The Reactions of 1,2,3-Trimethylindole and of *N*-Alkyltetrahydrocarbazoles with Trifluoroacetic Anhydride [1]

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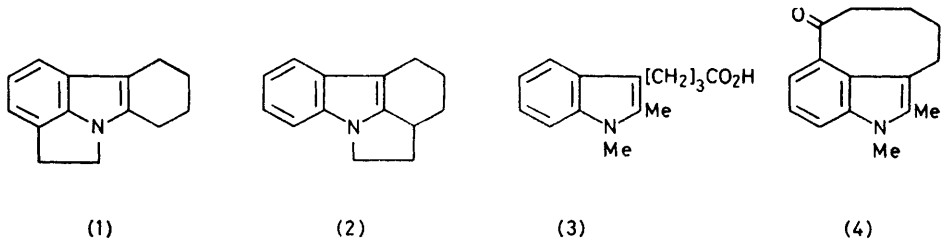
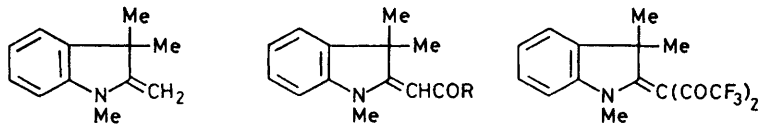
Treatment of 1,2,3-trimethylindole with trifluoroacetic anhydride results in attack on the C-2 methyl group of the indole, and trifluoroacetylation of *N*-alkyltetrahydrocarbazoles occurs at C-1.

We have examined the reactions of the ' strained ' indoles (1) and (2) with azides [2] and hoped to extend this work to cycloalkano[*c*,*d*]indole derivatives. Therefore we attempted to prepare compound (4) by cyclisation of the acid (3). Compound (3) was selected since the presence of a methyl group at C-2 would prevent the normal [1,3] ring closure onto C-2 of the indole ring.

5-Acetylvaleric acid [4] was condensed with *N*-methylphenylhydrazine in ethanolic sulphuric acid [5] affording



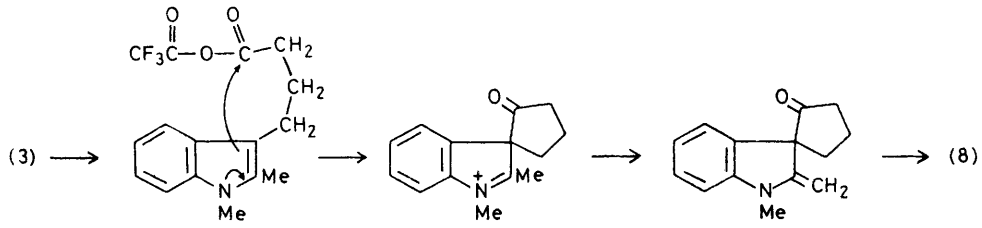
(1) (2) (3) (4) (5) (6) (7) (8)



(9) (10) (11)

(3). All attempts to make the acid chloride of (3) gave tars and therefore the acid (3) was treated with trifluoroacetic anhydride (TFAA) [6] in benzene solution. The expected ketone (4) was not obtained, but a crystalline solid of formula $C_{16}H_{14}F_3NO_2$ was isolated. The n.m.r. spectrum of the compound showed the absence of the Me group at C-2 and three structures, (6), (7), and (8) were considered; (6) and (7) would be formed by trifluoroacetylation on oxygen or on carbon of the ketone (5). The i.r. spectrum of the product showed the presence of two C=O groups (1 740 and 1 650 cm^{-1}) but no band in the OH region, and the u.v. spectrum ($\lambda_{max.}$ 372 nm) was similar to that of (10; R = Me), a compound obtained by acetylation of the Fischer base (9).[7] These data eliminated structures (6) and (7). Further support for structure (8) was provided by the ^{13}C n.m.r. spectrum which contained a signal at δ 66.7 [quaternary carbon, C-3] and at 171.1 p.p.m., characteristic [8] of N–*C*=C–CO. The ^1H n.m.r. spectrum contained a signal at τ 4.35, =CHCO and also two NMe signals (at τ 6.37 and 6.72; ratio 1 : 7) showing that the major component of the compound was the *trans-s-cis* form and the minor the *cis-s-cis* form.[7] The two ' model ' compounds (10; R = CF_3) and (11) were obtained by reaction of (9) with TFAA in pyridine solution; (10; R = CF_3) is best prepared by treating (11) with benzylamine. Compound (10; R = CF_3) exists mainly (8 : 1) in the *trans-s-cis* form; at 90 MHz the =C*H* signal appears as a singlet but at 300 MHz the signal is split: τ 4.54 (major component) and 4.61 (minor component); NMe 6.67 (major) and 6.26 (minor); CMe 8.24 (major) and 8.59 (minor).

We suggest that (8) is formed *via* the mixed anhydride (12) which cyclises to form the ion (13). Loss of a proton from the salt (13) gives the enamine (14), acylation of which yields compound (8) (Scheme 1). The alkylation of 3-substituted indoles at position 3 is well known [1,9] but there are few examples of acylation.[1]

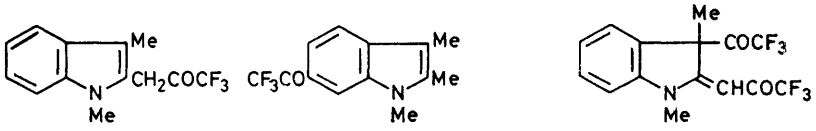


(12) (13) (14)

SCHEME 1

Friedel–Crafts reaction on 1,2,3-trisubstituted indoles leads to substitution at C-6 (ref. 9*a*, p. 36), and we therefore examined the reactions of trisubstituted indoles with TFAA to see whether attack occurred at C-3 or at C-6. Treatment of 1,2,3-trimethylindole with TFAA at 0 °C gave a compound of molecular formula $C_{13}H_{12}F_3NO$. The i.r. spectrum of the compound contained a band at 1 775 cm^{-1}, the u.v. spectrum was that of an indole, and the n.m.r. spectrum contained a signal at τ 5.8 (CH_2-$COCF_3$) but had no signal corresponding to C-2-CH_3. These data eliminated structure (16), and structure (15) was confirmed by alkaline hydrolysis of the material to 1,3-dimethyl-2-indolylacetic acid.[10]

