After the addition of the ceramide III (0.0066 mole) dissolved in dry chloroform (20 ml.) had been completed in 5–10 minutes, the temperature was maintained at 0– +5° for 4–5 hours. The clear reaction mixture was transferred to a vigorously stirred solution of 5% barium hydroxide (in slight excess), and the temperature was allowed to rise slowly to 20°. After 30 minutes, the mixture was recooled to 10° and cold ether was added slowly. Stirring was continued for 1 hour at a final temperature of 20–25°. The upper layer was separated, washed several times with water and left overnight in the refrigerator. The bulky precipitate which separated was washed with a little cold acetone and ether and air-dried. Owing to the greater solubility of the unsaturated derivatives, it was found advantageous in this case to cool the solution to −10° for about 30 minutes before filtering off the precipitated barium salt.

The barium salts isolated were decomposed by shaking with a mixture of ether and dilute hydrochloric acid, and the residue obtained on evaporation of the ether solution was crystallized from methanol at room temperature, giving 50–60% yields of the β-chloroethylphosphates; infrared spectra: significant bands at 5.8 and 7.9 μ (benzoate), 6.0 and 6.6 μ (amide), 7.9, 10.3 and 11.5 μ (phosphate), 10.3 μ (*trans*-ethylenic —C=C—) 9.05, 9.15, 9.65, 9.75 μ.

**Quaternization.**—The conversion of the free phosphoric acids to the pure barium salts and subsequent preparation of the sphingomyelins was carried out by the previous method,[5,6] and the pure materials were isolated in yields of 60–70%.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX S. A., MEXICO, D. F., MEX.]

# Steroids. CLXXXVIII.[1] New Fluorination Procedures. Part 3.[2] *cis*-Addition of Fluorine to a Steroid Olefin. A New Route to 6α-Fluoro-Δ⁴-3-ketones[3]

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An *in situ* preparation of lead tetrafluoride from lead tetraacetate and anhydrous hydrogen fluoride has been utilized for the controlled fluorination of pregnenolone and pregnenolone acetate. *cis*-Addition of fluorine takes place to afford the corresponding 5α,6α-difluoro analogs. Their ready conversion into 6α-fluoroprogesterone represents a new route to the biologically important 6α-fluoro-Δ⁴-3-ketones. The addition of hydrogen fluoride to pregnenolone acetate and the reaction between hydrogen fluoride and pregnenolone are described.

It has recently been demonstrated that introduction of a 6α-fluoro substituent[4–15] to a series of steroid hormones favorably influenced biological activity. Previous approaches to these compounds had proceeded *via* (a) fission of a 5α,6α-epoxide with boron trifluoride etherate[4,5,7–11,13–16] or anhydrous hydrogen fluoride,[6,12,15] (b) *trans*-addition of BrF to a Δ⁵-3β-alcohol[17] or (c) perchloryl fluoride treatment of the derived enol ether[18] or enol acetate[19] of a Δ⁴-3-ketone.

All of these approaches afforded 6α-fluoro-Δ⁴-3-ketones primarily through their 6β-fluoro epimers. The direct introduction of a 6α-fluorine atom is now described *via* the *cis*-addition of fluorine to a Δ⁵-olefin.

The addition of fluorine to carbon–carbon double bonds has found very little application because of the extremely vigorous and uncontrolled nature of the interaction of fluorine with both carbon–carbon and carbon–hydrogen bonds. Even dilution of fluorine with nitrogen or carbon dioxide and carrying out the reaction at low temperatures has had only very limited success.[20] Only in perhalogenated olefins has it been possible to effect the addition of fluorine to a double bond.[21] However in many instances chlorofluoroalkenes are fluorinated with addition, substitution and disproportionation taking place.[22] The controlled addition of fluorine to olefins thus posed an interesting problem.

An attractive approach appeared to be in a study of the potential of lead tetrafluoride for reactions of this type. In 1947, lead tetrafluoride was reported to be unsatisfactory as a fluorinating agent for hydrocarbons in the vapor phase,[23] but slightly prior to this work Henne and Waalkes showed that an *in situ* preparation of $PbF_4$ from $PbO_2$ and

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(5) A. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, **80**, 4423 (1958).

(6) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson and J. A. Campbell, *Chemistry & Industry*, 1002 (1958).

