Reactions of some Heterocyclic Quaternary Salts with Trifluoroacetic Anhydride

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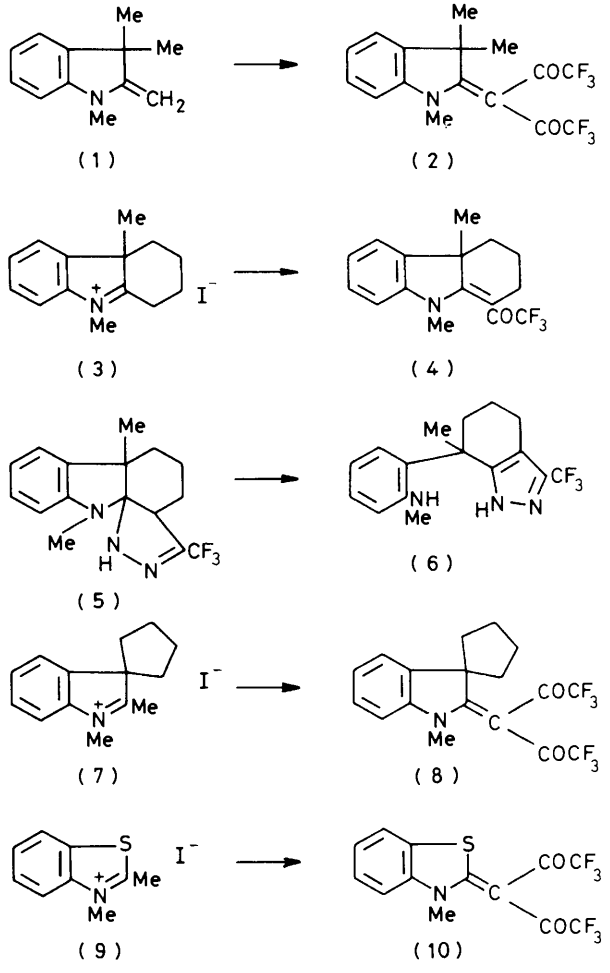
Treatment of the methiodides of 4a-methyl-1,2,3,4-tetrahydro-4a*H*-carbazole, 2-methyl-3*H*-indole-3-spirocyclopentane, 2-methylbenzothiazole, and 2-methylquinoline with trifluoroacetic anhydride afforded trifluoromethyl ketones. Some reactions of these enaminones with nitrogen-containing nucleophiles are described, attack taking place at the carbon–carbon and the carbon–oxygen double bonds.

We have shown [1] that the Fischer base (1) reacts with trifluoroacetic anhydride (TFAA) to form the bistrifluoroacetyl compound (2) in good yield. Since methylene bases of type (1) are often unstable [2] and are usually obtained *via* the corresponding salts we have examined the reactions of these salts with TFAA in pyridine solution.

Addition of TFAA to a solution of the salt (3) [2b,3] afforded the trifluoroacetyl compound (4) in 60% yield. The spectroscopic properties of the compound showed that acylation had occurred at C-1 and not in the aromatic ring. The compound was further characterised by reaction with hydrazine, the pyrazole (6) being obtained and not the pyrazoline (5) since the ^{1}H n.m.r. spectrum of the product contained signals at τ −0.2 to +0.2 [N(H)N] [4] and 6.8—7.0 (N*H*Me), and the ^{13}C spectrum (see Experimental section) indicated the presence of a pyrazole ring.[5] Formation of the pyrazole ring system by this type of reaction has already been reported.[6]

