Electrophilic Addition of Perfluorofluoro-oxy-compounds to Unactivated Double Bonds

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Whereas compounds containing unactivated double bonds generally react with trifluoro(fluoro-oxy)methane to afford complex mixtures of products, allylic alcohols and acetates each give cleanly two adducts which correspond to the *cis*-addition of CF_3OF and of F_2. Evidence is presented that the orientation of the allylic oxygen function is not important and that intramolecular nucleophilic participation is not involved.

In previous work we have demonstrated the usefulness of perfluorofluoro-oxy-compounds for mild and efficient fluorination of a variety of substrates.[1] With the notable exception of a marked tendency for *cis*-addition, these reactions exhibit characteristics which are typical of electrophilic additions. A discussion of factors relating to the unusual stereochemistry has already been given in connection with the reaction of trifluoro(fluoro-oxy)methane with *cis*- and *trans*-stilbene.[2] A significant attribute of perfluorofluoro-oxy-reagents is their ability to react with double bonds which are unactivated or even deactivated towards electrophilic attack.[3] We now report details of such reactions.

In general, the reaction of trifluoro(fluoro-oxy)-methane with isolated double bonds led to mixtures of products of a type that would be expected if rearrangement of an intermediate α-fluoro-carbocation were involved. Thus, a significant product from the reaction of the 9(11)-ene (I) with trifluoro(fluoro-oxy)methane was the 9β-methyl phenol (II).[4] The presence of an allylic oxygen function, however, had a pronounced and beneficial effect on the course of such reactions. Whereas (25*R*)-5α-spirost-9(11)-en-3β-ol (9,11-didehydrotigogenin) (III; R = X = H) gave a complex mixture of products, (25*R*)-5α-spirost-9(11)-ene-3β,12β-diol (9,11-didehydrorockogenin) (III; R = H, X = OH) reacted cleanly to afford two products. The major product (48%) corresponded to addition of the elements of CF_3OF and the minor one (14%) to the addition of F_2. In each case reaction with acetic anhydride in pyridine afforded a diacetate, which could also be formed directly by reaction of the diacetate (III; R = Ac, X = OAc) with trifluoro(fluoro-oxy)methane. Oxidation of the major product (IV; R = H, X = OCF_3) with Jones reagent afforded first a 3-monoketone ($\nu_{max.}$ 1 715 cm^{-1}) and then a 3,12-diketone ($\nu_{max.}$ 1 720 and 1 750 cm^{-1}). The position of the i.r. absorption of the 12-ketone suggested the presence of an electronegative substituent in the α-equatorial position.[5] On treatment with potassium acetate in methanol the diketone (V; X = OCF_3) readily formed the αβ-unsaturated ketone (VI). The full stereochemistry of (IV; R = H, X = OCF_3) was established unambiguously by n.m.r. spectroscopy. In particular, the H-11 signal appeared as a quartet, *J* 55 and 10 Hz (geminal H,F and vicinal *trans*-diaxial H,H coupling, respectively), and the H-12 signal as an apparent triplet, *J* 10 Hz (vicinal axial-equatorial H,F and vicinal *trans*-diaxial H,H coupling). Analogous

[1] D. H. R. Barton, R. H. Hesse, M. M. Pechet, and H. T. Toh, *J.C.S. Perkin I*, 1974, 732 and references therein; D. H. R. Barton, W. A. Bubb, R. H. Hesse, and M. M. Pechet, *ibid.*, p. 2095.

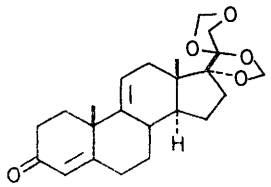
[2] D. H. R. Barton, R. H. Hesse, G. P. Jackman, L. Ogunkoya, and M. M. Pechet, *J.C.S. Perkin I*, 1974, 739.