(7) J. S. Mills, A. Bowers, C. Casas Campillo, C. Djerassi and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 1264 (1959); **82**, 3399 (1960).

(8) J. A. Edwards, A. Zaffaroni, H. J. Ringold and C. Djerassi, *Proc. Chem. Soc.*, 87 (1959).

(9) A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959).

(10) A. Bowers, E. Denot, M. B. Sánchez and H. J. Ringold, *ibid.*, **7**, 153 (1959).

(11) J. A. Edwards, H. J. Ringold and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3156 (1959); **82**, 2318 (1960).

(12) W. P. Schneider, F. H. Lincoln, G. B. Spero, H. C. Murray and J. L. Thompson, *ibid.*, **81**, 3167 (1959).

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(16) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4765 (1957).

(17) A. Bowers, *J. Am. Chem. Soc.*, **81**, 4107 (1959).

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

(19) B. M. Bloom, V. V. Bogert and R. Pinson, Jr., *Chemistry & Industry*, 1317 (1959).

(20) For a recent summary see A. M. Lovelace, D. A. Rausch and W. Postelnek, "Aliphatic Fluorine Compounds," Amer. Chem. Soc. Monographic Series, Reinhold Publishing Corp., New York, N. Y., 1958, pp. 20–23.

(21) *Cf.* the addition of fluorine to $CCl_2{=}CCl_2$ at −80° to give $CFCl_2{\cdot}CFCl_2$; W. Bockemüller, *Ann.*, **506**, 20 (1933).

(22) W. T. Miller, *J. Am. Chem. Soc.*, **62**, 341 (1940), and W. T. Miller, R. L. Ehrenfeld, J. M. Phelan, M. Prober and S. K. Reed, *Ind. Eng. Chem.*, **39**, 401 (1947).

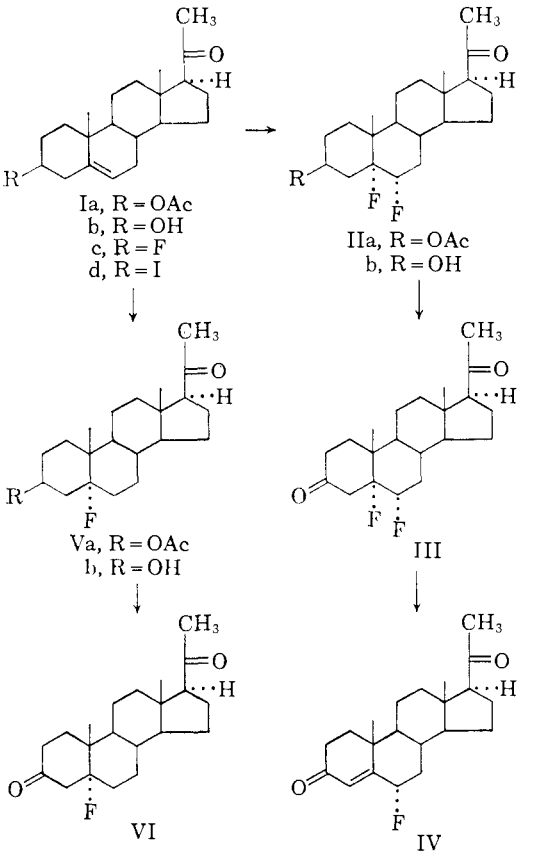
(23) R. D. Fowler, H. C. Anderson, J. M. Hamilton, Jr., W. B. Burford III, A. Spadett, S. B. Bitterlich and I. Litant, *Ind. Eng. Chem.*, **39**, 343 (1948).

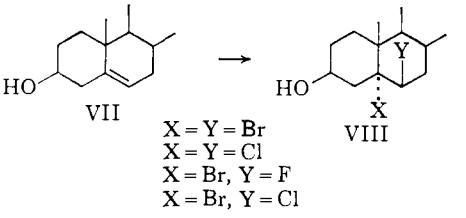
anhydrous hydrogen fluoride could be used to add fluorine to halogenated olefins.[24]

The only attempt to fluorinate a monohalogenated olefin appears to be due to Dimroth and Bockemüller[25] who treated 1,1-diphenylethylene with an *in situ* preparation of $PbF_4$ derived from lead tetraacetate and hydrogen fluoride. They obtained a difluoro compound which was later shown[26] to be 1,1-difluoro-1,2-diphenylethane, the reaction being accompanied by a molecular rearrangement.