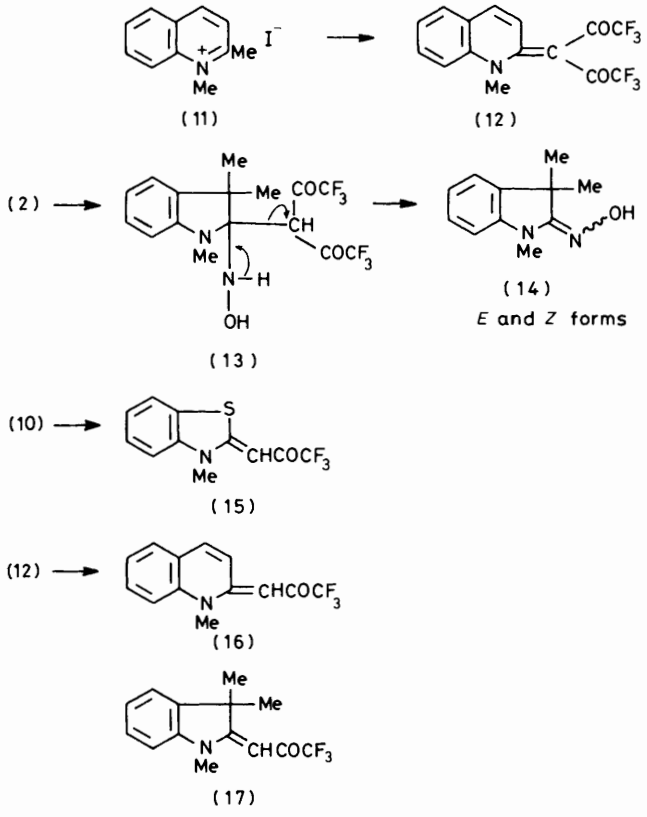
This trifluoroacetylation is applicable to a variety of salts, compounds (7), (9), and (11) yielding the bases (8), (10), and (12), respectively. The properties of these bistrifluoroacetyl derivatives have been investigated, most of the reactions being carried out on compound (2). We have reported [1] that treatment of compound (2) with benzylamine afforded the monotrifluoroacetyl derivative (17), the benzylamine attacking a carbonyl group of compound (2). Compound (17) is also obtained by treating compound (2) with potassium hydroxide, with ethyl carbazate, and with formic acid; the last reaction gives the highest yield (81%) of compound (17) and is the best method of preparation. In contrast, hydroxylamine reacted with compound (2) to give only a small yield of compound (17), the major product of the reaction being the amidoxime (14) arising by attack of the hydroxylamine on the C=C bond of compound (2) to form the hydroxylamine (13). The ^{1}H n.m.r. spectrum of compound (14) in $(CD_3)_2SO$ solution shows that the compound is a mixture of the (*E*)-isomer [τ 0.65 (OH), 7.0 (NMe), and 8.45 (CMe)] and the (*Z*)-isomer (τ 0.9, 6.4, and 8.75), the ratio *E*:*Z* being 4:1. These configurations were assigned by comparison with the chemical shifts of protons in amidoximes of known configuration.[7] The n.m.r. spectrum of compound (14) in trifluoroacetic acid (TFA) at 0 °C contained two sharp signals at τ 6.02 and 6.46 (NMe) and 8.18 and 8.35 (CMe). With increasing temperature the signals broadened, collapsed at *ca.* 40 °C, and at 55 °C formed two broad singlets at τ 6.23 and 8.26, indicating the interconversion of the *E* and *Z* forms.

Warming compound (10) with benzylamine gave a good yield of the monotrifluoroacetyl compound (15). The n.m.r. spectrum of this compound contained only one NMe signal, indicating the presence of a single isomer in solution, in contrast to that of compound (17) which is a mixture of *E* and *Z* forms in solution.[1] Treatment of compound (10) with hydroxylamine or with hydrazine also yielded compound (15) and no oxime corresponding to compound (14). Similarly,



compound (12) afforded the monotrifluoroacetyl compound (16).

Boiling an acetonitrile solution of compound (2) for five minutes with hydrazine did not remove the $C(COCF_3)_2$ group to give a structure similar to (14) (=NOH replaced by $=NNH_2$), but instead a compound with the formula $C_{16}H_{19}F_6N_5O$ was formed in high yield. The structure of this compound has been shown by *X*-ray crystallography to be (18a) in the solid state.[8] In the crystal the hydrazinium cation is hydrogen-bonded to the pyrazole nitrogen of another molecule [O⁻ . . . $\overset{+}{H}NH_2$–NH_2 . . . NH(pyrazole)]. The crystal structures of compounds (20) and (22; R^1 = Me, R^2 = Br) have also been determined.[8] Having established the 'open' structure of compound (20) and the 'closed' structure of compound



(22; R^1 = Me, R^2 = Br) it was possible to interpret the spectral properties of the compounds obtained in this present work. The n.m.r. spectrum of compound (18) (300 MHz) [$(CD_3)_2SO$] contained a very broad singlet at τ 3.9 (NH, exchanged with D_2O), and signals at τ 2.65—3.05 (m), 3.4—3.75 (m), 6.95 (NMe), 7.6 (NMe), 8.15 (CMe), and two (CMe) signals very close together at τ 8.3 (separation 0.01 p.p.m.). The multiplet at τ 3.4—3.75, and the NMe signal at τ 7.6, are assigned to the 'open' form (18b) by comparison with the spectral data obtained for compound (20), with the ratio of the 'closed' and 'open' forms (18a) : (18b) *ca.* 10 : 1. After the n.m.r. solution containing D_2O had been left for several hours the spectrum was rerun, the intensities of the signals at τ 3.5, 7.6, and 8.3 had decreased showing that addition of D_2O had increased the proportion of the 'closed' form (18a). The ^{19}F n.m.r. spectrum of compound (18a) contained two intense signals, downfield from that of TFA, at δ_F −19.0 and −2.2 p.p.m. ('closed' form) and two weak signals at δ_F −19.8 and −1.0 ('open' form). The signals at δ_F −19.0 and −19.8 are assigned to the pyrazolyl CF_3 group.[9] The CF_3 signal of compound (25) is 1.5 p.p.m. downfield of that of TFA and that of compound (26) 11.5 p.p.m. downfield.[10]

The i.r. spectrum of compound (18) (Nujol) contained no absorption in the carbonyl region but in dimethyl sulphoxide (DMSO) solution a carbonyl band (1 685 cm^{-1}) was detected. The ^1H n.m.r. spectrum of compound (18) in TFA contained signals at τ 2.0—2.45, 5.32 (NMe), 7.8 (CMe), and 8.4 (CMe). The downfield shift of the NMe signal (1.63 p.p.m.) on changing the solvent from DMSO to TFA is greater than the shift reported for the NMe signal for physostigmine.[11] At high resolution the NMe signal showed a small splitting (*ca.* 1.2 Hz); the ^{19}F spectrum contained a sharp quartet at δ_F −16.3 (*J* 10 Hz) (pyrazole CF_3) and a signal at δ −13.0 (br q, *J* 10 Hz, broadened by coupling with NMe). We suggest that, in TFA, compound (18) forms the cation (19).