From the reaction between 1,2,3-trimethylindole and TFAA in warm benzene a small (30%) yield of a compound of formula $C_{15}H_{11}F_6NO_2$ was isolated. The compound was very unstable and darkened on standing; its i.r. spectrum contained two C=O bands (1 655 and 1 750 cm^{-1}) and its u.v. spectrum ($\lambda_{max.}$ 373 nm) was similar to that of (10; R = CF_3). We assign structure (17) to this material, this structure being supported by the ^{13}C n.m.r. data [δ_C 61.4 (C-3) and 170.1 p.p.m., (C-2)]. The ^1H n.m.r. spectrum of the compound contained two NMe signals, *trans-s-cis* (τ 6.53), *cis-s-cis* (6.34), ratio 8 : 1. Warming (15) with TFAA yielded (17) and, on boiling in methanol, (17) was converted back into (15). Dissolving either (15) or (17) in aqueous pyridine gave the crystalline hydrate (18). In chloroform solution, (18) formed an equilibrium mixture with the anhydrous form. The hydration of fluorinated ketones is well known.[11] Compounds (15) and (17) arise by the addition of an electrophile E (E = either H^+ or CF_3CO^+) to C-3 of trimethylindole forming the ion (19). Loss of a proton then yields the enamine (20), and trifluoroacetylation of (20) then gives (21) (Scheme 2). Addition of H^+ and loss of E^+ from (21) forms compound (15). The Mannich reaction of 1,2,3-trimethylindole to form (22) [12]



(15) (16) (17)

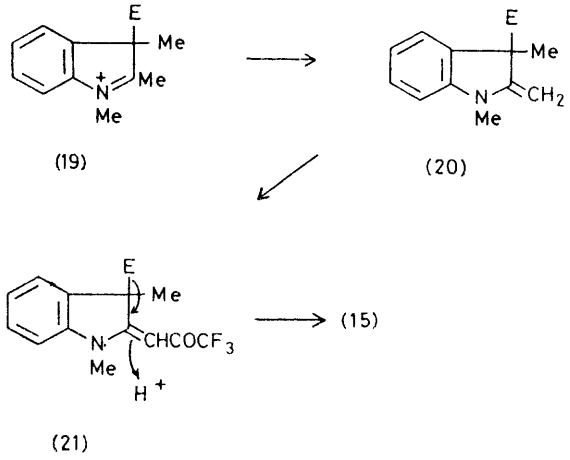
(18) (22)

probably occurs by the addition of (20; E = H) to $CH_2{=}\overset{+}{N}Me_2$.

Treatment of *N*-methyltetrahydrocarbazole with TFAA gave an 80% yield of the 1-trifluoroacetyl derivative (23; R = H). The structure of the compound was proved by alkaline hydrolysis to the acid (24), which was identical with the material obtained by a Fischer indole synthesis from 2-methoxycarbonylcyclohexanone (25) and *N*-methylphenylhydrazine. Compound (23; R = H) was heated with TFAA in benzene solution to see if the presence of a $COCF_3$ group in position 1 would result in substitution of $COCF_3$ in the aromatic ring. The product had the molecular formula $C_{15}H_{12}F_3N$, the u.v.

spectrum was that of a carbazole, and the n.m.r. spectrum contained a quartet [τ 6.08 J 10 Hz, (CH_2CF_3)]. Structure (29; R = H) was assigned to this compound. It is probably formed from the enol acetate (26) *via* (27) and (28) (Scheme 3). The aromatisation of cyclohexenones by treatment with pyridine hydrochloride has been reported.[13]

The ketone (23; R = H) was characterised by reduction to the corresponding alcohol and the formation of the oxime (30). When the oxime was treated with TFA in



SCHEME 2

an attempt [14] to carry out a Beckmann rearrangement a crystalline product, $C_{15}H_{15}F_3N_2O$, was isolated which was not the expected amide (absence of a CO band in the i.r. spectrum). The compound contained an NH group known (ref. 9, pp. 11 and 122). Normally dihydroisoxazoles contain a 2,3 (N=C) double bond rather than a 3,4 (C=C) bond,[16] although there is evidence for the tautomerism of oximes.[17] Dreiding models of (33)

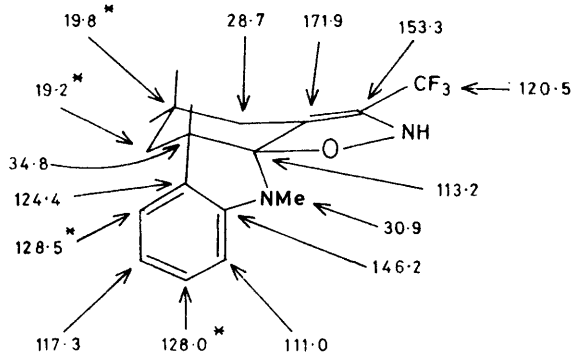
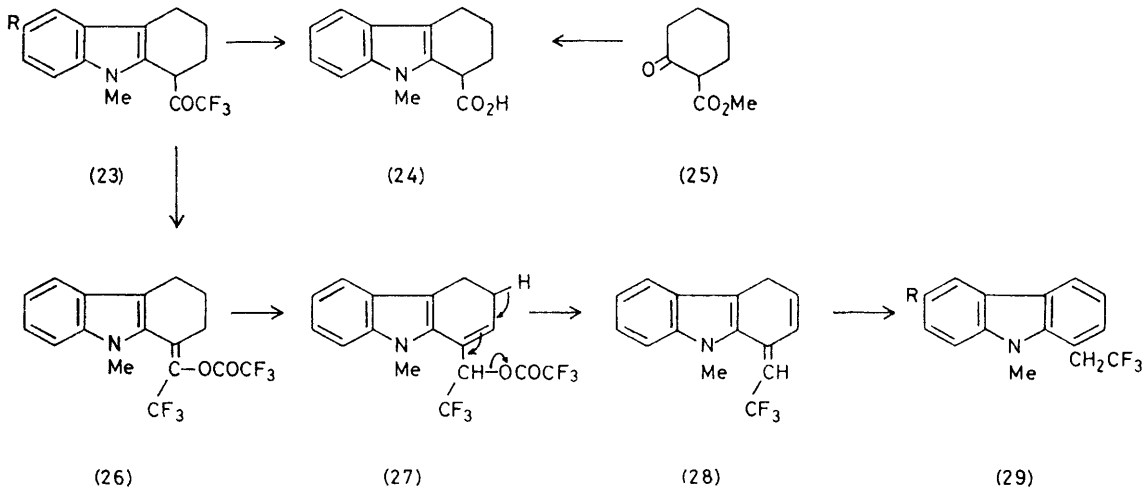


FIGURE 1 ^{13}C N.m.r. absorptions of compound (33)

(Figure 1) show that there is far less crowding in the structure than there is in structure (32) (Figure 2). The assignment of structure (33) to the compound is supported by the ^{13}C n.m.r. spectrum of the material (see Figure 1); the ^{13}C spectrum of a compound of structure (32) would contain signals from two aliphatic C–H groups.