Our initial experiments were directed toward the fluorination of pregnenolone acetate (Ia) and, after a certain amount of experimentation with respect to the reaction time, temperature and solvent systems, it was found that treatment of Ia in dry methylene dichloride with an excess of lead tetraacetate and anhydrous hydrogen fluoride for 15 minutes at −75° led after chromatography to a difluoro compound (IIa) in 27% yield together with a 63% recovery of pregnenolone acetate (Ia). Longer reaction times or higher temperatures did not afford a higher yield of IIa; instead a new product was obtained in low yield which appears to be formed as the result of a molecular rearrangement (see Experimental section). The difluoro compound IIa gave a correct analysis for $C_{23}H_{34}O_3F_2$ and exhibited bands in the infrared at 1733 and 1704 cm.$^{-1}$ characteristic of the 3β-acetoxy and C-20 carbonyl groups. Mild alkaline hydrolysis of IIa afforded the corresponding 3β-alcohol IIb which was also obtained by treatment of Δ⁵-pregnene-3β-ol-20-one (Ib) with the same *in situ* preparation of lead tetrafluoride. Oxidation of IIb with an excess of 8 *N* chromic acid[27] led to the C-3 ketone III. The structure and stereochemistry of the difluoro compound II then became clear when it was observed that treatment of III with sodium acetate in methanol under reflux for 3 hours led smoothly to 6α-fluoroprogesterone (IV) identical in every respect with an authentic sample.[4] This result is only compatible with the formulation of III as 5ξ,6α-difluoropregnane-3,20-dione since 6β-fluoro-Δ⁴-3-ketones are known[17] to be stable to the conditions of this β-halo ketone elimination reaction. It followed therefore that the C-6 fluorine atom in III and hence in II had the α-configuration. It only remained therefore to establish the stereochemistry of the fluorine atom at C-5.

Considerable experience has been obtained during the past ten years concerning the stereochemistry of halogen and mixed halogen addition to Δ⁵-olefins[28] and it is clear that when an ionic mechanism operates the product is always the *trans*-diaxial dihalide (5α,6β) (*cf.* VII→VIII). No instance of a 5β,6α-orientated addition of halogen to a Δ⁵-double bond has been reported; this would require diequatorial addition (with respect to ring B) and consequently a very unfavorable transition state.[29] *cis*-Addition to this double bond is governed mainly by steric factors. Osmium tetroxide, for example, affords in good yield the 5α,6α-diol[30] and *cis*-addition of chlorine using phenyl iodosodichloride[31] gives the 5α,6α-dichloro compounds.




On the basis of these analogies, the fluorine atom at C-5 was assigned the α-configuration.

Mechanistically the reaction is readily rationalized as proceeding through a cyclic transition state (IX→X). This reaction which represents the first example of the controlled addition of fluorine to a non-halogenated olefin may very well exemplify a general type for which the only necessary requirements are that two fluorine atoms should be attached to a central atom which is itself capable of undergoing reduction through two valency states. One other reagent which satisfies these

(24) A. L. Henne and T. P. Waalkes, *J. Am. Chem. Soc.*, **67**, 1639 (1945); **68**, 496 (1946); see also A. L. Henne and T. H. Newby, *ibid.*, **70**, 130 (1948).

(25) O. Dimroth and W. Bockemüller, *Ber.*, **64**, 516 (1931).

(26) J. Bornstein and M. R. Borden, *Chemistry & Industry*, 441 (1958).

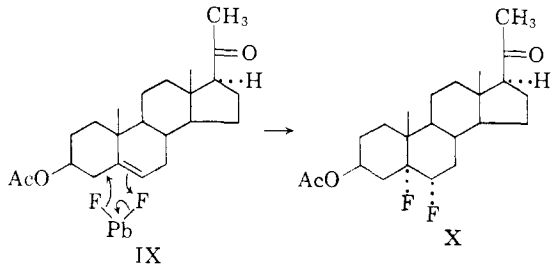
(27) A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(28) For recent summaries *cf.* ref. 2 and C. W. Shoppee, M. E. H. Howden and R. Lack, *ibid.*, 4874 (1960).

