hydrogen occurred during the experiment. After filtration of the reaction products to remove catalyst, the solvent was stripped at 20 mm. and 50°, yielding 98.5 g. of sirup. A sample of the sirup was analyzed by gas–liquid chromatography using a Podbielniak Chromacon isothermal unit equipped with thermal conductivity cells for detection. The three dianhydrohexitols were separated at 200° on a 2 ft. × 0.25 in. i.d. copper tubing column packed with 20% Carbowax 20M[9] on Chromosorb W.[10] Calibration with known samples of the three dianhydrohexitols established the identity of the three peaks found on the chromatogram. The composition of the mixture was estimated by measuring the areas under each peak by the peak height times width at half-height method. The absolute amounts were determined by the method of internal standardization using tetraethylene glycol as an internal standard (*cf.* Fig. 2). Analyses by the two methods were in close agreement.

(9) A product of the Union Carbide Chemicals Co., a division of Union Carbide Corp.

(10) A product of the Johns-Manville Corp.

The dianhydrohexitol mixture was separated on a macroscale by fractionation of a 100-g. distillation charge through a 12-in. glass column (23-mm. i.d.) packed with porous stainless steel packing. Three cuts were taken. Cut 1, 7.5% of the charge, b.p. 123–130° (2 mm.), was mainly isomannide contaminated with traces of isosorbide. Cut 2, 40.5% of the charge, b.p. 148–151° (2 mm.), was mainly isosorbide. Cut 3, 52.0% of the charge, b.p. 159–162° (2 mm.), was relatively pure isoidide. G.l.c. analysis of cut 3 indicated a purity of 99.9%. Recrystallization of a small sample of cut 3 from methyl ethyl ketone yielded isoidide, melting point and mixture melting point with an authentic sample of isoidide 63–64°.

**Acknowledgment.**—The authors wish to express their appreciation to Dr. A. D. Cooper for advice on the development of analytical procedures and to Dr. C. F Smullin, Dr. J. W. LeMaistre, and Mr. R. L. Birkmeier for helpful discussions during the course of this work.

# Reaction of Perchloryl Fluoride with Derivatives of Methyl 3,11-Diketo-4,17(20)-*cis*-pregnadien-21-oate. Synthesis of 4-Fluoro- and 6-Fluorohydrocortisone Acetate

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Treatment of the 3-enol ether, 3-enol acetate, and the 3-enamine of methyl 3,11-diketo-4,17(20)-*cis*-pregnadien-21-oate with perchloryl fluoride to form 4-fluoro and 6-fluoro steroids is described. These intermediates were converted to the corresponding cortical hormones.

Our continuing interest in the synthesis of 6-fluoro-[1] and 6,16-difluoro corticoids[2] made a simple method for the introduction of fluorine into a 3-keto-$\Delta^4$ steroid highly desirable. Particularly sought was a method to utilize the intermediates available from the unique synthesis of hydrocortisone described from these laboratories.[3]

Reaction of perchloryl fluoride with enol ethers and enol acetates of 3-keto-$\Delta^4$ steroids to yield 6-fluoro steroids[4,5] offered a means of attaining this goal. The 3-enol ether of methyl 3,11-diketo-4,17(20)-*cis*-pregnadien-21-oate[3] (**1**) was treated with an excess of perchloryl fluoride in pyridine or aqueous tetrahydrofuran solution. When the reaction was carried out in pyridine solution up to 52% yield of fluorinated product was obtained from which by chromatography the pure 6$\alpha$-fluoro and 6$\beta$-fluoro steroids **2** and **3** were isolated, the former predominating. A higher yield (86%) of a mixture of **2** and **3** was obtained when the fluorination was performed in aqueous tetrahydrofuran. From the reaction mixture in this solvent another fluorinated steroid was isolated in modest yield. This compound was assigned structure **4**, namely methyl 4$\alpha$-fluoro-3,11-diketo-5,17(20)-*cis*-pregnadien-21-oate, on the following evidence. Elemental analysis indicated a monofluoro steroid. An ultraviolet absorption maximum assigned to the unsaturated ester function was found at 222 m$\mu$, while infrared absorption bands were noted in the carbonyl region at 1739, 1710 and 1705 cm.$^{-1}$. The latter two bands were assigned to the unsaturated ester and 11-keto groupings, respectively. The band at 1739 cm.$^{-1}$ was assigned to the $\alpha$-halo-3-keto function. The hypsochromic shift in the infrared spectrum to 1739 cm.$^{-1}$ from that of an unsubstituted 3-keto steroid is consistent with the presence of a 4$\alpha$-fluoro substituent.[6] The ultraviolet and infrared absorption data for these compounds are summarized in Table I. When treated with hydrogen chloride in chloroform, **4** was isomerized to a monofluoro steroid possessing an ultraviolet absorption maximum at 237 m$\mu$ and infrared absorption in the carbonyl region at 1720, 1708, and 1690 cm.$^{-1}$. The spectral data indicate the presence of a newly formed unsaturated system. Structure **5** was assigned to this compound. The isolation of **4** is also consistent with the proposed mechanism of perchloryl fluoride reactions involving the electrophilic attack of the reagent at a center of high electron density.[5,6a]

Methyl 4$\alpha$-fluoro-3,11-diketo-5,17(20)-*cis*-pregnadien-21-oate (**4**) was converted to 4-fluorohydrocortisone acetate (**8**) *via* the 3-enamine by methods previously disclosed from this laboratory[3] (reaction sequence, **4** → **6** → **7** → **8**.) Owing to the difficulty of obtaining pure **4** on a large scale, partially purified material was usually used in the reduction sequence. Therefore a method to evaluate the purity of **6** and to purify this material prior to the introduction of the

(1) J. A. Hogg, *et al.*, *Chem. Ind.* (London), 1002 (1958).

