Infrared and ultraviolet spectra also confirmed the identity of the two compounds.

Physical Measurements.—Rotations were measured on a Rudolph Model 200A optical rotatory dispersion apparatus at the following settings: wave length, 589 mμ; slit width, 0.50 mm.; prism angle, 0.5°; temperature, 27°; source, sodium lamp. All solutions were made in chloroform. Infrared spectra were recorded on a Baird double beam instrument, Model ABB-2, ultraviolet spectra on a Beckman recording spectrophotometer, Model DK-2. Melting points were taken on a Fisher-Johns apparatus and are corrected.

Synthesis of 6α-Fluoromethyl Steroids

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The syntheses of 6α-fluoromethylprednisolone and the 9α-fluoro analog are reported, based on the application of the "oxo" reaction to 17,20;20 21-bismethylenedioxy-5-pregnene-3β,11β-diol 3-acetate (II), followed by conversion of the 6α-hydroxymethyl group to the fluoromethyl group by the action of potassium fluoride on the 6α-tosyloxymethyl derivative.

The modification of the hydrocortisone molecule, with the object of improving the anti-inflammatory activity, has led to the preparation of methyl and halogen analogs of steroids.[1] Other structural changes have included the introduction of double bonds, hydroxyl groups, and ring enlargement or contraction.[1] Since the substitution at C-6 by both methyl and fluorine to give the 6α-substituted derivatives has led to an enhancement of biological activity, it was decided to introduce other groups at this position. A valuable method for the introduction of substituents at C-6 is the application of the hydroformylation or "oxo" reaction to a steroidal 5,6-double bond, which has been shown to give a 6α-hydroxymethyl-5α-pregnane derivative,[2] *cis* addition occurring from the α-side of the molecule. The present work describes the conversion of the 6α-hydroxymethyl intermediates to the corresponding fluoromethyl derivatives and the elaboration of these latter to derivatives of prednisolone.[3]

The general utility of the bismethylenedioxy (BMD) blocking group for the preparation of cortical analogs has been amply demonstrated in the synthesis of 5,[4] 6,[5] 7,[6] 9[7] and 11[8]-methylated steroids. It seemed desirable, therefore, to prepare a Δ^5-steroid with the cortical side chain protected as its bismethylenedioxy derivative. Accordingly, cortisone was converted to cortisone BMD (I) as described earlier.[9] This latter was treated with isopropenyl acetate under acidic conditions to give the corresponding enol acetate[10] which on prolonged reduction with sodium borohydride, followed by reacetylation at C-3 with acetic anhydride in pyridine gave 17,20;20,21-bismethylenedioxy-5-pregnene-3β,11β-diol 3-acetate (II). Reaction of II with carbon monoxide and hydrogen at 91 kg./cm.^{2} total pressure in the presence of cobalt carbonate at 180° for eighteen hours gave 17,20;20,21-bismethylenedioxy-6α-hydroxymethyl-5α-pregnane-3β,11β-diol 3-acetate (III. R = H) in 54% yield, isolated readily by direct crystallization. The configuration of the "oxo" product is assigned the 5α,6α configuration by analogy with the previous examples. Conversion of this alcohol to the 6α-fluoromethyl derivative followed established methods.[11] Reaction of the corresponding tosylate ester (III. R = $SO_2C_6H_4CH_3$) with anhydrous potassium fluoride in diethylene glycol at 205–215° for one hour effected replacement with fluorine and at the same time partial hydrolysis of the 3-acetate. The ester hydrolysis was completed by a separate treatment with base to give 17,20;20,21-bismethylenedioxy-6α-fluoromethyl-5α-pregnane-3β,11β-diol (IV). An Oppenauer oxidation of the 3β-alcohol IV gave the corresponding 3-ketone (V), which on treatment with selenium dioxide in the presence of acetic acid,[12] introduced two double bonds into ring A to give 6α-fluoromethylprednisolone BMD (VI). Removal of the bismethylenedioxy pro-

(1) For a review see J. Fried and A. Borman, *Vitamins and Hormones*, **XVI**, 303 (1958); R. Hirschmann, G. A. Bailey, R. Walker, and J. M. Chemerda, *J. Am. Chem. Soc.*, **81**, 2822 (1959) and references cited there.

