,3-dihydrobenzofuran gave 3-trifluoromethoxybenzofuran (1b) on reaction with ethanolic potassium



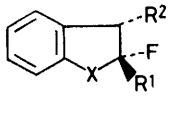
(1)

a; X = O, R^1 = R^2 = H
b; X = O, R^1 = H, R^2 = OCF_3
c; X = O, R^1 = H, R^2 = F
d; X = O, R^1 = H, R^2 = OMe
e; X = NH, R^1 = R^2 = H
f; X = NAc, R^1 = R^2 = H
g; X = NH, R^1 = H, R^2 = OCF_3
h; X = NH, R^1 = H, R^2 = F
i; X = NCHO, R^1 = Me, R^2 = H
j; X = NCHO, R^1 = Me, R^2 = OCF_3
k; X = NH, R^1 = Me, R^2 = OCF_3
l; X = NH, R^1 = Me, R^2 = F
m; X = NH, R^1 = H, R^2 = $CH_2 \cdot CO_2H$
n; X = NH, R^1 = H, R^2 = $CH_2 \cdot CO_2Me$
o; X = NAc, R^1 = H, R^2 = $CH_2 \cdot CO_2Me$
p; X = NH, R^1 = H, R^2 = $CO \cdot CO_2Me$
q; X = NAc, R^1 = H, R^2 = $CO \cdot CO_2Me$
r; X = NAc, R^1 = H, R^2 = $CH(OH) \cdot CO_2Me$



(2)

a; X = O, R^1 = H, R^2 = OCF_3
b; X = O, R^1 = H, R^2 = OMe
c; X = NAc, R^1 = H, R^2 = OCF_3



(3)

a; X = O, R^1 = H, R^2 = OCF_3
b; X = O, R^1 = H, R^2 = F
c; X = NAc, R^1 = H, R^2 = OCF_3
d; X = NAc, R^1 = H, R^2 = F

[1] D. H. R. Barton, L. J. Danks, A. K. Ganguly, R. H. Hesse, G. Tarzia, and M. M. Pechet, *J.C.S. Perkin I*, 1976, 101.

[2] M. P. Mertes, L. J. Powers, and E. Shelter, *J. Org. Chem.*, 1971, **36**, 1805.

hydroxide. That the n.m.r. spectrum of the product exhibited a singlet at δ 7.5 (2-H) supported the regiospecificity of the formation of the adducts (2a) and (3a). The presumed difluoride (3b) also reacted with ethanolic potassium hydroxide to give 3-fluorobenzofuran (1c). The *trans*-fluoro-methoxy-adduct (2b) with ethanolic potassium hydroxide gave 3-methoxybenzofuran (1d).

The reaction of indole (1e) and some derivatives with trifluorofluoro-oxymethane was also investigated. Indole (1e) and CF_3OF gave only complex mixtures. However, on protection of the nitrogen atom, as in 1-acetylindole (1f), a clean reaction with CF_3OF was observed. The three products, separated by chromatography, were identified as *trans*-1-acetyl-2-fluoro-3-trifluoromethoxy-2,3-dihydroindole (2c), the *cis*-isomer (3c), and 1-acetyl-2,3-difluoro-2,3-dihydroindole (3d). The structures were fully consistent with spectral data. Again the constitution and relative configurations followed from the n.m.r. spectra. The difluoride (3d) was probably of *cis*-stereochemistry. Reaction of the adducts with ethanolic potassium hydroxide gave 3-trifluoromethoxyindole (1g) and 3-fluoroindole (1h), thus confirming the assigned constitutions.

Fluorination of crystalline 2-methylindole-1-carbaldehyde (1i) with CF_3OF gave an unstable product. Spectral data showed that this contained the trifluoromethoxy-derivative (1j). When the indole (1i) was treated with CF_3OF and subsequently with sodium hydroxide in methanol a mixture of 2-methyl-3-trifluoromethoxyindole (1k) and 3-fluoro-2-methylindole (1l) was obtained. The two compounds were separated by fractional crystallisation.

