$[M]_{358}$ +3799°; $[M]_{345}$ +5328°; $[M]_{318}$ +11969° (peak); $[M]_{305}$ +10043°.

16α-Fluoromethyl-11-ketoprogesterone (VII). (*c*, 0.1028) $[M]_{559}$ +910°; $[M]_{375}$ +4237°; $[M]_{370}$ +4026°; $[M]_{360}$ +4412°; $[M]_{358}$ +4341°; $[M]_{345}$ +5882°; $[M]_{318}$ +12569° (max).

16α-Carbomethoxy-11-ketoprogesterone (VIII). (*c*, 0.0993) $[M]_{589}$ +538°; $[M]_{375}$ +3485°; $[M]_{370}$ +3485°; $[M]_{360}$ +3810°; $[M]_{355}$ +3849°; $[M]_{345}$ +5450°; $[M]_{315}$ +11900° (peak); $[M]_{300}$ +9140°.

11β-Hydroxyprogesterone (IX). (*c*, 0.098) $[M]_{589}$ +707°; $[M]_{385}$ +1860°; $[M]_{368}$ +1262°; $[M]_{358}$ +1814°; $[M]_{355}$ +1678°; $[M]_{350}$ +2340°; $[M]_{343}$ +4685°; $[M]_{330}$ +9105°; $[M]_{310}$ +13830°; $[M]_{300}$ +11810°.

11β-Hydroxy-16α-hydroxymethylprogesterone (X). (*c*, 0.097) $[M]_{589}$ +854°; $[M]_{380}$ +1965°; $[M]_{370}$ +1482°; $[M]_{360}$ +2001°; $[M]_{355}$ +2113°; $[M]_{343}$ +5487°; $[M]_{340}$ +5559°; $[M]_{330}$ +10070°; $[M]_{320}$ +13551°; $[M]_{313}$ +14827°; $[M]_{300}$ +12084°.

16α-Methylprogesterone (XI). (C 0.0998) $[M]_{589}$ +402°; $[M]_{380}$ +1635°; $[M]_{368}$ +1226°; $[M]_{360}$ +1602°; $[M]_{355}$ +1488°; $[M]_{343}$ +4414°; $[M]_{340}$ +4512°; $[M]_{315}$ +13094°; $[M]_{306}$ +12661°.

16β-Methylprogesterone (XII). (*c*, 1.0) $[M]_{589}$ +392°; $[M]_{385}$ +996°; $[M]_{373}$ −65° $[M]_{363}$ + 100°; $[M]_{355}$ −353°; $[M]_{343}$ + 1698°; $[M]_{340}$ +1698°; $[M]_{318}$ +5510° (peak); $[M]_{315}$ +5390°.

16β-Hydroxymethyl-17α-progesterone (XIII). (*c*, 0.0970) $[M]_{589}$ −81°; $[M]_{385}$ −879°; $[M]_{383}$ −858°; $[M]_{368}$ −1846°; $[M]_{360}$ −1719°; $[M]_{353}$ −2460°; $[M]_{343}$ −1006°; $[M]_{340}$ −1130°; $[M]_{328}$ +480°; $[M]_{323}$ +145°; $[M]_{305}$ +2040°.

16β-Fluoromethyl-17α-progesterone (XIV). (*c*, 0.0924) $[M]_{589}$ −37°; $[M]_{380}$ −835°; $[M]_{365}$ −1828°; $[M]_{363}$ −1760°; $[M]_{353}$ −2442°; $[M]_{343}$ −1030°; $[M]_{340}$ −1180°; $[M]_{330}$ +442°; $[M]_{323}$ −22°; $[M]_{315}$ +356°; $[M]_{312}$ +356°; $[M]_{300}$ +2386°.

16β-Carbomethoxy-11-keto-17α-progesterone (XV). (*c*, 0.0991) $[M]_{589}$ +268°; $[M]_{375}$ +1754°; $[M]_{368}$ +1241°; $[M]_{363}$ +1497°; $[M]_{353}$ +257°; $[M]_{345}$ +647°; $[M]_{338}$ −310°; $[M]_{330}$ −42°; $[M]_{310}$ −1448°; $[M]_{295}$ +1723°.

11-Keto-17α-progesterone (XVI). (*c*, 0.0982) $[M]_{589}$ +342°; $[M]_{380}$ +1287°; $[M]_{368}$ +854°; $[M]_{363}$ +856°; $[M]_{355}$ +186°; $[M]_{345}$ +736°; $[M]_{340}$ +502°; $[M]_{333}$ +1126°; $[M]_{325}$ +427°; $[M]_{305}$ +3730°.

16α-Cyano-3α-hydroxy-5β-pregnene-11,20-dione (XVII). (*c*, 0.0995) $[M]_{589}$ +280°; $[M]_{380}$ +1754°; $[M]_{318}$ +8803° (peak); $[M]_{300}$ +4080°.

16β-Carbomethoxy-3α-hydroxy-5β,17α-pregnane-11,20-dione (XVIII). (*c*, 0.1053) $[M]_{589}$ +19°; $[M]_{340}$ −683°; $[M]_{320}$ −2671°; $[M]_{318}$ −2604°; $[M]_{306}$ −3450°; $[M]_{300}$ −1150°.

KALAMAZOO, MICH.

[CONTRIBUTION OF THE RESEARCH LABORATORIES, THE UPJOHN CO.]

The Synthesis of 16α-Fluoromethyl Steroids

P. F. BEAL AND J. E. PIKE

Received March 6, 1961

The preparation of a series of 16α-fluoromethyl steroids is described. Addition of cyanide ion to a Δ^{16}-20-ketone gives a 16α-cyano 20-ketone, which after conversion to a 20-cycloethylene ketal can be converted to a variety of 16α-substituted derivatives. Transformation of one of these products, 16α-fluoromethyl-11-oxoprogesterone, to the corresponding hydrocortisone analogue is reported. Introduction of the Δ^1-double bond and a 9α-fluoro substituent follows established methods to give 9α-fluoro-16α-fluoromethylprednisolone 21-acetate (XIX) for which preliminary biological data are given.

In view of the biological change associated with the introduction of methyl, fluorine, and hydroxyl substituents at C-16 in corticoids,[1] the synthesis of other hydrocortisone derivatives substituted at this position was investigated.

A valuable method for the introduction of substituents at C-16 is the addition of cyanide ion to a Δ^{16}-20-ketone since the resulting 16-nitrile provides a versatile intermediate for futher transformations. Thus Romo[2] converted 16-dehydropregnenolone acetate to a 16α-cyano-20-ketone, which after alkaline hydrolysis, esterification, and Oppenauer oxidation gave a 16-carbomethoxyprogesterone.

Similar work has been reported by Petrow and coworkers.[3] Both groups of workers assigned the 16α,-17β configuration to the initial cyanide adduct and also to the subsequent transformation products. More recently Mazur and Cella[4] have recorded work in this series which makes it clear that the further transformations of the correctly assigned 16α-cyano-17β-acetyl adducts under alkaline equilibrating conditions give 17α-acetyl-16β-carboxylic acids. We had also reached the conclusion that a double inversion of configuration had occurred at C-16 and C-17 by an analysis of the optical rotatory dispersion curves of a series of 16β-substituted-17-iso transformation products, and by the conversion of 16β-hydroxymethyl-17-isoprogesterone to the known 16β-methyl-17-isoprogesterone.[5,6]

(1) (a) L. H. Sarett, *Ann. N. Y. Acad. Sci.*, **82**, 802 (1959); E. Oliveto, *Ann. N. Y. Acad. Sci.*, **82**, 808; and references cited therein; (b) W. M. Moreland, R. G. Berg, and D. P. Cameron, *J. Am. Chem. Soc.*, **82**, 504 (1960); (c) D. E. Ayer and W. P. Schneider, *J. Am. Chem. Soc.*, **82**, 1249 (1960); (d) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *J. Am. Chem. Soc.*, **82**, 1252 (1960).