(2) A. L. Nussbaum, T. L. Popper, E. P. Oliveto, S. Friedman, and I. Wender, *J. Am. Chem. Soc.*, **81**, 1228 (1959); P. F. Beal, M. A. Rebenstorf, and J. E. Pike, *ibid.*, **81**, 1231 (1959).

(3) After the completion of the present work, a Communication appeared describing the synthesis of 6α-fluoromethylpregnane derivatives by a similar route. A. L. Nussbaum, M. Kirtley, A. V. Maresco, and E. P. Oliveto, *J. Org. Chem.*, **26**, 2147 (1961).

(4) J. H. Fried, G. E. Arth, and L. H. Sarett, *J. Am. Chem. Soc.*, **82**, 1684 (1960).

(5) J. H. Fried, G. E. Arth, and L. H. Sarett, *ibid.*, **81**, 1235 (1959).

(6) R. E. Beyler, A. E. Oberster, F. Hoffman, and L. H. Sarett, *ibid.*, **82**, 170 (1960).

(7) F. Hoffman, R. E. Beyler, and M. Tishler, *ibid.*, **80**, 5322 (1958).

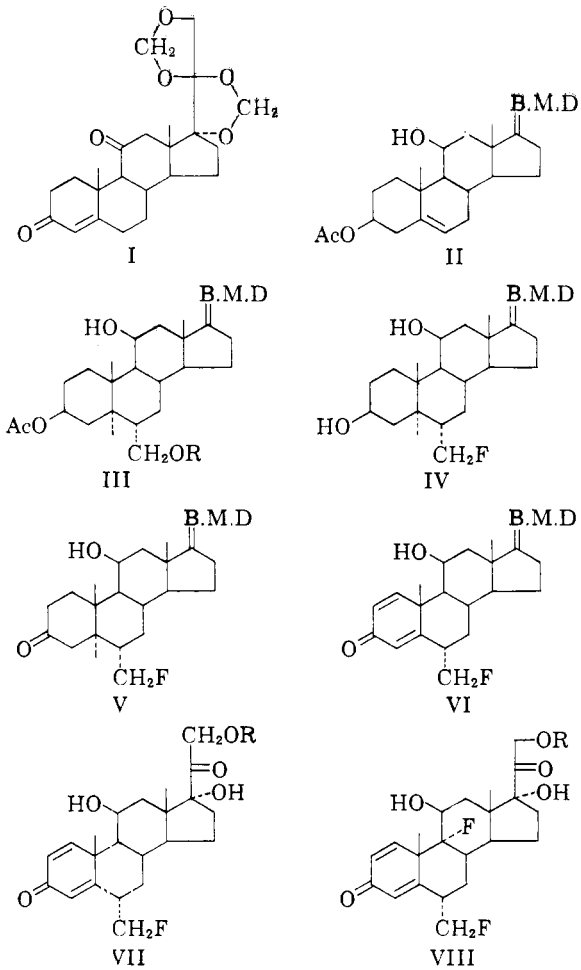
(8) R. E. Beyler, F. Hoffman, and L. H. Sarett, *ibid.*, **82**, 178 (1960).

(9) R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *ibid.*, **80**, 1517 (1958). See also ref. 13.

(10) After the completion of the present work the preparation of this enol acetate was described: J. H. Fried, A. N. Nutile, and G. E. Arth, *J. Org. Chem.*, **26**, 976 (1961).

(11) F. L. M. Pattison and J. E. Millington, *Can. J. Chem.*, **34**, 757 (1956); N. F. Taylor and P. W. Kent, *J. Chem. Soc.*, 872 (1958); E. D. Bergmann and I. Shahak, *Chem. & Ind.* (London), 157 (1958).