The reaction of benzofuran (1a) and of the various substituted indoles with CF_3OF must proceed by electrophilic fluorination at C-2 followed by nucleophilic capture of the C-3 cation. There is some analogy for this.[3] It is of interest that in the reactions of both benzofuran and *N*-acetylindole with CF_3OF the preponderant product (in total ratio $>4:1$) is the *cis*-isomer. This agrees with our earlier findings.[1] In contrast, in the reaction of benzofuran when the nucleophile (MeO^-) arises externally from the medium the only product detected is the *trans*-isomer (2b).

Since reactions of both 1-acetylindole (1f) and 1-acetyl-2-methylindole (1i) with CF_3OF followed by treatment with base gave the 3-fluoro- and 3-trifluoromethoxy-derivatives, it was of interest to examine the reaction of a 3-alkylindole. Indol-3-ylacetic acid (1m), an auxin, was chosen for study since substitution might provide biologically interesting derivatives. Reaction of methyl 1-acetylindol-3-ylacetate (1o) with CF_3OF gave a mixture of two $CF_3O(F)$ adducts. The n.m.r. spectra suggested formulation as the diastereoisomeric adducts (4). Clearly the fluoro- substituent was at the 2-position (δ_H 6.5, J 60 Hz). Since the products were unstable they were treated with base. Sodium hydrogen carbonate or methoxide in methanol, and 1,4-diazabicyclo[2.2.2]octane in dioxan or pyridine, gave mostly mixtures of polar products. 1,4-Diazabicyclo[2.2.2]-octane in THF gave a single major product. Analysis and mass spectral data indicated the composition $C_{13}H_{13}NO_4$. The ester and *N*-acetyl functions were retained intact. In addition the n.m.r. spectrum of the compound contained a proton signal coupled to both a hydroxy and a vinylic proton signal. Clearly the product was 1-acetyl-2-hydroxy-3-methoxycarbonylmethyleneindoline (5), although the stereochemistry could not be assigned. The u.v. spectrum suggested that the alternative methyl 1-acetylindol-3-ylglycolate (1r) was not formed. This was confirmed by synthesis of compound (1r) as follows.

Oxalylation and subsequent methanolysis of indole (1e) gave methyl indol-3-ylglyoxylate (1p). *N*-Acetylation and subsequent reduction with aluminium amalgam gave the known [4] but poorly characterised glycolate derivative (1r), clearly different from the fluorination product (5).

The methyleneindoline derivative (5) was inert to manganese dioxide, neutral permanganate, or Sarrett reagent at room temperature. Reaction with Jones reagent or dimethyl sulphoxide–acetic anhydride–pyridine gave, interestingly, the glyoxylate derivative (1q). In addition, on refluxing in aqueous acetic acid the methyleneindoline derivative (5) gave the glycolate derivative (1r), identical with synthetic material. Mechanisms for the preparation and subsequent reactions of the methyleneindoline derivative (5) are summarised in the Scheme.

In a recent publication on template functionalisation of steroids, Breslow [5] has commented on our demonstration [6] of selective functionalisation of steroids and other compounds at tertiary positions using fluorine and suggested that these reactions are radical reactions and not electrophilic replacements as we have advocated. Although most of the data can be interpreted in either way, the fact that steroids are substituted at C-14 with retention of configuration (14α) makes us disfavour the suggestion of a radical intermediate. A radical at C-14 would at once provide the mechanistic opportunity for the formation of the more stable 14β-configuration, which we do not detect. Our interpretation of electrophilic replacement of hydrogen at a tertiary centre has analogy in oxyfunctionalisation,[7] a process which is viewed in similar mechanistic terms.

A recent important publication [8] on radical fluorination by photolysis of CF_3OF also requires some modification. It is stated that ' Electrophilic fluorination of

[3] J. C. Powers, ' The Chemistry of Heterocyclic Compounds, (Indoles Part II),' Wiley–Interscience, New York, 1972, p. 131.

[4] W. Reeve, R. S. Hudson, and C. W. Woods, *Tetrahedron*, 1963, **19**, 1243.

