

lithium aluminum hydride reduction of (+)- α -methyl- α -isopropylsuccinic acid (X)¹⁸ (our measurements: $[\alpha]_D +14.8^\circ$ (*c* 0.85 in methanol)).

Anal. Found: C, 65.34; H, 11.98.

Attempts to prepare a crystalline 3,5-dinitrobenzoate, α -naphthylurethan or diphenylurethan failed.

(+)- α -Methyl- α -isopropylglutaric Acid (XII).—To a stirred and ice-cold solution of 0.4 g. of sodium hydroxide in 50 cc. of water was added dropwise 0.3 cc. of bromine, the temperature being maintained below 10°. After stirring for 30 min., a slightly basic aqueous solution of 200 mg. of (+)-2-methyl-2-isopropyl-5-oxocaproic acid (VIIa) was added dropwise and the mixture was stirred until it had decolorized (4 hr.). The basic solution was steam distilled, the distillate was discarded, the residue was acidified and again steam distilled. The aqueous residual solution from the second steam distillation was saturated with sodium chloride and extracted continuously with ether. Drying and evaporation of the ether left a viscous liquid (63 mg.) of the crude glutaric acid, which resisted initial attempts at crystallization. For purposes of purification, the entire material was heated under reflux for 1 hr. with 15 cc. of acetic anhydride and the excess acetic anhydride and acetic acid were removed by distillation at atmospheric pressure. The brownish residue solidified upon cooling and was sublimed

(18) J. Porath, *Arkiv Kemi*, 1, 385 (1949).

twice at 60° (0.05 mm.) to yield 41 mg. of colorless (–)- α -methyl- α -isopropylglutaric anhydride (XII), m.p. 55–56°, $[\alpha]_D -6.1^\circ$ (*c* 0.99), $\lambda_{\max}^{\text{CHCl}_3}$ 5.56 and 5.67 μ (typical¹⁹ bands of a glutaric anhydride).

Anal. Calcd. for C₉H₁₄O₃: C, 63.51; H, 8.29. Found: C, 63.05; H, 8.51.

The solid anhydride was mixed in an evaporating dish with water and placed in an oven heated to 100°. After the water had evaporated, the container was cooled and the residue was recrystallized from ether–pentane to afford colorless crystals of (+)- α -methyl- α -isopropylglutaric acid (XII), m.p. 60–62°, $[\alpha]_D +8.7^\circ$ (*c* 0.8).

Anal. Calcd. for C₉H₁₆O₄: C, 57.43; H, 8.57. Found: C, 56.90; H, 8.42.

α -Isopropylglutaric Anhydride.—For the quasi-racemate studies (see Fig. 1), the following anhydride was prepared by the above procedure:

(–)- α -Isopropylglutaric acid (XIV)¹⁶ (m.p. 90–92°, $[\alpha]_D -13.1^\circ$ (*c* 1.13)) was transformed into (–)- α -isopropylglutaric anhydride (XV), which was purified by sublimation, m.p. 60–62°, $[\alpha]_D -11.2^\circ$ (*c* 1.17).

Anal. Calcd. for C₉H₁₂O₃: C, 61.52; H, 7.75. Found: C, 61.24; H, 7.59.

(19) G. Stork and R. Breslow, *THIS JOURNAL*, 75, 3291 (1953).

STANFORD, CALIF.

COMMUNICATIONS TO THE EDITOR

THE PREPARATION OF 9-FLUOROSTEROIDS

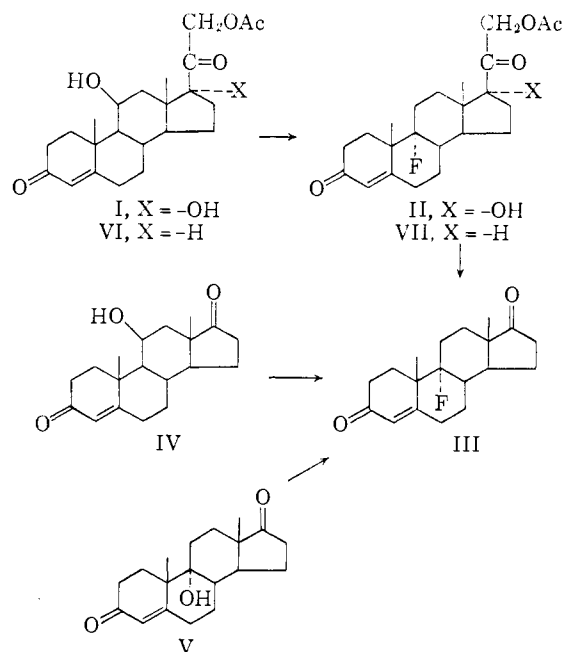
Sir:

In recent years a large number of 9 α -fluoro-11-oxygenated steroids have been prepared,¹ and the enhancement of the biological activity of the 11-oxygenated cortical hormones by a 9 α -fluoro group has been demonstrated clearly. However, no 9 α -fluoro-steroid devoid of further substitution in ring C has yet been reported. Here, we wish to report the preparation and properties of such steroids.

