Synthesis of 12-Fluoro-corticosteroids

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Methods for the preparation of various 11(12)-enol derivatives of steroidal 9α-fluoro-11-ketones are described. The reaction of metal enolates with perchloryl fluorides provides a convenient route to α-fluoro-ketones. Factors permitting control of the direction of enolisation of steroidal 11-ketones are defined. The synthesis of 12α- and 12β-monofluoro- and 12,12-difluoro-9α-fluoro-corticoids is reported.

We have previously shown that electrophilic fluorination of enolate derivatives with trifluorofluoro-oxymethane constitutes an attractive route to various fluorosteroids.[1] We now report extensions of this approach which make available corticosteroids with all possible substitutions of fluorine at positions 9α and 12.

In initial experiments we investigated the synthesis of 11(12)-enolates of 9α-halogeno-11-oxo-steroids. Treatment of 3,3-ethylenedioxy-9α-fluoro-17α,20;20,21-bismethylenedioxypregn-5-en-11-one[2] (I; R = F) with sodium bistrimethylsilylamide in tetrahydrofuran, followed by addition of trimethylsilyl chloride or benzoic anhydride gave in excellent yield the trimethylsilyl enol ether (IIa; $R^1 = F$, $R^2 = H$) or enol benzoate (IIb; $R^1 = F$, $R^2 = H$), respectively.[1c] The structure of these enolates followed from their n.m.r. spectra and from basic hydrolysis which regenerated the parent ketone quantitatively. α′-Enolates of α-halogeno-ketones have often been postulated as intermediates in the Favorskii rearrangement,[3a] but their isolation as derivatives had not been achieved at the time our work was carried out.[3b] Their particular stability in this case may be due, at least in part, to the known reluctance of axially oriented α-halogeno-ketones to undergo the Favorskii rearrangement.[4]

Neither the trimethylsilyl enol ether (IIa; $R^1 = F$, $R^2 = H$) nor the enol benzoate (IIb; $R^1 = F$, $R^2 = H$) reacted with trifluorofluoro-oxymethane at −78°. On warming to −28° a sluggish reaction leading to a multitude of products occurred. N.m.r. spectroscopy indicated that the 5,6-double bond was being attacked in preference to the sterically hindered 11(12)-enol. Attempts to reverse this situation by including the double bond in an electrophilically less reactive function were unsuccessful. Thus, the enol benzoates (III) and (IV)

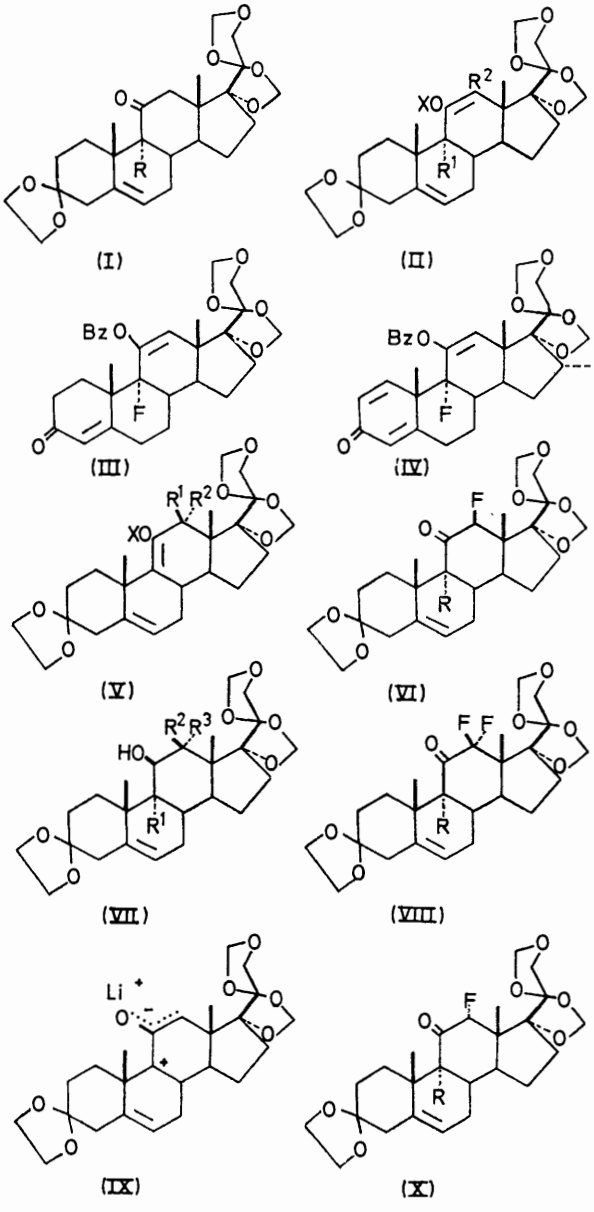
[1] (*a*) D. H. R. Barton, L. S. Godinho, R. H. Hesse, and M. M. Pechet, *Chem. Comm.*, 1968, 804; (*b*) D. H. R. Barton, L. J. Danks, A. K. Ganguly, R. H. Hesse, G. Tarzia, and M. M. Pechet, *ibid.*, 1969, 227; (*c*) D. H. R. Barton, R. H. Hesse, G. Tarzia, and M. M. Pechet, *ibid.*, 1969, 1497; (*d*) D. H. R. Barton, R. H. Hesse, M. M. Pechet, G. Tarzia, H. T. Toh, and N. D. Westcott, *J.C.S. Chem. Comm.*, 1972, 122.

[2] R. E. Beyler, F. Hoffman, and L. H. Sarett, *J. Amer. Chem. Soc.*, 1960, **82**, 178.

[3] (*a*) A. S. Kende, *Org. Reactions*, 1960, **11**, 262; F. G. Bordwell, R. G. Scamehorn and W. R. Springer, *J. Amer. Chem. Soc.*, 1969, **91**, 2087; F. G. Bordwell and M. W. Carlson, *ibid.*, 1970, **92**, 3370, 3377; (*b*) See H. O. House, W. F. Fischer, M. Gall, T. E. McLaughin, and N. P. Peet, *J. Org. Chem.*, 1971, **36**, 3429.