(12) Ch. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta.*, **39**, 734 (1956).



tecting group with 60% aqueous formic acid[13] was followed by hydrolysis with aqueous methanolic potassium bicarbonate solution to hydrolyze 21-formates which were apparently formed to some extent during this treatment, as suggested by absorption at 1176 cm.$^{-1}$ in the infrared spectrum of the crude acid hydrolysis product.[14] The resulting 6α-fluoromethylprednisolone (VII. R = H) was converted to the corresponding 21-acetate (VII. R = OAc), and then by the general Fried procedure[15] to the 9α-fluoro analog VIII. Dehydration of the 6α-fluoromethylprednisolone 21-acetate (VII. R = OAc) with *N*-bromoacetamide–sulfur dioxide–pyridine,[16] was followed by addition of hypobromous acid to the 9,11-double bond, ring closure to the 9,11β-oxide with potassium acetate, and oxide opening with hydrogen fluoride[17] in the presence of tetrahydrofuran[18] to give 9α-fluoro - 6α - fluoromethylprednisolone 21 - acetate (VIII).

Preliminary Biological Activity.—6α-Fluoromethylprednisolone had an anti-inflammatory potency three times that of hydrocortisone in the granuloma pouch assay,[19] and 4.7 times the activity of hydrocortisone in the seven-hour liver glycogen deposition assay.[20] The corresponding 9α-fluoro 21-acetate (VIII) in preliminary assays had an anti-inflammatory potency in the range of twelve times hydrocortisone, and a glucocorticoid activity of eighteen times hydrocortisone. This compound showed no sodium retaining properties at a subcutaneous dose of 0.5 mg.

Experimental

17,20;20,21-Bismethylenedioxy-4-pregnene-3,11-dione[9] or Cortisone-BMD (I).—A mixture of cortisone (200 g.), chloroform (4000 ml.), and 38% aqueous formaldehyde solution (2500 ml.), together with concd. hydrochloric acid (2000 ml.) was stirred at room temperature for 20 hr. The chloroform layer was separated, washed twice with water, sodium bicarbonate solution and finally with water. After drying (Na_2SO_4), removal of the solvent and crystallization of the residue from methanol gave 136 g., m.p. 244–248°, $[\alpha]_D$ ($CHCl_3$) +82°, reported,[9] m.p.258–261°. A second crop of 9 g., after recrystallization, was obtained from the mother liquors; final yield 145.2 g. (65%).

17,20;20,21-Bismethylenedioxy-5-pregnene-3β,11β-diol 3-Acetate (II).—Cortisone BMD (85.9 g.), isopropenyl acetate (750 ml.), *p*-toluenesulfonic acid monohydrate (2.5 g.), and toluene (1000 ml.) were heated and distilled so that 200 ml. of distillate was collected over a 2-hr. period. Additional toluene (500 ml.) and isopropenyl acetate (750 ml.) were added and 1200 ml. of distillate collected over a 4-hr. period. The reaction mixture was concentrated *in vacuo* to *ca.* 200 ml. (water temperature 70–80°). Additional toluene (1000 ml.) was again added and the solution again concentrated to *ca.* 200 ml. *in vacuo*. Benzene was added to the residue and the organic solution washed with 5% aqueous sodium bicarbonate solution, water and dried (Na_2SO_4). The benzene solution was stirred with Florisil (40.0 g.) and magnesol (40.0 g.) for 60 min. Filtration, evaporation of the solvent and crystallization of the residue from ether gave the enol acetate (48.1 g.; 51% yield, m.p. 170–182°), reported,[10] m.p. 172–175°. 17,20;20,21-Bismethylenedioxy-3-hydroxy-3,5-pregnadien-11-one 3-acetate (70.0 g.) was dissolved in dioxane (1750 ml.) and the solution cooled to 0–5°. To this was added 70.0 g. of sodium borohydride dissolved in 700 ml. of 0.1 *N* sodium hydroxide solution over 30 min. After 50 hr. at room temperature, the excess borohydride was decomposed by the addition of 50% aqueous acetic acid. Water (900 ml.) was added and after cooling to 0° for 1.5 hr. the product was collected by filtration, washed with water and dried. This solid was suspended in pyridine (500 ml.) and warmed to 30° and filtered. Acetic anhydride (150 ml.) was added to the filtrate and washings, and the reaction mixture heated on a steam bath for 1.5 hr. After cooling, the solution was poured into 3000 ml. of ice water, and after 1 hr. at 0–5° the product was collected by filtration, washed and dried to give 17,20;-20,21-bismethylenedioxy-5-pregnene-3β,11β-diol 3-acetate (52.6 g. (74%), m.p. 187–195°). Two recrystallizations

(13) R. E. Beyler, F. Hoffman, R. M. Moriarty, and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961).