Treatment of compound (18) with acid afforded the hydrazine-free compound (22; R^1 = R^2 = H); on dissolving this compound in acetonitrile and adding hydrazine, compound (18) was re-formed. Boiling a methanolic solution of the alcohol (22; R^1 = R^2 = H) yielded the methoxy-compound (22; R^1 = Me, R^2 = H). The n.m.r. spectrum of this compound contained signals at τ 2.5—3.1 (4 H, m, ArH), 6.9 (OMe), 7.0 (NMe), 8.2 (CMe), and 8.3 (CMe); the absence of any aromatic signals above τ 3.1 and the presence of two CMe signals indicate that this compound is in the 'closed' form.

Treatment of an acetic acid solution of the alcohol (18) with sodium borohydride gave the deoxy-compound (21), presumably by reduction of the cation (19). The ^1H n.m.r. spectrum of the compound contained no 'aromatic' signals above τ 3.0 and the $CHCF_3$ signal appeared as a quartet (τ 5.16, *J* 8 Hz); F–H coupling constants for this type of structure are reported as being of the order of *ca.* 9 Hz.[12] The ^{19}F spectrum contains two signals at δ_F −14.0 (pyrazole CF_3) and −6.4 p.p.m. ($CHCF_3$). Treatment of compound (18) with hydroxylamine gave the oxime (20). *X*-Ray crystallography of this oxime has shown [8] that the compound is in the 'open' form with the =N–OH group *Z* to the CF_3 group. In the n.m.r. spectrum of compound (20) two aromatic signals appear in the region τ = 3.25—3.55, the 'normal' positions

for protons *ortho* and *para* to NHMe,[13] in contrast to the signals from the aromatic protons in compounds (21) and (22; R^1 = Me, R^2 = H). The NMe signal appeared at τ 7.45 and only one CMe signal was seen, at τ 8.35. On boiling compound (18) with methyl iodide a mono-methyl derivative was obtained, methylation occurring on the pyrazole NH group.

On adding bromine to a solution of compound (18) in acetic acid the hydrobromide salt of the hydrazone (23; R = Br) separated out. The ^{1}H n.m.r. spectrum of this salt showed that it was in the 'open' form, with signals for one aromatic proton at τ 3.55, NMe (7.45), and one CMe signal (8.4). The oil obtained on dilution of the acetic acid mother-liquors with water was recrystallised from methanol to give the methoxy-compound (22; R^1 = Me, R^2 = Br), the n.m.r. spectrum of which showed signals for three aromatic protons (s, τ 2.6), NMe (7.02), and CMe_2 (8.15 and 8.3). The *X*-ray crystal structure of this compound showed the proximity of the CF_3 group to the NMe group. Dilution of the methanolic mother-liquors from the isolation of the methoxy-compound (22; R^1 = Me, R^2 = Br) with water gave the hydroxy-compound (22; R^1 = H, R^2 = Br) and attempted recrystallisation of this alcohol from methanol regenerated the ether (22; R^1 = Me, R^2 = Br). When compound (18) was dissolved in acetic acid and hydrogen bromide was added the hydrobromide of the hydrazone (23; R = H) separated out.

A solution of the spiro-compound (8) in acetonitrile was boiled with hydrazine; on cooling, no solid was deposited, but addition of water yielded the tetracycle (24).

The three *X*-ray crystallographic studies performed on compounds of this type have shown that in the solid state the pyrazole NH is as shown in the formulae and not as in the isomeric partial structure (27). The presence of the CF_3 group on the pyrazole ring will favour structures (18)—(24) rather than structures of type (27).[14]

There are clear differences in the mass spectra of compounds in the 'open' and 'closed' forms. The three compounds locked in the 'closed' form, (21), (22; R^1 = Me, R^2 = H), and (22; R^1 = Me, R^2 = Br), all give very small molecular-ion peaks, the base peaks being due to the $(M - CF_3)^+$ fragment ion; presumably the CF_3 group next to the NMe is lost to form ions of structure $^{-}\overset{+}{N}(Me)=C<$. All other compounds in this series gave the molecular ion as the base peak, the peak due to $(M - CF_3)^+$ being small in every case.

Experimental

General details and instruments used have already been reported;[1,15] u.v. spectra were measured for solutions in ethanol and n.m.r. spectra for $CDCl_3$ solutions unless otherwise stated. ^{1}H N.m.r. spectral data given in τ-values. I.r. spectra were measured for Nujol mulls.