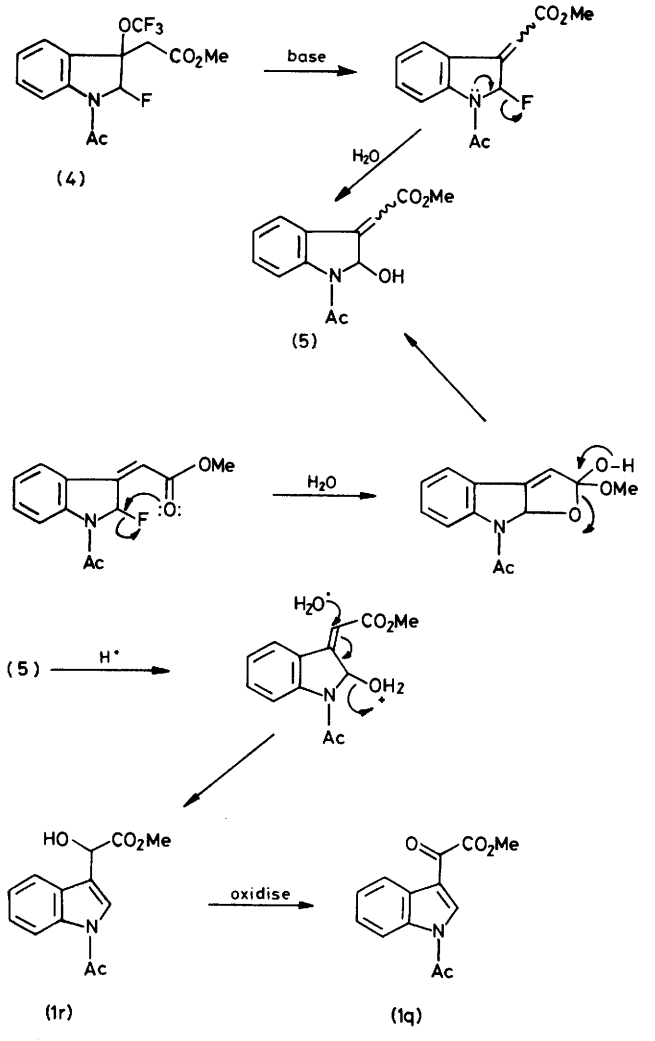
[5] R. Breslow, R. J. Corcoran, B. B. Snider, R. J. Doll, P. L. Khanna, and R. Kaleya, *J. Amer. Chem. Soc.*, 1977, **99**, 905.

[6] D. H. R. Barton, R. H. Hesse, R. F. Markwell, M. M. Pechet, and S. Rosen, *J. Amer. Chem. Soc.*, 1976, **98**, 3036.

[7] N. C. Deno, personal communication; G. A. Olah, N. Yoneda, and D. G. Parker, *J. Amer. Chem. Soc.*, 1977, **99**, 483, and references there cited; N. C. Deno and L. A. Messer, *J.C.S. Chem. Comm.*, 1976, 1051.

[8] J. Kollonitsch and L. Barash, *J. Amer. Chem. Soc.*, 1976, **98**, 5591.

olefins as well as of activated aromatics by CF_3OF was first described by Cady and Porter.'[9] This statement is untrue. Cady and Porter[9] made an important contribution to CF_3OF chemistry but all their reactions were



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radical in character and involved deactivated (fluorinated) olefins. The first reference to the concept of electrophilic fluorination by fluoro-oxy-compounds is from this Institute.[10]

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded for potassium bromide discs (solids) or liquid films. U.v. and n.m.r. spectra were recorded for solutions in methanol or deuteriochloroform (tetramethylsilane reference), respectively. Compounds from chromatography are listed in order of increasing polarity. Freon refers to trichlorofluoromethane.