The normal Beckmann rearrangement of (30) was attempted using phosphorus pentachloride in chloroform. A tar was obtained from which a small quantity of crystalline material was isolated by chromatography. The material melted over a wide range, the i.r. spectrum contained a band at 1 700 cm^{-1} (aromatic CO), and the n.m.r. spectrum indicated the absence of aliphatic



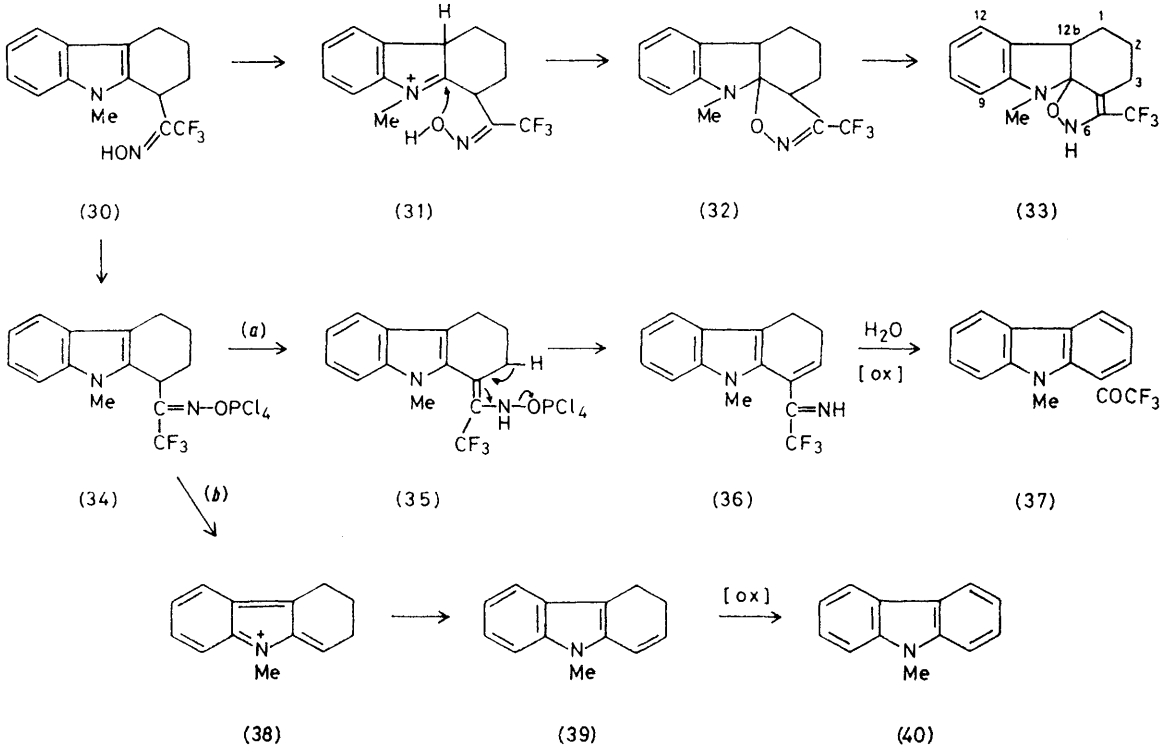
SCHEME 3

(i.r.) and the u.v. spectrum was that of an indoline. We assign structure (33) to this compound and suggest that it is formed by the addition of H^+ to (30) forming the ion (31) which cyclises to form (32) and this then isomerises to (33) (Scheme 4). The cyclisation of tryptamines [15] to form tricyclic systems *via* protonation at C-3 is well

protons, showing the compound to be 1-trifluoroacetyl-*N*-methylcarbazole (37); this was confirmed by dehydrogenation of (23; R = H) to (37). Compound (37) is probably formed by the route indicated *via* (35) and (36). Leuchs [18] has reported that treatment of the oxime (41) with acetyl chloride affords the ketone (42). The form-

ation of 1-naphthylamine from α-tetralone oxime (Semmler Wolff reaction) [19] proceeds by a similar mechanism. The mass spectrum of the sample of (37) obtained from (30) contained a strong signal at *m/e* 181 R = Me or OMe) and further action of TFAA gave the dehydration products (29; R = Me or OMe).

Jackson [22] has shown the effect of introducing a methoxy-group at C(6) [C-7 of tetrahydrocarbazole] on



SCHEME 4

suggesting that the impurity in the sample was *N*-methylcarbazole (40) formed from (34) by route (*b*) *via* (38) and (39); (39) is known [20] to form (40).

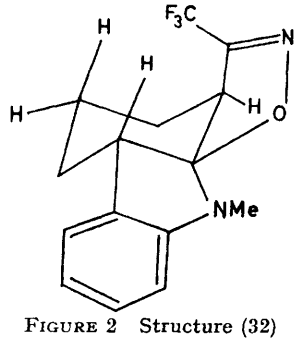
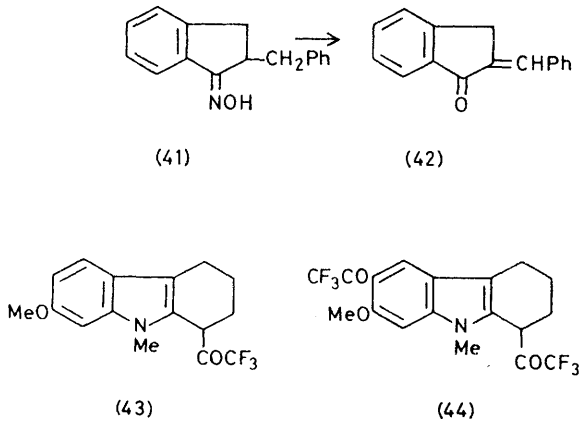


FIGURE 2 Structure (32)