[4] E. E. Smissman, T. L. Lemke, and O. Kristiansen, *J. Amer. Chem. Soc.*, 1966, **88**, 334 and references therein.

[the latter prepared by *slow* addition [1c] of sodium bistrimethylsilylamide to 9α-fluoro-16α-methyl-17α,20;20,-21-bismethylenedioxypregna-1,4-diene-3,11-dione [5]] reacted preferentially in ring A.



(I) (II) (III) (IV) (V) (VI) (VII) (VIII) (IX) (X)

a; X = Me_3Si
b; X = Bz
c; X = Na
d; X = Li

It was now clear that specific fluorination at C-12 would require a much more reactive enol derivative. Metal enolates were therefore considered. The reaction of sodium enolates with trifluorofluoro-oxymethane was too violent even at −78°. The less reactive perchloryl fluoride however, reacted smoothly at 0°. Thus, treatment of the 11-ketone [6] (I; R = H) with sodium bistrimethylsilylamide gave the sodium 9(11)-enolate (Vc; $R^1 = R^2 = H$) [characterised as the trimethylsilyl enol ether (Va; $R^1 = R^2 = H$)] which with perchloryl fluoride afforded the known 9α-fluoro-11-ketone (I; R = F) in high yield. Similarly, the sodium 11-enolate (IIc; $R^1 = F$, $R^2 = H$) gave 3,3-ethylenedioxy-9α,12β-difluoro-17α,20;20,21-bismethylenedioxypregn-5-en-11-one (VI; R = F) in 78% yield. The configuration of the new fluoro-substituent at C-12 was the more stable one (no epimerisation with base) and therefore probably β. This was confirmed by the coupling constants in the ^{19}F n.m.r. spectra of the product and of the corresponding 11β-alcohol (VII; $R^1 = R^2 = F$, $R^3 = H$) derived by reduction with sodium borohydride (see Table).

In an analogous series of experiments, treatment of the sodium 11-enolate (IIc; $R^1 = F$, $R^2 = H$) with bromine afforded the 12β-bromo-9α-fluoro-11-ketone, which with sodium borohydride gave the corresponding 11β-alcohol (VII; $R^1 = F$, $R^2 = Br$, $R^3 = H$). Reaction of the latter with sodium hydroxide in methanol proceeded with loss of bromine to give the 9α-fluoro-11-ketone (I; R = F), thereby confirming the equatorial nature of the original 12-bromo-substituent.

A disadvantage of this method of preparing fluorosteroids became apparent when the reaction of the sodium 11-enolate (IIc; $R^1 = F$, $R^2 = H$) was repeated on a larger (1 mmol) scale. The longer reaction time, a consequence of the need to introduce a greater volume of gaseous perchloryl fluoride (organic solutions of this reagent present considerable hazards), allowed equilibration between the original enolate (IIc; $R^1 = F$, $R^2 = H$) and the initial product (VI; R = F). As a result the final product was a mixture of the 9α-fluoro-11-ketone (I; R = F), the required 9α,12β-difluoro-11-ketone (VI; R = F), and the 9β,12,12-trifluoro-11-ketone (VIII; R = F). Lithium enolates are known to be considerably less prone to equilibration than their sodium counterparts,[7] and therefore offered a potential solution to this problem. The direct preparation of lithium enolates using lithium bistrimethylsilylamide gave erratic results and so an alternative method involving metathesis of sodium enolates was developed. Mixture of solutions of the sodium 11-enolate (IIc; $R^1 = F$, $R^2 = H$) and lithium chloride in tetrahydrofuran gave a precipitate of sodium chloride and a solution of the required lithium 11-enolate (IId; $R^1 = F$, $R^2 = H$). Addition of perchloryl fluoride to this mixture now afforded the required 9α,12β-difluoro-11-ketone (VI; R = F) in consistent yields of 65%, even on a 2 mmol scale. Further, treatment of the 9α,12β-difluoro-11-ketone (VI; R = F) with sodium bistrimethylsilylamide generated the sodium 11-enolate (IIc; $R^1 = R^2 = F$)

[5] L. J. Danks, Ph.D. Thesis, University of London, 1968.
[6] J. H. Fried, G. E. Arth, and L. H. Sarett, *J. Amer. Chem. Soc.*, 1959, **81**, 1235.
[7] H. O. House, *Rec. Chem. Progr.*, 1967, **28**, 99; ref. 1c.

which on reaction with perchloryl fluoride completed a convenient route to the 9α,12,12-trifluoro-11-ketone (VIII; R = F).

Use of an excess of lithium chloride in the particular metathesis quoted above gave significant amounts of a second product. This was isolated, after reduction of the mixture with sodium borohydride, as the corresponding 11β-alcohol. Spectroscopic data, particularly ^{19}F n.m.r. (see Table), indicated that this was the 9α-chloro-12β-fluoro-11β-alcohol (VII; R^1 = Cl, R^2 = F, R^3 = H). The formation of the 11-ketone (VI; R = Cl) is of considerable interest since it requires the intermediacy of a zwitterion such as (IX). Species of this type have been frequently postulated as intermediates in the Favorskii rearrangement.[3]