Reaction of Benzofuran (1a) *with Trifluorofluoro-oxymethane.*—(a) *In Freon.* Gaseous CF_3OF (600 ml) was added at 10 ml min^{-1} to benzofuran (1a) (2.16 g) in Freon (500 ml) at −78 °C. The solution was purged with nitrogen and added to aqueous sodium hydrogen carbonate. The organic phase was washed with water, dried, and evaporated, and the residue was chromatographed on silica (400 g) to give (monitoring by g.l.c.) trans-2-*fluoro*-3-*trifluoromethoxy*-2,3-*dihydrobenzofuran* (2a) (590 mg, 15%) as an oil, $\nu_{max.}$ 1 250 cm^{-1}, $\lambda_{max.}$ 271sh (ε 1 600), 276 (2 000), and 282 nm (1 700), δ 7.4 (4 H, m, aryl H), 6.2 (1 H, d, *J* 60 Hz, 2-H), and 5.57 (1 H, d, *J* 15 Hz, 3-H), ϕ^* (p.p.m. upfield from internal $CFCl_3$[6]) + 59 (3 F, OCF_3) and + 138 (1 F, dd, *J* 60 and 15 Hz, 2-F) (Found: C, 48.8; H, 2.9; F, 34.15. $C_9H_6F_4O_2$ requires C, 48.65; H, 2.7; F, 34.2%); cis-2-*fluoro*-3-*trifluoromethoxy*-2,3-*dihydrobenzofuran* (3a) (1.74 g, 43%) as an oil, $\nu_{max.}$ 1 250 cm^{-1}, $\lambda_{max.}$ 269sh (ε 1 500), 275 (2 100), and 280 nm (1 800), δ 7.0 (4 H, m, aryl H) and 6.5—5.1 (2 H, ABX, J_{AB} 4, 62, and 17 Hz), ϕ^* + 60 (3 F, d, *J* 3.5 Hz) and + 140 (1 F, ddq, *J* 62, 17, and 3.5 Hz) (Found: C, 48.8; H, 2.85; F, 34.05%); and *cis*-2,3-difluoro-2,3-dihydrobenzofuran (3b) (0.54 g, 19%) as an oil, $\nu_{max.}$ 1 040 cm^{-1}, $\lambda_{max.}$ 276 (ε 2 000) and 281 nm (1 900), δ 7.2 (4 H, m, aryl H) and 6.8—5.3 (2 H, m, 2- and 3-H), ϕ^* + 145 (1 F, m) and + 198 (1 F, m), *m/e* 156 (M^+).

(b) *In methanol.* Reaction of benzofuran (1a) (2 ml) and CF_3OF (600 ml gas) in methanol (200 ml) at −78 °C gave on chromatography on Florisil (eluant hexane) trans-2-*fluoro*-3-*methoxy*-2,3-*dihydrobenzofuran* (2b) (0.60 g, 40%) as an oil, $\nu_{max.}$ 1 000 cm^{-1}, $\lambda_{max.}$ 268sh (ε 1 800), 275 (2 400), and 282 nm (2 200), δ 7.2 (4 H, m, aryl H), 6.15 (1 H, d, *J* 60 Hz, 2-H), 4.8 (1 H, d, *J* 15 Hz, 3-H), and 3.5 (3 H, s, OMe), ϕ^* + 127 (dd, *J* 60 and 15 Hz) (Found: C, 64.5; H, 5.25; F, 11.15. $C_9H_9FO_2$ requires C, 64.3; H, 5.4; H, 11.3%).

Reaction of the cis-*Adduct* (3a) *with Base.*—*cis*-2-Fluoro-3-trifluoromethoxy-2,3-dihydrobenzofuran (3a) (600 mg) was added to ethanolic 10% potassium hydroxide (10 ml) and the mixture was heated to reflux for 24 h. The solution was partitioned between water and chloroform (3 × 10 ml) and the organic extract dried, evaporated, and distilled to give 3-*trifluoromethoxybenzofuran* (1b) (300 mg, 55%), b.p. 92° at 70 mmHg, $\nu_{max.}$ 1 250 cm^{-1}, $\lambda_{max.}$ 244 (ε 9 200), 275 (2 200), and 282 nm (2 400), δ 7.3 (4 H, m, aryl H) and 7.6 (1 H, s, 2-H), ϕ^* + 61 (s) (Found: C, 53.5; H, 2.35; F, 28.15. $C_9H_5F_3O_2$ requires C, 53.5; H, 2.5; F, 28.2%). Reaction of the *trans*-adduct (2a) and base also gave 3-trifluoromethoxybenzofuran (1b).