[3] D. H. R. Barton, L. J. Danks, A. K. Ganguly, R. H. Hesse, G. Tarzia, and M. M. Pechet, *Chem. Comm.*, 1969, 227.

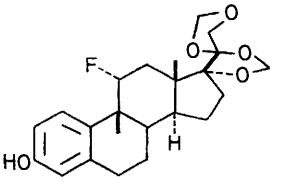
[4] For formation of an analogous rearrangement product, see J. W. ApSimon and R. R. King, *Chem. Comm.*, 1967, 1214.

[5] E. J. Corey and H. J. Burke, *J. Amer. Chem. Soc.*, 1955, **77**, 5418.

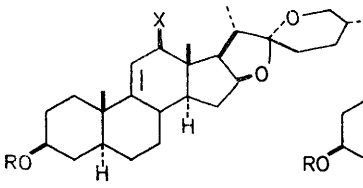
investigations established the structure of the minor product as (IV; R = H, X = F).



(I)



(II)



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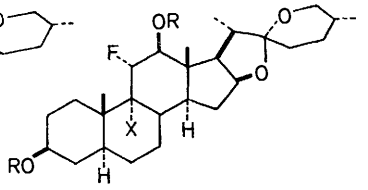

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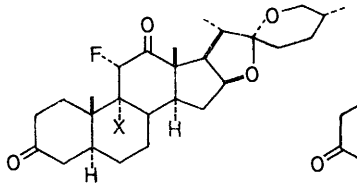
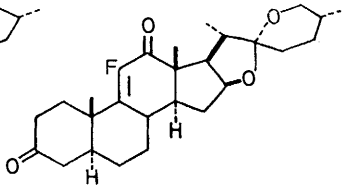


(V)

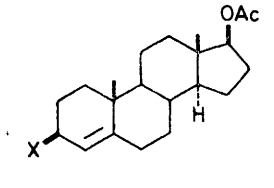


(VI)

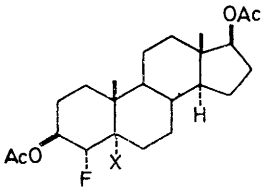
In similar experiments it was shown that whereas the 4-ene (VII; X = H) [6] reacted with trifluoro(fluoro-oxy)-methane to afford a complex mixture of products, the allylic acetate (VII; X = OAc) [7] gave the 4α-fluoro-5α-trifluoromethoxy-adduct (VIII; X = OCF_3) in good yield. A minor, uncharacterised product of the latter reaction was apparently the 4α,5α-difluoro-adduct (VIII; X = F). Details of these reactions are given in the Experimental section.

The persistence of Markovnikov, but *cis*-, addition rules out the occurrence of intramolecular nucleophilic participation in the fluorination of these allylic alcohols and acetates. As with related fluorinations,[8] the nature of the products was also unaffected when the reactions were carried out in a nucleophilic solvent such as methanol. To investigate further the role of the allylic oxygen function we studied the reaction of trifluoro-(fluoro-oxy)methane with the epimeric diacetate (IX), in which the 12α-acetate group is pseudoaxially orientated. Again two products were formed. The structure of the minor product (14%) was established as (X; $R^1 = R^2$ = Ac, X = F), by basic hydrolysis to the diol and oxidation to the 3,12-diketone (V; X = F), identical with material previously prepared from the 12β-epimer. Similar hydrolysis of the major product (59%) afforded a 12α-monoacetate which yielded elimination products on attempted further hydrolysis with methanolic sodium hydroxide or lithium aluminium hydride. Treatment with aluminium hydride,[9] however, gave the desired diol (X; $R^1 = R^2$ = H, X = OCF_3), which on oxidation gave the diketone (V; X = OCF_3), identical with an authentic sample. Thus, the major product must have structure (X; $R^1 = R^2$ = Ac, X = OCF_3) and it is to be concluded that the orientation of the acetate function at C-12 has little apparent effect on the outcome of the fluorination.