The products so far observed from the reaction of 11-ketones with sodium bistrimethylsilylamide have been the thermodynamically more stable sodium 9(11)-enolates. To test whether these are also the product of kinetic control, the 11-ketone (I; R = H) was titrated with lithium di-isopropylamide, with triphenylmethane as indicator. Treatment of the resulting lithium enolate with trimethylsilyl chloride gave a new trimethylsilyl enol ether. That this was the 11(12)-isomer (IIa; R^1 = R^2 = H) followed from the n.m.r. spectrum, and from basic hydrolysis which regenerated the parent ketone. Clearly then, the product of kinetic control of enolisation of this type of 11-ketone is the 11(12)-isomer, whereas the 9(11)-isomer is thermodynamically favoured. To illustrate the initial formation of the 11(12)-enol with sodium bases, the ketone (I; R = H) was added slowly to an excess of sodium bistrimethylsilylamide. Under these conditions the concentration of (I; R = H) available for intermolecular equilibration is minimised.[1c] Reaction with trimethylsilyl chloride now gave a mixture of the trimethylsilyl 9(11)-enol ether (Va; R^1 = R^2 = H) and its 11(12)-isomer (IIa; R^1 = R^2 = H). Reaction of the lithium 11-enolate (IId; R^1 = R^2 = H) with perchloryl fluoride and chromatography of the product on alumina gave the 12α-fluoro-11-ketone (X; R = H) (23%) and the 12β-fluoro-11-ketone (VI; R = H) (65%). The relative configuration of these products was suggested by their n.m.r. spectra, only the former showing coupling between fluorine and the C-13 methyl group.[8] Further evidence was obtained by reduction of each ketone to the corresponding 11β-alcohol and examination of the appropriate coupling constants in the ^1H and ^{19}F n.m.r. spectra (see Table and Experimental section). Finally, the former was isomerised by base into the more stable 12β-isomer.

^{19}F N.m.r. spectra

	9α-F		12α-F		12β-F	
Compound	δ	J/Hz	δ	J/Hz	δ	J/Hz
(VII; R^1 = R^2 = H, R^3 = F)			−184 (dd)	50, 12		
(VII; R^1 = R^3 = H, R^2 = F)					−186 (dd) *	
(VII; R^1 = Cl, R^2 = F, R^3 = H)					−191 (dd)	50, 5
(VII; R^1 = R^2 = F, R^3 = H)	−182 br (dd)	35, 15			−191 (dd) *	50, 5
(X; R = F)	−178 (dd)	35, 28	−188 (ddq)	50, 28, 2		
(X; R = H)			−185 (dq)	50, 2		
(VI; R = H)					−191 (d)	50
(VI; R = F)	−191 br (d)	35			−201 (d)	50
(VIII; R = F)	−179 (dd)	35, 28	−107 (dd)	258, 28	−115 (d)	258

* After addition of deuterium oxide.

Further confirmation of the mode of enolisation of 11-ketones was obtained for the 12α- and 12β-fluoro-11-ketones [(X; R = H) and (VI; R = H), respectively]. Treatment of (VI; R = H) with lithium di-isopropylamide gave the lithium 11-enolate (IId; R^1 = H, R^2 = F), isolated as the trimethylsilyl 11-enol ether (IIa; R^1 = H, R^2 = F), and utilised, by reaction with perchloryl fluoride, for the synthesis of the 12,12-difluoro-11-ketone (VIII; R = H). On the other hand slow addition of sodium bistrimethylsilylamide to the ketone (VI; R = H) afforded the sodium 9(11)-enolate (Vc; R^1 = F, R^2 = H), characterised as the trimethylsilyl 9(11)-enol ether (Va; R^1 = F, R^2 = H), and yielding with perchloryl fluoride the known 9α,12β-difluoro-11-ketone (VI; R = F). Finally, reaction of the ketone (X; R = H) with sodium bistrimethylsilylamide afforded the sodium 9(11)-enolate (Vc; R^1 = H, R^2 = F), which was further converted into the trimethylsilyl 9(11)-enol ether (Va; R^1 = H, R^2 = F) and the 9α,12α-difluoro-11-ketone (X; R = F). Treatment of the latter with mild base caused isomerisation to the 9α,12β-difluoro-11-ketone (VI; R = F).

Completion of the synthesis of the desired fluorinated corticosteroids required reduction of the 11-ketone function by sodium borohydride to 11β-ol, followed by removal of the ethylene acetal and bismethylenedioxy protecting groups. Brief treatment with concentrated hydrochloric acid was particularly effective for the latter transformation.[9]

EXPERIMENTAL

M.p.s were determined with a hot-stage microscope. N.m.r. data were recorded on a Varian T-60 instrument: ^1H spectra at 60 MHz in deuteriochloroform with tetramethylsilane as internal standard, and ^{19}F at 56·4 MHz in methylene chloride with trichlorofluoromethane as internal standard. Rotations are quoted for 1% solutions in chloroform, and i.r. spectra for potassium bromide discs. Alumina was of Brockmann grade III activity. Lithium di-isopropylamide [10] was prepared and used directly as a

[8] A. D. Cross and P. W. Landis, *J. Amer. Chem. Soc.*, 1964, **86**, 4005.

[9] F. Alvarez, J. B. Siddall, and A. Ruiz, U.S.P. 3,338,930/1967.

[10] H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, 1969, **34**, 2324.

solution in tetrahydrofuran. All enolisation reactions were performed in vacuum-dried glassware using as solvent tetrahydrofuran freshly distilled from lithium aluminium hydride under argon. Reactions were carried out in an atmosphere of argon. All solution transfers were made using hypodermic syringes *via* teflon-lined silicon rubber serum caps. General work-up procedures were as follows. (i) In the preparation of enol benzoates and trimethylsilyl enol ethers the reaction mixture was poured into ether and washed (×3) with aqueous buffer (pH 7), 5% sodium hydrogen carbonate solution, and saturated sodium chloride solution. (ii) In reactions involving perchloryl fluoride the reaction mixture was poured into potassium iodide solution and the liberated iodine was reduced by addition of sodium thiosulphate. The product was extracted with ether and the extracts washed with water, 5% sodium hydrogen carbonate solution, and saturated sodium chloride solution. Both procedures were completed by drying (Na_2SO_4) and evaporation under reduced pressure.