Reaction of the Difluoride (3b) *with Base.*—Similar reaction of the difluoride (3b) (300 mg) and ethanolic potassium hydroxide gave 3-fluorobenzofuran (1c) (160 mg, 61%) as an oil, b.p. 50° at 0.5 mmHg, $\lambda_{max.}$ 246 (ε 9 400), 276 (2 600), and 280 nm (2 200), δ 7.4 (1 H, d, *J* 4.5 Hz, 2-H) and 7.5—7.0 (4 H, m, aryl H), ϕ^* + 177 (dd, *J* 4.5 and 1.5 Hz).

Reaction of trans-2-*Fluoro*-3-*methoxy*-2,3-*dihydrobenzofuran* (2b) *with Base.*—Reaction of the adduct (2b) (200 mg) and ethanolic 10% potassium hydroxide overnight at room temperature gave 3-methoxybenzofuran (1d) (105 mg, 60%) as an oil, b.p. 80° at 20 mmHg, $\lambda_{max.}$ 245 (ε 9 500), 275 (2 200), and 281 nm (2 100), δ 7.1 (1 H, s, 2-H), 7.6—7.0 (4 H, m, aryl H), and 3.9 (3 H, s, OMe) (Found: C, 72.75; H, 5.25. Calc. for $C_9H_8O_2$: C, 72.95; H, 5.45%).

Fluorination of 1-*Acetylindole* (1f).—Reaction of 1-acetylindole (1f)[11] (2.0 g) and CF_3OF (400 ml gas) in Freon

[9] R. S. Porter and G. H. Cady, *J. Amer. Chem. Soc.*, 1957, **79**, 5625, 5628.

[10] D. H. R. Barton, L. S. Godinho, R. H. Hesse, and M. M. Pechet, *Chem. Comm.*, 1968, 804.

[11] I. M. Heilbron and H. M. Bunbury, 'Dictionary of Organic Compounds,' vol. III, Eyre and Spottiswood London, 1965, p, 1846.

(300 ml) at −78 °C gave on work-up and chromatography on Florisil (eluant hexane–benzene, 1 : 1) trans-1-*acetyl*-2-*fluoro*-3-*trifluoromethoxy*-2,3-*dihydroindole* (2c) (340 mg, 10%) as an oil, $\nu_{max.}$ 1 700 and 1 300—1 160 cm^{-1}, $\lambda_{max.}$ 237 (ε 14 000), 272 (1 080), 280 (1 250), and 287 nm (1 180), δ 8.4 and 7.2 (4 H, 2 m, C_6H_4), 6.4 (1 H, d, *J* 60 Hz, 2-H), 5.6 (1 H, d, *J* 16 Hz, 3-H), and 2.4 (3 H, s, NCOMe), ϕ^* + 59 (3 F, s, 3-OCF_3) and + 139 br (1 F, d, *J* 70 Hz) (Found: C, 50.2; H, 3.1; F, 28.95; N, 5.3. $C_{11}H_9F_4NO_2$ requires C, 50.2; H, 3.45; F, 28.9; N, 5.3%); a mixture of *trans*- (2c) and *cis*-adducts (3c) (0.83 g, 25%); cis-1-*acetyl*-2-*fluoro*-3-*trifluoromethoxy*-2,3-*dihydroindole* (3c) (1.3 g, 39%), m.p. 70—71°, $\nu_{max.}$ 1 700 and 1 300—1 150 cm^{-1}, $\lambda_{max.}$ 240 (ε 13 900), 276 (1 310), and 284 nm (1 130), δ 8.3 and 7.1 (4 H, s m, C_6H_4), 6.8—5.3 (2 H, AB of ABX, J_{AB} 5 Hz, 2- and 3-H), and 2.3 (3 H, s, NCOMe), ϕ^* + 61 (3 F, d, *J* 3 Hz, 3-OCF_3) and + 154br (1 F, d, *J* 70 Hz, 2-F) (Found: C, 50.3; H, 3.35; F, 29.05; N, 5.2%); a mixture of adducts (3c) and (3d) (0.20 g); and then 1-*acetyl*-2,3-*difluoro*-2,3-*dihydroindole* (3d) (0.32 g, 13%), m.p. 78—79°, $\nu_{max.}$ 1 700 cm^{-1}, $\lambda_{max.}$ 240 (ε 14 100), 278 (1 340), and 285 nm (1 190), δ 8.4 and 7.1 (4 H, 2 m, C_6H_4), 6.9—5.4 (2 H, m, 2- and 3-H), and 2.4 (3 H, s, NCOMe), ϕ^* +158br (1 F, d, *J* 70 Hz) and + 203br (1 F, d, *J* 70 Hz) (Found: C, 60.75; H, 4.9; F, 18.9; N, 7.25. $C_{10}H_9F_2NO$ requires C, 60.9; H, 4.6; F, 19.25; N, 7.1%).