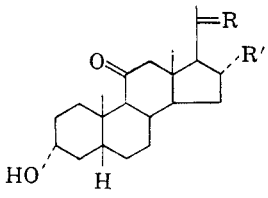
(2) J. Romo, *Tetrahedron*, Vol. **3**, 37 (1958).

(3) B. Ellis, V. Petrow, and D. Wedlake, *J. Chem. Soc.*, 3748 (1958).

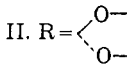
(4) R. H. Mazur and J. A. Cella, *Tetrahedron*, Vol. **7**, 130, 1959.

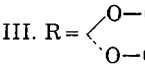
(5) The transformation in the non-11-oxygenated series will be described in detail in a publication from these Laboratories. For a detailed analysis of the optical rotatory dispersion curves in both series see W. A. Struck and R. Houtman, *J. Org Chem.*, **26**, 3883 (1961).

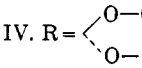
(6) J. Romo, J. Lepe, and M. Romero, *Bol. Inst. Quim. Univ. N. Auton. Mex.*, 125 (1952).

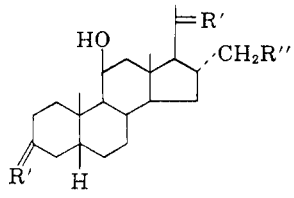


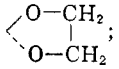
I. R = O; R′ = CN;

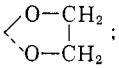
II. R =  ; R′ = CN

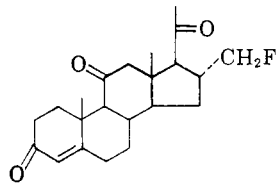
III. R =  ; R′ = CO_2H

IV. R =  ; R′ = CO_2CH_3



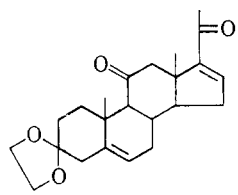
VI. R = R′ =  ; R″ = OH

VII. R = R′ =  ; R″ = F

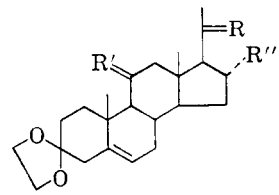


VIII. no Δ^4 bond

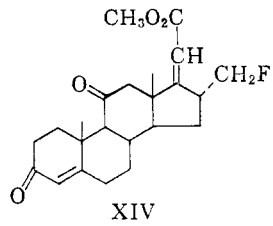
IX. Δ^4 bond present



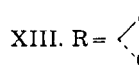
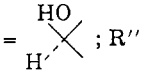
X

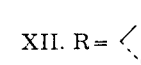
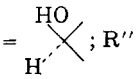


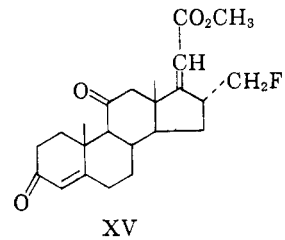
XI. R′ = R = O; R = CN



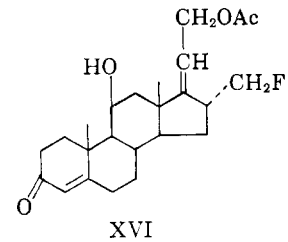
XIV

XIII. R =  ; R′ =  ; R″ = CH_2OH

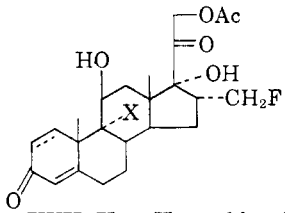
XII. R =  ; R′ =  ; R″ = CO_2R'''



XV



XVI



XVII. X = H no Δ^1 bond

XVIII. X = H Δ^1 bond present

XIX. X = F Δ^1 bond present

It was clear from these observations that, as it is normally necessary to maintain the 17β-acetyl configuration in order to elaborate the cortical side chain, some method was needed to prevent the isomerization of the initial nitrile adducts. 3α-Hydroxy-16-pregnen-11,20-dione acetate[7] was treated with potassium cyanide to give the corresponding 16α-cyano 20-ketone (I), hydrolysis of the 3-acetate occurring under the conditions of the reaction. By standard methods this was converted to the corresponding 20-cycloethylene ketal (II) in an attempt to fix the stereochemistry at C-16 and C-17. Alkaline hydrolysis of the nitrile with potassium hydroxide in refluxing ethylene glycol produced the corresponding carboxylic acid (III), which was esterified with ethereal diazomethane to the corresponding methyl ester (IV). Oxidation of this compound to the corresponding 3-ketone, followed by ketal formation gave the bisketal, which was reduced with lithium aluminum hydride to give the 11β-hydroxy-16α-hydroxymethyl bisketal (VI). Reaction of this diol with *p*-toluenesulphonyl chloride in pyridine formed the corresponding 16α-tosyloxymethyl derivative, which on treatment with anhydrous potassium fluoride in diethylene glycol[8] gave the corresponding 16α-fluoromethyl bisketal (VII). After oxidation of the 11β-hydroxy group with chromium trioxide–pyridine and removal of the ketal protecting groups by the action of acid, the 4,5-double bond was introduced into the resulting trione (VIII) by treatment with *t*-butyl hypochlorite to give the 4-chloro 3-ketone. Then dehydrochlorination with semicarbazide hydrochloride and pyruvic acid[9] produced 16α-fluoromethyl-11-oxoprogesterone (IX). Optical rotatory dispersion studies confirmed the retention of the 17β configuration for both VIII and IX.[5,10]

An alternate and preferable synthesis of 16α-fluoromethyl-11-oxoprogesterone employs interme-

(7) R. E. Marker and H. M. Crooks, Jr., *J. Am. Chem. Soc.*, **73**, 4765 (1951).

(8) (a) F. L. M. Pattison and J. E. Millington, *Can. J. Chem.*, **34**, 757 (1956); **35**, 141 (1957). (b) N. F. Taylor and P. W. Kent, *J. Chem. Soc.*, 872 (1958). (c) E. D. Bergman and I. Shahak, *Chem. & Ind.*, 157 (1958).

(9) R. H. Levin, B. J. Magerlein, A. V. McIntosh, Jr., A. R. Hanze, G. S. Fonken, J. L. Thompson, A. M. Searcy, M. A. Scheri, and E. S. Gutsell, *J. Am. Chem. Soc.*, **75**, 502 (1953); **76**, 546 (1954) and references cited there.

(10) Additional evidence for the correctness of the structural assignment for IX is its behavior in the Favorskiĭ sequence described below. Compounds with a 17-iso configuration do not behave normally. The configuration at C-16 also follows as 17β-acetyl-16β-methyl compounds are readily converted to 17-iso-16β-methyl derivatives, and a 17β-acetyl-16β-fluoromethyl compound would have presumably suffered inversion earlier under the conditions for the preparation of IX See also ref. (6).

NOTE ADDED IN PROOF: Confirmation of the stereochemical assignment has been obtained by converting XIII to the 16α-tosyloxymethyl derivative, reducing this with lithium aluminum hydride, oxidizing with chromium trioxide : pyridine and acid hydrolysis to give 16α-methyl-11-oxo-progesterone which was identical (I.R. and m.p.) with an authentic sample.

diates in which the Δ^4-3-ketone is protected as a cycloethylene ketal. 16-Dehydro-11-oxoprogesterone[11] was converted selectively to the monoketal (X). Addition of cyanide ion gave the corresponding 16α-cyano compound (XI). This intermediate was then transformed into the 16α-fluoromethyl derivative by the sequence described above, namely ketal formation at C-20, alkaline hydrolysis, esterification with diazomethane and lithium aluminum hydride reduction to give the diol (XIII) followed by replacement of the primary hydroxyl with fluorine *via* the tosylate as before. Oxidation with chromium trioxide–pyridine and acid hydrolysis gave 16α-fluoromethyl-11-oxoprogesterone (IX) which was identical with the material prepared in the first sequence. It was more convenient in this series to omit the esterification and to effect the lithium aluminum hydride reduction directly on the 16α-carboxylic acid (XII); R''' = H.

