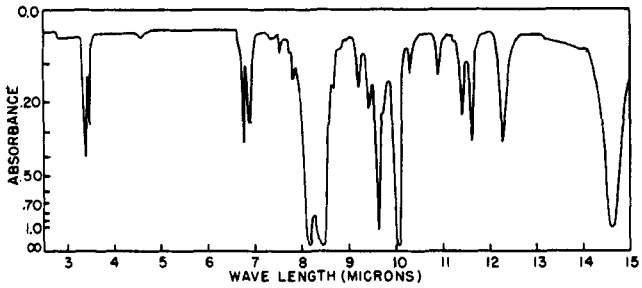


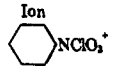
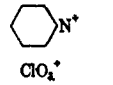

Fig. 1.—Infrared spectrum of liquid N-perchlorylpiperidine.

autocatalytic decomposition. Attempts to burn the pure compound during elemental analysis resulted in violent explosions and could only be carried out by first absorbing the compound on powdered alumina to desensitize it. Although the N-perchlorylpiperidine decomposes slowly at 25°, it may be stored indefinitely at −80°. The index of refraction ($n^{20}D$) of a freshly prepared sample is 1.4646.

*Anal.* Calcd. for $C_5H_{10}ClNO_3$: C, 35.8; H, 6.1; Cl, 21.2; N, 8.4; mol. wt., 167.6. Found: C, 37.4, 37.6; H, 8.8. 6.6; Cl, 21.2, 18.7; N, 9.1, 7.9; mol. wt., 169 (differential vapor pressure).

The above elemental analyses are only fair owing to instability of the compound; however, they do support the empirical formula. More positive evidence for the structure is provided by the mass cracking pattern of a freshly prepared sample (Table I). A

TABLE I

| m/e | Ion | Relative intensity |
|---|---|---|
| 167, 169 |  | 5.4/2.1 |
| 84 |  | 53.8 |
| 83, 85 | $ClO_4^+$ | 11.1/4.4 |

complex pattern below $m/e$ = 84 is similar to that observed for piperidine (API 618) and a relative intensity of 100 was assigned to mass peak 42.

The $-ClO_3$ group is bonded to the nitrogen as indicated by the infrared absorption spectrum and the absence of any N–H bond absorption at 2.7–3.0 μ. The major absorption peaks for the $-ClO_3$ group are found at 8.15, 8.42, and 14.63 μ. (See Fig. 1.)

The maximum yield to date of N-perchlorylpiperidine is 66% due to rapid hydrolysis of this compound by the basic solution in which it is formed. The hydrolysis products are being characterized now and will be reported on in a later publication.

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## Chloroethynyl Steroids. IV. The Synthesis of 16α-Fluoro-17α-chloroethynyl-4-androsten-17β-ol-3-one

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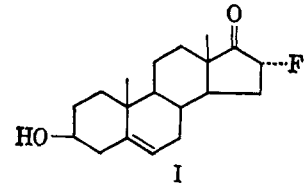
A possible rationale for the increased potency of the chloroethynylestrenones,[1] compared with the corresponding ethynylestrenones as inhibitors of pituitary gonadotrophin, is the acidification of the C-17β-ol owing to the inductive effect of the chlorine atom. It seemed possible that the substitution of additional electron-withdrawing groups around the C-17β-ol might lead to further increments in potency. In view of the ready availability of 16α-fluoro-5-androsten-3β-ol-17-one[2] (I) the synthesis of 16α-fluoro-17α-chloroethynyl-4-androsten-17β-ol-3-one (IV) appeared to provide an attractive test of this hypothesis.

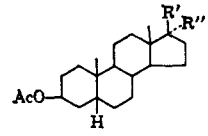
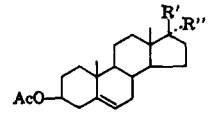
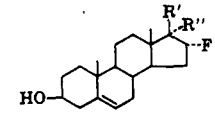
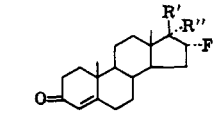


I

Chloroethynylation[3] of I afforded an approximately 2:3 mixture of II and III, which could be separated by crystallization. Jones[4] oxidation followed by acid-catalyzed isomerization of the Δ⁵-bond afforded the C-17 epimers, IV and V, of 16α-fluoro-17-chloroethynyl-4-androsten-17-ol-3-one.

The stereochemical assignments were made on the basis of rotation and the n.m.r. and infrared spectra of IV and V. Rotations[5] are summarized in Table I.