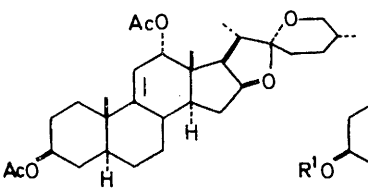
One compound in which intramolecular capture of an initially formed α-fluoro-carbocation was evident was the 17α-hydroxy-16-methylene steroid (XI). Here, reaction with trifluoro(fluoro-oxy)methane gave the epoxide (XII) in high yield. Analogous products are formed with more conventional electrophiles.[10] The formation of this epoxide (XII) is important evidence for the electrophilic fluorination capacity of trifluoro-(fluoro-oxy)methane. Certainly such a product could not result from a radical mechanism. The reaction also demonstrates the efficiency of an intramolecular nucleophile (17α-OH), in contrast with the failure of external



(VII)



(VIII)



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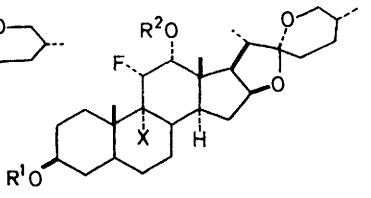

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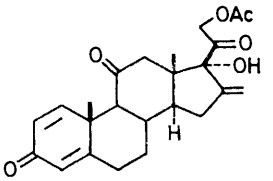

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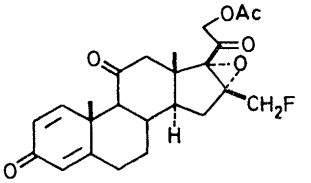

(XII)

nucleophiles like methanol, in the capture of the intermediate fluoro-carbocation.

Finally, also included in the Experimental section are details of the reaction of diphenylacetylene with an excess of trifluoro(fluoro-oxy)methane to afford, as the major product, 1,2,2-trifluoro-1,2-diphenyl-1-trifluoromethoxyethane.[3]

[6] A. C. de Paulet and J. Bascoul, *Bull. Soc. chim. France*, 1966, 939.
[7] A. Butenandt and A. Heusner, *Ber.*, 1938, **71**, 198.
[8] References 1—3 and references therein.
[9] H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, 1966, **88**, 1464.
[10] F. von Werder, K. Brückner, K. H. Bork, H. Metz, B, Hampel, and H. J. Mannhardt, *Chem. Ber.*, 1962, **95**, 2110.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. N.m.r. data refer to solutions in deuteriochloroform with tetramethylsilane as internal standard. I.r. data are for potassium bromide discs and rotations for solutions in chloroform. Alumina was neutral grade III.

Reaction of (25R)-5α-*Spirost*-9(11)-*ene*-3β,12β-*diol* (III; R = H, X = OH) *with Trifluoro*(*fluoro-oxy*)*methane*.—The 9(11)-ene (2 g) in dichloromethane (200 ml) and Freon (200 ml) at −78 °C was stirred with calcium oxide (800 mg) while an excess of trifluoro(fluoro-oxy)methane diluted with nitrogen was bubbled in. When no starting material remained (t.l.c.) the mixture was filtered into aqueous 5% sodium hydrogen carbonate (250 ml) and extracted with dichloromethane. The combined extracts were washed with brine, dried, and evaporated. The residue in methanol (250 ml) was treated with potassium carbonate (12 g) in water (30 ml) on a steam-bath for 30 min. Following normal work-up the residue was chromatographed on alumina (160 g). Elution with 30% ether–benzene afforded (25R)-11α-*fluoro*-9α-*trifluoromethoxy*-5α-*spirostan*-3β,12β-*diol* (IV; R = H, X = OCF_3) (48%), m.p. (from dichloromethane–hexane–ether) 129—133°, $[\alpha]_D$ −52° (*c* 3.9), $\nu_{max.}$ 3 500 and 1 260—1 120 cm^{-1}, τ 5.38 (1 H, q, *J* 55 and 10 Hz, 11β-H), 6.17 (1 H, t, *J* 10 Hz, 12α-H), 8.90 (3 H, s, 19-H_3), 8.99 (3 H, d, *J* 7 Hz, 21-H_3), 9.18 (3 H, s, 18-H_3), and 9.22 (3 H, d, *J* 5 Hz, 27-H_3) (Found: C, 63.1; H, 7.7; F, 14.4. $C_{28}H_{42}F_4O_5$ requires C, 62.9; H, 7.9; F, 14.2%). Further elution with 60% ether–benzene gave (25R)-9α,11α-*difluoro*-5α-*spirostan*-3β,12β-*diol* (IV; R = H, X = F) (14%), m.p. (from dichloromethane–hexane) 232—235°, $[\alpha]_D$ −59° (*c* 3.6) (Found: C, 69.0; H, 9.1; F, 8.0. $C_{27}H_{42}F_2O_4$ requires C, 69.2; H, 9.0; F, 8.1%).