3,3-*Ethylenedioxy*-9α-*fluoro*-17α,20;20,21-*bismethylenedioxypregn*-5-*en*-11-*one* (I; R = F).—Ethylene glycol (500 ml) containing 9α-fluoro-17α,20;20,21-bismethylenedioxypregn-4-ene-3,11-dione [2] (4 g) and toluene-*p*-sulphonic acid (250 mg) was slowly distilled (0·2 mmHg; still head temperature 60°). After 4 h the mixture was cooled, neutralised with sodium hydrogen carbonate, and extracted with methylene chloride to give the acetal (I; R = F) (3·1 g), m.p. 253°, $[\alpha]_D$ −94° (lit.,[2] m.p. 250—257°).

Similarly, 17α,20;20,21-bismethylenedioxypregn-4-ene-3,11-dione [11] (15 g) afforded 3,3-ethylenedioxy-17α,20;20,21-bismethylenedioxypregn-5-en-11-one (I; R = H) (12·8 g), m.p. 210—212°, $[\alpha]_D$ −85° (lit.,[6] m.p. 210—212°, $[\alpha]_D$ −87°).

9α-*Fluoro*-17α,20;20,21-*bismethylenedioxy*-3-*oxopregna*-4,11-*dien*-11-*yl Benzoate* (III).—9α-Fluoro-17α,20;20,21-bismethylenedioxypregn-4-ene-3,11-dione [2] (3·2 g) in 2,2-dimethoxypropane (50 ml) and *NN*-dimethylformamide (50 ml) containing toluene-*p*-sulphonic acid (400 mg) was heated under reflux for 4 h. The solution was poured into water and extracted with methylene chloride to give 9α-*fluoro*-3-*methoxy*-17α,20;20,21-*bismethylenedioxypregna*-3,5-*dien*-11-*one* (1·8 g), m.p. (from methanol–methylene chloride) 303°, $[\alpha]_D$ +12·6°, $\nu_{max.}$ 1725, 1660, and 1640 cm^{-1} (Found: C, 65·5; H, 6·9; F, 4·85. $C_{24}H_{31}FO_6$ requires C, 66·3; H, 7·2; F, 4·4%). This product (440 mg) in tetrahydrofuran (40 ml) was treated with sodium bistrimethylsilylamide (300 mg) in tetrahydrofuran (20 ml). After 5 min benzoic anhydride (400 mg) in tetrahydrofuran (10 ml) was added. After 1 min the solution was worked up to give an oil [$\nu_{max.}$ 1750, 1660, 1640, 1610, and 1260 cm^{-1}, δ 1·1 and 1·3 (each 3H, s, Me), 3·5 (3H, s, OMe), 4·0 (2H, s, 21-H_2), 5·1 (6H, complex, 4-H, 6-H, 2 × O·CH_2·O), 6·6 (1H, d, *J* 3 Hz, 12-H), and 7·9 (5H, m, Ph)]. This oil (300 mg) in acetone containing aqueous 0·5% hydrochloric acid was left at room temperature for 30 min. Work-up in the usual manner gave the *enol benzoate* (III) (183 mg), m.p. (from methanol–ether) 200—205°, $[\alpha]_D$ +5·4°, $\nu_{max.}$ 1750, 1660, 1610, and 1260 cm^{-1}, δ 1·1 and 1·3 (each 3H, s, Me), 5·9 (1H, s, 4-H), 6·6 (1H, d, *J* 3 Hz, 12-H), and 7·8 (5H, m, Ph) (Found: C, 67·1; H, 6·6; F, 3·0. $C_{30}H_{33}FO_7,CH_3OH$ requires C, 66·9; H, 6·7; F, 3·4%).

9α-*Fluoro*-16α-*methyl*-17α,20;20,21-*bismethylenedioxy*-3-*oxopregna*-1,4,11-*trien*-11-*yl Benzoate* (IV).—Concentrated hydrochloric acid (250 ml) and formaldehyde (250 ml; 40% aqueous solution) were added to 9α-fluoro-16α-methyl-3,20-dioxopregna-1,4-diene-11β,17α,21-triol (10 g) in chloroform (500 ml). After 40 min the chloroform layer was separated and worked up in the usual manner to afford 9α-fluoro-16α-methyl-17α,20;20,21-bismethylenedioxy-3-oxopregna-1,4-dien-11β-ol (6·4 g), m.p. 214—220°, $[\alpha]_D$ +40° (lit.,[5] m.p. 210—220°). A stirred solution of the 11β-alcohol (6 g) in acetone (1 l) was treated with Jones chromic acid (1·1 equiv.). After 1 h the solution was poured on ice, then filtered, to give, after crystallisation from methylene chloride–methanol, 9α-fluoro-16α-methyl-17α,20;20,21-bismethylenedioxypregna-1,4-diene-3,11-dione (5·0 g), m.p. 305—308°, $[\alpha]_D$ +30° (lit.,[5] m.p. 305—310°, $[\alpha]_D$ +28·4°). Sodium bistrimethylsilylamide (300 mg) in tetrahydrofuran (20 ml) was added *over* 2 *h* [1c] to the 11-ketone (500 mg) in tetrahydrofuran (40 ml). Benzoic anhydride (400 mg) in tetrahydrofuran (10 ml) was then added. After 1 min the solution was worked up. Chromatography of the product on alumina (elution with benzene) gave the *enol benzoate* (IV) (320 mg), m.p. 243—244°, $[\alpha]_D$ +50°, $\nu_{max.}$ 1750, 1670, 1615, and 1250 cm^{-1}, δ 1·0 (3H, d, *J* 7 Hz, 16α-Me), 1·17 and 1·43 (each 3H, s, 13- and 10-Me, respectively), 4·03 (2H, s, 21-H_2), 6·22 (1H, d, *J* 3 Hz, 12-H), and 7·5 (5H, m, Ph) (Found: C, 69·05; H, 6·3; F, 3·6. $C_{31}H_{33}FO_7$ requires C, 69·4; H, 6·2; F, 3·5%).