2,3,4,4a-*Tetrahydro*-4a,9-*dimethyl*-1-*trifluoroacetylcarbazole* (4).—1,2,3,4-Tetrahydro-4a,9-dimethyl-4a*H*-carbazolium iodide (3)[3,16] (2 g) was dissolved in dry pyridine (30 ml). To the cold (0 °C), stirred solution TFAA (6 ml) was added dropwise. After 15 min ice-water (150 ml) was added. The resultant gum crystallised on scratching. Recrystallisation (EtOH) gave yellow-green prisms of the *title vinylogous amide* (4) (1.1 g, 60%), m.p. 168—170 °C (Found: C, 65.3; H, 5.3; F, 19.3; N, 4.9. $C_{16}H_{16}F_3NO$ requires C, 65.1; H, 5.4; F, 19.3; N, 4.8%); $\lambda_{max.}$ 202, 240, and 387 nm (ε 13 800, 6 600, and 19 500); $\nu_{max.}$ 1 630 and 1 610 cm^{-1}; τ 2.65—3.05 (4 H, m), 6.75 (3 H, s), 7.0—7.4 (2 H, m), 7.65—8.4 (4 H, m), and 8.7 (3 H, s); *m/z* 295 (M^+, 52%), 280 (25), 226 (35), 198 (100), and 183 (40).

Compound (4) (1 g) was dissolved in ethanol (10 ml) containing hydrazine hydrate (1 ml). The solution was boiled under reflux (30 min), cooled, water was added, and the solid which formed was collected by filtration to afford 4,5,6,7-*tetrahydro*-7-*methyl*-7-[(2-*methylamino*)*phenyl*]-3-*trifluoromethyl*-1H-*indazole* (6) which was crystallised as prisms (from MeCN) (yield 58%), m.p. 136—137 °C (Found: C, 61.9; H, 5.7; F, 18.6; N, 13.6. $C_{16}H_{18}F_3N_3$ requires C, 62.1; H, 5.8; F, 18.5; N, 13.6%); $\lambda_{max.}$ 246 and 294 nm (ε 10 300 and 2 900); $\nu_{max.}$ 3 440 and 3 320 cm^{-1}; τ −0.2 to +0.2 (1 H, s, NH), 2.65—3.55 (4 H, m), 6.8—7.0 (1 H, s, NH), 7.2—8.55 (6 H, m), 7.45 (3 H, s), and 8.35 (3 H, s); δ_F −14.0 p.p.m. (from CF_3CO_2H); δ_C [$(CD_3)_2SO$] 19.7 (C-5), 20.1 (C-6), 26.6 (C*Me*), 30.9 (NMe), 34.3 (C-4), 38.3 (C-7), 111.4 (C-3'), 112.8 (C-3a), 116.3 (C-5'), 122.9 (CF_3), 128.1 (C-4'), 128.1 (C-6'), 129.5 (C-1'), 138.4 (C-3), 146.6 (C-2'), and 147.3 p.p.m. (C-7a); *m/z* 309 (M^+, 100%), 294 (44), and 266 (16).

2-*Bis*(*trifluoroacetyl*)*methylene*-1-*methylindoline*-3-*spirocyclopentane* (8).—Cyclopent-1-enyl methyl ketone[17] was hydrogenated (Pd–C, EtOAc) to give cyclopentyl methyl ketone,[17] b.p. 163 °C; $\nu_{max.}$ 1 720 cm^{-1}; *m/z* 112 (M^+). This ketone was treated with phenylhydrazine and the resulting phenylhydrazone was cyclised[18] to form 2-methyl-3*H*-indole-3-spirocyclopentane. Methylation (MeI, benzene, 30 min reflux) then afforded the methiodide (7) as needles (from EtOH), m.p. 200—202 °C (lit.,[19] 203—204 °C).

To a solution of compound (7) (1 g) in dry benzene (10 ml) was added TFAA (4 ml); the mixture was boiled (30 min), cooled, washed in turn with aqueous sodium carbonate and water, dried ($MgSO_4$), and the solvent was removed under reduced pressure. Two crystallisations of the residue (MeOH, then EtOH) gave the *ketone* (8) as yellow prisms (yield 71%), m.p. 134—135 °C (Found: C, 55.7; H, 4.0; N, 3.6. $C_{18}H_{15}F_6NO_2$ requires C, 55.2; H, 4.0; N, 3.7%); $\nu_{max.}$ 1 660 and 1 600 cm^{-1}; τ 2.5 (4 H, m), 6.35 (3 H, s), and 7.5—8.4 (8 H, m); δ_F −2.5 p.p.m.; *m/z* 391 (M^+, 30%), 350 (70), 294 (100), and 185 (20).

A solution of the methiodide (7) (1 g) in a mixture of pyridine (4 ml) and benzene (4 ml) was added dropwise to a cold solution of TFAA (4 ml) in a mixture of pyridine (4 ml) and benzene (4 ml). After 5 min water (50 ml) was added and the mixture was stirred for 25 min. The mixture was extracted with benzene and the extract was washed in turn with water and aqueous HCl. The solvent was removed under reduced pressure and the residue was recrystallised from MeOH to afford 1-*methyl*-2-*trifluoroacetylmethyleneindoline*-3-*spirocyclopentane* as needles (yield 68%), m.p. 111—113 °C (Found: C, 64.6; H, 5.6; N, 4.6. $C_{16}H_{16}F_3NO$ requires C, 65.0; H, 5.4; N, 4.7%); $\nu_{max.}$ 1 655 and 1 620 cm^{-1}; τ 2.5—3.2 (4 H, m), 4.5 (1 H, s), 6.6 and 6.62 (together 3 H, s, NMe) (*Z* and *E* forms[1]), and 7.0—8.5 (8 H, m); *m/z* 295 (M^+, 35%), 254 (100), and 198 (50).

