lithium aluminum hydride reduction of (+)-α-methyl-α-isopropylsuccinic acid (X)[18] (our measurements: $[\alpha]_D$ +14.8° (*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 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° (*c* 0.99), $\lambda_{max}^{CHCl_3}$ 5.56 and 5.67 μ (typical[19] bands of a glutaric anhydride).

Anal. Calcd. for $C_9H_{14}O_3$: 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° (*c* 0.8).

Anal. Calcd. for $C_9H_{16}O_4$: 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° (*c* 1.13)) was transformed into (−)-α-isopropylglutaric anhydride (XV), which was purified by sublimation, m.p. 60–62°, $[\alpha]_D$ −11.2° (*c* 1.17).

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found; C, 61.24; H, 7.59.

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

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

STANFORD, CALIF.

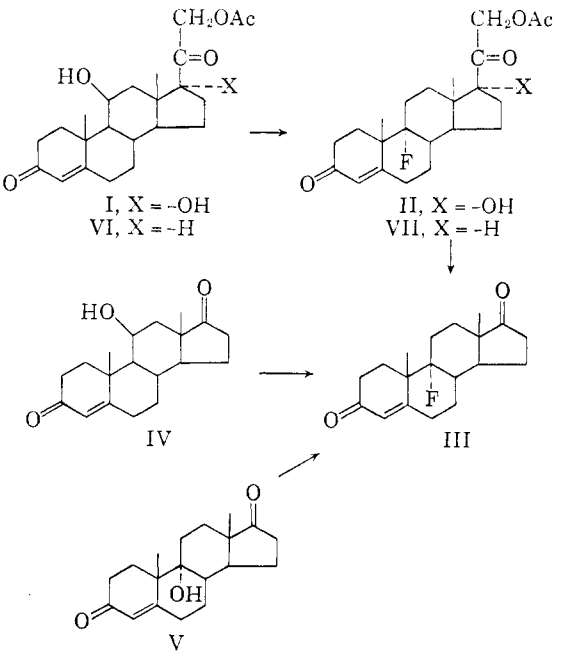
COMMUNICATIONS TO THE EDITOR

THE PREPARATION OF 9-FLUOROSTEROIDS

Sir:

In recent years a large number of 9α-fluoro-11-oxygenated steroids have been prepared,[1] and the enhancement of the biological activity of the 11-oxygenated cortical hormones by a 9α-fluoro group has been demonstrated clearly. However, no 9α-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 17α-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 9,11β-epoxide in the usual way,[2] gave, after chromatographic separation on silica gel, 9,11β-epoxy-17-hydroxydeoxycorticosterone 21-acetate[2] and 9α-fluoro-17-hydroxydeoxycorticosterone 21-acetate (II), m.p. 264–267°; $\lambda_{max}^{methanol}$ 238 mμ (ε 18,200); $[\alpha]_D$ +123° ($CHCl_3$); (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 9α-fluoro-17-hydroxydeoxycorticosterone, m.p. 235–238°; $\lambda_{max}^{methanol}$ 238 mμ (ε 17,100); $[\alpha]_D$ +105.5° ($CHCl_3$); (found: C, 69.37; H, 7.78); which in turn was oxidized to 9α-fluoro-4-androstene-3,17-dione (III), m.p. 227–228°; $\lambda_{max}^{methanol}$ 237 mμ (ε 17,800); $[\alpha]_D$ +158° ($CHCl_3$); (found: C, 74.98; H, 8.26). 9α-Fluoroandrostenedione (III) also could be obtained by treating either 11β-



hydroxyandrostenedione (IV) or 9α-hydroxyandrostenedione[3] (V) with the hydrogen fluoride–pyridine reagent. Compound III was not obtained from 11α-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

(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).