3,3-*Ethylenedioxy*-9α-*fluoro*-17α,20;20,21-*bismethylenedioxypregna*-5,11-*dien*-11-*ol Trimethylsilyl Ether* (IIa; R^1 = F, R^2 = H) *or Benzoate* (IIb; R^1 = F, R^2 = H).—Sodium bistrimethylsilylamide (300 mg) in tetrahydrofuran (20 ml) was added to the 11-ketone (I; R = F) (440 mg) in tetrahydrofuran (30 ml). The solution was stirred for 5 min and then trimethylsilyl chloride (0·15 ml) or benzoic anhydride (400 mg) in tetrahydrofuran (10 ml) was added. After a further 1 min the solutions were worked up to afford the *trimethylsilyl enol ether* (IIa; R^1 = F, R^2 = H) (320 mg after chromatography on silica with methylene chloride), m.p. (from methylene chloride–methanol) 176—180°, $[\alpha]_D$ −124·6°, $\nu_{max.}$ 1740 and 940 cm^{-1}, δ 0·15 (9H, s, Me_3Si), 0·9 and 1·15 (each 3H, s, 13- and 10-Me, respectively), and 6·1 (1H, d, *J* 2 Hz, 12-H) (Found: C, 62·9; H, 7·8; F, 3·7. $C_{28}H_{41}FO_7Si$ requires C, 62·65; H, 7·7; F, 3·5%), or the enol benzoate (IIb; R^1 = F, R^2 = H) as a glass, $\nu_{max.}$ 1745, 1650, 1600, and 1250 cm^{-1}, δ 1·05 and 1·25 (each 3H, s, 13- and 10-Me, respectively), 6·55 (1H, d, *J* 2 Hz, 12-H), and 7·8 (5H, m, Ph). Treatment of either product with sodium hydroxide in methanol gave the 11-ketone (I; R = F) quantitatively.

3,3-*Ethylenedioxy*-17α,20;20,21-*bismethylenedioxypregna*-5,9(11)-*dien*-11-*ol Trimethylsilyl Ether* (Va; R^1 = R^2 = H) *and* 3,3-*Ethylenedioxy*-9α-*fluoro*-17α,20;20,21-*bismethylenedioxypregn*-5-*en*-11-*one* (I; R = F).—Sodium bistrimethylsilylamide (300 mg) in tetrahydrofuran (20 ml) was added to the 11-ketone (I; R = H) (440 mg) in tetrahydrofuran (40 ml). After 5 min either trimethylsilyl chloride (0·15 ml) was added or the solution was cooled to 0° and perchloryl fluoride (35 ml) was passed in. After 1 min further the respective work-up procedures gave the *trimethylsilyl enol ether* (Va; R^1 = R^2 = H) (290 mg), m.p. (from ether–methanol) 153—155°, $[\alpha]_D$ −47°, $\nu_{max.}$ 1620 and 850 cm^{-1}, δ 0·2 (9H, s, Me_3Si), 0·8 and 1·2 (each 3H, s, 13- and 10-Me, respectively), 3·95 (6H, s, 21-H_2 and O·CH_2·CH_2·O), 5·1 (4H, d, 2 × O·CH_2·O), and 5·3br (1H, s, 6-H) (Found: C, 65·15; H, 7·85. $C_{28}H_{42}O_7Si$ requires C, 64·8; H, 8·2%) or the 9α-fluoro-11-ketone (I; R = F) (330 mg), identical with an authentic sample.

[11] P. F. Beal, R. W. Jackson, and J. E. Pike, *J. Org. Chem.*, 1962, **27**, 1752.

3,3-*Ethylenedioxy*-9α,12β-*difluoro*-17α,20;20,21-*bismethylenedioxypregn*-5-*en*-11-*one* (VI; R = F).—(*a*) Sodium bistrimethylsilylamide (150 mg) in tetrahydrofuran (20 ml) was added to the 9α-fluoro-11-ketone (I; R = F) (220 mg) in tetrahydrofuran (40 ml). The solution was stirred and after 5 min was cooled to 0°, and perchloryl fluoride (20 ml) was passed in. After a further 1 min, work-up gave the 9α,12β-*difluoro*-11-*ketone* (VI; R = F) (180 mg), m.p. (from methylene chloride–methanol) 260—262°, $[\alpha]_D$ −102°, $\nu_{max.}$ 1745 cm^{-1}, δ 0·85 and 1·3 (each 3H, s, 13- and 10-Me, respectively), and 5·5 (1H, dd, *J* 50 and 5·5 Hz, 12-H) (Found: C, 62·6; H, 6·7; F, 7·3. $C_{25}H_{32}F_2O_7$ requires C, 62·2; H, 6·7; F, 7·9%). Much lower yields were obtained when this method was repeated on a larger scale.

(*b*) Sodium bistrimethylsilylamide (1·5 g) in tetrahydrofuran (40 ml) was added to the 9α-fluoro-11-ketone (I; R = F) (2·2 g) in tetrahydrofuran (120 ml). After 5 min anhydrous lithium chloride (300 mg) in tetrahydrofuran (40 ml) was added, and 5 min later perchloryl fluoride (140 ml) was passed in. Work-up gave the 9α,12β-difluoro-11-ketone (VI; R = F) (1·43 g), identical with material prepared as in (*a*). Repetition of this method but using lithium chloride (2 g) and allowing 20 min before addition of the perchloryl fluoride led to a mixture of two products. Reduction of this mixture followed by chromatography on alumina gave the 9α,12β-difluoro-11β-ol (VII; $R^1 = R^2 =$ F, R^3 = H) and then 9α-*chloro*-3,3-*ethylenedioxy*-12β-*fluoro*-17α,20;20,21-*bismethylenedioxypregn*-5-*en*-11β-*ol* (VII; R^1 = Cl, R^2 = F, R^3 = H) (187 mg), m.p. (from methylene chloride–methanol) 226—228°, δ 4·8 (1H, dd, *J* 50 and 3·5 Hz, 12-H) (Found: C, 59·9; H, 6·7; Cl, 7·1; F, 4·1. $C_{25}H_{34}ClFO_7$ requires C, 59·9; H, 6·8; Cl, 7·1; F, 3·8%).