The conversion of 16α-fluoromethyl-11-oxoprogesterone to the corresponding derivative of hydrocortisone follows the procedure described earlier.[12] Formation of a 2,21-dialkoxyoxalyl derivative of (IX) by the action of diethyl oxalate in the presence of sodium methoxide was followed by bromination with three moles of bromine. Reaction of the intermediate bromo compound, without isolation, with excess sodium methoxide effected Favorskii rearrangement and, after treatment with zinc and acetic acid gave a mixture of the methyl *cis*-17-(20)-ene-21-oate(XIV) and the corresponding *trans* isomer (XV), separable by chromatography on Florisil. Employing the mixture of *cis* and *trans* isomers and protecting the Δ^4-3-ketone as its pyrrolidine enamine both the 11-ketone and the methyl ester were reduced with lithium aluminum hydride. After hydrolysis of the enamine and acetylation at C-21, 16α-fluoromethyl-11β,21-dihydroxy-4,17(20)-pregnadien-3-one 21-acetate (XVI) was obtained as a mixture of geometric isomers. Separation of these two isomers was possible on Florisil chromatography, but only one pure crystalline compound was obtained. Reaction of the 17(20)-double bond with *N*-methylmorpholine oxide-hydrogen peroxide reagent in the presence of a catalytic amount of osmium tetroxide[13] gave 16α-fluoromethylhydrocortisone 21-acetate (XVII).

The 1,2-double bond was introduced by the action of selenium dioxide[14] to give 16α-fluoromethylprednisolone 21-acetate (XVIII). The 9α-fluoro group was introduced by the general Fried procedure,[15] dehydration of the 11β-hydroxyl group employing *N*-bromoacetamide–sulfur dioxide–pyridine[16] followed by the addition of hypobromous acid to the 9,11-double bond, ring closure to the 9,11β-oxide with potassium acetate in acetone, and conversion to the fluorohydrin (XIX) by the action of hydrogen fluoride[17] in the presence of tetrahydrofuran.[18]

Preliminary biological activity. 9α-Fluoro-16α-fluoromethylprednisolone 21-acetate has twenty times the activity of hydrocortisone in the granuloma pouch assay for anti-inflammatory activity,[19] and seventy-two times the activity of hydrocortisone in the seven-hour liver glycogen deposition assay,[20] parenterally in the rat. Since this compound induces mild sodium, potassium, and water excretion at doses of 10–40 μg. the 16α-fluoromethyl group, like the 16α-hydroxy group, the 16-methyl group and the 16-fluoro group,[1] appears to counteract the marked sodium retaining properties of 9α-fluoroprednisolone.

EXPERIMENTAL

Melting points were determined on a Kofler block. The infrared spectra were determined as Nujol mulls, and ultraviolet spectra in 95% ethanol.

16α-Cyano-3α-hydroxy-5β-pregnane-11,20-dione (I). A mixture of 3α-hydroxy-16-pregnene-11,20-dione acetate (20.0 g.), potassium cyanide (30.0 g.) methanol (11.) and dioxane (200 ml.) was heated to boiling under reflux for 3 hr. After cooling, water was added and the organic material extracted with methylene chloride. The combined extracts were washed with water, dried (sodium sulfate) and the solvent removed. The crystalline residue was recrystallized from acetone–petroleum ether (b.p. 64–70°) to give crop 1 (9.5 g., m.p. 222–226°). Further crystallization raised the m.p. to 238–240°.

Anal. Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; N, 3.92. Found: C, 74.34; H, 9.04; N, 4.11. ν_{max}^{Nujol} 3470, 2225, 1702, 1693, 1078, 1055, 1033, 1014 cm.$^{-1}$

16α-Cyano-3α-hydroxy-5β-pregnane-11,20-dione 20-cycloethyleneketal (II). 16α-Cyano-3α-hydroxy-5β-pregnane-11,20-dione (5.5 g.) was heated to reflux incorporating a water separator, with ethylene glycol (25 ml.), *p*-toluenesulfonic acid monohydrate (250 mg) in benzene (500 ml.) for 6 hr. Isolation was effected, after ice cooling, with the aid of benzene and saturated aqueous sodium bicarbonate solution. After washing the combined extracts with water until neutral, drying (sodium sulfate), removal of the solvent gave an oil. This was dissolved in methylene chloride and chromatographed on Florisil (300 g.) made up in petroleum ether (b.p. 64–70°). Crystalline material was obtained from the fractions eluted with petroleum ether:20% acetone. These fractions were combined and crystallized from ether

(11) B. J. Magerlein, D. A. Lyttle, and R. H. Levin, *J. Org. Chem.*, 20, 1709 (1955).

(12) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R Hanze, and R. W. Jackson, *J. Am. Chem. Soc.*, 77, 4436 (1955).

(13) W. P. Schneider and A. R. Hanze, U. S. Pat. 2,769,-823 (Nov. 6, 1956); see also G. S. Fonken, J. A. Hogg, and A. V. McIntosh, *J. Org. Chem.*, 24, 1600 (1959).

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

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

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

(17) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman, and F. Singer, *J. Am. Chem. Soc.*, 77, 4181 (1955).

(18) R. F. Hirschmann, R. Miller, J. Wood, and R. E. Jones, *J. Am. Chem. Soc.*, 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).

to give the monoketal (II), crop 1, 3.25 g.; m.p. 164–170°; crop 2, 0.54 g. Further crystallization raised the melting point to 168–170°.

Anal. Calcd. for $C_{24}H_{35}O_4N$: C, 71.79; H, 8.79; N, 3.49. Found: C, 71.40; H, 8.53; N, 3.68. ν_{max}^{Nujol} 3560, 3490, 3410, 2230, 1690, 1100, 1085, 1047, 1018 cm.$^{-1}$

16α-Carbomethoxy-5β-pregnane-3,11,20-trione-3,20-biscycloethyleneketal (IV) and (V). A solution of 16α-cyano-3α-hydroxy-5β-pregnane-11,20-dione 20-ketal (2.85 g., m.p. 164–170°) in ethylene glycol (80 ml.), and water (20 ml.) and potassium hydroxide (5.0 g.) was heated to boiling under reflux in a nitrogen atmosphere for 24 hr. After cooling, the solution was diluted with water (*ca.* 250 ml.) and extracted twice with methylene chloride. The aqueous layer was then carefully acidified to *ca.* pH 4 first with sodium dihydrogen phosphate and then with ice cold dilute hydrochloric acid, and rapidly extracted with ethyl acetate. The combined extracts were washed with water until neutral, dried (sodium sulfate) and the solvent evaporated *in vacuo*. The crude acid was dissolved in methanol (250 ml.) and methylene chloride (50 ml.) and esterified with excess ethereal diazomethane at room temperature for 3 hr. The ester (after removal of the solvent) was crystallized from acetone–petroleum ether to give (IV) crop 1, 2.21 g., m.p. 221–223°. Further crystallization raised the m.p. to 222–223°.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.29; H, 8.89. ν_{max}^{Nujol} 3430, 1720, 1685, 1260, 1245, 1220, 1210, 1165, 1130, 1105, 1083, 1053, 1040, 1027 cm.$^{-1}$

A portion of this ester (2.05 g.) in acetone (200 ml.) was oxidized for 5–10 min. at 0° with the standard chromium trioxide sulfuric acid reagent[21] (1.85 ml.) (prepared by dissolving 26.72 g. of chromium trioxide in 25 ml. of concd. sulfuric acid and diluting with water to 100 ml.). Isolation with saturated aqueous sodium bicarbonate solution and filtration through Supercel was followed by extraction with methylene chloride. The combined extracts were washed with water, dried (sodium sulfate) and the solvent removed. Crystallization of the residual oil from acetone–petroleum ether gave the corresponding 3-ketone, 1.73 g., m.p. 154–156°. A portion of this ketone (1.68 g.) was heated to reflux incorporating a water separator for 16 hr. in the presence of ethylene glycol (10 ml.) *p*-toluenesulfonic acid monohydrate (150 mg.) and benzene (200 ml.). Isolation after cooling with sodium bicarbonate solution and subsequent washing with water, drying (sodium sulfate), and solvent removal gave the bisketal (V). This was crystallized from acetone–petroleum ether to give 1.74 g., m.p. 220–225°.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.74; H, 8.48. ν_{max}^{Nujol} 1730, 1702, 1250, 1242, 1230, 1213, 1188, 1165, 1125, 1100, 1085, 1057, 1040, 1010 cm.$^{-1}$