Similarly, the diacetate (III; R = Ac, X = OAc) afforded the *adduct* (IV; R = Ac, X = OCF_3) (57%), m.p. (from dichloromethane–methanol–ether) 189—190°, $[\alpha]_D$ −36° (*c* 3.5), $\nu_{max.}$ 1 750, 1 730, 1 250, 1 220, and 1 200 cm^{-1} (Found: C, 62.5; H, 8.1; F, 11.8. $C_{32}H_{46}F_4O_7$ requires C, 62.1; H, 7.5; F, 12.3%), and the *adduct* (IV; R = Ac, X = F) (19%), m.p. (from dichloromethane–ether) 273—274°, $[\alpha]_D$ −38° (*c* 2.3), $\nu_{max.}$ 1 750, 1 730, and 1 230 cm^{-1} (Found: C, 67.1; H, 8.3; F, 6.9. $C_{31}H_{46}F_2O_6$ requires C, 67.4; H, 8.4; F, 6.9%). Identical material was also obtained by treatment of the respective diol adducts (IV; R = H, X = OCF_3 or F) with acetic anhydride and pyridine at room temperature overnight.

Treatment of the 9(11)-ene (III; R = H, X = OH) or the diacetate with trifluoro(fluoro-oxy)methane as above but with, as solvent, methanol containing just sufficient dichloromethane to effect complete dissolution gave identical products (IV; R = H or Ac, X = OCF_3 or F). With either solvent system (25*R*)-5α-spirost-9(11)-en-3β-ol (III; R = X = H) reacted under the same conditions to give a complex mixture.

(25R)-11α-*Fluoro*-12β-*hydroxy*-9α-*trifluoromethoxy*-5α-*spirostan*-3-*one*.—The adduct (IV; R = H, X = OCF_3) (705 mg) in acetone (10 ml) was treated with an excess of Jones chromium trioxide reagent at room temperature. The mixture was immediately poured into ice–water and the solid filtered off. Recrystallisation from dichloromethane afforded the 3-*ketone* (90%), m.p. 199—200°, $[\alpha]_D$ −40° (*c* 4.3), $\nu_{max.}$ 3 500, 1 715, 1 240, 1 190, and 1 140 cm^{-1}, τ 5.21 (1 H, q, *J* 46 and 10 Hz, 11β-H), 6.09 (1 H, t, *J* 10 Hz, 12α-H), 8.69 (3 H, s, 19-H_3), 8.96 (3 H, d, *J* 6.5 Hz, 21-H_3), 9.13 (3 H, s, 18-H_3), and 9.22 (3 H, d, *J* 5.5 Hz, 27-H_3) (Found: C, 63.3; H, 7.6; F, 14.1. $C_{28}H_{40}F_4O_5$ requires C, 63.15; H, 7.6; F, 14.3%). A similar oxidation carried out at 5 °C overnight gave the 3,12-*diketone* (V; X = OCF_3), m.p. (from dichloromethane–hexane) 193—195°, $[\alpha]_D$ −7° (*c* 4.6), $\nu_{max.}$ 1 750, 1 720, 1 250, 1 190, and 1 160 cm^{-1}, τ 4.63 (1 H, d, *J* 43 Hz, 11β-H), 8.63 (3 H, s, 19-H_3), 8.90 (3 H, s, 18-H_3), 8.90 (3 H, d, *J* 6 Hz, 21-H_3), and 9.22 (3 H, d, *J* 6 Hz, 27-H_3) (Found: C, 63.6; H, 6.8; F, 14.05. $C_{28}H_{38}F_4O_5$ requires C, 63.4; H, 7.2; F, 14.3%).