12β-*Bromo*-3,3-*ethylenedioxy*-9α-*fluoro*-17α,20;20,21-*bismethylenedioxypregn*-5-*en*-11β-*ol* (VII; R^1 = F, R^2 = Br, R^3 = H).—Sodium bistrimethylsilylamide (300 mg) in tetrahydrofuran (40 ml) was added to the 9α-fluoro-11-ketone (I; R = F) (440 mg) in tetrahydrofuran (40 ml). After 5 min bromine (0·18 ml) was added. The solution was poured into ether, washed with sodium sulphite solution, and further processed in the usual manner. Chromatography on alumina (elution with benzene) gave the 12β-*bromo*-9α-*fluoro*-11-*ketone* (280 mg), m.p. 201—203° (decomp.), $\nu_{max.}$ 1740 cm^{-1}, δ 4·8 (1H, d, *J* 3 Hz, 12-H). This 11-ketone (220 mg) in tetrahydrofuran (20 ml) and propan-2-ol (8 ml) was treated with sodium borohydride (100 mg) in water (3 ml). After 1 h the solution was poured into methylene chloride, washed with water and sodium carbonate solution, dried, and evaporated. Crystallisation from methylene chloride–methanol gave the *bromohydrin* (VII; R^1 = F, R^2 = Br, R^3 = H) (160 mg), m.p. 184—185°, $\nu_{max.}$ 3300 cm^{-1}, δ 4·3 (1H, dd after addition of deuterium oxide, *J* 12 and 3 Hz, 11β-H) (Found: C, 55·0; H, 6·3; F, 3·5; Br, 14·6. $C_{25}H_{34}BrFO_7$ requires C, 55·05; H, 6·3; F, 3·5; Br, 14·65%). The bromohydrin was treated with refluxing methanol containing 1% sodium hydroxide for 1 h to give the 9α-fluoro-11-ketone (I; R = F), identical with an authentic sample.

3,3-*Ethylenedioxy*-9α,12-*difluoro*-17α,20;20,21-*bismethylenedioxypregna*-5,11-*dien*-11-*ol Trimethylsilyl Ether* (IIa; $R^1 = R^2$ = F) *and* 3,3-*Ethylenedioxy*-9α,12,12-*trifluoro*-17α,20;20,21-*bismethylenedioxypregn*-5-*en*-11-*one* (VIII; R = F).—Sodium bistrimethylsilylamide (300 mg) in tetrahydrofuran (20 ml) was added to the 9α,12β-difluoro-11-ketone (VI; R = F) (460 mg) in tetrahydrofuran (40 ml). After 5 min either trimethylsilyl chloride (0·15 ml) was added or the solution was cooled to 0° and perchloryl fluoride (35 ml) was passed in. The respective work-up procedures then afforded the *trimethylsilyl enol ether* (IIa; $R^1 = R^2$ = F) (330 mg), m.p. (from methylene chloride–methanol) 174—176°, $[\alpha]_D$ −116°, $\nu_{max.}$ 1640 and 950 cm^{-1}, δ 0·2 (9H, d, *J* 1·2 Hz, Me_3Si), and 1·0 and 1·08 (each 3H, s, 13- and 10-Me) (Found: C, 60·9; H, 7·2; F, 6·5. $C_{28}H_{40}F_2O_7Si$ requires C, 60·6; H, 7·3; F, 6·85%) or the 9α,12,12-*trifluoro*-11-*ketone* (VIII; R = F) (220 mg), m.p. (from methylene chloride–methanol) 239—245°, $[\alpha]_D$ −87·4°, $\nu_{max.}$ 1750 cm^{-1}, δ 0·8 and 1·3 (each 3H, s, 13- and 10-Me) (Found: C, 59·9; H, 6·2; F, 12·2. $C_{25}H_{31}F_3O_7$ requires C, 59·9; H, 6·2; F, 11·4%).

3,3-*Ethylenedioxy*-17α,20;20,21-*bismethylenedioxypregna*-5,11-*dien*-11-*ol Trimethylsilyl Ether* (IIa; $R^1 = R^2$ = H).—The 11-ketone (I; R = H) (420 mg) in tetrahydrofuran (40 ml) was treated with lithium di-isopropylamide solution [10] containing triphenylmethane as indicator until a pink colour persisted. Trimethylsilyl chloride (0·15 ml) was added and the solution worked up. Crystallisation from methanol gave the *trimethylsilyl enol ether* (IIa; $R^1 = R^2$ = H) (360 mg), m.p. 170—172°, $[\alpha]_D$ −120°, $\nu_{max.}$ 1625 and 850 cm^{-1}, δ 0·2 (9H, s, Me_3Si), 0·95 and 1·15 (each 3H, s, 13- and 10-Me, respectively), 4·0 (6H, s, 21-H_2 and O·CH_2·CH_2·O), 5·1 (4H, d, 2 × O·CH_2·O), 5·4br (1H, s, 6-H), and 5·6 (1H, s, 12-H) (Found: C, 65·2; H, 7·8. $C_{28}H_{42}O_7Si$ requires C, 64·8; H, 8·2%).