11β-Hydroxy-16α-(hydroxymethyl)-5β-pregnane-3,20-dione-biscycloethyleneketal (VI). A solution of 16α-carbomethoxy-5β-pregnane-3,11,20-trione-3,20-bisketal (1.6 g., m.p. 220–225°) in benzene (50 ml.) was added dropwise with stirring to a suspension of lithium aluminum hydride (2.0 g.) in diethyl ether (30 ml.) and benzene (20 ml.) at 0°. The mixture was then heated under reflux for 4.25 hr. After cooling, ethyl acetate was added, followed by water (*ca.* 5 ml.). Filtration of the organic layer with the aid of Supercel, washing the filtrate with water and drying (sodium sulfate), gave after removal of the solvent the crude alcohol 1.605 g. Crystallization from acetone–petroleum ether gave VI 1.18 g. (two crops, m.p. 196–203°). Two further crystallizations from acetone–petroleum ether raised the m.p. to 204–205°.

Anal. Calcd. for $C_{26}H_{42}O_6$: C, 69.30; H, 9.40. Found: C, 69.53; H, 9.41. ν_{max}^{Nujol} 3380, 3320, 1245, 1220, 1185, 1150, 1121, 1093, 1053, 1040, 1025, 1005 cm.$^{-1}$

16α-Fluoromethyl-11β-hydroxy-5β-pregnane-3,20-dione-biscycloethyleneketal (VIII). A solution of 11β-hydroxy-16α-(hydroxymethyl)-5β-pregnane-3,20-dione bisketal (0.82 g., m.p. 196–202°), and *p*-toluenesulfonyl chloride (0.82 g.) in pyridine (16 ml.) was allowed to stand 18 hr. at room temperature. The organic material was isolated with ice water and methylene chloride. The combined extracts were washed with sodium bicarbonate solution, water, dried (sodium sulfate), and the solvent removed. The crude 16α-tosyloxymethyl derivative (1.418 g.) was dissolved in diethylene glycol (25 ml. redistilled) and heated with anhydrous potassium fluoride (2.0 g.) for 18 hr. under nitrogen at 110°. Isolation, after cooling, with water and ethyl acetate gave after washing the organic layer with water, drying (sodium sulfate), and solvent removal, an oil (814 mg.). This was chromatographed on Florisil (100 g.). Crystalline material was obtained from the fractions eluted with 5% acetone–petroleum ether (404 mg.). This was recrystallized from acetone–petroleum ether to give VII, 310 mg., m.p. 115–120°. Two further crystallizations from the same solvent raised the m.p. to 125–127°.

Anal. Calcd. for $C_{26}H_{41}FO_5$: C, 69.04; H, 9.07; F, 4.2. Found: C, 68.90; H, 9.46; F, 3.99. ν_{max}^{Nujol} 3495, 1090, 1067 cm.$^{-1}$

16α-Fluoromethyl-5β-pregnane-3,11,20-trione (VIII). 16α-Fluoromethyl-11β-hydroxy-5β-pregnane-3,20-dione-bisketal (283 mg.) in pyridine (5 ml.) was added to a suspension of chromium trioxide pyridine complex [prepared from chromium trioxide (300 mg.) and pyridine (5 ml.)].

After 18 hr. at room temperature isolation was effected with benzene:ether (1:1) and water, followed by filtration through Supercel. The organic layer was washed with water, dried (sodium sulfate), and the solvent removed. The residue was dissolved in 50 ml. of acetone, 5 ml. of water and hydrolyzed by standing at room temperature for 30 hr. with 0.5 ml. of 25% sulfuric acid. At the end of this time excess sodium bicarbonate solution was added and the acetone removed *in vacuo* at room temperature until crystallization commenced. Water (*ca.* 100 ml.) was then added and the crystallization allowed to proceed at 0°. The crystalline solid was collected by filtration, washed with water, dried to give 200 mg. of crude material. This was crystallized from acetone–petroleum ether to give 16α-fluoromethyl-5β-pregnan-3,11,20-trione (VIII), 130 mg., m.p. 162–165°. Final crystallization from the same solvent raised the m.p. to 164–166°.

Anal. Calcd. for $C_{22}H_{31}FO_3$: C, 72.90; H, 8.56; F, 5.25. Found: C, 72.80; H, 8.92; F, 5.26. ν_{max}^{Nujol} 1690, 1064, 1014, 1001, 968, 938, 822 cm.$^{-1}$

16α-Fluoromethyl-11-oxoprogesterone (IX). 16α-Fluoromethyl-5β-pregnane-3,11,20-trione (VIII) (1.05 g.) in *t*-butyl alcohol (35 ml.) and dioxane (2 ml.) was stirred in the dark at room temperature with concentrated hydrochloric acid (0.3 ml.), water (1.5 ml.), and *t*-butyl hypochlorite (0.35 ml.) for 24 hr. Isolation with methylene chloride and water gave after washing the extracts with sodium bicarbonate solution, water, drying (sodium sulfate) and solvent removal, the crude 4-chloro compound, 1.283 g. This was dissolved in dimethylformamide (35 ml.) and heated at 50–60° in a nitrogen atmosphere with semicarbazide hydrochloride (1.38 g.), sodium acetate (1.03 g.) and water (7 ml.). After 2 hr. pyruvic acid (3.45 ml.) and water (3.45 ml.) were added and the solution maintained at the same temperature for a further 2.5 hr. After cooling benzene and sodium bicarbonate solution were added, and the organic layer washed with water and dried (sodium sulfate). Removal of the solvent gave an oil (1.28 g.) which was dissolved in methylene chloride and chromatographed on Florisil (100 g.) made up in ether. Crystalline material was obtained from the fractions eluted from 10–15% acetone–petroleum ether. These were combined and crystallized from acetone–petroleum ether to give, 0.45 g. (2 crops; crop 1, m.p. 203–208°). Two further crystallizations raised the m.p. to 223–226°.

Anal. Calcd. for $C_{22}H_{29}FO_3$: C, 73.33; H, 8.06; F, 5.28. Found: C, 73.31; H, 7.63; F, 5.52. $\lambda_{max}^{C_2H_5OH}$ 238 mμ, a_M 15,400 ν_{max}^{Nujol} 1700, 1670, 1618, 1240, 1230 cm.$^{-1}$

(21) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

4,16-Pregnadiene-3,11,20-trione-3-cycloethyleneketal (X). A mixture of 4,16-pregnadiene-3,11,20-trione (31.68 g., m.p. 198.5–201°), 2-methyl-2-ethyldioxolane (500 ml.) and *p*-toluenesulfonic acid monohydrate (300 mg.) was heated to reflux and incorporating a water separator for 4 hr. Isolation was effected after cooling by the addition of methylene chloride, and subsequent washing with sodium bicarbonate solution and then water. After drying the solvent was removed. The residue was dissolved in benzene and chromatographed on acid washed alumina (1000 g.). Crystalline material was obtained from the fractions eluted from benzene until 50% ether:benzene. These were combined and crystallized from acetone–petroleum ether to give the monoketal (X) (crop 1, 8.5 g., m.p. 228–233°; crop 2, 1.0 g., m.p. 205–211°). Further crystallization from acetone–petroleum ether raised the melting point to 233–235°.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.43; H, 8.37. $\lambda_{max}^{C_2H_5OH}$ 234.5 mμ, a_M 9,500. ν_{max}^{Nujol}; 1697, 1660, 1625, 1595, 1147, 1130, 1093, 1053, 1037, 1002, 973 cm.$^{-1}$

16α-Cyano-4-pregnene-3,11,20-trione-3-cycloethyleneketal (XI). 4,16-Pregandiene-3,11,20-trione-3-cycloethyleneketal (9.5 g., m.p. 228–235°), potassium cyanide (15.0 g.), dioxane (100 ml.), and methanol (500 ml.) were heated in a nitrogen atmosphere under reflux for 3 hr. Isolation was effected, after cooling with water and methylene chloride. The combined extracts were washed with water, dried over sodium sulfate, and the solvent removed. The residue was dissolved in benzene and filtered through a column of acid-washed alumina (20.0 g.) made up in benzene. After evaporation of the eluate, the residue was crystallized from acetone–petroleum ether to give crop 1 (6.15 g., m.p. 236– 242°); and crop 2 (1.93 g., m.p. 190–200°). Recrystallization of crop 2 gave 0.83 g., m.p. 200–220°, and this may be contaminated with the 16β-cyano-17α-compound, and was not combined with the main crop. Two recrystallizations of crop 1 from acetone–methanol gave 16α-cyano-4-pregnene-3,11,20-trione 3-cycloethyleneketal, m.p. 242–244°.