Treatment of 17 α -hydroxycorticosterone acetate (I) with a solution of hydrogen fluoride in pyridine (ca. 70% hydrogen fluoride by weight), and conversion of the $\Delta^9,11$ -olefin in the mixture to the 9,11 β -epoxide in the usual way,² gave, after chromatographic separation on silica gel, 9,11 β -epoxy-17-hydroxydeoxycorticosterone 21-acetate² and 9 α -fluoro-17-hydroxydeoxycorticosterone 21-acetate (II), m.p. 264–267°; $\lambda_{\max}^{\text{methanol}}$ 238 μ (ϵ 18,200); $[\alpha]_D +123^\circ$ (CHCl₃); (found: C, 67.73; H, 7.59; F, 4.5, 4.3). The fact that the fluorine was attached to the steroid nucleus and not to the side chain was demonstrated by the hydrolysis of I to 9 α -fluoro-17-hydroxydeoxycorticosterone, m.p. 235–238°; $\lambda_{\max}^{\text{methanol}}$ 238 μ (ϵ 17,100); $[\alpha]_D +105.5^\circ$ (CHCl₃); (found: C, 69.37; H, 7.78); which in turn was oxidized to 9 α -fluoro-4-androstene-3,17-dione (III), m.p. 227–228°; $\lambda_{\max}^{\text{methanol}}$ 237 μ (ϵ 17,800); $[\alpha]_D +158^\circ$ (CHCl₃); (found: C, 74.98; H, 8.26). 9 α -Fluoroandrostenedione (III) also could be obtained by treating either 11 β -

(1) J. Fried and A. Borman, "Vitamins and Hormones," Vol. XVI. Academic Press, Inc., New York, N. Y., 1958, p. 303.

(2) J. Fried and E. F. Sabo, *THIS JOURNAL*, 79, 1130 (1957).



hydroxyandrostenedione (IV) or 9 α -hydroxyandrostenedione³ (V) with the hydrogen fluoride–pyridine reagent. Compound III was not obtained from 11 α -hydroxyandrostenedione when treated under the same conditions as IV or V. It was formed slowly and only in very small quantities (paper chromatographic study) from 9(11)-dehydroandrostenedione. In fact, semi-quantitative paper chromatographic studies showed that

(3) R. M. Dodson and R. D. Muir, *ibid.*, 80, 6148 (1958).

the formation of III from 11 β -hydroxyandrostenedione could not have resulted primarily from an intermediate 9,11-olefin.

The structure of the 9 α -fluorosteroids was based on these considerations: (1) the biological activity of 9 α -fluorodeoxycorticosterone acetate (see below) suggested the presence of an intact steroid nucleus. (2) The molecular rotatory contribution of the fluorine ($\Delta M_D^{XF-H} -45$ to -93) corresponded to that found in other 9 α -fluoro-11- or 12-hydroxylated steroids ($\Delta M_D -24$ to -86).⁴ (3) The n.m.r. spectrum of III in deuteriochloroform with added tetramethylsilane as an internal standard showed no hydrogen on the carbon atom holding the fluorine (region from 150 to 352 cps. was free of resonance bands) and showed angular methyl resonances (56 and 80 cps.) within 2 cps. of those expected from 9 α -fluorosteroids.⁵

When corticosterone 21-acetate (VI) was treated with the hydrogen fluoride-pyridine reagent 9 α -fluorodeoxycorticosterone 21-acetate (VII), m.p. 188–190°, $\lambda_{\max}^{\text{methanol}}$ 238 (ϵ 17,900); $[\alpha]_D +169.5^\circ$ (CHCl₃); (found: C, 70.49; H, 7.83); was obtained. Compound VII is twelve times as potent in the sodium retaining assay as deoxycorticosterone acetate.⁶ This clearly indicates that the enhancement of hormonal activity by the introduction of a 9 α -fluoro group is not necessarily mediated through the inductive effect of the fluoro group on an adjacent oxygen function.¹ It seems more probable that the 9 α -fluoro group interferes with one of the normal metabolic mechanisms for the degradation of steroids, possibly with one involving 9-hydroxylation.^{3,7}

(4) J. Fried, J. E. Herz, E. F. Sabo and M. H. Morrison, *Chem. and Ind.*, 1232 (1950); and references given in reference 1.

(5) We are indebted to Dr. LeRoy F. Johnson of Varian Associates, Palo Alto, California, for the determination and interpretation of this spectrum.

(6) C. M. Kagawa and R. S. Jacobs, Jr., *Proc. Soc. Exptl. Biol. Med.*, **104**, 60 (1960).

(7) R. M. Dodson and R. D. Muir, *THIS JOURNAL*, **80**, 5004 (1958).