(2) B. J. Magerlein, F. H. Lincoln, R. D. Birkenmeyer, and F. Kagan, *ibid.*, 2050 (1961).

(3) J. A. Hogg, *et al.*, *J. Am. Chem. Soc.*, **77**, 4436 (1955).

(4) S. Nakanishi, K. Morita, and E. V. Jensen, *ibid.*, **81**, 5259 (1959).

(5) B. M. Bloom, V. V. Bogert, and R. Pinson, Jr., *Chem. Ind.* (London), 1317 (1959).

(6) (a) R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958); (b) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960); (c) see also R. Joly and J. Warnant, *Bull. soc. chim. France*, **28**, 569 (1961), who described the synthesis 4-fluoro steroids from steroidal 3-enamines subsequent to the completion of this work.

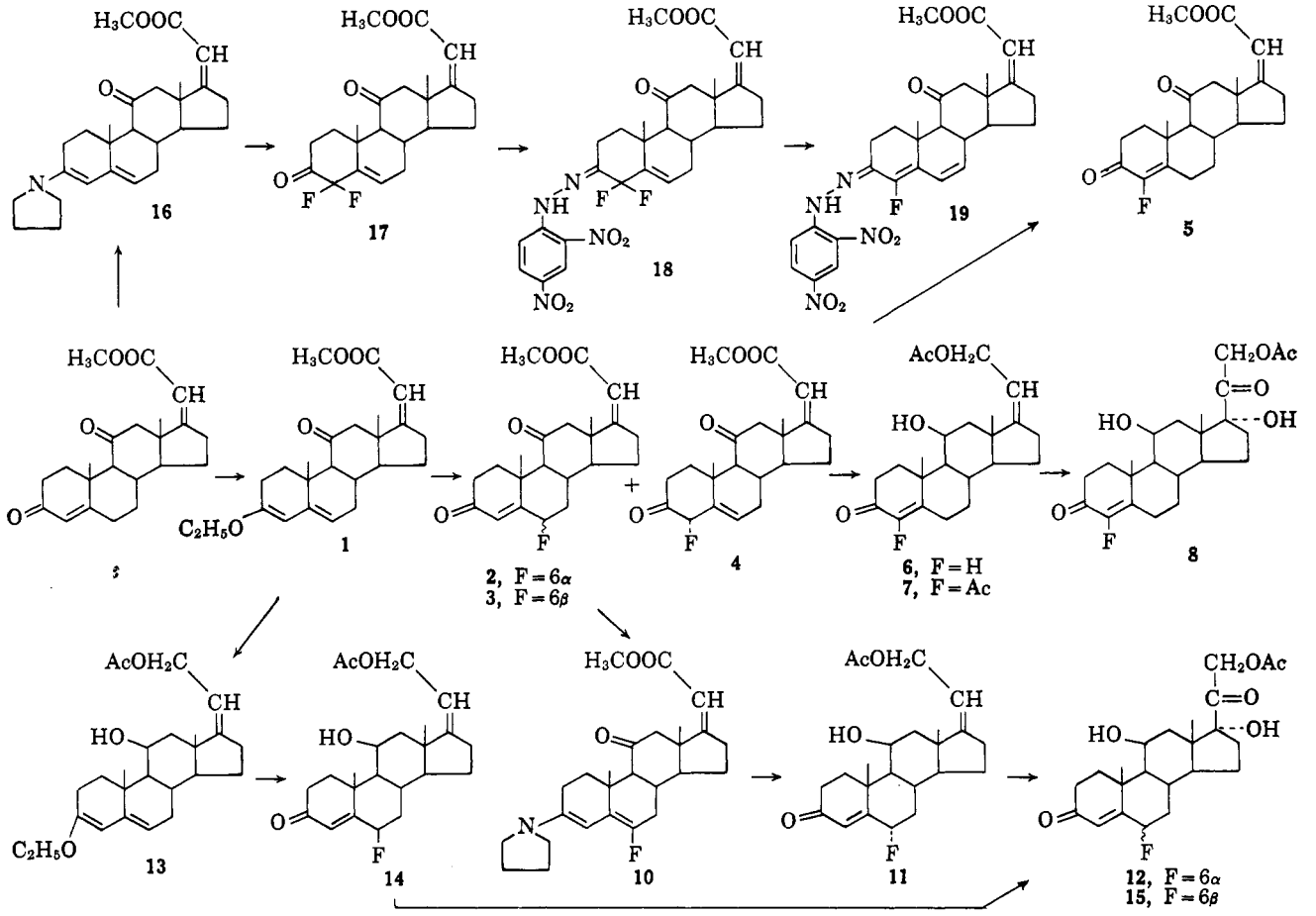
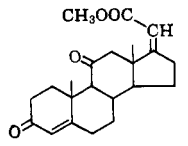
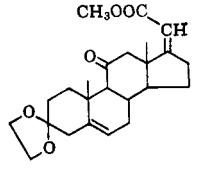
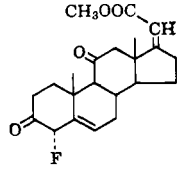
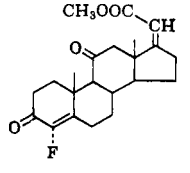
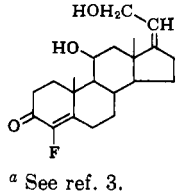