(29) *Cf.* D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

(30) V. Prelog and E. Tagmann, *Helv. Chim. Acta*, **27**, 1867 (1944).

(31) C. J. Berg and E. S. Wallis, *J. Biol. Chem.*, **162**, 683 (1946). D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, **72**, 370 (1950).




requirements is phenyl iodoso difluoride[32] and the effect of this reagent on a variety of steroid olefins is presently under investigation.

The addition of hydrogen fluoride to cyclic olefins is often complicated by the fact that the instability of monofluoroalkanes makes the reaction reversible. They are also difficult to purify since trace amounts of water or acid often result in their decomposition. It was noted that pregnenolone acetate (Ia) in methylene dichloride was not attacked by anhydrous hydrogen fluoride at low temperatures. However, when an organic proton acceptor such as tetrahydrofuran was added to increase the effective concentration of fluoride ion[33] a reaction product was obtained which afforded after chromatography in 12% yield a monofluoro compound (Va) which analyzed for $C_{23}H_{35}O_3F$. Mild hydrolysis of Va gave the 3β-alcohol Vb which underwent oxidation to the C-3 ketone VI. This latter compound readily eliminated the elements of hydrogen fluoride upon treatment under reflux with sodium acetate in methanol for 2 hours to afford progesterone identical in all respects with an authentic specimen. This reaction sequence clearly showed that hydrogen fluoride had added across the 5,6-double bond to furnish the 5-fluoro dihydro analog. This is in accord with expectation since it is well known that hydrogen chloride and hydrogen bromide add to $\Delta^5$-olefins to afford the 5-halo analogs.[34]

On this basis the C-5 fluorine atom was tentatively assigned the 5α-stereochemistry. When pregnenolone (Ib) was treated with anhydrous hydrogen fluoride in tetrahydrofuran under similar conditions to those described above for the acetate, no addition to the double bond resulted. Instead, substitution of the hydroxyl by fluorine occurred with retention of configuration to give 3β-fluoro-$\Delta^5$-pregnene-20-one (Ic) in 30.0% yield together with a 51.5% recovery of pregnenolone (Ib). This 3β-fluoro compound has previously been prepared by fluoride ion displacement of the corresponding 3β-iodo compound (Id)[35] and by the action of 40% hydrofluoric acid on the corresponding 6β-hydroxy-*i*-steroid.[36]

## Experimental[37]

**5α,6α-Difluoropregnane-3β-ol-20-one Acetate (IIa).**—A solution of pregnenolone acetate (Ia, 25.0 g.) in methylene dichloride (400 ml.) was chilled to −50° and added to a stirred mixture of hydrogen fluoride (55.0 g.), lead tetraacetate (80.0 g.) and methylene dichloride (200 ml.) at −75°. After 15 minutes at this temperature the mixture was poured into iced water (2.0 l.), neutralized with potassium carbonate, and the lead oxide was removed by filtration, the precipitate being washed well with methylene dichloride (200 ml.). The aqueous phase was separated and extracted with methylene chloride (2 × 500 ml.). The combined organic layer was washed with water, dried and evaporated. The residue was chromatographed in hexane–benzene (60:40) on washed alumina (1.0 kg.). Development and elution with the same solvent gave first recovered pregnenolone acetate (15.80 g.). On further elution there was obtained 7.55 g. of crude difluoro compound, m.p. 165–175°, which on crystallization from acetone–ether gave 4.64 g. of pure 5α,6α-difluoropregnane-3β-ol-20-one acetate (IIa), m.p. 178–180°, $[\alpha]_D$ +98.5°; $\nu_{max}$ 1733 and 1248 (ester), 1704 cm.$^{-1}$ (C=O).

*Anal.* Calcd. for $C_{23}H_{34}O_3F_2$: C, 69.67; H, 8.64; F, 9.58. Found: C, 70.11; H, 8.62; F, 9.11.

Under more forcing conditions (16 hr. at +5°), the reaction took a different course, affording an isomeric difluoro compound, m.p. 126–127° (from benzene), $[\alpha]_D$ +83°; $\nu_{max}$ 1734 and 1248 (ester), 1703 cm.$^{-1}$ (C=O).