(14) The value of this treatment to hydrolyze formates has been also reported by W. T. Moreland, R. G. Berg, and D. P. Cameron, *J. Am. Chem. Soc.*, **82**, 504 (1960).

(15) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957) and earlier papers.

(16) H. A. Drake, R. B. Howard, and A. E. Fonken, German Patent 1,054,991, October 1, 1959.

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(18) R. F. Hirschmann, R. Miller, J. Wood, and R. E. Jones, *ibid.*, **78**, 4956 (1956).

(19) A. Robert and J. E. Nezamis, *Acta. Endocrinol.*, **25**, 105 (1957).

(20) R. O. Stafford, L. E. Barnes, B. J. Bowman, and M. M. Meinzinger, *Proc. Soc. Exp. Biol. Med.*, **89**, 371 (1955).

from acetone–petroleum ether (b.p. 64–70°) raised the m.p. to 198–199°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.75; H, 7.99.

ν_{max}^{Nujol} 3500, 1722, 1663, 1245, 1140, 1117, 1100, 1085, 1037, 1015, 1005 cm.$^{-1}$.

6α-Hydroxymethyl-17,20;20-21-bismethylenedioxy-5α-pregnane-3β,11β-diol 3-Acetate (III. R = H).—A 2000-ml. Magne-Dash autoclave was charged with 36.4 g. of 17,20;20,21-bismethylenedioxy-5-pregnene-3β,11β-diol 3-acetate, 1150 ml. of toluene, and 9.1 g. of cobalt carbonate. After flushing three times with carbon monoxide the carbon monoxide pressure was raised to 46 kg./cm.^{2} then hydrogen introduced to 91 kg./cm.^{2}. The reaction was heated at 180° with agitation for 18 hr. The gases were then vented and the reaction mixture removed from the autoclave. After filtration through Celite, the toluene was evaporated *in vacuo* and the residue boiled for 1 hr. with 1 l. of ethanol. The solution was filtered through Celite and the alcohol evaporated *in vacuo*. Crystallization of the residue from acetone–petroleum ether gave 15.8 g., crop 1, m.p. 193–199°. Chromatography of the mother liquors on Florisil gave further hydroxymethyl compound (eluted with 20–30% acetone–petroleum ether). Crystallization of the combined fractions from acetone–petroleum ether gave a further 4.9 g., crop 2, m.p. 193–199°.

Two crystallizations from acetone–petroleum ether gave material with m.p. 202–204°.

Anal. Calcd. for $C_{26}H_{40}O_8$: C, 64.98; H, 8.39. Found: C, 64.63; H, 8.65.

ν_{max}^{Nujol} 3510, 3480, 1727, 1245, 1082, 1041, 1025, 985, 935 cm.$^{-1}$.

6α-Fluoromethyl-17,20;20,21-bismethylenedioxy-5α-pregnan-3β,11β-diol (IV).—6α-Hydroxymethyl-17,20;20,21-bismethylenedioxy-5α-pregnane-3β,11β-diol 3-acetate (1.2 g., m.p. 199–201°), *p*-toluenesulfonyl chloride (1.2 g.) and pyridine (20 ml.) were allowed to stand for 18 hr. at room temperature. The reaction mixture was then poured into sodium bicarbonate solution and the organic material extracted with benzene. The extracts were washed successively with water, ice-cold dilute sulfuric acid, water, sodium bicarbonate solution, water, and dried (Na_2SO_4). Removal of the solvent gave a crystalline tosylate, which was crystallized from acetone–petroleum ether to give 1.25 g., m.p. 200–208° dec.