TABLE I

| Compd. | $\lambda_{max}^{EtOH}$, mμ (ε) | $\nu_{max}^{Nujol}$ (C=O region) |
|---|---|---|
|  | 233 (24,375)[a] | 1715, 1689, 1675–1660 |
|  | 225 (13,525)[a] | 1705, 1695 |
|  | 222 (13,050) | 1739, 1710, 1705 |
|  | 237 (20,000) | 1720, 1708, 1690 |
|  | 249 (14,750) | 1690 |

[a] See ref. 3.

corticoid side chain was imperative. Gas–liquid chromatography (g.l.c.) proved an ideal analytical tool after paper chromatography and thin layer chromatography had failed.[7] 4-Fluoro-11β,21-dihydroxy-4,17(20)-*cis*-pregnadien-3-one (**6**) was obtained free from 6-fluoro and difluoro impurities (as shown by g.l.c.) by a countercurrent extraction process using 600 transfers and a system composed of Skellysolve B, benzene, water, and acetone. Acylation of **6**, thus purified, followed by treatment with osmium tetroxide–N-methylmorpholine oxide peroxide[8] afforded 4-fluorohydrocortisone acetate (**8**) in low yield.

Preliminary biological assay of 4-fluorohydrocortisone acetate (**8**) indicated that this compound possessed a low order of antiinflammatory activity.

The mixture of methyl 6α- and 6β-fluoro-3,11-diketo-4,17(20)-*cis*-pregnadien-21-oates (**2** and **3**), obtained as described above, when treated with acid was converted to the pure 6α-fluoro compound (**2**). Reduction of the 11-keto function, after blocking of the 3-ketone as the enamine, gave after acylation 6α-fluoro-21-acetoxy-11β-hydroxy-4,17(20)-*cis*-pregnadien-3-one (**7**) in good yield. In practice the mixture of 6α- and 6β-fluoro steroids **2** and **3** was not separated or isomerized but the crude product was used in the reduction sequence. Following removal of the blocking group and acylation pure 6α-fluoride **7** was then isolated. Oxidative hydroxylation of **11** with phenyl iodosoacetate or N-methylmorpholine oxide peroxide

(7) The authors are indebted to Dr. N. A. Nelson of these laboratories for his assistance in the g.l.c. of these steroids.

(8) W. P. Schneider and A. R. Hanze, U. S. Patent 2,769,823 (Nov. 6, 1956).

afforded 6α-fluorohydrocortisone acetate (**12**). In an alternative synthesis of 6α-fluorohydrocortisone acetate from **1**, the fluorination and reduction steps were reversed. Thus, the enol ether **1** was reduced, and the product acylated to yield **13** which when treated with perchloryl fluoride gave 6β-fluoride **14**. Introduction of the 17 and 20 oxygen functions in the usual manner afforded 6β-fluorohydrocortisone acetate **15** whose isomerization to 6α-fluorohydrocortisone acetate was previously recorded.[1,9]

Finally the reaction of the 3-pyrrolidyl enamine of methyl 3,11-diketo-4, 17(20)-*cis*-pregnadien-21-oate-(**16**)[3] with perchloryl fluoride was investigated in the quest for 6-fluorinated steroids. The only product isolated was methyl 4,4-difluoro-3,11-diketo-5,17(20)-*cis*-pregnadien-21-oate (**17**), which proved to be in accord with subsequent reports of the action of perchloryl fluoride on enamines of 3-keto-$\Delta^4$ steroids.[4,10] The 2,4-dinitrophenylhydrazone of **17**, when treated with acetic acid, was dehydrohalogenated to the monofluoro steroid (**19**).

## Experimental[11]

**Methyl 3-Ethoxy-11-keto-3,5,17(20)-*cis*-pregnatrien-21-oate (1).**[12]—A solution of 1.5 g. of methyl 3,11-diketo-4,17(20)-*cis*-pregnadien-21-oate,[3] 300 mg. of *p*-toluenesulfonic acid monohydrate, and 25 ml. of ethyl orthoformate was heated under reflux for 1.5 hr. The excess orthoformate was removed by distillation *in vacuo*, and the residue was dissolved in benzene. After washing with sodium bicarbonate solution and drying, the solvent was removed to yield 1.47 g. of crystalline residue. Recrystallization from acetone–Skellysolve B[13] afforded 0.78 g. of **1**, m.p. 165–170°, $[\alpha]_D$ −69° (acetone).

*Anal.* Calcd. for $C_{24}H_{32}O_4$: C, 74.96; H, 8.40. Found: C, 74.57; H, 8.46.