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RECEIVED MARCH 3, 1960

THE BIOLOGICAL HYDROXYLATION OF 9 α -FLUOROANDROSTENEDIONE

Sir,

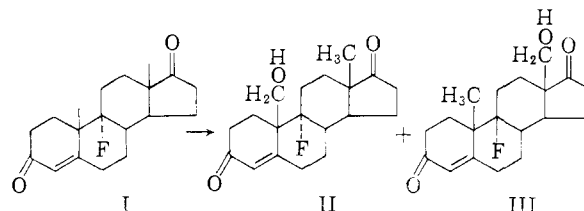
In order to provide further evidence for the position and configuration of the fluorine atom in 9 α -fluoro-4-androstene-3,17-dione (I),¹ an attempt was made to convert I to the known 9 α -fluoro-11 β -hydroxyandrostenedione² by perfusion of a solution in blood through surviving adrenal glands.³ However, none of the desired 11 β -hydroxylated material was isolated. Instead, two new monohydroxy-9 α -fluoro-4-androstene-3,17-diones were obtained: II, m.p. 238.5° dec., $\lambda_{\max}^{\text{ethanol}}$ 240 m μ (ϵ 15,300); $\lambda_{\max}^{\text{KBr}}$ 3.01, 5.74, 6.02, 6.18, 9.16, 9.42-

(1) C. G. Bergstrom and R. M. Dodson, *THIS JOURNAL*, **82**, 3479 (1960).

(2) R. H. Lenhard and S. Bernstein, *ibid.*, **77**, 6665 (1955).

(3) R. W. Jeanloz, H. Levy, R. P. Jacobsen, O. Hechter, V. Schenker and G. Pineus, *J. Biol. Chem.*, **203**, 453 (1953). We are indebted to Dr. James J. Carlo and The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts, for this perfusion.

9.48, 9.81 μ ; (found: C, 71.19; H, 7.74). III, m.p. 236–239°, slight dec.; $\lambda_{\max}^{\text{methanol}}$ 237 m μ (ϵ 15,100); $\lambda_{\max}^{\text{KBr}}$ 2.95, 5.78, 6.00, 6.20, 9.46, 9.73 μ ; $[\alpha]_D +134.8^\circ$ (CHCl₃); (found: C, 71.09; H, 7.73). Both compounds gave qualitative tests⁴ for the presence of fluorine.



The distillates obtained after treatment of compounds II and III with aqueous sodium hydroxide gave positive reactions with chromotropic acid⁵ indicating the presence of hydroxylated methyl groups in both steroids. A similar reaction was given by 19-hydroxyandrostenedione,⁶ but reactions run with 9 α -fluoro-11 β -hydroxyandrostenedione² or without the addition of steroid were negative. A study of the change in ultraviolet spectrum with time of III and of 9 α -fluoroandrostenedione (I) in 0.1 *N* ethanolic potassium hydroxide⁷ showed no dramatic shifts, but only a slight decrease in extinction coefficient. The hydroxyl group in III is, therefore, isolated from the 3-keto- Δ^4 -chromophore and should be at C₁₈. The molecular rotatory contribution of the new hydroxy group ($\Delta M_D^{18\text{OH-H}} -49^\circ$) is in good agreement with that calculated from 18-hydroxyestrone (-28°).⁵

The ultraviolet spectrum of II in 0.1 *N* ethanolic potassium hydroxide at zero time (approximately two minutes after preparing the solution) showed a maximum at 302 m μ (ϵ 17,400) and a point of inflection at 238 m μ (ϵ 5,850). After 24 hr. these changed to λ_{\max} 292 m μ (ϵ 4,770) and λ_{\max} 246 m μ (ϵ 9,250), respectively. Apparently, basic elimination of the 19-hydroxymethyl group occurred rapidly with concurrent elimination of the 9 α -fluoro group to form 19-nor-4,10(9)-androstadiene-3,17-dione, which, in the basic solution slowly equilibrated with the δ,ϵ -unsaturated isomer(s). Thus, the sodium hydroxide chromotropic acid test and the study of change of ultraviolet spectra in ethanolic potassium hydroxide not only provided strong evidence for the positions of the hydroxyl groups in II and III, but also lent confirmatory evidence for the 9 α -position of the fluoro group. The small bathochromic shift (2–3 *m μ*) associated with a 19-hydroxyl group is also noticed in a comparison of the ultraviolet spectra of 9 α -fluoro-19-hydroxy-4-androstene-3,17-dione (II) ($\lambda_{\max}^{\text{ethanol}}$ 240 m μ) and 9 α -fluoro-18-hydroxy-4-androstene-3,17-dione (III) ($\lambda_{\max}^{\text{methanol}}$ 237 m μ).⁵

(4) E. L. Bennett, C. W. Gould, B. H. Swift and C. Nizmann, *Anal. Chem.*, **19**, 1035 (1947).

(5) K. H. Løtse, G. F. Marrian and E. J. D. Watson, *Biochim. J.*, **71**, 43 (1959).

(6) A. S. Meyer, *Experientia*, **11**, 99 (1955); A. S. Meyer, M. Hayano, M. C. Lindberg, M. Gut and O. G. Rodgers, *Acta Endocrin.*, **18**, 148 (1955).

(7) A. S. Meyer, *J. Org. Chem.*, **20**, 1240 (1955).

(8) F. W. Kahnt, R. Neher and A. Wettstein, *Helv. Chim. Acta*, **38**, 1237 (1955).