We have examined the reactions of a number of tetrahydrocarbazoles with TFAA to establish the scope of the reaction. *N*-Ethyltetrahydrocarbazole [21] gave the 1-trifluoroacetyl derivative in approximately the same yield as (23; R = H) was obtained from *N*-methyltetrahydrocarbazole. The presence of either a methyl group or a methoxy-group at C-6 did not lead to substitution in the benzene ring. Both 6,9-dimethyltetrahydrocarbazole and 6-methoxy-9-methyltetrahydrocarbazole gave the 1-trifluoroacetyl compounds (23;

the reactivity of the indole nucleus towards electrophilic substitution. We therefore examined the reaction of 7-methoxy-9-methyltetrahydrocarbazole with TFAA. The product was a mixture of two compounds which could be separated by chromatography. The first product to be eluted was the 1-trifluoroacetyl compound (43) followed by a bis-trifluoroacetyl compound. The



^{19}F n.m.r. spectrum indicated two different types of $COCF_3$ groups and we assigned structure (44) to this material. This structure was supported by the ^{1}H n.m.r.

spectrum of the compound which contained two singlets [5-H and 8-H] in the aromatic region. The proportions of the two compounds (43) and (44) in the reaction mixtures was estimated by integration of the ^{19}F n.m.r spectrum. As the reaction time increased from 15 min to 24 h the ratio (43) : (44) changed from 2 : 1 to 1 : 3 showing that trifluoroacetylation was occuring first at position 1 giving (43) which was then further acylated forming (44).

EXPERIMENTAL

General details and instruments used have been reported.[2] U.v. spectra were determined for solutions in ethanol and n.m.r. spectra for solutions in $CDCl_3$ unless otherwise stated. ^{13}C Chemical shifts (δ_C) are in p.p.m. from Me_4Si and ^{19}F shifts (δ_F) in p.p.m. from CF_3CO_2H. ^{13}C Assignments are supported by the observation of C–H coupling but only the completely proton-decoupled spectra are reported. I.r. spectra were recorded for Nujol mulls.

4-(1,2-*Dimethylindol*-3-*yl*)*butyric Acid* (3).—5-Acetylvaleric acid (5 g)[4] was mixed with *N*-methylphenylhydrazine (4.2 g); after 15 min the mixture was heated (100 °C, 10 min). To this hydrazone was then added a mixture of EtOH (93 ml), H_2O (13 ml), and concentrated H_2SO_4 (10 ml).[5] The solution was boiled under reflux (1 h), cooled, and poured onto ice. The mixture was extracted (Et_2O, 3 × 50 ml), the extracts washed (aqueous $NaHCO_3$), and the solvent removed. The residue was boiled (30 min) with a mixture of EtOH (25 ml) and 2M-NaOH (25 ml). The solution was cooled, diluted with water, acidified with hydrochloric acid, and the solid collected. Recrystallisation from benzene–light petroleum (b.p. 60—80 °C) gave the *acid* (3) as tiny cubes, m.p. 109—110 °C (4.85 g) (Found: C, 72.8; H, 7.5; N, 6.2. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%); $\lambda_{max.}$ 230 and 282 nm (ε 27 400 and 4 800); $\nu_{max.}$ 1 700 and 2 500—3 400 cm^{-1}; τ −0.55 (1 H, OH), 2.4—3.0 (4 H, m), 6.37 (3 H, s, NMe), 7.2 (2 H, t, *J* 7 Hz), 7.67 (3 H, s, CMe), 7.5—7.8 (2 H, m), and 7.8—8.2 (2 H, quintuplet, *J* 7 Hz); *m/e* 231 (M^+, 9), 159% (13), 158 (100), and 134 (5).

1-*Methyl*-2-*trifluoroacetylmethyleneindoline*-3-*spirocyclopentan*-2′-*one* (8).—The acid (3) (3 g) in dry benzene (60 ml) was treated dropwise with TFAA (6 ml) at 0 °C. After the initial reaction had subsided the solution was boiled gently under reflux (45 min), cooled, and carefully treated with aqueous sodium carbonate solution. The organic phase was separated, washed with water, dried ($MgSO_4$), and the solvent removed. The oily residue was dissolved in a little MeOH, and the solid which separated was collected and recrystallised (from EtOH). The *ketone* (8) formed needles (yield 33%), m.p. 179—180 °C (Found: C, 62.3; H, 4.7; F, 18.3; N, 4.5. $C_{16}H_{14}F_3NO_2$ requires C, 62.1; H, 4.5; F, 18.4; N, 4.5%); $\lambda_{max.}$ 210, 228sh, 253, and 372 nm (ε 13 200, 9 300, 8 800, and 20 500); $\nu_{max.}$ 1 650 and 1 740 cm^{-1}; τ 2.4—3.2 (4 H, m), 4.35 (1 H, s), 6.37 (NMe, *cis-s-cis*), 6.72 (NMe, *trans-s-cis*), and 6.7—8.0 (6 H, m); δ_F +1; δ_C 20.0 (4′-C), 30.5 (NMe), 34.7 (5′-C), 37.7 (3′-C), 66.7 (3-C), 84.9 (=CH), 109.5 (7-C), 122.2 (5-C), 124.4 (4-C), 128.9 (6-C), 134.3 (3a-C), 143.0 (7a-C), 171.1 (2-C), 174.3 ($COCF_3$), and 210.2 (2′-C); *m/e* 309 (M^+, 31%), 254 (100, *m** 208.9), 252 (4), 212 (7), 185 (15), and 184 (26).

1,3,3-*Trimethyl*-2-*bis*(*trifluoroacetyl*)*methyleneindoline* (11).—Pyridine (6 ml) was added dropwise with stirring to ice-cold TFAA (14.4 g). After 10 min 2-methylene-1,3,3-trimethylindoline (9) (5 g) was added slowly and the mixture stirred (10 min). Ice-water (30 ml) was then added, the solid was collected, and twice recrystallised (EtOH). The *ketone* (11) formed yellow laths, m.p. 135—136 °C, (yield 7.0 g) (Found: C, 52.8; H, 3.7; F, 31.0; N, 4.0. $C_{16}H_{13}F_6NO_2$ requires C, 52.6; H, 3.6; F, 31.2; N, 3.8%); $\lambda_{max.}$ 241, 303, and 380 nm (ε 6 700, 7 900, and 13 500); $\nu_{max.}$ 1 635 cm^{-1}; τ 2.4—2.8 (4 H, m), 6.59 (3 H, s), and 8.50 (6 H, s); δ_F − 1.7; *m/e* 365 (M^+, 13%), 296 (83), 268 (16), 184 (51), 158 (100), and 156 (22).