3,3-*Ethylenedioxy*-12α- *and* 12β-*fluoro*-17α,20;20,21-*bismethylenedioxypregn*-5-*en*-11-*one* (X; R = H) *and* (VI; R = H).—The 11-ketone (I; R = H) (2·2 g) in tetrahydrofuran (100 ml) containing triphenylmethane as indicator was titrated with lithium di-isopropylamide. The solution was cooled to 0° and perchloryl fluoride (145 ml) passed in. Work-up and chromatography on alumina (elution with methylene chloride) gave the 12α-*fluoro*-11-*ketone* (X; R = H) (520 mg), m.p. (from methylene chloride–ether) 234·5°, $[\alpha]_D$ −62·7°, $\nu_{max.}$ 1725 cm^{-1}, δ 0·7 (3H, d, *J* 2 Hz, 13-Me) and 4·75 (1H, d, *J* 50 Hz, 12-H) (Found: C, 64·6; H, 7·0; F, 4·1. $C_{25}H_{33}FO_7$ requires C, 64·6; H, 7·2; F, 4·1%) followed by the 12β-*fluoro*-11-*ketone* (VI; R = H) (1·48 g), m.p. (from methylene chloride–ether) 208—214°, $[\alpha]_D$ −98·1°, $\nu_{max.}$ 1725 cm^{-1}, δ 5·05 (1H, d, *J* 50 Hz, 12-H) (Found: C, 65·1; H, 7·0; F, 4·0%).

3,3-*Ethylenedioxy*-12-*fluoro*-17α,20;20,21-*bismethylenedioxypregna*-5,11-*dien*-11-*ol Trimethylsilyl Ether* (IIa; R^1 = H, R^2 = F) *and* 3,3-*Ethylenedioxy*-12,12-*difluoro*-17α,20;20,21-*bismethylenedioxypregn*-5-en-11-*one* (VIII; R = H).—The 12β-fluoro-11-ketone (VI; R = H) (450 mg) in tetrahydrofuran (40 ml) was titrated with lithium di-isopropylamide. Either trimethylsilyl chloride (0·15 ml) was added or the solution was cooled to 0° and perchloryl fluoride (35 ml) passed in. The respective work-up procedure then gave the *trimethylsilyl enol ether* (IIa; R^1 = H, R^2 = F) (390 mg), m.p. (from methanol) 190—192°, $[\alpha]_D$ −77·6°, $\nu_{max.}$ 1640 and 850 cm^{-1}, δ 0·16 (9H, d, *J* 2 Hz, Me_3Si), 1·1 (6H, s, 13- and 10-Me), 3·95 (6H, s, 21-H_2 and O·CH_2·CH_2·O), 5·1 (4H, t, 2 × O·CH_2·O), and 5·4 (1H, s, 6-H) (Found: C, 62·9; H, 7·55; F, 3·6. $C_{28}H_{41}FO_7Si$ requires C, 62·65; H, 7·7; F, 3·5%) or the 12,12-*difluoro*-11-*ketone* (VIII; R = H) (355 mg), m.p. (from methylene chloride) 231—233°, $[\alpha]_D$ −61° (Found: C, 61·8; H, 6·5; F, 7·95. $C_{25}H_{32}F_2O_7$ requires C, 62·2; H, 6·7; F, 7·9%).

3,3-*Ethylenedioxy*-12β-*fluoro*-17α,20;20,21-*bismethylenedioxypregna*-5,9(11)-*dien*-11-*ol Trimethylsilyl Ether* (Va; R^1 = F, R^2 = H).—Sodium bistrimethylsilylamide (600

mg) in tetrahydrofuran (35 ml) was added *over* 2·5 *h* to the 12β-fluoro-11-ketone (VI; R = H) (880 mg) in tetrahydrofuran (50 ml). Trimethylsilyl chloride (0·3 ml) was added and the solution worked up to afford the *trimethylsilyl enol ether* (Va; R^1 = F, R^2 = H) (750 mg), m.p. (from methanol–ether) 161°, $[\alpha]_D$ −38°, $\nu_{max.}$ 1640 and 950 cm^{-1}, δ 0·2 (9H, d, *J* 2 Hz, Me_3Si), 0·8 (3H, d, *J* 2 Hz, 13-Me), and 5·25 (1H, d, *J* 48 Hz, 12-H) (Found: C, 62·7; H, 7·45; F, 3·7. $C_{28}H_{41}FO_7Si$ requires C, 62·65; H, 7·7; F, 3·5%).

3,3-Ethylenedioxy-12α-fluoro-17α,20;20,21-bismethylenedioxypregna-5,9(11)-dien-11-ol Trimethylsilyl Ether (Va; R^1 = H, R^2 = F) *and* *3,3-Ethylenedioxy-9α,12α-difluoro-17α,20;20,21-bismethylenedioxypregn-5-en-11-one* (X; R = F).—The 12α-fluoro-11-ketone (X; R = H) (460 mg) in tetrahydrofuran (30 ml) was added to sodium bistrimethylsilylamide (340 mg) in tetrahydrofuran (30 ml) over 2 h. Either trimethylsilyl chloride (0·15 ml) was added or the solution was cooled to 0° and perchloryl fluoride (35 ml) passed in. The respective work-up procedures then gave the *trimethylsilyl enol ether* (Va; R^1 = H, R^2 = F) (380 mg), m.p. (from methanol) 168—170°, $[\alpha]_D$ −39°, δ 0·15 (9H, s, Me_3Si), 0·8 and 1·2 (each 3H, s, 13- and 10-Me, respectively), and 4·8 (1H, d, *J* 50 Hz, 12-H) (Found: C, 62·4; H, 7·5; F, 3·3. $C_{28}H_{41}FO_7Si$ requires C, 62·65; H, 7·7; F, 3·5%) or the *9α,12α-difluoro-11-ketone* (X; R = F) (295 mg), m.p. (from ether) 263—265°, $[\alpha]_D$ −115°, $\nu_{max.}$ 1740 cm^{-1}, δ 0·8 (3H, d, *J* 2 Hz, 13-Me) and 4·9 (1H, d, *J* 50 Hz, 12-H) (Found: C, 62·1; H, 6·4; F, 8·3. $C_{25}H_{32}F_2O_7$ requires C, 62·2; H, 6·7; F, 7·9%).