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

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

The structure of the 9α-fluorosteroids was based on these considerations: (1) the biological activity of 9α-fluorodeoxycorticosterone acetate (see below) suggested the presence of an intact steroid nucleus. (2) The molecular rotatory contribution of the fluorine (ΔM_D^{XF-H} -45 to -93) corresponded to that found in other 9α-fluoro-11- or 12-hydroxylated steroids (ΔM_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 9α-fluorosteroids.[5]

When corticosterone 21-acetate (VI) was treated with the hydrogen fluoride–pyridine reagent 9α-fluorodeoxycorticosterone 21-acetate (VII), m.p. 188–190°, $\lambda_{max}^{methanol}$ 238 (ϵ 17,900); $[\alpha]_D$ +169.5° ($CHCl_3$); (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 9α-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 9α-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 (1956); 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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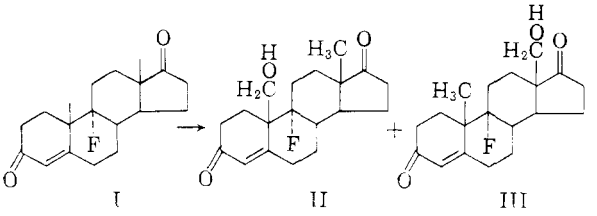
RECEIVED MARCH 3, 1960

THE BIOLOGICAL HYDROXYLATION OF 9α-FLUOROANDROSTENEDIONE

Sir.

In order to provide further evidence for the position and configuration of the fluorine atom in 9α-fluoro-4-androstene-3,17-dione (I),[1] an attempt was made to convert I to the known 9α-fluoro-11β-hydroxyandrostenedione[2] by perfusion of a solution in blood through surviving adrenal glands.[3] However, none of the desired 11β-hydroxylated material was isolated. Instead, two new monohydroxy-9α-fluoro-4-androstene-3,17-diones were obtained: II, m.p. 238.5° dec., $\lambda_{max}^{ethanol}$ 240 mμ (ϵ 15,300); λ_{max}^{KBr} 3.01, 5.74, 6.02, 6.18, 9.16, 9.42–9.48, 9.81 μ; (found: C, 71.19; H, 7.74). III, m.p. 236–239°, slight dec.; $\lambda_{max}^{methanol}$ 237 mμ (ϵ 15,100); λ_{max}^{KBr} 2.95, 5.78, 6.00, 6.20, 9.46, 9.73 μ; $[\alpha]_D$ +134.8° ($CHCl_3$); (found: C, 71.09; H, 7.73). Both compounds gave qualitative tests[4] for the presence of fluorine.



I II III

The distillates obtained after treatment of compounds II and III with aqueous sodium hydroxide gave positive reactions with chromotropic acid[5] indicating the presence of hydroxylated methyl groups in both steroids. A similar reaction was given by 19-hydroxyandrostenedione,[6] but reactions run with 9α-fluoro-11β-hydroxyandrostenedione[2] or without the addition of steroid were negative. A study of the change in ultraviolet spectrum with time of III and of 9α-fluoroandrostenedione (I) in 0.1 *N* ethanolic potassium hydroxide[7] 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 C_{18}. The molecular rotatory contribution of the new hydroxy group (ΔM_D^{18OH-H} $-49°$) 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 mμ (ϵ 17,400) and a point of inflection at 238 mμ (ϵ 5,850). After 24 hr. these changed to λ_{max} 292 mμ (ϵ 4,770) and λ_{max} 246 mμ (ϵ 9,250), respectively. Apparently, basic elimination of the 19-hydroxymethyl group occurred rapidly with concurrent elimination of the 9α-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 9α-position of the fluoro group. The small bathochromic shift (2–3 mμ) associated with a 19-hydroxyl group is also noticed in a comparison of the ultraviolet spectra of 9α-fluoro-19-hydroxy-4-androstene-3,17-dione (II) ($\lambda_{max}^{ethanol}$ 240 mμ) and 9α-fluoro-18-hydroxy-4-androstene-3,17-dione (III) ($\lambda_{max}^{methanol}$ 237 mμ).[8]

(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. Pincus, *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.

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

(5) K. H. Lo'te, G. F. Marrian and E. J. D. Watson, *Biochem. 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).