**Methyl 6α- and Methyl 6β-Fluoro-3,11-diketo-4,17(20)-*cis*-pregnadien-21-oate (2 and 3).**—Methyl 3-ethoxy-11-keto-3,5,17-(20)-*cis*-pregnatrien-21-oate (4.0 g.) was dissolved in 200 ml. of pyridine and, after cooling to 0 to −5°, perchloryl fluoride was bubbled through the solution for 5 min. The reaction mixture was distilled to half-volume *in vacuo* and was poured into ice and dilute hydrochloric acid. The organic material was removed by extraction with ether. After washing with sodium bicarbonate and drying over sodium sulfate, evaporation of the solvent *in vacuo* gave the crude product as an oil. This oil was dissolved in 100 ml. of methylene chloride and chromatographed over Florisil[14] (150 g.) to yield two main fractions. The first fraction (which is the 6α-fluoro isomer) was eluted with 15% acetone–Skellysolve B, and after crystallization from methanol gave 250 mg. of **2**, m.p. 224–226° dec.; further crystallization from methanol gave raised m.p. 226–228° dec., $\lambda_{max}^{EtOH}$ 229 mμ (ε 27,900), $[\alpha]_D$ +178° ($CHCl_3$). The infrared spectrum of this compound is the same as that of an authentic sample of the 6α-fluoro isomer.[15]

*Anal.* Calcd. for $C_{22}H_{27}FO_4$: C, 70.60; H, 7.26; F, 5.07. Found: C, 69.88; H, 7.06; F, 4.16.

The second fraction eluted from the chromatogram with 20% acetone–Skellysolve B was crystallized from methanol to give 250 mg. of the 6β-isomer **3**, m.p. 155–160° dec., raised on further crystallization to 165–168° dec., $[\alpha]_D$ +88° ($CHCl_3$), $\lambda_{max}^{EtOH}$ 227 mμ (ε 23,100).

*Anal.* Calcd. for $C_{22}H_{27}FO_4$: C, 70.60; H, 7.26; F, 5.07. Found: C, 69.62; H, 7.58; F, 4.70.

The infrared spectrum of this compound is identical with the spectrum of the authentic 6β-fluoro isomer.[16] A subsequent run gave 52% of combined column fractions of 6α- and 6β-isomers.

**Methyl 4α-Fluoro-3,11-diketo-5,17(20)-*cis*-pregnadien-21-oate (4).**—Perchloryl fluoride was bubbled for 30 min. through a solution of 300 g. of methyl 3-ethoxy-11-keto-3,5(6),17(20)-*cis*-pregnatrien-21-oate in 7.5 l. of tetrahydrofuran and 1.8 l. of water cooled to 10°. The reaction mixture was evaporated *in vacuo*, until the solution became turbid, and at this point a crystalline product precipitated which was crude **4**. Further concentration of the mother liquor led to the crystallization of a mixture of methyl 6α- and 6β-fluoro-3,11-diketo-4,17(20)-*cis*-pregnadien-21-oate (**2** and **3**).

Thirty grams of crude **4** was dissolved in 270 ml. of boiling methylene chloride and clarified by filtration. The solution was concentrated to 200 ml. and 300 ml. of boiling acetone was added. Concentration was continued until crystals formed. The white crystals were collected by filtration and dried. The fluoride **4**, $[\alpha]_D$ −9° ($CHCl_3$), weighed 25.4 g. and melted at 202° dec.

*Anal.* Calcd. for $C_{22}H_{27}FO_4$: F, 5.07. Found: F, 5.02.

After five recrystallizations, material prepared in a similar manner had m.p. 208° dec.; $[\alpha]_D$ −21° ($CHCl_3$); $\lambda_{max}^{EtOH}$ 222 mμ (ε 13,050); $\nu_{max}^{Nujol}$ (C=O region) 1739, 1710, and 1705 cm.$^{-1}$.

*Anal.* Calcd. for $C_{22}H_{27}FO_4$: C, 70.56; H, 7.27; F, 5.07. Found: C, 70.60; H, 7.15; F, 5.09.

**Methyl 4-Fluoro-3,11-diketo-4,17(20)-*cis*-pregnadien-21-oate (5).**—A solution of 2 g. of methyl 4α-fluoro-3,11-diketo-5,17(20)-*cis*-pregnadien-21-oate (**4**) in 100 ml. of chloroform was cooled to 0–5°. Anhydrous hydrogen chloride was bubbled through the solution for 3 hr. The temperature was kept below 5°. The solution was washed with 10% potassium bicarbonate solution and water. The washes were combined and extracted with chloroform. The chloroform solutions were combined, dried over anhydrous sodium sulfate, and poured over a column of Florisil. The crystalline fractions, eluted with Skellysolve B containing increasing amounts of acetone, were combined and recrystallized twice from acetone to give **5**, $[\alpha]_D$ +176° ($CHCl_3$), which weighed 550 mg. and had m.p. 224.5–226.5°; $\lambda_{max}^{EtOH}$ 237 mμ (ε 20,200); $\nu_{max}^{Nujol}$ 1720, 1708, and 1690 cm.$^{-1}$.