1,3 3-*Trimethyl*-2-*trifluoroacetylmethyleneindoline* (10; R = CF_3).—(*a*) A mixture of acetic acid (2.1 g) and TFAA (7.4 g) was kept at room temperature for 15 min and then cooled to 0 °C. Dry pyridine (3 ml) was then added and after 5 min compound (9) (2.5 g) was added dropwise and the mixture kept at 0 °C for 15 min. Ice–water (25 ml) was then added and the solid collected. Two recrystallisations (from EtOH) gave needles, m.p. 149—150 °C (yield 31%).

(*b*) A mixture of benzylamine (8 g), pyridine (5 ml), and compound (11) (4 g) was boiled under reflux (30 min), cooled, and poured into water. The solid was collected and recrystallised (yield 68%). The *ketone* (10; R = CF_3) had m.p. 149—150 °C (Found: C, 62.6; H, 5.2; F, 20.9; N, 5.3. $C_{14}H_{14}F_3NO$ requires C, 62.5; H, 5.2; F, 21.9; N, 5.2%); $\lambda_{max.}$ 241 and 365 nm (ε 27 800 and 35 200); $\nu_{max.}$ 1 650 cm^{-1}; δ_C 22.1 (CCH_3), 30.1 (NCH_3), 49.6 (3-C), 84.9 (=CH), 109.1 (7-C), 122.1 (5-C), 124.2 (4-C), 127.9 (6-C), 140.4 (3a-C), 142.7 (7a-C), 175.0 (C=O), and 177.6 (2-C); *m/e* 269 (M^+, 71%), 268 (20), 254 (28), 200 (100), 185 (54), and 157 (32).

1-(1,3-*Dimethylindol*-2-*yl*)-3,3,3-*trifluoropropanone* (15).—1,2,3-Trimethylindole (5 g) in benzene (20 ml) was added dropwise to a cold (0 °C) solution of TFAA (8 g) in benzene (20 ml). The mixture was stirred at 0 °C for 6 h and at room temperature for 2 h. Water was then added, followed by sodium carbonate solution. The organic phase was washed with water, dried, and the solvent removed. Chromatography (SiO_2; CH_2Cl_2) of the resulting oil gave the *ketone* (15) (4.45 g) as plates, m.p. 78 °C [from light petroleum (b.p. 60—80 °C)] (Found: C, 61.0; H, 4.9; F, 22.2; N, 5.5. $C_{13}H_{12}F_3NO$ requires C, 61.2; H, 4.7; F, 22.4; N, 5.5%); $\lambda_{max.}$ 230 and 286 nm (ε 34 800 and 7 300); $\nu_{max.}$ 1 775 cm^{-1}; τ 2.4—3.0 (4 H, m), 5.8 (2 H, s), 6.55 (3 H, s), and 7.8 (3 H, s); δ_C 8.7 (CCH_3), 29.7 (NCH_3), 32.9 (CH_2), 109.1 (3-C), 110.5 (7-C), 118.0 (4-C), 119.2 (6-C), 122.0 (5-C), 124.0 (2-C), 127.0 (3a-C), 137.0 (7a-C), and 187.5 (C=O); *m/e* 255 (M^+, 28%), 158 (100, m* 97.8), 143 (11), and 115 (7).

1,3-*Dimethyl*-3-*trifluoroacetyl*-2-*trifluoroacetylmethyleneindoline* (17).—1,2,3-Trimethylindole (4 g) in benzene (20 ml) was added slowly to a stirred solution of TFAA (10 g) in benzene (20 ml). The solution was boiled under reflux (1 h), cooled, and treated with aqueous sodium carbonate. The benzene layer was washed with water, dried, and the solvent removed. The residual oil solidified at 0 °C. Recrystallisation (benzene–light petroleum) gave the *ketone* (17) as pale yellow needles (2.53 g), m.p. 113—115 °C (Found: C, 51.3; H, 3.3; F, 32.6; N, 4.1. $C_{15}H_{11}F_6NO_2$ requires C, 51.3; H, 3.1; F, 32.5; N, 4.0%); $\lambda_{max.}$ 232, 252sh, 290, and 373 nm (ε 23 100, 4 200, 3 900, and 12 900); $\nu_{max.}$ 1 655 and 1 750 cm^{-1}; τ 2.3—3.1 (4 H, m), 4.15 (1 H, s), 6.34 (s, NMe, *cis-s-cis*), 6.53 (s, NMe, *trans-s-cis*), 7.75 (C-Me), and 8.25 (C-Me); δ_C 21.3 (CCH_3), 30.7 (NCH_3), 61.4 (3-C), 86.3 (=CH), 110.0 (7-C), 119.9 (5-C), 123.4 (4-C), 130.4 (6-C), 138.0 (3a-C), 143.4 (7a-C), 170.1 (2-C), 176.8 (C=O), and 183.5 (C=O); *m/e* 351 (M^+, 77%), 255 (35), 254 (100), 185 (53), and 158

(61). The same compound was obtained by reaction of 1,2,3-trimethylindole (4 g) with TFAA (12 g) at 0 °C in pyridine solution and also by treating compound (15) with TFAA in warm benzene. Boiling compound (17) in MeOH for 1 h gave (15) (89%). When either compound (15) or compound (17) was dissolved in pyridine and water added until the solution became turbid the *hydrate* (18) separated. Recrystallisation (benzene–light petroleum) gave thick rods, m.p. 112—113 °C (Found: C, 56.9; H, 5.2; N, 5.2. $C_{13}H_{14}F_3NO_2$ requires C, 57.1; H, 5.1; N, 5.2%); $\lambda_{max.}$ 230 and 288 nm (ε 38 900 and 7 600); $\nu_{max.}$ 3 400 cm^{-1}; τ 2.2—3.1 (4 H, m), 5.92 (s, CH_2CO), 6.38 (s, NMe), 6.50 (s NMe), 6.80 [s, $CH_2C(OH)_2$], 6.9—7.5br [s, OH, exchanged with D_2O], 7.72 (s, CMe), and 7.8 (s, CMe); *m/e* 273 (M^+, 1%), 255 (44), 158 (100), and 143 (14).