Anal. Calcd. for $C_{24}H_{31}O_4N$: C, 72.51; H, 7.86. Found: C, 72.49; H, 7.94. ν_{max}^{Nujol} 2240, 1700, 1693, 1663, 1100, 1090, 1075, 1012 cm.$^{-1}$

16α-Cyano-11-oxoprogesterone-3,20-biscycloethyleneketal. 16α-Cyano-11-oxoprogesterone-3-ketal (1.1 g., m.p. 236–242°) benzene (150 ml.), ethylene glycol (3.0 ml.) and *p*-toluenesulfonic acid monohydrate (25 mg.) were heated to boiling under reflux and incorporating a water separator for 5.5 hr. Isolation after cooling was effected by the addition of sodium bicarbonate solution. The organic extract was washed with water, dried (sodium sulfate) and the solvent removed *in vacuo*. Two crystallizations of the residue from acetone–petroleum ether gave 16α-cyano-11-oxoprogesterone 3,20-biscycloethyleneketal, crop 1, 640 mg., m.p. 251–253°; crop 2, 340 mg., m.p. 215–223°.

16α-Cyano-11-oxoprogesterone-3-monoketal (1.01 g., m.p. 225–230°) was dissolved in acetone (60 ml.) and allowed to stand 18 hr. at room temperature with water (5 ml.) and 3 drops of 25% sulfuric acid. Sodium bicarbonate solution was then added and the acetone removed *in vacuo* at room temperature until crystallization commenced. Further water (*ca.* 100 ml.) was then added and the crystallization allowed to proceed at 0°. The solid material was collected by filtration, dried and twice crystallized from acetone–petroleum ether to give 16α-cyano-11-ketoprogesterone, 500 mg., m.p. 230–235°. A final crystallization from methanol raised the m.p. to 238–230°.

Anal. Calcd. for $C_{22}H_{27}O_3N$: C, 74.75; H, 7.70. Found: C, 74.63; H, 7.60. $\lambda_{max}^{C_2H_5OH}$ 238 mμ, a_M 14,500. ν_{max}^{Nujol} 2210, 1698, 1672, 1612 cm.$^{-1}$

16α-Carbomethoxy-11-oxoprogesterone-3,20-biscycloethyleneketal (XII.R'''=CH_3). A mixture of 16α-cyano-11-oxoprogesterone-3,20-bisketal (13.7 g., m.p. 245–252°), ethylene glycol (400 ml.), potassium hydroxide (25.0 g.), and water (100 ml.) was heated at reflux under nitrogen for 20 hr. After cooling, water was added and the alkaline solution extracted with methylene chloride. The aqueous layer was cooled to 0° then carefully acidified to *ca.* pH 4 and rapidly extracted with ethyl acetate–methylene chloride. The combined extracts were washed with water until neutral, dried (sodium sulfate), and the solvent removed. The residue was dissolved in methylene chloride (200 ml.) and methanol (500 ml.), and esterified with excess ethereal diazomethane solution for 3 hr. at room temperature. After removal of the solvent the residue was crystallized from acetone–petroleum ether to give XII, R'''=CH_3; 9.8 g., m.p. *ca.* 200°. Two crystallizations (same solvent) raised the m.p. to 224–225°.

Anal. Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.29; H, 7.94. ν_{max}^{Nujol} 3340, 1663, 1168, 1108, 1060, 1050, 1040, 1023, 1003.

11β-Hydroxy-16α-(hydroxymethyl)progesterone-3,20-biscycloethyleneketal (XIII). A solution of 16α-carbomethoxy-11-oxoprogesterone-3,20-bisketal (9.7 g., m.p. *ca.* 200°) in benzene (200 ml.) was added to a stirred suspension of lithium aluminum hydride (12.0 g.) in ether (150 ml.) and benzene (150 ml.) at 0°. The mixture was heated under reflux for 4 hr. cooled in ice and the excess hydride decomposed with ethyl acetate and then water. After filtration the organic layer was washed with water, dried (sodium sulfate), and the solvent removed. The crude residue was crystallized from ethyl acetate–petroleum ether to give XIII, crop 1, 2.4 g., m.p. 195–205°; crop 2, 0.3 g. The melting point was raised on crystallization from acetone–petroleum ether to 209–211°. Chromatography on Florisil gave further material (eluted with 20% acetone–petroleum ether), 0.79 g., m.p. 195–205°.

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 69.61; H, 8.99. Found: C, 69.61; H, 8.61. ν_{max}^{Nujol} 3440, 1663, 1168, 1108, 1060, 1050, 1040, 1023, 1003 cm.$^{-1}$

A solution of 11β-hydroxy-16α-(hydroxymethyl)progesterone-3,20-bisketal (300 mg., m.p. 195–205°) in acetone (40 ml.) and water (4 ml.) was hydrolyzed by standing for 40 hr. at room temperature with 25% sulfuric acid (1 ml.). Initially the mixture was boiled for 10 min. At the end of the reaction excess sodium bicarbonate solution was added and the acetone removed *in vacuo* at room temperature until crystallization commenced. Further water (*ca.* 50 ml.) was added and the crystallization allowed to proceed at 0°. The solid material was then collected by filtration and dried *in vacuo* to give 11β-hydroxy-16α-(hydroxymethyl)progesterone; 150 mg., m.p. 234–238°. Crystallization from acetone–petroleum ether raised the m.p. to 244–246°.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.24; H, 9.35. ν_{max}^{Nujol} 3430, 1690, 1685, 1662, 1615, 1076, 1053, 1025, 1000 cm.$^{-1}$ $\lambda_{max}^{C_2H_5OH}$ 238 mμ, a_M 15,800.

16α-Carboxy-11-oxoprogesterone-3,20-biscycloethyleneketal (XIII. *R''' = H*). 16α-Cyano-11-oxoprogesterone-3-monocycloethyleneketal (47.0 g.) was converted to the 20-ketal, as described above. The total crude product was suspended in ethylene glycol (2 l.), with potassium hydroxide (100 g.) in water (100 ml.), and the mixture heated to reflux under nitrogen for 18 hr. with stirring. After cooling in ice:salt to +5° excess ice-cold dilute sulfuric acid was added until the pH of the solution was 4. The precipitated solid was collected by filtration, washed with water until the washings were neutral, and dried *in vacuo* at 65°. This gave 48.75 g. of the crude 16α-carboxylic acid, m.p. 225–245°. A portion of this acid was esterified as described earlier to give the corresponding ester, which was identical (melting point; infrared spectrum) with the material previously characterized.

11β-Hydroxy-16α-(hydroxymethyl)progesterone-3,20-biscycloethyleneketal (XIII). 16α-Carboxy-11-oxoprogesterone-3,20-bisketal (5.07 g., m.p. 225–245°) was reduced with lithium aluminum hydride (3.5 g.) in tetrahydrofuran, employing the technique in which the carboxylic acid was placed in a Soxhlet thimble, because of its low solubility. After 2 hr. of refluxing, the mixture was cooled and the excess hydride decomposed by the successive addition of ethyl acetate and water. After filtration of the inorganic salts with the aid of Celite the solvent was evaporated *in vacuo*. Crystallization of the residue from methanol–acetone gave 16α-

hydroxymethyl-11β-hydroxyprogesterone-3,20-bis-ketal, crop 1, 3.52 g.; crop 2, 0.32 g. The infrared spectrum of crop 1 was identical with that of the sample prepared earlier from the ester.