The tosyloxymethyl derivative (1.2 g., m.p. 200–208° dec.), anhydrous potassium fluoride (2.0 g.) and diethylene glycol (20 ml.) were heated with stirring at 205–215° under nitrogen for 1 hr. After cooling, dioxane (20 ml.) and a solution of potassium hydroxide (0.5 g.) in water (10 ml. were added and the solution allowed to stand 18 hr. at room temperature. Isolation was effected by pouring the reaction mixture into water and extracting with ethyl acetate. The combined extracts were washed with water until neutral, dried (Na_2SO_4), and the solvent removed. The total material was dissolved in methylene chloride (25 ml.) and chromatographed on Florisil (100 g.) made up in petroleum ether. Crystalline material was obtained from the 20–30% acetone–petroleum ether eluates. These were combined and recrystallized from methanol to give crop 1, 240 mg., m.p. 215–217°; a second crop was obtained from acetone–petroleum ether to give crop 2, 140 mg., m.p. 215–217°, and crop 3, 130 mg., m.p. 213–215°. The infrared spectra of all crops were the same and the total yield was therefore 510 mg. (61%).

Further crystallization from acetone–petroleum ether raised the m.p. to 217–219°.

Anal. Calcd. for $C_{24}H_{37}O_6F$: C, 65.45; H, 8.41; F, 4.32. Found: C, 65.08; H, 8.21; F, 4.57.

ν_{max}^{Nujol}, 3580, 3460, 1132, 1108, 1063, 1057, 1045, 1021, 1008, 990 cm.$^{-1}$.

6α-Fluoromethyl-17,20;20,21-bismethylenedioxy-11β-hydroxy-5α-pregnan-3-one (V).—6α-Fluoromethyl-17,20;20,21-bismethylenedioxy-5α-pregnane-3β,11β-diol (380 mg., m.p. 215–217°), cyclohexanone (20 ml., redistilled) and toluene (30 ml.) were distilled incorporating a Dean-Stark trap until *ca.* 10 ml. of distillate was collected. Then aluminum isopropoxide (500 mg.) was added and the mixture was refluxed for 4 hr. After cooling, the organic layer was washed with ice-cold dilute hydrochloric acid, then water until neutral, dried (Na_2SO_4), and the organic solvents removed by steam distillation. After cooling at 0°, the solid material was collected by filtration, washed with water and dried (380 mg., m.p. 190–205°). Crystallization from acetone–petroleum ether gave 240 mg., m.p. 208–212°. Further crystallization from acetone–petroleum ether raised the m.p. to 211–213°.

Anal. Calcd. for $C_{24}H_{35}O_6F$: C, 65.75; H, 7.99; F, 4.34. Found: C, 65.74; H, 8.19; F, 4.53.

ν_{max}^{Nujol}, 3490, 3400, 1708, 1183, 1163, 1143, 1132, 1107, 1093, 1068, 1037, 1030, 1000 cm.$^{-1}$.

6α-Fluoromethylprednisolone BMD (VI).—6α-Fluoromethyl - 17,20;20,21 - bismethylenedioxy - 11β - hydroxy-5α-pregnan-3-one (200 mg.), selenium dioxide (400 mg.), acetic acid (0.1 ml.), and *t*-butyl alcohol (20 ml.) were heated to reflux for 48 hr. After the first 24 hr. further selenium dioxide (400 mg.) was added and the same amount added again after 34 hr. Isolation was effected, after cooling, by filtration through Celite–magnesol. The filtrate was evaporated to dryness and the residue taken up in ethyl acetate, which was washed successively with potassium bicarbonate solution, freshly prepared ice-cold ammonium sulfide solution, ice-cold ammonia, dilute hydrochloric acid, potassium bicarbonate solution, water, and dried (Na_2SO_4). Removal of the solvent gave crystalline material (281 mg.). This was dissolved in methylene chloride and chromatographed on Florisil (20 g.) made up in petroleum ether. Crystalline material was obtained from the 15–20% acetone–petroleum ether eluates. These were combined (93 mg.) and crystallized from acetone–petroleum ether to give 6α-fluoromethylprednisolone B.M.D. (67 mg., m.p. 255–265°). ν_{max}^{Nujol} 3450, 1663, 1625, 1610, 1170, 1145, 1095, 1065, 1055, 1043, 1025, 1017, 995 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{31}O_6F$: C, 66.36; H, 7.14. Found: C, 66.40; H, 7.41.