TABLE I

| Compd. | [M]D R′ = OH; R″ = C≡CX | [M]D R′ = C≡CX; R″ = OH | Δ[M]D |
|---|---|---|---|
|  | X = H −153° | X = H +97° | +250° |
|  | X = H −357° | X = H −94° | +263° |
|  | II, X = Cl −534° | III, X = Cl −136° | +398° |
|  | IV, X = Cl + 17° | V, X = Cl +496° | +479° |

The rotational evidence is satisfactory as far as the stereochemistry at C-17 is concerned, but does not exclude the possibility of epimerization of the C-16 fluorine during the chloroethynylation step. The later possibility appear rather remote since the mechanism of the epimerization would require formation of a Δ¹⁶-enolate which would resist chloroethynylation under the conditions of the reaction. Furthermore, long-range, spin–spin coupling between the protons at C-18 and fluorine at C-16β has been observed by Cross and Lan-

(1) J. H. Fried, T. S. Bry, A. E. Oberster, R. E. Beyler, T. B. Windholz, J. Hannah, L. H. Sarett, and S. L. Steelman, *J. Am. Chem. Soc.*, **83**, 4663 (1961).

(2) S. Nakanishi and E. Jensen, *J. Org. Chem.*, **27**, 702 (1962).

(3) H. G. Viehe, *Chem. Ber.*, **92**, 1950 (1959).

(4) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **12**, 1547 (1956).

(5) T. Reichstein and C. Meystre, *Helv. Chim. Acta*, **22**, 728 (1939).

dis.[6] In the present instance compounds I, IV, and V exhibited only a sharp singlet for the C-18 methyl at $\tau$ 8.95, 8.99, and 9.00.[7]

Examination of the infrared spectrum[8] of IV demonstrated the presence of both free and hydrogen-bonded hydroxyl at 3609 cm and 3390 cm.$^{-1}$. The latter disappeared after a *ca.* 50-fold dilution, indicating intermolecular hydrogen bonding for this compound. Compound V showed only a single peak at 3589 cm.$^{-1}$. The shift of 20 cm.$^{-1}$ with V compared with IV is in accord with the $\Delta\mu$ of 19 cm.$^{-1}$ observed by Schleyer and West[9] for intermolecular hydrogen bonding with a methanol–*n*-butyl fluoride system.

It is interesting to note that polarities could not be used with confidence for structure determinations in this series. Compounds II and III were not separated by silica gel, thin layer chromatography using ether–benzene (3:2) as the eluent. However, compounds IV and V showed the expected polarities, with IV slightly more polar than V [$\Delta R_f$ 0.08 on silica gel using ether–benzene (2:3) as the eluent].

Compounds IV and V were tested in the Merck Institute for Therapeutic Research.[10] Compound IV was 0.5 times as active as 21-chloroethisterone, s.c. (2.5 times ethisterone), in the Clauberg assay.[11] In the pituitary gonadotrophin inhibition test[12] IV was 0.2 times as active as Norlutin, s.c. Compound V was inactive in both assays.

### Experimental[13]

**16α-Fluoro-17α-chloroethynyl-4-androstene-3β,17β-diol (II) and 16α-Fluoro-17β-chloroethynyl-4-androstene-3β,17α-diol (III).**—A solution consisting of 3.84 g. of *cis*-1,2-dichloroethylene in 15 ml. of sodium-dried ether was added to a stirred solution consisting of 7.6 ml. of 1.30 *N* methyllithium in 15 ml. of sodium-dried ether maintained under 1 atm. of nitrogen and cooled by an ice bath. Stirring was continued for an additional 15 min. after removal of the ice bath, followed by the dropwise addition of 500 mg. of 16α-fluoro-Δ$^5$-androsten-3β-ol-17-one in 45 ml. of sodium-dried ether over a 5-min. period. After an additional 1.7 hr. the reaction mixture was poured into ice–water and ether. The ether layer was separated, washed with water, dried over potassium carbonate, and concentrated *in vacuo* to yield 614 mg. of an off-white foam. Crystallization from ether afforded 308 mg. of 16α-fluoro-17β-chloroethynyl-5-androstene-3β,17α-diol (III), m.p. ~185–238°. A sample for analysis, prepared in an analogous reaction with protection of the C-3β-ol as the tetrahydropyranyl ether, was crystallized several times from methanol, m.p. 255–256°, $[\alpha]_D$ −37°.

*Anal.* Calcd. for $C_{21}H_{25}ClFO_2$: C, 68.74; H, 7.69; F, 5.18. Found: C, 68.38; H, 7.54; F, 4.94.

Evaporation of the filtrate afforded a yellow gum which on crystallization from cyclohexane with a trace of methylene chloride yielded 225 mg. of 16α-fluoro-17α-chloroethynyl-5-androstene-3β,17β-diol (II), m.p. 100–105°. A sample for analysis was crystallized from benzene, m.p. 100–105°; $[\alpha]_D$ −145°.

*Anal.* Found: C, 69.28; H, 8.18; F, 4.80.