*Anal.* Calcd. for $C_{23}H_{34}O_3F_2$: C, 69.67; H, 8.64; F, 9.58. Found: C, 70.26; H, 8.77; F, 8.55.[38]

**5α,6α-Difluoropregnane-3β-ol-20-one (IIb).** (a) **By Saponification of (IIa).**—5α,6α-Difluoropregnane-3β-ol-20-one acetate (IIb, 580 mg.) was dissolved in methanol (27.5 ml.) containing potassium hydroxide (275 mg.) and the solution was heated under reflux for 2 hours. After neutralizing with acetic acid the solution was concentrated to small bulk and poured into water. The crude product was collected and crystallized from acetone–hexane to give 330 mg. of 5α,6α-difluoropregnane-3β-ol-20-one (IIb), m.p. 222–224°. The analytical sample had m.p. 224–226°, $[\alpha]_D$ +88°, $\nu_{max}$ 3600 (OH) and 1704 cm.$^{-1}$ (C=O).

*Anal.* Calcd. for $C_{21}H_{32}O_2F$: C, 70.94; H, 9.07; F, 10.69. Found: C, 71.29; H, 9.29; F, 8.45.

(b) **By Reaction of Pregnenolone (Ib) with Lead Tetraacetate and Hydrogen Fluoride.**—A solution of pregnenolone (Ib, 5.0 g.) in methylene dichloride (100 ml.) was added to a stirred mixture of anhydrous hydrogen fluoride (13.0 g.) and methylene dichloride (50 ml.) containing lead tetraacetate (10.0 g.) at −75°. After 30 minutes at this temperature, the mixture was poured into water, neutralized with sodium carbonate and filtered. The precipitate of lead salts was washed well with methylene dichloride and the aqueous layers were extracted with methylene dichloride (2 × 100 ml.). The combined organic solutions were dried and evaporated. The residue was chromatographed in benzene on alumina (200 g.). Elution with benzene gave first recovered pregnenolone (Ib) (2.6 g., m.p. 182–187°). Further elution with benzene ether (80:20) and crystallization of the resulting material from acetone–hexane gave 1.02 g. of IIb, m.p. 218–220°. A recrystallized sample had m.p. 224–226°, $[\alpha]_D$ +88°, and was identical in all respects with that obtained in (a) above.

Under more forcing conditions (20 hr. at 0°) there was obtained an isomeric difluoro acetate, m.p. 194–196° (from acetone–ether), $[\alpha]_D$ +83°, $\nu_{max}$ 3600 (OH) and 1705 cm.$^{-1}$ (C=O).

(32) W. Bockemüller, *Ber.*, **64**, 522 (1931).

(33) R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, *J. Am. Chem. Soc.*, **78**, 4956 (1956).

(34) *Inter alia:* C. W. Shoppee and R. Lack, *J. Chem. Soc.*, 4864 (1960); T. Kon, *J. Chem. Soc.* (Japan), **64**, 405 (1943); Y. Urushibara and S. Mori, *ibid.*, **64**, 1285 (1943); H. Aebli, C. A. Grob and E. Schumacher, *Helv. Chim. Acta*, **44**, 774 (1958). In such instances the halogen atom has been assigned a 5α-configuration. For an X-ray study of 3β,5α-dichlorocholestane which confirms the α-orientation of the chlorine atom at C-5, *cf.* J. D. Bernal, D. Crowfoot and I. Fankucken, *Trans. Roy. Soc.* (London), **A239**, 135 (1940). For recent optical rotatory dispersion studies of 5α-halo-3-ketones *cf.* J. C. Jacquesy and J. Levisalles, *Chemistry and Industry*, 1310 (1961) and C. S. Barnes and C. Djerassi, *ibid.*, in press.

(35) T. N. Jacobsen and E. V. Jensen, *ibid.*, 172 (1957).

(36) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 4813 (1957).

(37) Melting points are uncorrected. Optical rotations were measured in chloroform solution at 25°. Ultraviolet absorption spectra were measured in ethanol using a Beckman DK2 spectrophotometer. Infrared absorption spectra were determined in potassium bromide disks on a Perkin–Elmer model 21 spectrometer equipped with sodium chloride optics. Alumina for chromatography was neutralized by heating under reflux in ethyl acetate for 6 hr. and reactivated by heating for 72 hours at 120°.