2-*Bis*(*trifluoroacetyl*)*methylene*-2,3-*dihydro*-3-*methylbenzothiazole* (10).—To a solution of 2-methylbenzothiazole methiodide (9)[2a,20] (4 g) in pyridine (10 ml) at 0 °C was added dropwise TFAA (20 ml). After 15 min water was added and the solid which formed was collected by filtration, dried, and recrystallised (MeCN). The *ketone* (10) formed pale-green needles (2.2 g), m.p. 155—156 °C (Found: C, 43.6; H, 1.9; F, 31.8; N, 4.0; S, 9.2. $C_{13}H_7F_6NO_2S$ requires C, 43.9; H, 2.0; F, 32.1; N, 3.9; S, 9.0%); $\lambda_{max.}$ 232, 292, and 365 nm (ε 5 200, 8 400, and 5 900); $\nu_{max.}$ 1 650 cm^{-1}; τ[$(CD_3)_2SO$] 1.55—2.35 (4 H, m) and 6.0 (3 H, s); δ_F −4.5 p.p.m.

Compound (10) (1.3 g) was dissolved in MeCN (10 ml) and benzylamine (1.5 ml) was added. The mixture was boiled under reflux (30 min), cooled, and the solid which formed was

collected by filtration (yield 85%). Recrystallisation gave 2,3-*dihydro*-3-*methyl*-2-*trifluoroacetylmethylenebenzothiazole* (15) as pale-yellow prisms from MeCN, m.p. 187—188 °C (Found: C, 51.0; H, 3.0; F, 21.9; N, 5.5; S, 12.5. $C_{11}H_8F_3NOS$ requires C, 51.0; H, 3.1; F, 22.0; N, 5.4; S, 12.4%); $\lambda_{max.}$ 214, 246, 356, and 367 nm (ε 4 600, 1 500, 6 300, and 6 900); $\nu_{max.}$ 1 605 cm^{-1}; τ 2.25—2.85 (4 H, m), 3.9 (1 H, s), and 6.3 (3 H, s); δ_F +0.3 p.p.m.; *m/z* 259 (M^+, 34%), 190 (100), 175 (8), and 162 (12). Compound (15) was also obtained on treating compound (10) with either hydroxylamine or hydrazine.

2-*Bis*(*trifluoroacetyl*)*methylene*-1,2-*dihydro*-1-*methylquinoline* (12).—A solution of 2-methylquinoline methiodide (11) [21] in cold pyridine was treated with TFAA as described above. Work-up afforded the *ketone* (12) as bright-yellow prisms from MeCN (yield 47%), m.p. 193—194 °C (Found: C, 51.7; H, 2.6; F, 32.5; N, 4.0. $C_{15}H_9F_6NO_2$ requires C, 51.6; H, 2.6; F, 32.7; N, 4.0%); $\lambda_{max.}$ 239, 307, and 406 nm (ε 17 800, 10 600, and 3 400); $\nu_{max.}$ (1 660 cm^{-1}; τ[$(CD_3)_2SO$] 0.9 (1 H, d, *J* 9 Hz) 1.35—2.15 (5 H, m), and 5.6 (3 H, s); δ_F −4.0 p.p.m.; *m/z* 349 (M^+, 27%), 280 (100), and 230 (76).

Compound (12) was boiled with benzylamine in MeCN as described above and the bulk of the solvent was removed under reduced pressure. Work-up gave 1,2-*dihydro*-1-*methyl*-2-*trifluoroacetylmethylenequinoline* (16) as yellow prisms from MeCN (yield 88%), m.p. 194—195 °C (Found: C, 61.6; H, 4.0; F, 21.8; N, 5.7. $C_{13}H_{10}F_3NO$ requires C, 61.7; H, 4.0; F, 22.5; N, 5.5%); $\lambda_{max.}$ 222, 298, 410, and 428 nm (ε 25 000, 13 400, 25 600, and 21 000); $\nu_{max.}$ 1 645 cm^{-1}; τ[$(CD_3)_2SO$] 1.1 (1 H, d, *J* 9 Hz), 1.9—2.7 (5 H, m), 4.45 (1 H, s) and 6.2 (3 H, s); δ_F −0.5 p.p.m.; *m/z* 253 (M^+, 82%) and 184 (100). Compound (16) was also obtained by heating compound (12) with hydroxylamine hydrochloride in MeCN (yield 69%).

Reactions of 2-*Bis*(*trifluoroacetyl*)*methylene*-1,3,3-*trimethylindoline* (2).—(*a*) Compound (2) (0.25 g) was dissolved in formic acid (2 ml) and the solution was boiled (15 min), cooled, and water (2 ml) was added. Compound (17) separated out (yield 81%), identical with the material obtained previously [1] (m.p. and i.r.).