6α-Fluoromethylprednisolone and 21-Acetate (VII. R = H and R = Ac).—Nitrogen was bubbled for 5 min. through 10 ml. of 60% formic acid, while the solution was heated on a steam bath. Then 6α-fluoromethylprednisolone BMD (60 mg.) was added to the hot solution and the mixture heated on the steam bath, while keeping a nitrogen stream bubbling through the solution, for 15 min. After cooling the solution was poured into ice–sodium bicarbonate solution, and the organic material extracted with methylene chloride. These extracts were washed with water, dried (Na_2SO_4), and the solvent removed. This crystalline solid (57 mg.) was dissolved in 20 ml. methanol (previously purged for 20 min. with nitrogen), and an aqueous solution of potassium bicarbonate (100 mg. in 10 ml. water similarly treated with nitrogen), added and the solution allowed to stir 48 hr. at room temperature. Acetic acid was then added, until the *p*H was neutral and the solvent removed *in vacuo*. The organic material was isolated using methylene chloride; the extract was dried (Na_2SO_4) and evaporated to give 58 mg. crystalline material. This was dissolved in methylene chloride: ethyl acetate and chromatographed on Florisil (5.0 g.) made up in petroleum ether. Crystalline material was obtained from the 30% acetone–petroleum ether eluates. These fractions were combined and crystallized from acetone–petroleum ether to give 6α-fluoromethylprednisolone [19 mg., m.p. 232–235°, VII. R = H].

Anal. Calcd. for $C_{22}H_{29}O_5F$: C, 67.35; H, 7.40; F, 4.85, Found: C, 67.77; H, 7.95; F, 5.24.

ν_{max}^{Nujol} 3380, 3290, 1712, 1650, 1598, 1115, 1105, 1057, 1044, 1030, 1020 cm.$^{-1}$.

6α-Fluoromethylprednisolone (0.338 g.) was allowed to stand overnight at room temperature in pyridine (10 ml.) and acetic anhydride (2.5 ml.). After 18 hr. at room temperature, isolation was effected with ice–sodium bicarbonate solution, and extraction with ethyl acetate. The combined extracts were washed with water, dilute sulfuric acid, water until neutral, and dried (Na_2SO_4). Removal of the solvent gave a crystalline solid, which was crystallized from acetone–petroleum ether to give 6α-fluoromethylprednisolone 21-acetate (VII. R = Ac), 248 mg., m.p. 226–229°. Further crystallization from the same solvent gave material with m.p. 231–233°.

Anal. Calcd. for $C_{24}H_{31}O_6F$: C, 66.36; H, 7.14; F, 4.38. Found: C, 66.23; H, 7.34; F, 4.81.

ν_{max}^{Nujol}, 3470, 3250, 1747, 1722, 1653, 1610, 1600, 1235, 1115, 1045, 1030, 1022 cm.$^{-1}$. $\lambda_{max}^{C_2H_5OH}$ 244 mμ, ε, 15,350.