(38) In almost all instances we were unable to obtain sufficiently high values for fluorine analyses.

*Anal.* Calcd. for $C_{21}H_{32}O_2F_2$: C, 71.07; H, 9.03; F, 10.13. Found: C, 70.89; H, 9.12; F, 10.21.

Saponification of the isomeric difluoro acetate obtained from pregnenolone acetate (Ia) under similar conditions gave the same substance as above. This compound does not appear to be a 5,6-difluoro compound, since the corresponding diketone [m.p. 174–176° (from methylene dichloride–ether), $[\alpha]_D$ +73°, $\nu_{max}$ 1710 and 1715 cm.$^{-1}$ (C=O). *Anal.* Calcd. for $C_{21}H_{30}O_2F_2$: C, 71.55; H, 8.52; F, 10.70. Found: C, 71.19; H, 8.52; F, 10.70] obtained by oxidation with 8 *N* chromic acid gave neither 6α- nor 6β-fluoroprogesterone on attempted elimination with sodium acetate in methanol or hydrogen chloride in ethyl acetate.

**5α,6α-Difluoropregnane-3,20-dione (III).**—A solution of 5α,6α-difluoropregnane-3β-ol-20-one (IIb, 150 mg.) in acetone (40 ml.) was treated with a slight excess of 8 *N* chromium trioxide at 0°. After 2 minutes, the mixture was poured into water and the crude diketone III (120 mg.) was collected. After two recrystallizations from acetone–hexane it had m.p. 224–227°, $[\alpha]_D$ +80°.

*Anal.* Calcd. for $C_{21}H_{30}O_2F_2$: C, 71.55; H, 8.52; F, 10.70. Found: C, 71.29; H, 8.57; F, 9.42.

**6α-Fluoroprogesterone (IV).**—A solution of 5α,6α-difluoropregnane-3,20-dione (30 mg.) in methanol (3 ml.) containing sodium acetate (90 mg.) was heated under reflux for 3 hours. The cooled solution was poured into water (20 ml.) and the product, m.p. 134–139°, $\lambda_{max}$ 236 mμ, log ε 4.14, was collected. Recrystallization from acetone–hexane gave 6α-fluoroprogesterone (IV), m.p. 145–147°, $\lambda_{max}$ 236 mμ, log ε 4.16. A mixed melting point with an authentic sample[4] was undepressed and the infrared spectra were identical.

**5α-Fluoropregnane-3β-ol-20-one Acetate (Va).**—A cooled solution of pregnenolone acetate (Ia, 25.0 g.) in methylene dichloride (300 ml.) was added to a mixture of hydrogen fluoride (176.5 g.) and tetrahydrofuran (296 g.) at −75° and the solution was left at 0° for 20 hr. The mixture was poured into iced water (3.0 l.) and neutralized with sodium carbonate. The organic layer was separated and the aqueous phase was extracted with methylene dichloride (2 × 250 ml.). Evaporation of the dried organic extracts gave a semi-crystalline residue (24.8 g.) which was chromatographed in hexane–benzene (70:30) on alumina (750 g.). Elution with the same solvent mixture first gave recovered pregnenolone acetate (Ia) (18.2 g.), followed by mixed fractions (2.5 g.) and finally 5α-fluoropregnane-3β-ol-20-one acetate (Va), 2.2 g., m.p. 172–177°. Rechromatography of the mixed fractions gave a further 1.0 g. of Va. Recrystallization from acetone–methanol gave a total of 2.36 g., m.p. 194–196°, $[\alpha]_D$ +86°; $\nu_{max}$ 1733 and 1248 (acetate) and 1704 cm.$^{-1}$ (C=O).

*Anal.* Calcd. for $C_{23}H_{35}O_3F$: C, 72.97; H, 9.39; F, 5.09. Found: C, 73.06; H, 9.36; F, 4.04.

**5α-Fluoropregnane-3β-ol-20-one (Vb).**—A solution of the above acetate Va (420 mg.) in methanol (20 ml.) containing potassium hydroxide (200 mg.) was heated on the steam-bath for 2 hr. The cooled solution was neutralized with acetic acid, concentrated and poured into water. The precipitate of the 3β-alcohol Vb was collected, washed well with water and dried (360 mg., m.p. 178–180°). A recrystallized sample had m.p. 188–189°, $[\alpha]_D$ +105°, $\nu_{max}$ 3530 (OH) and 1704 cm.$^{-1}$ (C=O).