16α-Fluoromethyl-11-oxoprogesterone (IX). 11β-Hydroxy-16α-(hydroxymethyl)progesterone-3,20-bisketal (47.6 g.), *p*-toluenesulfonyl chloride (50.0 g.), and pyridine (600 ml.) were allowed to stand for 18 hr. at room temperature. The reaction mixture was then poured into ice water, and the organic material extracted with benzene. These combined extracts were washed successively with ice-cold dilute sulfuric acid, water, sodium bicarbonate solution, water, and dried (sodium sulfate). Removal of the solvent gave the crude tosylate, which was crystallized from acetone–petroleum ether to give 30.5 g., m.p. 155–165° dec. This material was suspended in diethylene glycol (redistilled; 1 l.) together with anhydrous, freshly fused potassium fluoride (35.0 g.), and the mixture was heated with stirring under nitrogen at 200–210° for 1 hr. After cooling the organic material was isolated with ethyl acetate, and the combined extracts washed with water and dried (sodium sulfate). Removal of the solvent gave an oil which was dissolved in methylene chloride and chromatographed on Florisil (1500 g.). Elution with increasing proportions of acetone in petroleum ether gave crystalline material from the 15% acetone—petroleum ether eluates. These fractions were combined and crystallized from acetone–petroleum ether to give the 16α-fluoromethyl derivative, 8.46 g., crop 1, m.p. 179–181°; crop 2, 0.44 g., m.p. 169–175°. Recrystallization of crop 1 from acetone–petroleum ether gave 16α-fluoromethyl-11β-hydroxyprogesterone-3,20-bisketal, m.p. 183–185°.

Anal. Calcd. for $C_{26}H_{39}FO_5$: C, 69.34; H, 8.67; F, 4.22. Found: C, 69.61; H, 9.03; F, 3.74. ν_{max}^{Nujol} 3470, 1674, 1093, 1085, 1080, 1052, 1042, 1035, 1000 cm.$^{-1}$

The bisketal (8.8 g.) was dissolved in pyridine (100 ml.) and oxidized for 18 hr. at room temperature with chromium trioxide (10 g.) and pyridine (100 ml.). Isolation was effected by the addition of benzene-ether (1:1) and water,, followed by filtration through Supercel. The aqueous layer was separated, and re-extracted with benzene-ether. The combined extracts were washed successively with dilute hydrochloric acid and then with water until neutral. These extracts were dried (sodium sulfate) and the solvent removed. The residue was dissolved in 1 l. of acetone, and 6 ml. of 25% aqueous sulfuric acid was added. After heating the solution to reflux for 5 min., the hydrolysis was allowed to proceed for 40 hr. at room temperature. Aqueous saturated sodium bicarbonate solution was added until the *p*H was 8, and the acetone was removed *in vacuo* at room temperature until the total volume was 150 ml. Water (500 ml.) was then added and the crystallization allowed to proceed at 0°. The crystalline material was collected by filtration, washed with water and dried at 40° *in vacuo* to give 16α-fluoromethyl-11-oxo-progesterone (IX), 6.43 g.; m.p. 215–219°. Further crystallization raised the m.p. to 219–222°.

Anal. Calcd. for $C_{22}H_{29}FO_3$: F, 5.28. Found: F, 5.26.

The infrared spectrum was the same as the sample prepared and characterized above.

Methyl-3,11-dioxo-16α-fluoromethyl-4,17(20)-pregnadiene-21-oate (cis and trans) (XIV) *and* (XV). A solution of 16α-fluoromethyl-11-oxoprogesterone (8.9 g.) in *t*-butyl alcohol (200 ml.) was heated to 60° with stirring, under nitrogen and treated with diethyl oxalate (17.0 ml.) followed by methanolic sodium methoxide solution (16.4 g., 24.1%). A yellow precipitate formed almost at once. The mixture was stirred for 15 min. while cooling from 60° to 25°. Then an ice-cooled solution of 4.14 g. anhydrous sodium acetate and acetic acid (4.23 ml.) in methanol (190 ml.) was added. After cooling to 0° the mixture was treated dropwise with a cooled solution of bromine (11.84 g.) in methanol (120 ml.). The cooling bath was removed and 38.0 g. of 24.1% methanolic sodium methoxide was added and stirring continued for 1 hr. Zinc (8.0 g.) and acetic acid (18 ml.) were added and the stirring continued for 40 min. Filtration through Supercel was followed by isolation with water and methylene chloride. The organic layer was dried (sodium sulfate) and the solvent removed. The crude product was dissolved in 30 ml. of methylene chloride and chromatographed on 600 g. of Florisil. Three main peaks were eluted:

1. Crystalline material was obtained from the 10% acetone–petroleum ether eluates. This is formulated as the *trans* isomer. This assignment is made in two grounds. First, the *trans* Favorskii esters are always less polar than the *cis* isomers in their behavior on Florisil chromatography. Secondly, an analysis of a series of isomer pairs shows characteristic infrared spectral patterns which allow structural assignment (private communication, R. Rinehart, these laboratories). Crystallization of a portion (69 mg.) of this from acetone-petroleum ether gave methyl 3,11-dioxo-16α-fluoromethyl-*trans*-4,17(20)-pregnadiene-21-oate, (XV) m.p. 157–159°. ν_{max}^{Nujol}; 1718, 1710, 1675, 1650, 1620, 1210, 1190, 1177, 1165 cm.$^{-1}$ $\lambda_{max}^{C_2H_5OH}$ 232 mμ (24,450).

Anal. Calcd. for $C_{23}H_{29}FO_4$: C, 71.14; H, 7.47; F, 4.9. Found: C, 71.09; H, 7.71; F, 5.1.

2. Crystalline material was obtained from the 10–15% acetone-petroleum ether eluates. This is formulated as the *cis* isomer. Crystallization of a portion (62 mg.) of this material from acetone–petroleum ether gave methyl 3,11-dioxo-16α-fluoromethyl-*cis*-4,17(20)-pregnadiene-21-oate, (XIV) m.p. 169–172°. ν_{max}^{Nujol} 1718, 1710, 1675, 1650, 1620 cm.$^{-1}$ $\lambda_{max}^{C_2H_5OH}$ 231 mμ (22,050).

Anal. Calcd. for $C_{23}H_{29}FO_4$: C, 71.14; H, 7.47; F, 4.9. Found: C, 71.01; H, 7.58; F, 5.29.

The combined *cis* and *trans* isomers amounted to 5.672 g.

3. The fractions with 15–20% acetone–petroleum ether gave, after crystallization from acetone–petroleum ether, recovered starting material, 1.25 g., m.p. 199–210°.