6α-Fluoromethyl-9,11β-oxido-17α,21-dihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate.—A mixture of 6α-fluoromethylprednisolone 21-acetate (1.87 g.), pyridine (30 ml.), and *N*-bromoacetamide (0.866 g.) was stirred at room temperature under nitrogen for 20 min. The solution was then cooled to *ca.* 10° and a slow stream of sulfur dioxide passed over the surface for 10 min. The reaction mixture was then poured onto 300 ml. of ice water and the organic material extracted with methylene chloride. The extracts were washed with water, dried (Na_2SO_4), and the solvent removed. The noncrystalline residue was dissolved in 15 ml. methylene chloride and chromatographed on Florisil (100 g.). Elution with increasing concentrations of acetone in petroleum ether gave a main peak (1.608 g.) eluted with 15–20% acetone–petroleum ether. Since the fractions did not crystallize, the 9,11-dehydro compound was not further purified but converted directly to the corresponding oxide. Papergram (benzene—formamide) showed one spot moving fast relative to the starting 11β-hydroxy compound. The 9,11-dehydro steroid (1.358 g.) was dissolved in *t*-butyl alcohol (54 ml.) and methylene chloride (27 ml.), and a solution of 70% aqueous perchloric acid (3.57 ml.) in 18 ml. water was added followed by *N*-bromoacetamide (0.652 g.) in *t*-butyl alcohol (11 ml.). After stirring at room temperature for 20 min., a solution of sodium sulfite (0.652 g.) in 12 ml. water was added and the solution evaporated *in vacuo* at *ca.* 30°. Further water was added and the crystalline bromo compound was collected by filtration, washed thoroughly with water and dried. The total bromohydrin from 1.608 g. of the $\Delta^{9,11}$ derivative (and showing essentially one spot on a benzene–formamide papergram, moving slowly relative to the starting $\Delta^{9,11}$ compound) was dissolved in acetone (110 ml.) and heated to boiling under reflux with potassium acetate (1.7 g.). After 18 hr. the mixture was cooled and the acetone removed in a nitrogen stream at room temperature. The residue was partitioned between methylene chloride and water. The organic layer was separated, dried (Na_2SO_4), and the solvent *in vacuo*. The residue was dissolved in methylene chloride and chromatographed on Florisil (110 g.). Elution with increasing proportions of acetone in petroleum ether gave crystalline material from the 20% acetone–petroleum ether eluates. These fractions were combined and crystallized from acetone–petroleum ether to give 6α-fluoromethyl-9,11β-oxido-17α,21-dihydroxy-1,4-pregnadiene-3,20-dione 21-acetate; crop 1, 660 mg., m.p. 220–225°; crop 2, 140 mg., m.p. 210–215°. Two further crystallizations of crop 1 from acetone–petroleum ether gave material with m.p. 225–228°.

ν_{max}^{Nujol} 3240, 1750, 1726, 1660, 1618, 1230, 1150, 1127, 1100, 1082, 1062, 1052, 1040, 1035 cm.$^{-1}$ $\lambda_{max}^{C_2H_5OH}$ 250 mμ; $\epsilon_{1cm.}^{1\%}$ 268, 300 mμ; $\epsilon_{1cm.}^{1\%}$ 106. Satisfactory analyses could not be obtained for this material. The ultraviolet spectrum suggests some loss of the fluorine to give partly, material with extended conjugation in the A–B rings.

6α-Fluoromethyl-9α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (VIII. R = Ac).—A solution of the 9,11β-oxide (730 mg.) in methylene chloride (25 ml.) was added to a mixture of hydrogen fluoride (9.13 g.) and tetrahydrofuran (15.7 ml.) at −10°. After standing for 20 min. at −10°, the solution was left for 18 hr. at 0–5°. Isolation was then effected by pouring the reaction mixture onto ice–sodium bicarbonate and extraction with further methylene chloride. The combined extracts were washed with water, dried (Na_2SO_4), and the solvent evaporated. The residue was dissolved in methylene chloride (10 ml.) and chromatographed on Florisil (50 g.) and elution effected with increasing proportions of acetone in petroleum ether. Crystalline material was obtained from the 30–40% acetone–petroleum ether elutates. These were combined and crystallized from acetone–petroleum ether to give the 9α-fluoro compound, crop 1, 0.265 g., m.p. 202–207°; crop 2, 0.125 g. Two further crystallizations of crop 1 from acetone–petroleum ether gave m.p. 215–217°.

Anal. Calcd. for $C_{24}H_{30}O_6F_2$: C, 63.72; H, 6.64; F, 8.41. Found: C, 63.82; H, 6.90; H, 8.47.

ν_{max}^{Nujol} 3220, 1748, 1724, 1656, 1613, 1220 cm.$^{-1}$. $\lambda_{max}^{C_2H_5OH}$ 239 mμ; ε 15,200.

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