(*b*) A solution of compound (2) (2 g) in dry pyridine (20 ml) containing hydroxylamine hydrochloride (1.5 g) was heated at 100 °C, for 30 min. The pyridine was removed under reduced pressure, water (20 ml) added to the residue, and the mixture was brought to pH 6 by the addition of dilute HCl (*ca.* 2 ml). The solid which formed was filtered off, dried, and recrystallised (MeCN) to give 1,3,3-*trimethyloxindole oxime* (14) as prisms, m.p. 217—218 °C (yield 67%) (Found: C, 69.4; H, 7.2; N, 14.8. $C_{11}H_{14}N_2O$ requires C, 69.5; H, 7.4; N, 14.7%); $\nu_{max.}$ 3 280 cm^{-1}; τ[$(CD_3)_2SO$] 0.65 and 0.9 (OH), 2.75—3.45 (m, ArH), 6.4 and 7.0 (NMe), and 8.45 and 8.75 (CMe_2); *m/z* 190 (M^+, 100%), 175 (9), and 158 (42).

The acetonitrile mother-liquors from the recrystallisation of compound (14) were evaporated to dryness to afford compound (17) (yield 8%).

Hydrazinium 1,4,5,10-*Tetrahydro*-5,10,10-*trimethyl*-3,4-*bis*(*trifluoromethyl*)*pyrazolo*[4,3-c][1]*benzazepin*-4-*olate* (18a).—To a solution of compound (2) (4 g) in hot MeCN (10 ml) was added hydrazine hydrate (2 ml) and the mixture was boiled for 5 min. The solution was then cooled and the solid which formed was collected by filtration (yield 85%). Recrystallisation gave the *pyrazole* (18a) as rods from MeCN, m.p. 138—140 °C (Found: C, 46.6; H, 4.8; F, 27.5; N, 17.0. $C_{16}H_{19}F_6N_5O$ requires C, 46.7; H, 4.6; F, 27.7; N, 17.0%); $\lambda_{max.}$ 273 and 279 nm (ε 25 400 and 23 000); $\nu_{max.}$ (Nujol) 3 365, 3 345, and 3 230br; (Me_2SO) 1 685 cm^{-1}; *m/z* 379 (100%), 364 (18) and 310 (17). The n.m.r. data for this compound are discussed in the main text of this paper.

1,4,5,10-*Tetrahydro*-5,10,10-*trimethyl*-3,4-*bis*(*trifluoromethyl*)*pyrazolo*[4,3-c][1]*benzazepin*-4-*ol* (22; $R^1 = R^2 =$ H).—(*a*) Compound (18) (1 g) was finely powdered and was dissolved in glacial acetic acid (4 ml). Water (10 ml) was then added to the mixture. Work-up afforded the free alcohol.

(*b*) Compound (18) (1.2 g) was added to aqueous hydrochloric acid (10 ml; 2M) and the mixture was shaken for 30 min. The solid which formed was collected by filtration and washed with water. Recrystallisation (MeCN) gave the free *alcohol* (22; $R^1 = R^2 =$ H) as prisms, m.p. 134—137 °C (Found: C, 50.5; H, 4.1; F, 30.2; N, 11.1. $C_{16}H_{15}F_6N_3O$ requires C, 50.7; H, 4.0; F, 30.1; N, 11.1%); $\nu_{max.}$ 3 320br cm^{-1}; τ(CF_3CO_2H) 2.05—2.5 (4 H, m), 5.32 (3 H, s, NMe), 7.75 (3 H, s, CMe), and 8.4 (3 H, s, CMe); *m/z* 379 (M^+, 100%).

A sample of this compound was dissolved in warm MeCN and hydrazine was added; on cooling, crystals of compound (18) separated out, identical (m.p. and i.r.) with the compound prepared above.

A solution of (22; $R^1 = R^2 =$ H) in methanol was boiled for 5 min and allowed to cool whence 1,4,5,10-*tetrahydro*-4-*methoxy*-5,10,10-*trimethyl*-3,4-*bis*(*trifluoromethyl*)*pyrazolo*-[4,3-c][1]*benzazepine* (22; R^1 = Me, R^2 = H) separated out as prisms, m.p. 193—194 °C (Found: C, 51.7; H, 4.4; N, 10.7. $C_{17}H_{17}F_6N_3O$ requires C, 51.9; H, 4.4; N, 10.7%); $\nu_{max.}$ 3 250 cm^{-1}; δ_F −4.0 (br s) and −17.0 p.p.m. (q, *J* 10 Hz); τ *; *m/z* 393 (M^+, 2%) 379 (10), 362 (10), and 324 (100); on a cold probe with chemical ionisation: 394 [$(M + 1)^+$, 80%], 380 (20), 362 (100), and 324 (24).