**16α-Fluoro-17α-chloroethynyl-4-androsten-17-β-ol-3-one (IV).**—To a stirred solution consisting of 1.0 g. of II in 50 ml. of acetone and maintained under 1 atm. of nitrogen was added 0.63 ml. of 8 *N* Jones[4] reagent. Stirring was continued for 5 min., followed by dilution of the reaction mixture with 200 ml. of ether. The ether suspension was washed with water, saturated aqueous sodium bicarbonate solution, and water, and then dried over potassium carbonate and concentrated *in vacuo* to yield 855 mg. of a colorless foam. The crude 3-keto Δ$^5$-steroid and 86 mg. of *p*-toluenesulfonic acid were dissolved in 25 ml. of acetone and left at room temperature overnight. The solution was concentrated to about 5 ml. *in vacuo*, diluted with ether, and washed with saturated aqueous sodium bicarbonate solution and water, dried over magnesium sulfate, and concentrated *in vacuo* to yield 825 mg. of a colorless foam. After setting aside 50 mg., the remainder was chromatographed on 47 g. of acid-washed alumina. Elution with benzene–ether (3:1) afforded 289 mg. of 16α-fluoro-17α-chloroethynyl-4-androsten-17β-ol-3-one (IV), double m.p. 100–105°, 166–169°. Three crystallizations from ethyl acetate afforded a sample for analysis: double m.p. 100–105°, 191–193°; $[\alpha]_D$ +47°; ultraviolet spectrum, $\lambda_{max}^{MeOH}$ 241 mμ (ε 16,600).

*Anal.* Calcd. for $C_{21}H_{26}ClFO_2$: C, 69.12; H, 7.18; F, 5.21. Found: C, 69.15; H, 6.87; F, 5.36.

**16α-Fluoro-17β-chloroethynyl-4-androsten-17α-ol-3-one (V).**—Starting with 1.50 g. of III, Jones oxidation and acid-catalyzed isomerization afforded 714 mg. of V. A sample for analysis was crystallized two times from ethyl acetate: m.p. 198–200°; $[\alpha]_D$ +136°; ultraviolet spectrum, $\lambda_{max}^{MeOH}$ 242 mμ (ε 16,950).

*Anal.* Found: C, 69.14; H, 7.10; F, 5.10.

(6) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 3784 (1962).

(7) N.m.r. spectra were taken in deuteriochloroform with a Varian HR-60 spectrometer. We are indebted to B. Arison and Dr. N. R. Trenner for these determinations.

(8) Infrared spectra were measured on a Perkin Elmer 421 spectrometer in $CCl_4$ solution. We are indebted to R. Walker for the infrared analysis.

(9) P. von R. Schleyer and R. West, *J. Am. Chem. Soc.*, **81**, 3164 (1959).

(10) We are indebted to Drs. S. L. Steelman and D. Patanelli for carrying out this determination.

(11) M. K. McPhail, *J. Physiol.* (London), **83**, 145 (1934).

(12) J. A. Epstein, H. S. Kupperman, and A. Cutler, *Ann. N. Y. Acad. Sci.*, **71**, 560 (1958).

(13) Melting points were taken on a micro hot stage and are corrected. Rotations were determined in chloroform at *ca.* 25° at a concentration of 7 mg./ml. We are indebted to A. Kalowski for the ultraviolet spectra and to R. Boos and his associates for the microanalysis herein reported.

## Synthesis of 4-(2-Methyl-5-isopropenyl-1-cyclopenten-1-yl)butan-2-one. A By-Product in the Synthesis of Pseudoionone

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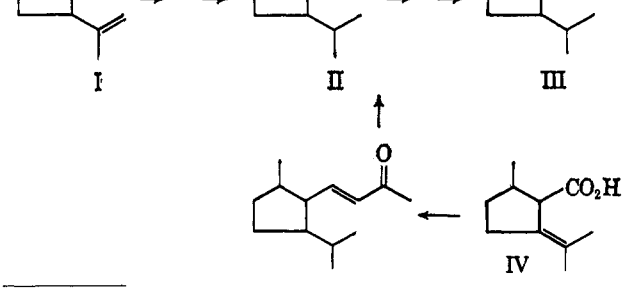
The thermal isomerization of dehydrolinalyl acetoacetate produces, in addition to the commercially valuable pseudoionone, an appreciable amount of a ketone $C_{13}H_{20}O$.[2-5] Kimel[3] and Saucy[5] identified this by-product as ketone I on the basis of a comparison of its degradation products II and III with authentic II and




(1) Participant in the National Science Foundation Undergraduate Research Program, summer, 1963.

(2) P. Teisseire, *Recherches* (Paris), **5**, 3 (1955).

(3) W. Kimel, N. W. Sax, S. Kaiser, G. G. Eichmann, G. O. Chase, and A. Ofner, *J. Org. Chem.*, **23**, 153 (1958).

(4) O. Isler, L. H. Chopard, W. Geux, G. Ryser, and G. Saucy, *Chimia* (Aarau), **11**, 103 (1957).

(5) G. Saucy, L. H. Chopard, W. Geux, G. Ryser, and O. Isler, *Helv. Chim. Acta*, **41**, 160 (1958).