*Anal.* Calcd. for $C_{22}H_{27}FO_4$: C, 70.57; H, 7.27; F, 5.07. Found: C, 70.58; H, 7.46; F, 4.90.

**4-Fluoro-11β,21-dihydroxy-4,17(20)-*cis*-pregnadien-3-one (6).**—To a heated solution of 20 g. of methyl 4α-fluoro-3,11-diketo-5,17(20)-*cis*-pregnadien-21-oate (**4**) in 400 ml. of benzene was added 380 mg. of *p*-toluenesulfonic acid monohydrate and 8.6 ml. of pyrrolidine under an atmosphere of nitrogen. Heating was continued until reflux temperature was reached and maintained for 1 hr., passing the condensate through a water trap. The solvent was then removed *in vacuo*. The solid residue was dissolved in 520 ml. of ether and 75 ml. of benzene. This solution was added slowly to a slurry of 6.2 g. of lithium aluminum hydride in 280 ml. of ether. After the addition was complete, the mixture was heated under reflux for 1 hr. Water (150 ml.) was added slowly and the organic solvent was removed *in vacuo*. Under an atmosphere of nitrogen, 640 ml. of methyl alcohol was added followed by 3 g. of sodium hydroxide in 60 ml. of water. After heating under reflux for 1 hr., the reaction mixture was cooled to room temperature and neutralized with glacial acetic acid. The methyl alcohol was removed *in vacuo* and 30 ml. of hydrochloric acid in 140 ml. of water was added. The mixture was extracted three times with methylene chloride; the extracts were washed with water, and dried over sodium sulfate. Chromatography over Florisil gave 1.3 g. of material in the 85% Skellysolve B–15% acetone fractions. The combined fractions were crystallized from acetone to give 800 mg. (4%) of **6**, melting at 170–172°, $\lambda_{max}^{EtOH}$ 249 mμ (ε 14,750). G.l.c. showed varying amounts of at least two impurities to be present. The retention time of **6** was 12.8 min. using a column of 1.5% SE-52 on purified and silanized Gas-Chrom P 100–200-mesh with column temperature of 240°.

*Anal.* Calcd. for $C_{21}H_{29}FO_3$: C, 72.38; H, 8.39. Found: C, 72.26; H, 7.92.

**Purification of 4-Fluoro-11β,21-dihydroxy-4,17(20)-*cis*-pregnadien-3-one (6).**—Three grams of crude **6** from above was subjected to countercurrent distribution in a 200-tube machine using a system composed of Skellysolve B, water, benzene, and acetone in a ratio of 4:4:1:16. After 200 transfers, analysis by g.l.c. showed that one component was well separated from the other

(9) G. B. Spero and J. A. Hogg, U. S. Patent 2,838,497 (1958), Example 9.

(10) S. Nakanishi, R. L. Morgan, and E. V. Jensen, *Chem. Ind.* (London), 1136 (1960); S. Nakanishi, *Steroids*, **2**, 765 (1963).

(11) Melting points were taken in capillary tubes and are uncorrected. Rotations were observed at 26°.

(12) The authors are indebted to Dr. P. F. Beal of these laboratories, who first prepared this compound.

(13) A saturated hydrocarbon fraction, b.p. 60–71°, available from Skelly Oil Co., Kansas City, Mo.

(14) A synthetic, magnesia–silica gel manufactured by the Floridin Co., Warren, Pa.

(15) Unpublished data of R. W. Jackson of these laboratories.

(16) Unpublished data of J. A. Campbell of these laboratories.

two components. This material (contained in the first 95 tubes) was removed. The emptied tubes were refilled with fresh solvent and 400 more transfers were made. Assay by g.l.c. once more showed the pure 4-fluorodienediol (**6**) to be in tubes 107–132. The solutions in these tubes were removed and combined. The organic solvents were removed by vacuum distillation and the solids were extracted with methylene chloride. The solvent was removed *in vacuo* and pure **6** was crystallized from acetone–Skellysolve B. It melted at 169.5–171°.

*Anal.* Calcd. for $C_{21}H_{28}FO_3$: F, 5.45. Found: F, 5.37.

**4-Fluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione 21-Acetate (8).**—To a solution of 800 mg. of 4-fluoro-11β,21-dihydroxy-4,17(20)-*cis*-pregnadien-3-one (**6**) in 2 ml. of pyridine was added 2 ml. of acetic anhydride. After standing at ambient temperature overnight, ice was added until the exothermic reaction ceased. Dilute hydrochloric acid was added. The acid mixture was extracted three times with methylene chloride. The combined extracts were washed with 10% potassium bicarbonate and water. The solvent was removed *in vacuo* after drying over sodium sulfate to afford the 21-acetate **8** (850 mg., 95% yield) which was used without purification. The noncrystalline **8** was dissolved in 34 ml. of *t*-butyl alcohol. Pyridine (1 ml.) was added followed by 2.75 mole equiv. of N-methylmorpholine oxide peroxide and 17 mg. of osmium tetroxide (added in 8.5 ml. of a 2.0-mg./ml. solution of *t*-butyl alcohol). After standing overnight at ambient temperature, a slight excess of a 1% sodium hydrosulfite solution was added. The solvent was removed *in vacuo*, and the residue was partitioned between dilute hydrochloric acid and methylene chloride. The layers were separated and the aqueous layer was extracted two more times with methylene chloride. The combined extracts were washed with water and dried over sodium sulfate. Chromatography over Florisil with Skellysolve B–acetone gave three crystalline fractions possessing a positive Tollens test and absorbing ultraviolet light. These fractions were combined and crystallized from ethyl acetate to yield 100 mg. of **8** with m.p. 190–193°, $\lambda_{max}^{EtOH}$ 248 mμ (ε 14,850).