A solution of (15) (2 g) in EtOH (10 ml) was added to a solution of NaOH (2 g) in water (10 ml). The mixture was boiled under reflux (1 h), the EtOH removed *in vacuo*, and the residue acidified. Recrystallisation (light petroleum) of the precipitate gave 1,3-dimethylindol-2-ylacetic acid as prisms, m.p. 83—84 °C (0.85 g), identical with a sample obtained by the hydrolysis of the corresponding thiomorpholide; [10] $\nu_{max.}$ 1 710 and 2 450—3 300 cm^{-1}; τ — 0.34 (1 H, s, OH), 2.3—3.1 (4 H, m), 6.33 (2 H, s), 6.47 (3 H, s, NMe), and 7.78 (3 H, s, CMe); *m/e* 203 (M^+, 1%), 159 (73), 158 (100), 144 (34), and 143 (12).

1,2,3,4-*Tetrahydro*-9-*methyl*-1-*trifluoroacetylcarbazole* (23; R = H).—A solution of *N*-methyltetrahydrocarbazole (4 g) in dry pyridine (12 ml) was added slowly with stirring to TFAA (12 ml) at 0 °C. After 15 min ice-water was added, the mixture was kept at 0 °C for 1 h, and then the solid was collected, washed, dried, and recrystallised (from MeOH). The *ketone* (23; R = H) formed pale yellow prisms, m.p. 106—107 °C (yield 5.0 g) (Found: C, 64.2; H, 5.0; F, 20.0; N, 5.1. $C_{15}H_{14}F_3NO$ requires C, 64.1; H, 5.0; F, 20.3; N, 5.0%); $\lambda_{max.}$ 228 and 282 nm (ε 41 300 and 6 900); $\nu_{max.}$ 1 755 cm^{-1}; τ 2.3—3.0 (4 H, m), 5.6 [1 H, t, *J* 6 Hz, 1-H], 6.55 (3 H, s, NMe), 6.9—7.4 (2 H, m), 7.5—7.9 (2 H, m), and 7.9—8.4 (2 H, m); δ_C 19.8 (3-C)*, 20.7 (4-C) *, 26.4 (2-C), 29.1 (N-CH_3), 40.9 (1-C), 109.0 (8-C), 113.2 (4a-C), 118.6 (5-C), 119.1 (7-C), 122.1 (6-C), 126.7 (9a-C), 129.0 (4b-C), 137.4 (8a-C), and 191.5 (C=O); *m/e* 281 (M^+, 40%), 185 (100), 169 (10), and 168 (12). The ketone (23; R = H) (2 g) was boiled (1 h) with a mixture of EtOH (15 ml), water (10 ml), and NaOH (2 g). Most of the EtOH was removed *in vacuo* and the residual solution acidified. The solid which separated was recrystallised (AcOH–H_2O, 9 : 1) giving the acid (24) as plates (0.91 g), m.p. 141—142 °C (decomp.) (lit.,[23] 143 °C) (Found: C, 73.5; H, 6.8; N, 6.1. Calc. for $C_{14}H_{15}NO_2$: C, 73.4; H, 6.8; N, 6.1%); $\lambda_{max.}$ 231 and 282 nm (ε 40 400 and 9 600); $\nu_{max.}$ 1 700 and 2 500—3 400 cm^{-1}; *m/e* 229 (M^+, 36%), 185 (46), 184 (100), and 157 (60). *N*-Methylphenylhydrazine (16.7 g) and methyl cyclohexanone-2-carboxylate (21.2 g) were heated together on a water bath for 30 min. The resulting hydrazone was boiled under reflux (1 h) with MeOH (180 ml) containing concentrated H_2SO_4 (20 ml). Dilution with water and Et_2O extraction gave an oil which crystallised on standing. Recrystallisation (MeOH) gave *methyl* 9-*methyl*-1,2,3,4-*tetrahydrocarbazole*-1-*carboxylate* (46%) as prisms, m.p. 51 °C (Found: C, 74.1; H, 7.1; N, 5.9. $C_{15}H_{17}NO_2$ requires C, 74.1; H, 7.0; N, 5.8%); $\lambda_{max.}$ 228 and 285 nm (ε 53 100 and 11 400); $\nu_{max.}$ 1 730 cm^{-1}; τ 2.4—3.2 (4 H, m), 6.25 (1 H, m), 6.38 (3 H, s, OMe), 6.62 (3 H, s, NMe), and 7.0—8.3 (6 H, m); *m/e* 243 (M^+, 30%), 184 (100), and 157 (10). Alkaline hydrolysis of this ester gave the acid (24), identical with material obtained from (23; R = H).

9-*Methyl*-1-(βββ-*trifluoroethyl*)*carbazole* (29; R = H).—A solution of (23; R = H) (2.5 g) in benzene (30 ml) was cooled in ice and TFAA (10 ml) added dropwise. The solution was boiled under reflux (4 h), cooled, and treated with water followed by sodium carbonate solution. The organic phase was separated, washed with water, dried, and the solvent removed. The solid residue was recrystallised (EtOH) giving the *carbazole* (29; R = H) (yield 56%) as prisms, m.p. 110—111 °C (Found: C, 68.5; H, 4.7; F, 21.4; N, 5.2. $C_{15}H_{12}F_3N$ requires C, 68.4; H, 4.6; F, 21.7; N, 5.3%); $\lambda_{max.}$ 237, 249sh, 263, 282sh, and 293 nm (ε 40 100, 20 400, 21 000, 8 300, and 16 700); τ 1.8—2.0 [2 H, m, 4-H and 5-H], 2.4—3.0, (5 H, m), 6.01 (3 H, s, NMe), and 6.08 (2 H, q, *J* 10 Hz, CH_2CF_3); τ (C_5D_5N) 1.8—2.0 (2 H, m), 2.0—3.0 (5 H, m), 6.12 (3 H, s), and 5.95 (2 H, q, *J* 10 Hz); δ_F — 10.2 (t, *J* 10 Hz); *m/e* 263 (M^+, 100%), 194 (72), 179 (4), 165 (5), and 152 (6).

Reduction of compound (23; R = H) with $NaBH_4$ in EtOH gave 1-[1-(9-*methyl*-1,2,3,4-*tetrahydrocarbazoyl*)]-2,2,2-*trifluoroethanol* as prisms, m.p. 87—90 °C (from light petroleum) (Found: C, 63.6; H, 5.7; F, 20.2; N, 5.0. $C_{15}H_{16}F_3NO$ requires C, 64.0; H, 5.7; F, 20.2; N, 5.2%); $\lambda_{max.}$ 233 and 287 nm (ε 38 000 and 8 000); $\nu_{max.}$ 3 250—3 640 cm^{-1}; τ 2.45—3.1 (4 H, m), 5.90—6.15 (1 H, m), 6.40 (3 H, s), 6.45—6.80 (1 H, m), 7.10—7.50 (2 H, m), and 7.80—8.35 (5 H, m, 1 H exchanged with D_2O); *m/e* 283 (M^+, 22%) and 184 (100).