1,4,5,10-*Tetrahydro*-5,10,10-*trimethyl*-3,4-*bis*(*trifluoromethyl*)*pyrazolo*[4,3-c][1]*benzazepine* (21).—To a stirred solution of compound (18) (1 g) in glacial acetic acid (10 ml) was added $NaBH_4$ (0.5 g); after 2 h water was added to the mixture and the solid which formed was collected by filtration (yield 90%). Recrystallisation (MeOH) gave *compound* (21) as flakes, m.p. 155—157 °C (Found: C, 52.6; H, 4.1; F, 31.0; N, 11.7. $C_{16}H_{15}F_6N_3$ requires C, 52.8; H, 4.1; F, 31.4; N, 11.6%); $\nu_{max.}$ 3 500—3 250br cm^{-1}; τ −1.4 (1 H, br, NH, exchanged with D_2O), 2.6—3.0 (4 H, m), 5.16 (1 H, q, *J* 8 Hz), 6.78 (NMe), 8.09 (CMe), and 8.42 (CMe); δ_F −14.0 (sharp q, *J* 8 Hz) and −6.4 p.p.m. (quintet, coupled CF_3 and CH); *m/z* 363 (M^+, 24%), 348 (18), 294 (100), and 279 (10).

5-[α,α-*Dimethyl*-2-(*methylamino*)*benzyl*]-4-*trifluoroacetyl*-3-*trifluoromethylpyrazole Oxime* (20).—To a solution of compound (18) (1 g) in pyridine was added hydroxylamine hydrochloride (0.5 g). The solution was heated at 100 °C for 30 min, cooled, and water (50 ml) was added. The mixture was acidified to pH 6 (dilute H_2SO_4) and the solid which formed was collected by filtration and recrystallised from methanol (yield 70%) to give the *oxime* (20) as prisms, m.p. 105—107 °C, which contained methanol of crystallisation (Found: C, 48.0; H, 5.0; F, 27.0; N, 13.2. $C_{16}H_{16}F_6N_4O{\cdot}CH_3OH$ requires C, 47.9; H, 4.7; F, 26.8; N, 13.2%); $\nu_{max.}$ 3 560, 3 485, 3 200, and 1 605 cm^{-1}; τ[$(CD_3)_2SO$] −3.03 (1 H, NH, exchanged with D_2O), 2.65—2.95 (2 H, m), 3.25—3.55 (2 H, m), 5.9 (total 3 H, br, NH and 2 × OH, exchanged with D_2O), 6.8 (3 H, s, OMe), 7.45 (3 H, s, NMe), and 8.35 (6 H, s, CMe_2); τ(CF_3CO_2H) 2.1—2.55 (4 H, m), 5.95 (OMe), 7.2 (NMe), and 8.15 (6 H); δ_F −16.0 and −11.5 p.p.m.; *m/z* 394 (M^+, 100%) and 378 (15).

* ^1H N.m.r. data given in main text.

1,4,5,10-*Tetrahydro*-1,5,10,10-*tetramethyl*-3,4-*bis*(*trifluoromethyl*)*pyrazolo*[4,3-c][1]*benzazepin*-4-*ol*.—Compound (18) (1 g) was dissolved in a mixture of MeI (10 ml) and benzene (10 ml). The mixture was boiled for 1 h, the solvents were removed under reduced pressure, and the residue was recrystallised (MeOH) to yield the *title compound* as prisms, m.p. 154—157 °C (yield 78%) (Found: C, 51.6; H, 4.5; F, 29.1; N, 10.6. $C_{17}H_{17}F_6N_3O$ requires C, 51.9; H, 4.3; F, 29.0; N, 10.7%); $\nu_{max.}$ 3 260 cm^{-1}; τ[$(CD_3)_2SO$] −4.2 to −2.8 (1 H, br, exchanged with D_2O), 2.45—3.45 (ArH), 6.85 (pyrazole NMe), 7.0 (NMe), 8.15 (CMe), and 8.3 (CMe); τ(CF_3CO_2H) 2.05—2.4 (4 H, m), 5.3 (3 H, q, *J* 1.2 Hz, NMe), 5.95 (3 H, NMe), 7.75 (3 H, CMe), and 8.4 (3 H, CMe); δ_F (CF_3CO_2H) −13.5 (q, *J* 9 Hz) and −10.5 p.p.m. (m, *J* 9 and 1.2 Hz).

5-[α,α-*Dimethyl*-2-(*methylamino*)*benzyl*]-4-*trifluoroacetyl*-3-*trifluoromethylpyrazole Hydrazone Hydrobromide* (23; R = H)·HBr.—Compound (18) (1 g) was dissolved in glacial acetic acid (3 ml) and aqueous HBr (48%) was added slowly until a solid precipitate ceased to separate out. The solid was collected by filtration and recrystallised (MeCN) to afford the *hydrazone salt* (23; R = H)·HBr as prisms, m.p. 203—204 °C (yield 71%) (Found: C, 40.8; H, 3.6; N, 14.7. $C_{16}H_{18}BrF_6N_5$ requires C, 40.5; H, 3.8; N, 14.8%); $\nu_{max.}$ 3 460, 3 320, 3 230, 3 120, and 1 580 cm^{-1}; τ[$(CD_3)_2SO$] 2.4 (4 H, br, exchanged with D_2O), 2.5—2.9 (2 H, m), 3.0—3.35 (1 H, m), 3.5 [1 H, d (br), *J* 8 Hz], 7.4 (3 H, s, NMe), and 8.35 (6 H, CMe_2); *m/z* 393 (M^+, 100%) and 362 (38).