The analytical sample prepared from similar material by recrystallization from ethyl acetate melted at 194–196°.

*Anal.* Calcd. for $C_{23}H_{31}FO_6$: C, 65.38; H, 7.40; F, 4.50. Found: C, 65.40; H, 7.65; F, 4.58.

**6α-Fluoro-11β,21-dihydroxy-4,17(20)-*cis*-pregnadiene-3-one 21-Acetate (11).**—A mixture of 6α- and 6β-isomers of methyl 6-fluoro-3,11-diketo-4,17(20)-pregnadien-21-oate (**2** and **3**), 8.0 g., was dissolved in 200 ml. of benzene in a flask fitted with a stirrer, Dean–Stark water trap, and and reflux condenser. Pyrrolidine, 3.5 ml., and toluenesulfonic acid monohydrate (200 mg.) were added and the mixture was stirred and heated under reflux for 45 min. The benzene and excess pyrrolidine were removed by distillation *in vacuo*. The crude enamine was taken up in 200 ml. of fresh benzene and added dropwise to a previously prepared suspension of 2.0 g. of lithium aluminum hydride in 500 ml. of anhydrous ether. The reaction mixture was stirred for 1 hr. at room temperature and then the excess lithium aluminum hydride was decomposed by the cautious addition of ethyl acetate and water, respectively. The ether and benzene were distilled from the mixture *in vacuo* and the residue was stirred in 200 ml. of methyl alcohol. The enamine moiety was removed by treating the methanol slurry at reflux for 1 hr. with 30 ml. of a 1:1 mixture of acetic acid and water. The mixture was distilled *in vacuo* to a thick slurry, cooled to 20°, and treated with a solution of 25 ml. of concentrated hydrochloric acid in 200 ml. of cold water. The crude product was extracted with methylene chloride, washed with water and saturated sodium bicarbonate solution, and dried over anhydrous sodium sulfate. The extract was concentrated to dryness by distillation *in vacuo*.

The residue was dissolved in 100 ml. of pyridine and was treated with 30 ml. of acetic anhydride overnight at room temperature. This mixture was poured into water and crushed ice, and extracted with methylene chloride. The extract was washed with water, ice-cold dilute hydrochloric acid, and finally with saturated sodium bicarbonate solution before drying over anhydrous sodium sulfate. The methylene chloride solution was chromatographed over 400 g. of Florisil. The column was developed with 200-ml. fractions of 5, 10, and 15% acetone in Skellysolve B, respectively. The product was eluted in the last two of ten fractions of 10% acetone in Skellysolve B and the first five fractions of 15% acetone in Skellysolve B. The peak, amounting to 2.86 g., was recrystallized from acetone and Skellysolve B to give 1.72 g., 20.6%, of **11**, m.p. 180–191°, $[\alpha]_D$ +135° ($CHCl_3$).

*Anal.* Calcd. for $C_{23}H_{31}FO_4$: C, 70.74; H, 8.00; F, 4.86. Found: C, 70.88; H, 8.26; F, 4.68.

**3-Ethoxy-11β,21-dihydroxy-3,5,17(20)-*cis*-pregnatriene 21-Acetate (13).**—Lithium aluminum hydride (17.0 g.) was suspended in 3.5 l. of ether and a solution of 100 g. of methyl 3-ethoxy-11-keto-3,5,17(20)-*cis*-pregnatrien-21-oate in 700 ml. of benzene was added with stirring over a period of 5 min. The reaction mixture was stirred at room temperature for 2 hr. The excess lithium aluminum hydride was decomposed by the cautious addition of ethyl acetate and water, respectively. The organic layer was decanted from the thick mass of inorganic salts and the latter was washed with ethyl acetate. After drying over anhydrous sodium sulfate, the organic phase was concentrated to dryness by distillation *in vacuo*. The crystalline residue, 95.0 g., melted at 105–120, and was not further purified. The entire crystalline mass was dissolved in 600 ml. of pyridine and was treated with 150 ml. of acetic anhydride at room temperature for 16 hr. The reaction mixture was poured into ice and water and allowed to stand for 1 hr. The product was extracted with methylene chloride and the extract was washed thoroughly with water and dried over anhydrous sodium sulfate. The extract was concentrated to dryness by distillation *in vacuo*. The residue was dissolved in 200 ml. of ether and diluted with 600 ml. of Skellysolve B. The solution was concentrated to a volume of approximately 350 ml. Crystallization started and the mixture was allowed to cool slowly to room temperature. The light yellow crystalline solid was collected by filtration. The yield was 56.0 g., 54%, m.p. 98–110°, $\lambda_{max}^{EtOH}$ 240 mμ (ε 19.726), $[\alpha]_D$ +17° ($CHCl_3$).