Reaction of the cis-*Adduct* (3c) *and Base*.—Reaction of the *cis*-adduct (3c) (50 g) and potassium hydroxide (100 mg) in ethanol (5 ml) for 1 h at room temperature, work-up, and chromatography on silica (eluant benzene) gave 3-*trifluoromethoxyindole* (1g) (30 mg, 65%), m.p. 49—50° (from hexane), $\nu_{max.}$ 3 450 and 1 250 cm^{-1}, $\lambda_{max.}$ 266sh (ε 5 480), 270 (5 720), 277 (5 620), and 280sh nm (5 400), δ 7.8—6.9 (5 H, m, 1 H exch. D_2O) and 7.3 (1 H, s, 2-H), ϕ^* + 61 (s) (Found: C, 53.6; H, 3.05; F, 28.5; N, 7.05. $C_9H_6F_3NO$ requires C, 53.75; H, 3.0, F, 28.35; N, 6.95%). Reaction of the *trans*-adduct (2c) with ethanolic potassium hydroxide (complete in 5 min) gave 3-trifluoromethoxyindole (1g).

Reaction of the Difluoride (3d) *with Base*.—The difluoride (3d) (25 mg) and ethanolic potassium hydroxide (1 h at room temperature) gave, on work-up, 3-*fluoroindole* (1h) (25 mg, 100%), m.p. room temp., $\nu_{max.}$ 3 500 cm^{-1}, $\lambda_{max.}$ 274 (ε 5 750), 280 (5 960), 284sh (5 600), and 290 nm (4 680), δ 7.9—6.9 (5 H, m, 1 H exch D_2O), and 7.3br (1 H, s, 2-H), ϕ^* + 175br (s, $W_{\frac{1}{2}}$ 6 Hz) (Found: C, 70.9; H, 4.35; F, 14.05; N, 10.35. C_8H_6FN requires C, 71.1; H, 4.5; F, 14.05; N, 10.35%).

Fluorination of 2-*Methylindole*-1-*carbaldehyde* (1i).—CF_3OF (450 ml gas) was added to 2-methylindole-1-carbaldehyde (1i) [12] (2.5 g) in Freon (250 ml) and chloroform (5 ml) at −78 °C. Excess of CF_3OF was removed by purging with nitrogen and sodium hydroxide (10 g) in methanol (200 ml) was added. After 1 h at −78 °C benzene (300 ml) was added and the solution washed with water (3 × 200 ml), dried, evaporated, and chromatographed on Florisil (eluant benzene–hexane 2 : 1) to give 3-*fluoro*-2-*methylindole* (1l) (0.25 g, 11%) as pale yellow plates, m.p. 89—90° (from hexane), $\nu_{max.}$ 3 500 cm^{-1}, $\lambda_{max.}$ 224 (ε 29 100), 275 (6 400), 281 (6 500), and 290 nm (5 300), δ 7.6—6.9 (5 H, m) and 2.3 (3 H, d, *J* 2 Hz), ϕ^* + 180br (s, $W_{\frac{1}{2}}$ 7 Hz) (Found: C, 72.6; H, 5.55; F, 12.6; N, 9.4. C_9H_8FN requires C, 72.45; H, 5.4; F, 12.75; N, 9.4%). Repeated crystallisation of material from the mother liquors from hexane and rechromatography on Florisil (eluant hexane) gave 2-*methyl*-3-*trifluoromethoxyindole* (1k) (0.42 g, 12%) as pale yellow plates, m.p. 49—50°, $\nu_{max.}$ 3 500 and 1 240 cm^{-1}, $\lambda_{max.}$ 217 (ε 36 300), 230sh (8 100), 271 (10 300), 280 (10 000), and 287 nm (8 200), δ 7.6—6.9 (5 H, m) and 2.4 (3 H, s), ϕ^* + 60 (s) (Found: C, 55.75; H, 4.0; F, 26.55; N, 6.55. $C_{10}H_8F_3NO$ requires C, 55.8; H, 3.75; F, 26.5; N, 6.5%). Reaction of 2-methylindole-1-carbaldehyde (1i) with CF_3OF and work-up without base gave an unstable oil, $\nu_{max.}$ (film) 1 710 and 1 250 cm^{-1}, ϕ^* + 60.