16α-Fluoromethyl-11β,21-dihydroxy-4,17(20)-pregnadien-3-one 21-acetate (XVI). A solution of mixed *cis*- and *trans*-methyl 3,11-oxo-16α-fluoromethyl-4,17(20)-pregnadien-21-oate (6.21 g.) in benzene (400 ml.) was heated with stirring under reflux, incorporating a water separator, for 1.5 hr. with *p*-toluenesulfonic acid monohydrate (200 mg.) and pyrrolidine (5 ml.; freshly distilled). After cooling this benzene solution was added dropwise with stirring to a suspension of lithium aluminum hydride (6.5 g.) in ether (500 ml.) cooled to 0°, and in a nitrogen atmosphere. After 1 hr. at room temperature the mixture was heated to reflux for 0.5 hr. It was then cooled and 60 ml. of ethyl acetate was added followed by water (90 ml.). Most of the solvent was removed *in vacuo*, and the residue stirred for 15 min. with a mixture of acetic acid (9.0 ml.) and methanol (204 ml.). A solution of sodium hydroxide (6.0 g.) in water (60 ml.) was then added followed by removal of the solvent until the volume was diminished by about half. A mixture of 12 ml. of concd. sulfuric acid and water (210 ml.) was added and after stirring for 15 min. the product was isolated with methylene chloride. The combined extract was washed with water, dried (sodium sulfate) and the solvent evaporated. The residue was treated overnight at room temperature with acetic anhydride (20 ml.) and pyridine (30 ml.). Isolation was effected with ice–sodium bicarbonate solution and ether:benzene. The organic extracts were washed with dilute hydrochloric acid and water, and dried (sodium sulfate). Removal of the solvent gave an oil. Chromatography of the total product in methylene chloride (30 ml.) on Florisil (500 g.) gave the required "diene diol" acetate eluted with 15–20% acetone–petroleum ether. Less clear isomer separation was obtained in this case than with the corresponding Favorskii esters. A portion of the later (20% acetone–petroleum ether elutates) fractions was crystallized from acetone–petroleum ether to give 16α-fluoromethyl-11β,21-dihydroxy-4,17(20)-pregnadiene-3-one 21-acetate, m.p. 183–186°. ν_{max}^{Nujol}; 3470, 1732, 1657, 1611, 1245, 1232, 1047, 1035. 1023, 1004, 998 cm.$^{-1}$ $\lambda_{max}^{C_2H_5OH}$ 241 mμ (16,400).

Anal. Calcd. for $C_{24}H_{33}FO_4$: C, 71.29; H, 8.17; F, 4.7. Found: C, 70.91; H, 8.13; F, 4.88.

The combined *cis* and *trans* isomers amounted to 3.702 g. (57% yield).

16α-Fluoromethylhydrocortisone 21-acetate (XVII). A solution of 16α-fluoromethyl-11β,21-dihydroxy-4,17(20)-pregnadiene-3-one 21-acetate (*cis* and *trans;* 3.66 g.) in *t*-butyl alcohol (183 ml.) was stirred at room temperature with pyridine (2.6 ml.) and *N*-methylmorpholine oxide–hydrogen peroxide reagent (17.6 ml.; titration 1 ml. = 42 ml, 0.1*N* sodium thiosulfate) together with osmium tetroxide (16 ml. of a solution containing 117 mg./50 ml. = 37.5 mg. of osmium tetroxide). Isolation after 17.5 hr. was effected by addition of a solution of sodium hydrosulphite (0.37 g.) in water (350 ml.) and stirring the resulting mixture for 30 min. The organic material was isolated with methylene chloride and water. The combined extracts were washed with water, dried (sodium sulfate), and the solvent removed to give an oil. This material was dissolved in methylene chloride (30 ml.) and chromatographed on Florisil (300 g.). Elution with increasing proportions of acetone in petroleum ether gave from the 15% acetone–petroleum ether eluates recovered starting material (0.939 g.). The 20–25% acetone–petroleum ether eluates gave the required 16α-fluoromethylhydrocortisone 21-acetate (0.697 g.) (A). 30–40% Acetone–petroleum ether gave the "triol" side chain by-product (0.388 g.).

The recovered starting material (0.989 g.) was retreated with osmium tetroxide-*N*-methylmorpholine oxide–hydrogen peroxide in the above fashion to give further product (0.178 g. combined column fractions). Crystallization of the combined fractions (A) gave 16α-fluoromethylhydrocortisone 21-acetate; crop 1, 0.399 g., m.p. 198–201°; crop 2 from ether–methanol, 84 mg., m.p. 193–198°. Further crystallization of crop 1 from acetone–petroleum ether gave m.p. 203–205°. $\lambda_{max}^{C_2H_5OH}$ 242 mμ (15,750). ν_{max}^{Nujol} 3550, 3410, 1740, 1727, 1655, 1624, 1237, 1123, 1060, 1040 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{33}FO_6$: C, 66.06; H, 7.57; F, 4.36. Found: C, 65.72; H, 7.61; F, 4.77.

16α-Fluoromethylprednisolone 21-acetate (XVIII. X = H). A mixture of 16α-fluoromethylhydrocortisone 21-acetate (290 mg. m.p. 198–201°), selenium dioxide (290 mg.), acetic acid (0.5 ml.) and *t*-butyl alcohol (25 ml.) was heated to boiling under reflux for 15.5 hr. Further selenium dioxide (200 mg.) was then added and the reflux period continued for a further 24 hr. The mixture was then cooled and filtered through Celite using ethyl acetate to wash the solid material. The resulting filtrate was evaporated to dryness in a nitrogen stream, and the residue extracted with ethyl acetate. This extract was washed successively with potassium bicarbonate solution, freshly prepared ice-cold ammonium sulfide, ice-cold dilute ammonia, dilute hydrochloric acid, potassium bicarbonate solution, water, and dried (sodium sulfate). Removal of the solvent gave an oil, which was dissolved in 15 ml. of methylene chloride and chromatographed on Florisil (30 g.). Elution with increasing proportions of acetone in petroleum ether gave crystalline material (177 mg.) from the 25–30% acetone–petroleum ether eluates. Crystallization from acetone–petroleum ether gave crop 1, 114 mg., m.p. 194–197°; crop 2, 17 mg. Paper chromatography of crop 1 (benzene-formamide system) showed essentially one spot moving slowly relative to 16α-fluoromethylhydrocortisone 21-acetate. A further crystallization of crop 1 from acetone–petroleum ether gave 16α-fluoromethylprednisolone 21-acetate (XVIII), acetone solvate, m.p. 197–199°. ν_{max}^{Nujol} 3480, 1730, 1723, 1662, 1615, 1600, 1257, 1240, 1130, 1060, 1043, 1030, 1020 cm.$^{-1}$. $\lambda_{max}^{C_2H_5OH}$ 243 (14,800) A243/A263 = 1.66.

Anal. Calcd. for $C_{24}H_{31}FO_6 \cdot C_3H_6O$: C, 65.85; H, 7.52; F, 3.86. Found: C, 65.57; H, 7.34; F, 4.06.

Paper chromatography showed only one spot in two solvent systems (Mattox-1 and carbitol-methylcyclohexane).

16α-Fluoromethyl-9α-fluoroprednisolone 21-acetate (XIX). 16α-Fluoromethylprednisolone 21-acetate (XVIII) (123 mg.) was dissolved in pyridine (5 ml.; freshly redistilled from barium oxide) and *N*-bromoacetamide (63 mg.) was added. The solution was stirred for 20 min. at room temperature and then cooled to *ca.* 10° in an ice bath. A slow stream of sulfur dioxide was passed over the solution until a negative starch : iodide test was given by the solution. Ice water (100 ml.) was then added and with precipitated solid was collected by filtration (77 mg.). The aqueous mother liquors were extracted with methylene chloride to furnish an additional 56 mg. These two products were combined, dissolved in methylene chloride and chromatographed on Florisil (50 g.). One main peak was eluted with 20% acetone– petroleum ether. These crystalline fractions were combined to give 117 mg. Paper chromatography of this material (benzene–formamide system) showed one spot moving fast relative to 16α-fluoromethylprednisolone 21-acetate.

The total chromatographic fractions from the above dehydration (116 mg.) were dissolved in 2 ml. of methylene chloride and *t*-butyl alcohol (5.8 ml.); 70% perchloric acid, 0.375 ml. in 2.5 ml. of water, was then added, followed by a solution of *N*-bromoacetamide (50 mg.) dissolved in 2.2 ml. of *t*-butyl alcohol. After stirring this mixture for 15 min. at room temperature, a solution of sodium sulfite (88 mg.) in 4 ml. of water was added. Most of the solvent was then removed *in vacuo* at room temperature. Water (15 ml.) was then added to the residue and the crystalline solid formed was refrigerated for 1 hr. at +5°, collected by filtration, washed thoroughly with water and dried *in vacuo* at 40° to give 123 mg. Paper chromatography (benzene-formamide) showed mainly one spot moving slowly relative to the 9,11-dehydro compound. The total crude bromohydrin prepared above (123 mg.) was heated to boiling under reflux in acetone (15 ml.) with potassium acetate (300 mg.). After 18 hr. the solution was cooled and the acetone removed in a nitrogen stream at room temperature. The residue was partitioned between water and methylene chloride. The methylene chloride extract was dried (sodium sulfate) and the solvent removed *in vacuo*. The residue was dissolved in methylene chloride and applied to a 5.0-g. Florisil column. Crystalline material (102 mg.) was obtained from the 10–20% acetone–petroleum ether eluates. Paper chromatography (benzene-formamide) showed essentially one spot moving fast relative to the bromohydrin.