*Anal.* Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.74; H, 9.52.

**6β-Fluoro-11β,21-dihydroxy-4,17(20)-*cis*-pregnadien-3-one 21-Acetate (14).**—3-Ethoxy-11β,21-dihydroxy-3,5,17(20)-*cis*-pregnatriene 21-acetate (**13**), 20.0 g., was added to a solution of 8.0 g. of perchloryl fluoride in 1 l. of pyridine cooled to −20°. The reaction mixture was stirred for 5 min. at −20° to −15°. The mixture was poured into 1.2 l. of hydrochloric acid in 2 l. of ice and water. The product was extracted with methylene chloride and the extract was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The extract was concentrated to dryness by distillation *in vacuo*. The residue (17.1 g.) was redissolved in 400 ml. of methylene chloride and chromatographed over 1.2 kg. of Florisil. The column was eluted with 500 ml. portions of 10% acetone–Skellysolve B (**10**), 20% acetone–Skellysolve B (**12**), and 30% acetone–Skellysolve B (**6**). Fractions 14–20 gave 6.49 g. of **14** which was recrystallized from acetone and Skellysolve B to give 4.95 g. of **14**, m.p. 155–162°.

*Anal.* Calcd. for $C_{23}H_{31}FO_4$: C, 70.74; H, 8.00; F, 4.87. Found: C, 70.97; H, 8.08; F, 4.35.

**6β-Fluorohydrocortisone Acetate (15).**—6β-Fluoro-11β,21-dihydroxy-4,17(20)-*cis*-pregnadien-3-one 21-acetate (4.95 g.) was dissolved in 200 ml. of *t*-butyl alcohol. This solution was treated with 3 ml. of pyridine, 25 ml. of N-methyl morpholine oxide peroxide (titration of 42.0 ml. of 0.1 *N* sodium thiosulfate/ml.), and 9.9 mg. of osmium tetroxide (7.9 ml. of a solution containing 1.26 mg./ml.) for 20 hr. at room temperature. The reaction mixture was stirred with 140 ml. of 0.5% sodium hydrosulfite solution for 30 min. Magnesol,[17] 5 g., was added and the stirring was continued for 15 min. The mixture was filtered through a bed of Celite 45 and the bed was rinsed with hot *t*-butyl alcohol. The filtered solution of the product was concentrated by distillation *in vacuo* until the crude product precipitated. The mixture was extracted with methylene chloride and the extract was dried over anhydrous sodium sulfate.

The crude product, dissolved in approximately 200 ml. of methylene chloride, was chromatographed over 300 g. of Florisil. The product was eluted with 20% acetone in Skellysolve B. Crystalline fractions 15–22 inclusive, weighing 2.47 g., were combined and recrystallized from acetone and Skellysolve B to give a first crop of 1.9 g., 27.8%, m.p. 197–199°, $[\alpha]_D$ +112° ($CHCl_3$).

*Anal.* Calcd. for $C_{23}H_{31}FO_6$: C, 65.38; H, 7.39; F, 4.50. Found: C, 65.36; H, 7.63; F, 4.47.

**Methyl 4,4-Difluoro-3,11-diketo-5(6),17(20)-*cis*-pregnadien-21-**

(17) Synthetic magnesium silicate obtained from Waverly Chemical Co., Inc., 628 Waverly Avenue, Mamaroneck, N.Y.

oate (17).—Perchloryl fluoride was bubbled through a solution of 10 g. of methyl 3,11-diketo-4,17(20)-*cis*-pregnadien-21-oate 3-pyrrolidyl enamine (16) in 2 l. of dry benzene for 5 min. The reaction mixture was washed with saturated sodium bicarbonate solution. The solution was dried over anhydrous sodium sulfate and evaporated. The crude material, weighing 10 g., was crystallized from ethyl acetate. The crystals, melting at 212–214° and weighing 2.0 g. (21%), were collected by filtration. After two recrystallizations, the material had m.p. 228° dec., $\lambda_{max}^{EtOH}$ 224 mμ (ε 11,900).

*Anal.* Calcd. for $C_{22}H_{26}F_2O_4$: C, 67.33; H, 6.68; F, 9.68. Found: C, 67.13; H, 7.10; F, 9.1.

**Methyl 4,4-Difluoro-3,11-diketo-5(6)-*cis*-pregnadien-21-oate 3-(2,4-Dinitrophenylhydrazone) (18).**—A solution of 110 mg. of 2,4-dinitrophenylhydrazone in 3 ml. of 30% perchloric acid was added to a solution of 200 mg. of (17) in 60 ml. of 95% ethyl alcohol. The mixture was stirred for 90 min., crystals forming within 10 min. The orange crystals, weighing 200 mg. (65%) and melting above 360°, were collected by filtration. Ultraviolet absorptions were at 260 mμ (ε 14,750) and 351 (25,500).

**Methyl 4-Fluoro-3,11-diketo-4,6,17(20)-*cis*-pregnadien-21-oate 3-(2,4-Dinitrophenylhydrazone) (19).**—A solution of 50 mg. of 2,4-dinitrophenylhydrazone (18) in 20 ml. of glacial acetic acid was heated under reflux for 15 min. Crystals formed after concentration to 10 ml. The red product, weighing 30 mg. (19) and melting at 305° dec., showed the following ultraviolet absorptions: $\lambda_{max}^{CHCl_3}$ 269 mμ (ε 16,150), 296 (12,500), 309 (15,400), and 392 (39,450).