Acetylation of Methyl Indol-3-*ylacetate* (1n).—The ester (1n) (9.5 g) was dried by azeotropic distillation with benzene (2 × 20 ml). The residue, potassium acetate (10 g), and acetic anhydride (50 ml) were heated to reflux for 1 h and poured into water (500 ml), and the solution was extracted with dichloromethane (2 × 50 ml). The extracts were dried, evaporated, and distilled to give *methyl* 1-*acetylindol*-3-*ylacetate* (1o) (11.5 g, 85%) as a pale yellow solid, b.p. 165° at 0.1 mmHg, m.p. 65—67°, $\nu_{max.}$ 1 745 and 1 710 cm^{-1}, $\lambda_{max.}$ 238 (ε 19 100), 260 (8 800), 268sh (7 700), 290 (6 650), and 299 nm (7 100), δ 8.5—7.1 (5 H, m, aryl H), 3.7 (5 H, s, OMe, CH_2CO_2), and 2.6 (3 H, s, NCOMe) (Found: C, 67.55; H, 5.6; N, 6.2. $C_{13}H_{13}NO_3$ requires C, 67.6; H, 5.65; N, 6.05%).

Reaction of the Ester (1o) with *Trifluorofluoro-oxymethane*.—Reaction of the ester (1o) (0.46 g) and CF_3OF (100 ml gas) in dichloromethane (50 ml) at −78 °C gave on work-up and chromatography on silica (eluant benzene) an oil, δ 8.4—7.0 (4 H, m), 6.5 (1 H, d, *J* 60 Hz), 3.6 (3 H, 2 s, ratio 5 : 1), and 2.4 (3 H, 2 s, ratio 5 : 1), ϕ^* + 52 (3 F, 2 d, *J* 10 Hz, ratio 5 : 1) and + 145br (1 F, d, *J* 60 Hz). The mixture in tetrahydrofuran (25 ml) and 1,4-diazabicyclo[2.2.2]octane (400 mg) was stirred overnight. P.l.c. on silica (developing solvent chloroform) gave 1-*acetyl*-2-*hydroxy*-3-*methoxycarbonylmethyleneindoline* (5) (295 mg, 60%) as needles, m.p. 134—136° (from hexane), $\nu_{max.}$ 3 400, 1 740, and 1 710 cm^{-1}, $\lambda_{max.}$ 250 (ε 21 200), 256 (21 500), 285 (16 200), 294sh (13 400), and 350 nm (7 300), δ 8.2—6.7 (4 H, m, C_6H_4), 6.4 [1 H, dd, *J* 4 and 2 Hz (with D_2O d, *J* 2 Hz), 2-H], 6.2 (1 H, d, *J* 2 Hz, vinylic H), 5.0 (1 H, d, *J* 4 Hz, exch. D_2O, OH), 3.8 (3 H, s, CO_2Me), and 2.4 (3 H, s, NCOMe) (Found: C, 62.8; H, 5.45; N, 5.65%; *m/e*, 247.0854. $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.3; N, 5.65%; *M*, 247.084 5).