1,2,3,12b-*Tetrahydro*-8-*methyl*-5-*trifluoromethylisoxazolo*-[4,5-k]*carbazole* (33).—The ketone (23; R = H) reacted with hydroxylamine hydrochloride in pyridine solution (reflux, 45 min) to form the oxime (30). Recrystallisation (MeOH–H_2O) gave *prisms*, m.p. 185—188 °C (yield 90%) (Found: C, 60.6; H, 5.3; F, 19.4; N, 9.5. $C_{15}H_{15}F_3N_2O$ requires C, 60.8; H, 5.1; F, 19.3; N, 9.5%); $\nu_{max.}$ 3 310 cm^{-1}; *m/e* 296 (M^+, 14%), 280 (13), 184 (48), 183 (62), 182 (100), and 167 (53). A solution of the oxime (2.0 g) in TFA (3.8 g) was heated under reflux (water bath, 80 min). Water was then added to the cold solution and the resulting gum washed by decantation. The gum crystallised on scratching with MeOH. Recrystallisation (MeOH) gave the *dihydroisoxazole* (33) (1.1 g) as needles, m.p. 124—126 °C (Found: C, 60.7; H, 5.1; F, 19.3; N, 9.3. $C_{15}H_{15}F_3N_2O$ requires C, 60.8; H, 5.1; F, 19.3; N, 9.5%); $\lambda_{max.}$ 209, 243, and 297 nm (ε 31 700, 16 000, and 3 800); $\nu_{max.}$ 3 450 cm^{-1}; τ 2.70—2.92 (1 H, m), 3.20—3.46 (3 H, m), 5.75—5.93 (1 H, m), 7.11 (3 H, s, NMe), 7.23—7.50 [3 H, m, 3-H_2 + NH, one H exchanged with D_2O], and 7.80—8.40 (4 H, m) δ_F — 12.6, *m/e* 296 (M^+, 100%), 200 (19), 199 (47), 159 (24), 130 (31), and 118 (54).

9-*Methyl*-1-*trifluoroacetylcarbazole* (37).—(*a*) A mixture of the ketone (23; R = H) (2 g) and Pd–C (30%, 0.5 g) was heated (270 °C, 20 min), cooled, and chloroform added to the melt. The catalyst was filtered off, the solvent removed, and the residue recrystallised (from MeOH). The *carbazole* (37) formed yellow prisms (yield 42%), m.p. 108—111 °C (Found: C, 64.5; H, 4.0; N, 5.1. $C_{15}H_{10}F_3NO$ requires C, 65.0; H, 3.6; N, 5.1%); $\lambda_{max.}$ 230, 265, and 305 nm (ε 35 000, 7 900, and 9 200); $\nu_{max.}$ 1 690 cm^{-1}; τ 1.70 (1 H, dd, *J* 8 and 2 Hz, 2-H], 1.87—2.15 (2 H, m), 2.42—2.85 (4 H, m), and 6.32 (3 H, s, NMe); δ_F — 5.3; *m/e* 277 (M^+, 76%), 208 (100), 180 (56), and 152 (30).

(*b*) The oxime (30) (2 g) was dissolved in dry chloroform (25 ml) and PCl_5 (2.8 g) added slowly (over 3 min). The

mixture was stirred (2.5 h), poured into ice–water, and the aqueous phase extracted with chloroform (3 × 15 ml). The combined organic extracts were washed (aqueous Na_2CO_3), dried ($MgSO_4$), and the solvent removed. The resulting tar was chromatographed (SiO_2; CH_2Cl_2). Recrystallisation (from MeOH) gave yellow prisms (0.43 g), m.p. 105—106 °C (Found: C, 65.2, 64.5; H, 4.9, 5.3; N, 4.7, 5.2; F, 19.6%). The i.r. and n.m.r. spectra of this sample were identical with those of the sample obtained by dehydrogenation, but the mass spectrum of the sample contained a signal at *m/e* 181 (*N*-methylcarbazole).

9-*Ethyl*-1,2,3,4-*tetrahydro*-1-*trifluoroacetylcarbazole*.— *N*-Ethyltetrahydrocarbazole was prepared by the alkylation of tetrahydrocarbazole [NaH–$(CH_3)_2SO$–EtBr]; b.p. 145—150 °C at 2 mmHg (lit.,[21] 188 °C at 17 mmHg); τ 2.6—3.2 (4 H, m), 6.13 (2 H, q, *J* 8 Hz), 7.2—7.6 (4 H, m), 8.0—8.2 (4 H, m), and 8.8 (3 H, t, *J* 8 Hz). This compound reacted with TFAA in pyridine at 0 °C (3 h) [see preparation of (23; R = H)] to form 9-*ethyl*-1,2,3,4-*tetrahydro*-1-*trifluoroacetylcarbazole* as pale yellow plates (77%), m.p. 99—100 °C (from EtOH) (Found: C, 65.1; H, 5.5; F, 19.1; N, 4.8. $C_{16}H_{16}F_3NO$ requires C, 65.1; H, 5.4; F, 19.3; N, 4.7%); $\lambda_{max.}$ 227 and 280 nm (ε 36 200 and 7 100); $\nu_{max.}$ 1 760 cm^{-1}; τ 2.4—3.2 (4 H, m), 5.63 (1 H, t, *J* 6 Hz), 6.15 (2 H, q, *J* 7 Hz), 7.1—7.4 (2 H, m), 7.65—7.9 (2 H, m), 8.0—8.33 (2 H, m), and 8.80 (3 H, t, *J* 7 Hz); δ_F + 1.2; *m/e* 295 (M^+, 21%), 195 (100), and 167 (12).