Reduction of 11-Ketones to 11β-Alcohols.—Sodium borohydride (200 mg) in water (1 ml) was added to the 11-ketone (VIII; R = F) (800 mg) in tetrahydrofuran (10 ml) and propan-2-ol (5 ml). After 1 h the solution was poured into methylene chloride, washed with water and sodium hydrogen carbonate solution, dried, and evaporated. Crystallisation from methylene chloride–ether afforded *3,3-ethylenedioxy-9α,12,12-trifluoro-17α,20;20,21-bismethylenedioxypregn-5-en-11β-ol* (620 mg), m.p. 239—240° (Found: C, 59·75; H, 6·6; F, 11·3. $C_{25}H_{33}F_3O_7$ requires C, 59·75; H, 6·6; F, 11·3%). The following compounds were prepared similarly: *3,3-ethylenedioxy-9α,12β-difluoro-17α,20;20,21-bismethylenedioxypregn-5-en-11β-ol* (VII; R^1 = R^2 = F, R^3 = H), m.p. (from methylene chloride–ether) 231—232°, $[\alpha]_D$ −128° (Found: C, 61·9; H, 7·1; F, 7·9. $C_{25}H_{34}F_2O_7$ requires C, 62·0; H, 7·1; F, 7·8%); *3,3-ethylenedioxy-9α,12α-difluoro-17α,20;20,21-bismethylenedioxypregn-5-en-11β-ol* (VII; R^1 = R^3 = F, R^2 = H), m.p. [after chromatography on alumina (elution with chloroform) and crystallisation from methylene chloride–methanol] 268°, $[\alpha]_D$ −131° (Found: C, 62·1; H, 6·9; F, 7·9%); *3,3-ethylenedioxy-12β-fluoro-17α,20;20,21-bismethylenedioxypregn-5-en-11β-ol* (VII; R^1 = R^3 = H, R^2 = F), m.p. (from methylene chloride–methanol) 198—200°, $[\alpha]_D$ −136°, δ 1·1 and 1·3 (each 3H, s, 13- and 10-Me, respectively), 3·95 (4H, s, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 4·0 (2H, s, 21-$H_2$), and 4·5 (2H, m, 11α- and 12α-H) (Found: C, 64·1; H, 7·4; F, 4·35. $C_{25}H_{35}FO_7$ requires C, 64·4; H, 7·6; F, 4·1%); *3,3-ethylenedioxy-12α-fluoro-17α,20;20,21-bismethylenedioxypregn-5-en-11β-ol* (VII; R^1 = R^2 = H, R^3 = F), m.p. (from methylene chloride–ether) 209—212°, $[\alpha]_D$ −101°, δ 1·0 (3H, d, *J* 2 Hz, 13-Me), 1·25 (3H, s, 10-Me), 3·95 (4H, s, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 4·0 (2H, s, 21-$H_2$), and 4·2 (2H, m, 11α- and 12α-H) (Found: C, 64·1; H, 7·3; F, 4·0%).

Removal of Protecting Groups.—The 9α,12α-difluoro-11β-alcohol (VII; R^1 = R^3 = F, R^2 = H) (800 mg) was dissolved in acetone containing 1% hydrochloric acid. After 30 min the acetone was removed under vacuum. The residue was dissolved in concentrated hydrochloric acid and shaken for 2 min, and water was added. The precipitate was filtered off, dissolved in pyridine (2 ml) and acetic anhydride (2 ml), and left at room temperature overnight to yield *9α,12α-difluoro-11β,17α-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate* (610 mg), m.p. (from methanol–ether) 223—227°, $[\alpha]_D$ +129°, $\nu_{max.}$ 3400, 1750, and 1650 cm^{-1}, δ 0·9 (3H, d, *J* 2 Hz, 13-Me), 1·5 (3H, s, 10-Me), 2·05 (3H, s, OAc), 4·2 (1H, ddd, *J* 15, 15, and 2 Hz, 11α-H), and 5·1 (1H, dd, *J* 50 and 2 Hz, 12β-H) (Found: C, 63·2; H, 7·0; F, 8·3. $C_{23}H_{30}F_2O_6$ requires C, 62·7; H, 6·9; F, 8·6%). Similar series of reactions gave the following compounds: *9α,12β-difluoro-11β,17α-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate*, m.p. 234—237°, $[\alpha]_D$ +144°, $\nu_{max.}$ 3400, 1750, 1730, and 1650 cm^{-1}, δ 0·9 and 1·35 (each 3H, s, 13- and 10-Me, respectively) and 2·05 (3H, s, OAc) (Found: C, 62·55; H, 7·1; F, 7·6%); *9α,12,12-trifluoro-11β,17α-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate*, m.p. (from methanol) 252—257°, $[\alpha]_D$ +121°, $\nu_{max.}$ 3400, 1750, 1725, and 1650 cm^{-1}, δ 1·0 and 1·4 (each 3H, s, 13- and 10-Me, respectively) and 2·0 (3H, s, OAc) (Found: C, 60·0; H, 6·4; F, 12·7. $C_{23}H_{29}F_3O_6$ requires C, 60·25; H, 6·4; F, 12·4%); *12,12-difluoro-11β,17α-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate*, m.p. 225—236°, $[\alpha]_D$ +118°, $\nu_{max.}$ 3400, 1750, 1725, and 1660 cm^{-1}, δ 1·0 and 1·4 (each 3H, s, 13- and 10-Me, respectively) and 2·1 (3H, s, OAc) (Found: C, 63·0; H, 6·9; F, 7·9%) ; *12β-fluoro-11β,17α-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate*, m.p. 240—244°, $[\alpha]_D$ +168°, $\nu_{max.}$ 3400, 1750, 1735, and 1660 cm^{-1}, δ 0·9 and 1·4 (each 3H, s, 13- and 10-Me, respectively) and 2·1 (3H, s, OAc) (Found: C, 65·2; H, 7·2; F, 4·4. $C_{23}H_{31}FO_6$ requires C, 65·4; H, 7·4; F, 4·5%); 12α-fluoro-11β,17α-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate, m.p. 224—226°, $[\alpha]_D$ +111° (lit.,[12] m.p. 226—228°, $[\alpha]_D$ +106°).

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