The combined chromatographic fractions containing the 9,11β-oxide (102 mg.) were dissolved in methylene chloride (4 ml.); the solution was cooled to −10° and added to a cooled mixture of anhydrous hydrofluoric acid (2.0 g.) and tetrahydrofuran (3.45 ml., freshly distilled from lithium aluminum hydride), together with methylene chloride (2 ml.) This mixture was allowed to stand at +5° for 18 hr. After pouring the mixture cautiously onto ice–sodium bicarbonate solution, the organic material was extracted with methylene chloride. These extracts were washed with water, dried (sodium sulfate) and the solvent removed. The residue was dissolved in methylene chloride (*ca.* 10 ml.) and chromatographed on 5.0 g. of Florisil. Elution with increasing proportions of acetone in petroleum ether gave crystalline material from the 30% acetone–petroleum ether eluates. These were combined and crystallized from acetone–petroleum ether to give crop 1, 40 mg., m.p. 235–238°; crop 2, 24 mg., m.p. 225–230°. Crop 1 showed only one spot on paper chromatography (benzene-formamide) moving slowly relative to prednisolone 21-acetate. Recrystallization of both crops separately from aqueous acetone gave (e. crop 1), 35 mg., m.p. 235–238° and (e. crop 2), 17 mg., m.p. 228–235°. A third crop was obtained from the combined mother liquors, 11 mg., m.p. 224–230°. The material, m.p. 235–238°, had an analysis corresponding to 16α-fluoromethyl-9α-fluoroprednisolone 21-acetate monohydrate (XIX). ν_{max}^{Nujol} 3580, 3450, 3320, 3190, 1735, 1723, 1660, 1615, 1605, 1248, 1140, 1063 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{30}F_2O_6 \cdot H_2O$: C, 61.28; H, 6.86; F, 8.1. Found: C, 61.21; H, 7.09; F, 8.7.

Acknowledgment. The authors are indebted to J. L. Johnson, W. A. Struck, and associates for the analyses, ultraviolet, and infrared spectra.

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

Degradation of Corticosteroids. IV. Preparation of 3,5-Seco-4-nor-6-androstene-5,11,17-trione-3-oic Acid and 3,5-Seco-4-nor-11β-hydroxyandrostane-5,17-dione-3-oic Acid 3,11-Lactone[1,2]

ELIAHU CASPI, (MRS.) BADAR TAQUI KHAN,[3a] AND WALTER SCHMID[3b]

Received March 6, 1961

The 3,5-seco-4-norandrostane-5,11,17-trione-3-oic acid was converted to 5-en-3,5-lactone III which on treatment with *N*-bromosuccinimide gave 3,5-seco-4-nor-6-androstene-5,11,17-trione-3-oic acid (IVa), presumably *via* an unstable 7-bromo-5-en-3,5-lactone which was not isolated. The Δ^6-acid IVa rearranges with base to the thermodynamically more stable Δ^8 isomer V. The utilization of the Δ^6-acid IVa for the degradation of ring B and isolation of carbons 5, 6 and 7 is described. Attempts to prepare the 3,5-seco-4-nor-11β-hydroxy-5-androsten-17-one-3-oic acid 3,5-lactone failed and instead the 3,5-seco-4-nor-11β-hydroxyandrostane-5,17-dione-3-oic acid 3,11-lactone (X) was obtained. The seven-membered 3,11-lactone was formed in preference to the enol lactone and must therefore be the thermodynamically more stable of the two.

As part of a broad program of studies directed toward the stepwise degradation and isolation of individual carbon atoms of corticosteroids, approaches to the cleavage of ring B were explored. Economy of biosynthetic material required development of methods leading to the isolation of a large number of atoms. The 4-nor acid II, having an exposed ring B, was considered an attractive starting material for isolation of carbons 5, 6 and 7. Additional activation, necessary for directing the chemical attack, preferentially towards ring B, was achieved by enol lactone formation. The degradation of ring B and certain reactions of the 11-keto-enol lactone III as well as observations on the course of lactone formation in the 11β-hydroxy acid IXa are the subject of this communication.

Ozonolysis of adrenosterone at −70° in ethyl acetate gave in high yield the 3,5-sec-4-nor acid II as well as a low yield of an unidentified neutral product of m.p. 180–184°. Treatment of the acid II with acetic anhydride and fused sodium acetate[4] yielded the enol lactone III. Bromination of the enol lactone with *N*-bromosuccinimide did not lead to the isolation of the 7-bromo enol lactone. When, at the completion of the bromination, the reaction mixture was processed in ethyl acetate and partitioned with sodium hydrogen carbonate, two products, an acid and a neutral substance, were obtained. The acid, m.p. 205–207°, with an analysis for a $C_{18}H_{22}O_5$ compound, absorbed ultraviolet light at 224 mμ, indicative of a β-monosubstituted α,β-unsaturated ketone[5,6] and its infrared spectrum had bands at 3600, 3100 (broad), 2750 (shoulder), 1750, 1710, 1640, 1600 (shoulder), 1170 cm.$^{-1}$ These results are consistent with the structure IVa assigned to the acid which was subsequently confirmed by degradation experiments (see below). The neutral product, m.p. 105–107°, also absorbed ultraviolet light at $\lambda_{max}^{CH_3OH}$ 224 mμ and its infrared spectrum exhibited bands at 1730, 1710, 1670, 1610, 1160 cm.$^{-1}$ The possibility of the compound being the 1-dehydro enol lactone, formed *via* bromination[7] at C-2 followed by dehydrobromination was excluded, as the product had an analysis of a $C_{26}H_{26}O_5$ substance and its infrared spectrum did not show a band in the 1680–1690-cm.$^{-1}$ region, characteristic for enol lactones.[8] Furthermore, the NMR spectrum showed only two protons on a double bond while the 1-dehydro enol lactone requires three. In addition the NMR spectrum showed a quartet and triplet of bands characteristic of an ethyl ester.[9] These results suggested that the neutral product is the ethyl ester IVc and attempts were made to saponify the substance to the acid IVa. However on treatment of the neutral product

---

(1) This investigation was supported by grants from the American Cancer Society P102 and P103.

(2) Previous papers of this series: (a) *J. Org. Chem.*, **21**, 814 (1956). (b) *J. Org. Chem.*, **22**, 326 (1957). (c) *J. Org. Chem.*, **24**, 669 (1959).

(3)(a) Postdoctoral Fellow 1959–1961. On leave of absence from Osmania University, Hyderabad, India. (b) Postdoctoral Fellow 1958–1960. Present address: Sandoz, A.G., Basel, Switzerland.

(4) R. B. Woodward, F. Sondheimer, D. Taub, K. Hensler, and M. W. MacLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(5) R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941); **64**, 76 (1942). L. F. Fieser and M. Fieser, *Steroids*, Reinhold, New York, 1959, p. 19.

(6) E. Caspi and M. M. Pechet, *J. Biol. Chem.*, **230**, 843 (1958).

(7) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

(8) H. Rosenkrantz and M. Gut, *Helv. Chim. Acta*, **36**, 1000 (1953); T. L. Jacobs and N. Takahashi, *J. Am. Chem. Soc.*, **80**, 4865 (1958).

(9) J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw Hill, New York, 1959, p. 31, 67; *Catalog of NMR Spectra of Hydrogen and Hydrocarbons and Their Derivatives*, Humble Oil and Refining Co., 1959, p. 147.