6,9-*Dimethyl*-1,2,3,4-*tetrahydro*-1-*trifluoroacetylcarbazole* (23; R = Me).—6,9-Dimethyltetrahydrocarbazole [24] gave the *ketone* (23; R = Me) (71%) as prisms, m.p. 139—140 °C (from EtOH) (Found: C, 65.3; H, 5.4; F, 19.1; N, 4.8. $C_{16}H_{16}F_3NO$ requires C, 65.1; H, 5.4; F, 19.3; N, 4.7%); $\nu_{max.}$ 1 755 cm^{-1}; τ 2.6—3.1 (3 H, m), 5.7 (1 H, t, *J* 6 Hz), 6.64 (3 H, s), 7.0—7.45 (2 H, m), 7.58 (3 H, s), 7.65—8.0 (2 H, m), and 8.0—8.4 (2 H, m); *m/e* 295 (M^+, 37%), 198 (100), and 171 (49). Boiling compound (23; R = Me) with TFAA in benzene solution gave the *carbazole* (29; R = Me) (79%) as needles, m.p. 162—163 °C (from EtOH) (Found: C, 69.4; H, 5.0; F, 20.4; N, 5.0. $C_{16}H_{14}F_3N$ requires C, 69.3; H, 5.1; F, 20.6; N, 5.1%); $\lambda_{max.}$ 239, 250sh, 265, 285, and 296 nm (ε 36 700, 17 800, 18 700, 8 700, and 16 800); τ 1.9—3.0 (6 H, m), 6.11 (3 H, s), 6.15 (2 H, q, *J* 10 Hz), and 7.5 (3 H, s); *m/e* 277 (M^+, 100%) and 208 (60).

1,2,3,4-*Tetrahydro*-6-*methoxy*-9-*methyl*-1-*trifluoroacetylcarbazole* (23; R = OMe).—6-Methoxy-9-methyltetrahydrocarbazole [25] (m.p. 87—89 °C) reacted with TFAA in pyridine at 0 °C to form the *ketone* (23; R = OMe) as needles (59%), m.p. 94—95 °C (from MeOH) (Found: C, 61.6; H, 5.1; F, 18.4; N, 4.5. $C_{16}H_{16}F_3NO_2$ requires C, 61.7; H, 5.1; F, 18.3; N, 4.5%); $\nu_{max.}$ 1 750 cm^{-1}; τ 2.68—3.34 (3 H, m), 5.63 (1 H, t, *J* 6 Hz), 6.18 (3 H, s), 6.61 (3 H, s), 7.1—7.4 (2 H, m), 7.6—7.9 (2 H, m), and 7.95—8.25 (2 H, m); *m/e* 311 (M^+, 35%), 214 (100), and 199 (11). Heating compound (23; R = OMe) with TFAA in benzene afforded the *carbazole* (29; R = OMe) as yellow prisms, m.p. 131—133 °C (from MeOH) (yield 84%) (Found: C, 65.1; H, 4.9; F, 19.6; N, 4.7. $C_{16}H_{14}F_3NO$ requires C, 64.6, H, 4.8; F, 19.2; N, 4.8%); $\lambda_{max.}$ 234, 254, 267, 301, and 345 nm (ε 32 500, 17 100, 16 100, 17 800, and 3 400); τ 2.04 (1 H, dd, *J* 8 and 2 Hz), 2.53 (1 H, d, *J* 2 Hz), 2.7—3.05 (4 H, m), 6.13 (6 H, s, OMe and NMe), and 6.22 (2 H, q, *J* 10 Hz); δ_F − 10.5 (t, *J* 10 Hz); *m/e* 293 (M^+, 90%), 278 (100), 250 (16), and 181 (12).

Reaction of 7-Methoxy-9-methyl-1,2,3,4-*tetrahydrocarbazole with TFAA*.—2-Hydroxycyclohexanone [26] was converted into 7-hydroxytetrahydrocarbazole, and then into 7-methoxytetrahydrocarbazole,[27] which was methylated [NaH–Me_2SO–MeI] forming 7-methoxy-9-methyltetrahydrocarbazole, m.p. 93—95 °C, (lit.,[28] 95—96 °C). A solution of 7-methoxy-9-methyltetrahydrocarbazole (4 g) in pyridine (12 ml) was added dropwise to TFAA (16 ml) which had been cooled to 0 °C. After 15 min ice–water was added and the solid which separated was collected after 12 h at 0 °C. The solid was dried and then separated by chromatography [SiO_2; light petroleum (b.p. 40—60 °C)–ether, 4 : 1, v/v]. The first compound to be eluted was recrystallised from light petroleum (b.p. 60—80 °C). 1,2,3,4-Tetrahydro-7-*methoxy*-9-*methyl*-1-*trifluoroacetylcarbazole* (43) formed yellow needles (20%), m.p. 110—112 °C (Found: C, 61.7; H, 5.1; F, 18.6; N, 4.6. $C_{16}H_{16}F_3NO_2$ requires C, 61.7; H, 5.1; F, 18.3; N, 4.5%); $\lambda_{max.}$ 229 and 295 nm (ε 38 000 and 7 500); $\nu_{max.}$ 1 760 cm^{-1}; τ 2.66 (1 H, dd, *J* 8 and 2 Hz, 6-H), 3.20—3.35 (2 H, m), 5.68 (1 H, t, *J* 6 Hz), 6.18 (3 H, s), 6.65 (3 H, s), 7.17—7.40 (2 H, m), 7.65—7.90 (2 H, m), and 8.04—8.25 (2 H, m); δ_F + 0.7; *m/e* 311 (M^+, 19%), 214 (100), 199 (8), and 184 (6). Further elution gave 1,2,3,4-*tetrahydro*-7-*methoxy*-9-*methyl*-1,6-*bistrifluoroacetyltetrahydrocarbazole* (44) as yellow needles (45%), m.p. 139—142 °C (from benzene–light petroleum) (Found: C, 53.2; H, 3.6; F, 28.3; N, 3.6. $C_{18}H_{15}F_6NO_3$ requires C, 53.1; H, 3.7; F, 28.0; N, 3.4%); $\lambda_{max.}$ 219, 266, and 317 nm (ε 18 800, 22 200, and 9 500); $\nu_{max.}$ 1 680 and 1 770 cm^{-1}; τ 2.13 (1 H, s, 5-H), 3.32 (1 H, s, 8-H), 5.66 (1 H, t, *J* 6 Hz), 6.10 (3 H, s), 6.59 (3 H, s), 7.16—7.42 (2 H, m), 7.62—7.88 (2 H, m), and 8.00—8.35 (2 H, m); δ_F + 0.7 (1-$COCF_3$) and −2.8 (6-$COCF_3$); *m/e* 407 (M^+, 18%), 388 (4), 310(100), and 266 (8). This reaction was repeated, the mixtures left to stand for varying times, and the crude products so obtained analysed by integration of the ^{19}F n.m.r. spectra; after 15 min the ratio (43) : (44) was 2 : 1, after 2 h 1 : 2, and after 24 h 1 : 3.

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