*Anal.* Calcd. for $C_{28}H_{29}FN_4O_7$: F, 3.2. Found: F, 3.3.

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# Geometric Isomers of 2,3-Dimethyl-5-aryl-2,4-pentadienoic Acids. The Steric Factors Favoring 2-*cis* Formation

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The n.m.r. data for the 2-*cis*-4-*trans*- and 2,4-di-*trans*-2,3-dimethyl-5-aryl-2,4-pentadienoic acids and their esters (IV and V) and the nonconjugated isomeric acid (VI) and mixtures thereof have been analyzed and used to determine the relative amounts of the isomers obtained in the formation and dehydration of the Reformatsky product (II). The preponderance of 2-*cis* isomer (45%) over 2-*trans* (30%) and nonconjugated methylene acids (25%) is accounted for in terms of the relative overlap of the groups in the 2- and 3-positions in the transition complexes and in the resulting hydroxy esters. The result indicates less hindrance in the overlapping $CH_3$–$CH_3$ and R″–H groups in the transition complex VII leading to the *cis* isomer *via* E2 elimination from IX than in the overlapping $CH_3$–H and $CH_3$–R″ in VIII which leads to the *trans* isomer *via* X.

We have described tautomeric and geometric isomers of 3-methyl- and 3,4-dimethyl-5-aryl-2,4-pentadienoic acids and the n.m.r. techniques used in establishing their structures in preceding papers.[1–5] We wish at this time to describe the results of related studies of the 2,3-dimethyl-5-aryl-2,4-pentadienoic acids in which n.m.r. characteristics have been used to assign structures and to analyze the steric factors controlling the proportions in which they are formed.

The Reformatsky reaction of 4-aryl-3-buten-2-ones (I, aryl = phenyl, *p*-tolyl, *p*-chlorophenyl, *p*-methoxyphenyl) and ethyl α-bromopropionate gives β-hydroxy esters (II) in 74–86% yield. Dehydration with *p*-toluenesulfonic acid catalysis gives *cis–trans* mixtures (III) of the ethyl 2,3-dimethyl-5-aryl-2,4-pentadienoates along with the 3-methylene structures (VI) also formed in the 3,4-series. Alkaline saponification gives the *cis–trans* mixture of the acids from which the pure isomers (IV and V) were separated by fractional crystallization. The unfractionated mixture of dehydrated esters (for the phenyl series) contained 45% *cis*, 30% *trans*, and 25% methylene isomers as determined by the integrated areas of characteristic n.m.r. peaks associated with each isomer. The peaks at τ 4.79 and 4.86 (C-3 methylene protons of VI), at 7.87 and 7.95 (C-3 methyl protons *cis* to carbethoxy and C-2 methyl protons of IV), and at 8.09 and 8.04 (C-2 methyl protons and C-3 methyl protons *trans* to carbethoxy of V) were used.

The configurations of the acids in this series were assigned on the basis of the n.m.r. characteristics of their solutions in deuteriochloroform, pyridine, and piperidine.[3] The pyridine solutions are useful in that peaks associated with 3-methyl groups *cis* to carboxy groups are subjected to an enhanced deshielding effect which distinguishes the peak associated therewith from the 2-methyl peak. Pyridine obscures the C-4 and C-5 olefinic proton absorption which can, however, be observed in deuteriochloroform or piperidine solutions. With the data available for the pure acids, it is possible to make appropriate assignments to the peaks observed in mixtures of the esters and to determine the relative quantities of each present.

The n.m.r. data for the three acids in the phenyl series (IVa, Va, and VIa, R′ = H) are typical and will be summarized briefly. Complete data on the n.m.r. characteristics of the substituted products are given in Table I. The 2-*cis*-4-*trans* configuration (Va) is assigned to the acid, m.p. 130–131°, on the basis of peaks at τ 7.83 (C-2 methyl), 8.02 (C-3 methyl), 2.22 ($J$ = 16 c.p.s., C-4 proton), and 3.68 (J = 16 c.p.s., C-5 proton). The low-field doublet is assigned to the C-4 proton deshielded by the *cis* carboxy. The τ 8.02 peak is assigned to the C-3 methyl protons on the basis of its position, which is typical of that for methyl protons trans to a carboxyl group, and on the basis of splitting (in pyridine and in piperidine) into a doublet ($J$ = 1–2 c.p.s.) due to long-range coupling with the C-4 proton. Under these conditions the τ 7.83 peak shows

(1) R. H. Wiley, *J. Chem. Soc.*, 3831 (1958).
(2) R. H. Wiley, H. C. Van der Plas, and N. F. Bray, *J. Org. Chem.*, **27**, 1989 (1962).
(3) R. H. Wiley, T. H. Crawford, and C. E. Staples, *ibid.*, **27**, 1535 (1962).
(4) R. H. Wiley and C. E. Staples, *ibid.*, **28**, 3408 (1963).
(5) R. H. Wiley and C. E. Staples, *ibid.*, **28**, 3413 (1963).