(25R)-11-*Fluoro*-5α-*spirost*-9(11)-*ene*-3,12-*dione* (VI).—The diketone (V; X = OCF_3) (50 mg) in methanol (30 ml) was refluxed with potassium acetate (300 mg) for 3.5 h. Evaporation and trituration of the residue with water precipitated the *enedione* (VI), m.p. (from dichloromethane–hexane) 256—257°, $[\alpha]_D$ −12° (*c* 3.2), $\nu_{max.}$ 1 715, 1 685, and 1 600 cm^{-1}, $\lambda_{max.}$ (MeOH) 247 nm (ε 14 700) (Found: C, 72.9; H, 8.5; F, 4.3. $C_{27}H_{37}FO_4$ requires C, 72.9; H, 8.4; F, 4.3%).

(25R)-9α,11α-*Difluoro*-5α-*spirostane*-3,12-*dione* (V; X = F).—The adduct (IV; R = H, X = F) (100 mg) in acetone (5 ml) was treated with Jones chromium trioxide reagent (0.1 ml) at room temperature for 10 min. The diketone (84%) crystallised as plates from dichloromethane–hexane, m.p. 240—241°, $[\alpha]_D$ −5° (*c* 2.0), $\nu_{max.}$ 1 745 and 1 720 cm^{-1}, τ 4.63 (1 H, q, *J* 45 and 10 Hz, 11β-H), 8.87 (3 H, s, 19-H_3), 8.95 (3 H, d, *J* 6 Hz, 21-H_3), 9.17 (3 H, s, 18-H_3), and 9.21 (3 H, d, *J* 5 Hz, 27-H_3).

Reaction of 17α,20:20,21-*Bismethylenedioxypregna*-4,9(11)-*dien*-3-*one* (I) *with Trifluoro*(*fluoro-oxy*)*methane*.—The 9(11)-ene (I) [11] was treated with trifluoro(fluoro-oxy)methane (1 equiv.) as described above. Repeated chromatography of the resulting mixture gave in low yield 11α-*fluoro*-9β-*methyl*-17α,20:20,21-*bismethylenedioxy*-19-*norpregna*-1,3,5-(10)-*trien*-3-*ol* (II), m.p. (from water) 109—112°, $[\alpha]_D$ −39.8° (*c* 7.8), $\nu_{max.}$ 3 500, 1 610, 1 590, 1 500, 1 250, and 1 080 cm^{-1}, $\lambda_{max.}$ 281 nm (log ε 3.13) (Found: C, 67.1; H, 7.2. $C_{23}H_{29}FO_5$,0.5H_2O requires C, 66.9; H, 7.35%); *benzoate*, m.p. (from hexane) 98—100°, $[\alpha]_D$ −64.3° (Found: C, 70.6; H, 6.3%; M^+, 508.2222. $C_{30}H_{33}FO_6$ requires C, 70.9; H, 6.5%; *M*, 508.2261).