Oxalylation of Indole (1e).—Oxalyl chloride (2.5 ml) was added with stirring over 15 min to indole (1e) (3g) in anhydrous ether (50 ml) at 0—5 °C. After a further 1 h anhydrous methanol (5 ml) was added. Overnight stirring gave methyl indol-3-ylglyoxylate (1p) (2 g, 38%) as plates, m.p. 234—236° (from methanol) (lit.,[4] 230°), $\nu_{max.}$ 3 300, 1 740, and 1 630 cm^{-1}, $\lambda_{max.}$ 255 (ε 9 600), 268 (9 500), 274 (8 100), and 322 nm (9 700), δ 8.4 (1 H, s, 2-H), 8.2 (1 H, m, 7-H), 7.3 (3 H, m), and 4.0 (3 H, s, CO_2Me).

Acetylation of the Glyoxylate (1p).—The glyoxylate (1p) (0.50 g), potassium acetate (2 g), and acetic anhydride (10 ml) were stirred together overnight, poured into water, and extracted with ether (2 × 50 ml). The extracts were washed with aqueous ammonia and water, dried, and evaporated to give methyl 1-acetylindol-3-ylglyoxylate (1q) (0.55 g, 91%) as plates, m.p. 130—132° (from benzene–hexane) (lit.,[4] 130—132°), $\nu_{max.}$ 1 740 and 1 670 cm^{-1}, $\lambda_{max.}$ 224sh (ε 13 300), 250 (10 100), 264sh (7 400), 274 (6 100), and 317 nm (9 500), δ 8.8 (1 H, s, 2-H), 8.3 and 7.4 (4 H, 2 m, C_6H_4), 4.0 (3 H, s, CO_2Me), and 2.8 (3 H, s, NCOMe).

Reduction of the Glyoxylate (1q).—Aluminium amalgam [from aluminium (100 mg)] was added to the glyoxylate

[12] L. Alessandri and M. Passerini, *Gazzetta*, 1921, **51**, 262.

(0.20 g) in diethyl ether (10 ml), methanol (1 ml), and water (0.5 ml). The solution was stirred for 1 h and filtered, and the product was separated by p.l.c. on silica (developing solvent chloroform–methanol, 50 : 1) to give methyl 1-acetylindol-3-ylglycolate (1r) (150 mg, 74%) as needles, m.p. 120—121° (from hexane–diethyl ether) (lit.,[4] 121—123°), $\nu_{max.}$ 1 740 and 1 720 cm^{-1}, $\lambda_{max.}$ 238 (ε 16 800), 260 (7 700), 267sh (6 900), 290 (6 100), and 299 nm (6 700), δ 8.4 (1 H, m, 2-H), 7.4 (4 H, m, C_6H_4), 5.4 (1 H, s, $CH{\cdot}CO_2$), 3.7 (3 H, s, CO_2Me), and 2.6 (3 H, s, NCOMe).

Jones Oxidation of the Indoline Derivative (5).—The indoline (5) (100 mg) in acetone (2 ml) was titrated with Jones reagent until an orange colour persisted. The solution was added to water (20 ml) and extracted with chloroform (2 × 5 ml). Evaporation of the organic phase and chromatography on silica gave methyl 1-acetylindol-3-ylglyoxylate (1q), m.p. and mixed m.p. 130—133° (Found: C, 63.85; H, 4.75; N, 5.75. Calc. for $C_{13}H_{11}NO_4$: C, 63.65; H, 4.5; N, 5.7%).

Oxidation of the Indoline Derivative (5) *with Dimethyl Sulphoxide.*—Acetic anhydride (0.5 ml) and pyridine (1 drop) were added with stirring to the indoline derivative (5) (50 mg) in dimethyl sulphoxide (1 ml). After 1 h water (20 ml) was added and the solution extracted with ether (20 ml). The ether phase was washed with water (2 × 20 ml), dried, and evaporated to give methyl 1-acetylindol-3-ylglyoxylate (1q) (32 mg, 65%) (from hexane), identical with authentic material.

Isomerisation of the Indoline Derivative (5).—1-Acetyl-2-hydroxy-3-methoxycarbonylmethyleneindoline (5) (50 mg) and 50% aqueous acetic acid (2 ml) were heated on a steam-bath for 4 h. Ether (30 ml) was added and the solution washed with water (3 × 50 ml), dried, and evaporated. Crystallisation from hexane gave methyl 1-acetylindol-3-ylglycolate (1r) (40 mg, 80%) as needles, identical with authentic material.

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