*Anal.* Calcd. for $C_{21}H_{33}O_2F$: C, 74.96; H, 9.88; F, 5.63. Found: C, 75.12; H, 9.80; F, 4.76.

**5α-Fluoropregnane-3,20-dione (VI).**—To a solution of 5α-fluoropregnane-3β-ol-20-one (290 mg.) in acetone (20 ml.) at 0° was added a slight excess of 8 *N* chromium trioxide in acetone. After 1 minute, the solution was poured into water and the dione VI was collected (245 mg., m.p. 200–203°). After two recrystallizations from acetone–hexane, the product had m.p. 204–205°, $[\alpha]_D$ +100°.

*Anal.* Calcd. for $C_{21}H_{31}O_2F$: C, 75.41; H, 9.34; F, 5.68. Found: C, 75.08; H, 9.04; F, 5.76.

**Treatment of 5α-Fluoropregnane-3,20-dione (VI) with Sodium Acetate.**—A solution of the 5α-fluoro-3,20-dione VI (50 mg.) in methanol (5.0 ml.) containing sodium acetate (150 mg.) was heated under reflux for 2 hr. It was then concentrated to small volume and diluted with water (50 ml.). Extraction with methylene dichloride (2 × 20 ml.) afforded a product which was dissolved in hexane–benzene (20:30) and adsorbed onto alumina (1.0 g.). Elution with hexane–benzene (50:50) (60 ml.) gave progesterone (27 mg., m.p. 112–119°) which after crystallization from methylene dichloride–hexane had m.p. 126–128°, $\lambda_{max}$ 240–242 mμ, log ε 4.22, and was identical in all respects with an authentic specimen.

**3β-Fluoro-Δ$^5$-pregnene-20-one (Ic).**—A solution of pregnenolone (Ib) (20.0 g.) in methylene dichloride (260 ml.) was cooled to −40° and added to a mixture of anhydrous hydrogen fluoride (167 g.) and tetrahydrofuran (281 g.) at −75°. The mixture was stirred at 6° for 18 hr., poured into iced water (3 l.) and neutralized with sodium carbonate. The aqueous layer was separated and extracted with methylene dichloride (2 × 250 ml.). The combined organic extracts were dried and evaporated. The residue was chromatographed in hexane–benzene (50:50) on alumina (500 g.). Elution with the same solvent pair gave first fractions of m.p. 145–155° (8.5 g.), then low melting material (m.p. 110–140°) and finally recovered pregnenolone (Ib, m.p. 185–189°, 9.2 g.). The first eluted fractions were rechromatographed on alumina (300 g.) in hexane–benzene (80:20) to give 6.1 g. of 3β-fluoro-Δ$^5$-pregnene-20-one (Ic), m.p. 161–162°, and a further 1.1 g. of recovered pregnenolone (m.p. 186–189°). Recrystallization of the 3β-fluoro-Δ$^5$-pregnene-20-one raised the m.p. to 167–168°, $[\alpha]_D$ +14°, $\nu_{max}$ 1705 cm.$^{-1}$ (C=O). Jacobson and Jensen[35] report m.p. 164–165°, $[\alpha]_D$ +14° and Shoppee and Summers[36] erroneously report m.p. 170–172°, $[\alpha]_D$ +114°.

# COMMUNICATIONS TO THE EDITOR

## THE USE OF REMOTE DEUTERATION FOR THE DETERMINATION OF COUPLING CONSTANTS AND CONFORMATIONAL EQUILIBRIA IN CYCLOHEXANE DERIVATIVES

*Sir:*

The application of high-resolution proton nuclear magnetic resonance (n.m.r.) to the study of conformational equilibria is often made difficult or impossible by the complexity of the spectra. For example, cyclohexanol[1] (see also Fig. 1) and its alkyl derivatives[2,3] and cyclohexyl halides[4] give a broad unresolved band for the tertiary ring proton (Hl) even though Hl is well chemically shifted from all the other protons in the molecule. It is therefore not possible to make full use of the difference in the magnitude of coupling constants which should exist[2,5] between *gauche* (a,e or e,e) and conformationally *trans* (a,a) vicinal protons.

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