Reaction of Androst-4-*ene*-3β,17β-*diol Diacetate* (VII; X = OAc) *with Trifluoro*(*fluoro-oxy*)*methane*.—The 4-ene (VII; X = OAc) [7] was treated with an excess of trifluoro(fluoro-oxy)methane as above. The crude product was dissolved in methanolic 10% potassium hydroxide and left overnight at room temperature. Crystallisation of the material thus obtained from acetone–hexane afforded 4α-*fluoro*-5α-*trifluoromethoxyandrostane*-3β,17β-*diol*, m.p. 196—198°, $[\alpha]_D$ +2.05° (Found: C, 58.3; H, 7.8. $C_{20}H_{30}F_4O_3$,H_2O requires C, 58.1; H, 7.3%). The *diacetate* had m.p. (from acetone–hexane) 206—207°, $[\alpha]_D$ +26° (Found: C, 60.4; H, 7.3; F, 15.7. $C_{24}H_{34}F_4O_5$ requires C, 60.3; H, 7.2; F, 15.9%). Oxidation of the diol in acetone with Jones reagent for 2 min at 0 °C gave a 17-*monoketone*, m.p. (from chloroform–methanol) 205—206°, $[\alpha]_D$ +61°, $\nu_{max.}$ 3 500 and 1 740 cm^{-1} (Found: C, 61.1; H, 7.0; F, 19.2. $C_{20}H_{28}F_4O_3$ requires C, 61.3; H, 7.2; F, 19.4%). Prolonged oxidation under the same conditions afforded 4α-*fluoro*-5α-*trifluoromethoxyandrostane*-3,17-*dione*, m.p. (from methanol) 210—212°, $[\alpha]_D$ +74.6°, $\nu_{max.}$ 1 740 and 1 710 cm^{-1} (Found: C, 61.4; H, 7.0. $C_{20}H_{26}F_4O_3$ requires C, 61.6; H, 6.7%).

[11] R. E. Beyler and L. H. Sarett, U.S.P. 2,888,457 (*Chem. Abs.*, 1959, **53**, 22090i).

The 3,17-dione (15 mg) in methanol (1 ml) was refluxed with potassium acetate (15 mg) for 2.5 h to yield 4-fluoroandrost-4-ene-3,17-dione, m.p. (from ether) 184—185°, $\nu_{max.}$ 1 740 and 1 665 cm^{-1}, identical with material prepared by oxidation of 4-fluorotestosterone.[12]

When androst-4-en-17β-yl acetate (VII; X = H) [prepared in 70% yield by refluxing testosterone semicarbazone with potassium t-butoxide in dry toluene for 60 h; m.p. 97—98° (lit.,[6] 98—102°)] was treated with trifluoro(fluoro-oxy)methane under the same conditions as for (VII; X = OAc), a complex mixture of products was formed.

Reaction of (25R)-5α-*Spirost*-9(11)-*ene*-3β,12α-*diol Diacetate* (IX) *with Trifluoro(fluoro-oxy)methane.*—The 9(11)-ene-3β,12α-diol was treated as described for the 12β-epimer. Chromatography on alumina (elution with an increasing proportion of ether in hexane) gave first the *adduct diacetate* (X; $R^1 = R^2 = Ac$; X = OCF_3) (36%), m.p. (from methanol–dichloromethane) 127—133°, resolidifying at *ca.* 145°, then remelting at 215°, $[\alpha]_D$ −47° (*c* 3.6), $\nu_{max.}$ 1 735, 1 730, 1 240, 1 200, 1 130, and 1 110 cm^{-1}, τ 8.83 and 9.09 (each 3 H, s, 19- and 18-H_3, respectively) and 9.13 and 9.25 (each 3 H, d, *J* 6 Hz, 21- and 27-H_3, respectively), M^+ 618 (Found: C, 62.4; H, 7.4; F, 12.5. $C_{32}H_{46}F_4O_7$ requires C, 62.1; H, 7.5; F, 12.3%). After mixed fractions the *difluoride diacetate* (X; $R^1 = R^2$ = Ac, X = F) (4%) was obtained; m.p. 205—207°, $[\alpha]_D$ −45° (*c* 2.1) (Found: C, 68.1; H, 8.5; F, 6.8. $C_{31}H_{46}F_2O_6$ requires C, 67.4; H, 8.4; F, 6.9%). Superior yields were obtained when the total product was treated with methanolic 1% sodium hydroxide overnight at room temperature. Chromatography on alumina then afforded the easily separated adduct 12-monoacetate (X; R^1 = H, R^2 = Ac, X = OCF_3) (59%) and the difluoride diol (X; $R^1 = R^2$ = H, X = F) (14%). The former product could not be induced to crystallise and was characterised by treatment with acetic anhydride in pyridine at room temperature to afford the diacetate described above, and by oxidation with Jones reagent at room temperature to give a monoketone, m.p. 162°, $[\alpha]_D$ −35° (*c* 1.2), $\nu_{max.}$ 1 755 and 1 725 cm^{-1}. The diol (X; $R^1 = R^2$ = H, X = F) had m.p. 238—242°, $[\alpha]_D$ −47°. On oxidation with Jones reagent it gave the diketone (V; X = F), identical with previously prepared material.