Bromination of Compound (18).—Bromine (1 ml) was dissolved in glacial acetic acid (20 ml); a portion (2.66 ml) of this solution was added to a solution of compound (18) (1 g) in glacial acetic acid (10 ml). The mixture was kept overnight at 0 °C and the solid which had formed was collected by filtration (yield 25%) and recrystallised (MeCN) to give 5-[5-*bromo*-α,α-*dimethyl*-2-(*methylamino*)*benzyl*]-4-*trifluoroacetyl*-3-*trifluoromethylpyrazole hydrazone hydrobromide* (23; R = Br)·HBr as flakes, m.p. 204—206 °C (Found: C, 35.3; H, 3.3; Br, 29.6; N, 12.1. $C_{16}H_{17}Br_2F_6N_5$ requires C, 35.3; H, 3.3; Br, 29.6; N, 12.7%); $\nu_{max.}$ 3 475, 3 378, and 3 280 cm^{-1}; τ[$(CD_3)_2SO$] (after D_2O exchange) 2.6—2.85 (2 H, m), 3.55 (1 H, d, *J* 9 Hz), 7.45 (3 H, NMe), and 8.4 (6 H, CMe_2); τ(CF_3CO_2H) 2.0—2.6 (3 H, m), 7.42 (NMe) and 8.09 (CMe); δ_F [$(CD_3)_2SO$] −14.8 (q, *J* 4 Hz) and −11.0 p.p.m. (q, *J* 4 Hz); *m/z* 471 (M^+, 100%), 402 (5), and 440 (21).

The acetic acid mother-liquors were diluted with water and the oil which separated was washed by decantation. This oil was then triturated with methanol and kept overnight at 0 °C. The solid which formed was collected by filtration and recrystallised from methanol (yield 20%) to give 8-*bromo*-1,4,5,10-*tetrahydro*-4-*methoxy*-5,10,10-*trimethyl*-3,4-*bis*(*trifluoromethyl*)*pyrazolo*[4,3-c][1]*benzazepine* (22; R^1 = Me, R^2 = Br) as prisms, m.p. 177—178 °C (Found: C, 43.1; H, 3.6; Br, 17.1, N, 8.7. $C_{17}H_{16}BrF_6N_3O$ requires C, 43.2; H, 3.4; Br, 16.9; N, 8.8%); $\nu_{max.}$ 3 280 cm^{-1}; τ[$(CD_3)_2SO$] 2.6 (3 H, s), 6.88 (3 H, s, OMe), 7.02 (3 H, s, NMe), 8.15 (3 H, s, CMe), and 8.3 (3 H, s, CMe); τ(CF_3CO_2H) 2.1—2.5 (3 H, m), 5.33 (NMe), 5.97 (OMe), 7.78 (CMe), and 8.4 (CMe); δ_F [$(CD_3)_2SO$] −17.0 (q, *J* 12 Hz) and −4.0 p.p.m. (br); *m/z* 471 (M^+, 10%), 440 (10), and 402 (100).

Addition of water to the methanolic mother-liquors gave 8-*bromo*-1,4,5,10-*tetrahydro*-5,10,10-*trimethyl*-3,4-*bis*(*trifluoromethyl*)*pyrazolo*[4,3-c][1]*benzazepin*-4-*ol* (22; R^1 = H, R^2 = Br) (yield 10%) as prisms from acetonitrile, m.p. 134—135 °C (Found: C, 46.2; H, 3.6; N, 10.8. $C_{16}H_{14}BrF_6N_3O·CH_3CN$ requires C, 43.4; H, 3.4; N, 11.2%); τ[$(CD_3)_2SO$] 2.5—2.8 (3 H, m), 6.99 (3 H, br s, NMe), 8.05 (MeCN), 8.13 (CMe), and 8.3 (CMe). When a sample of this compound was boiled in methanol the methoxy-derivative (22; R^1 = Me, R^2 = Br) was formed.

1,4,5,10-*Tetrahydro*-4-*hydroxy*-5-*methyl*-3,4-*bis*(*trifluoromethyl*)*pyrazolo*[4,3-c][1]*benzazepine*-10-*spirocyclopentane* (24).—Compound (8) (1 g) was dissolved in MeCN (5 ml) and hydrazine hydrate (0.5 ml) was added. The mixture was boiled for 5 min and cooled. However, no solid separated out and so water (5 ml) was added. The solid which then separated was washed by decantation, dried, and recrystallised from MeCN (yield 77%) to give *compound* (24) as prisms, m.p. 133—135 °C (Found: C, 53.3; H, 4.4; N, 10.9. $C_{18}H_{17}F_6N_3O$ requires C, 53.3; H, 4.2; N, 10.4%); $\nu_{max.}$ 3 600 and 3 250 cm^{-1}; τ[$(CD_3)_2SO$] −3.25 (1 H, br, exchanged with D_2O), 2.5—3.1 (4 H, m), 6.99 (3 H, s, NMe), 7.5 (4 H, br), and 7.95 (4 H, br); *m/z* 405 (M^+ 100%).

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