Hydrolysis of the 12-*Monoacetate* (X; R^1 = H, R^2 = Ac, X = OCF_3).—The monoacetate (20 mg) in dry tetrahydrofuran (7 ml) was treated with aluminium hydride [9] (2 equiv.). After 4 days at room temperature (no *apparent* change on t.l.c.) the mixture was poured into dilute acetic acid and extracted with dichloromethane. The product was purified (p.l.c.) and then treated in acetone with Jones reagent at room temperature for 10 min. The diketone obtained was identical with compound (V; X = OCF_3) described above.

21-*Acetoxy*-16α,17α-*epoxy*-16β-*fluoromethylpregna*-1,4-*diene*-3,11,20-*trione* (XII).—16-Methyleneprednisone 21-acetate (XI) (1 g) in chloroform (100 ml) at −20 °C was treated under nitrogen and in the presence of calcium oxide (0.3 g) with a slow stream of trifluoro(fluoro-oxy)-methane until no starting material remained (t.l.c.). Work-up as before gave material containing one major (*ca.* 80%) product. Purification was best achieved by p.l.c. (silica gel GF_{254}; benzene–methanol, 20 : 1). Crystallisation from chloroform–ether afforded the *epoxide* (XII), m.p. 176—177°, $[\alpha]_D$ +187°, $\nu_{max.}$ 1 750, 1 710, 1 680, 1 640, and 1 620 cm^{-1}, $\lambda_{max.}$ 238 nm (ε 16 900), τ 5.3 (2 H, q, *J* 47 and 5.5 Hz, 16-CH_2F), 7.83 (3 H, s, OAc), and 8.5 and 8.9 (each 3 H, s, 19- and 18-H_3) (Found: C, 67.1; H, 6.2; F, 4.2. $C_{24}H_{27}FO_6$ requires C, 67.0; H, 6.3; F, 4.4%).

1,2,2-*Trifluoro*-1,2-*diphenyl*-1-*trifluoromethoxyethane.*—Diphenylacetylene (500 mg) in Freon (75 ml) at −78 °C was treated under nitrogen and in the presence of calcium oxide with trifluoro(fluoro-oxy)methane (2.5 equiv.). After work-up as above the major product (*ca.* 75%) was separated by chromatography on alumina (elution with hexane). Crystallisation from methanol followed by vacuum sublimation at room temperature gave 1,2,2-*trifluoro*-1,2-*diphenyl*-1-*trifluoromethoxyethane*, m.p. 52—54°, $\lambda_{max.}$ 235, 254, 260, and 267 nm (ε 3 300, 1 500, 1 400, and 1 100), M^+ 320 (Found: C, 56.5; H, 3.3; F, 35.5. $C_{15}H_{10}F_6O$ requires C, 56.3; H, 3.15; F, 35.6%).

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