sure to remove most of the solvent. The resulting product was extracted with ether (5 times) and benzene (7 times) and the aqueous layer was acidified with 10% hydrochloric acid (*p*H 5), was extracted with ether and benzene 3 times each. The organic solvent was distilled off under a reduced pressure and atrolactic acid was obtained as the residue; yield 0.27 g. (62%), α_D + 9.4° (*c* 12.6%).

Phenylglyoxylates of IVa (oil), IVb (m.p. 68–71°), VIIIa (m.p. 149–151°) and VIIIb (m.p. 182–185°), prepared as described above, were converted to atrolactic acid by the same procedure as 4,4-dimethylcholesteryl phenylglyoxylate and the results are summarized in Table II.

HONGO, BUNKYO-KU, TOKYO, JAPAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SYNTEX, S.A.]

Steroids. CXXVIII.[1] Synthesis of Halogenated Steroid Hormones: 6α-Fluoro-17α-acetoxyprogesterone and Some Unsaturated Analogs. A New Class of Highly Active Oral Progestational Hormones[2]

BY A. BOWERS, LAURA CUÉLLAR IBÁÑEZ AND H. J. RINGOLD

RECEIVED MAY 25, 1959

A synthesis of 6α-fluoro-17α-acetoxyprogesterone (V) from Δ⁵-pregnen-3β,17α-diol-20-one 3-formate 17-acetate (Ia) is described. Oxidation of V by a modified chloranil procedure led to the Δ⁶-dehydro analog VII. Selenium dioxide oxidation of V and VII afforded the corresponding Δ¹-dehydro compounds VI and VIII, respectively. Compounds V, VI, VII and VIII exhibited extremely high oral progestational activities.

The utility of oral progestational hormones such as 19-nor-17α-ethinyltestosterone[3] (Norlutin) and its Δ⁵⁽¹⁰⁾-isomer (Enovid)[4] in various gynecologic and obstetric dysfunctions and their possible mass application as oral contraceptive agents has stimulated considerable efforts to find cheaper and more effective compounds. In particular, it was desirable to find compounds which still retained the C-10 methyl group since the C-19 nor compounds are all derived from the relatively expensive ring A-aromatic compounds by a Birch reduction[5] process.

Spectacular success in this direction was achieved recently when it was reported independently from three laboratories that the oral progestational activity of 17α-acetoxyprogesterone[6,7] was remarkably increased by the introduction of a 6α-methyl group.[8–10] This activity was further enhanced by the introduction of an additional double bond at C-1[10] or C-6.[10]

It has been shown recently that the addition of a 6α-fluoro substituent[2,11–16] to a series of steroid hormones favorably influenced biological activity and it was clearly desirable therefore to prepare the 6α-fluoro analogs of 17α-acetoxyprogesterone and its Δ¹ and Δ⁶-dehydro analogs.[17]

A convenient starting material was Δ⁵-pregnen-3β,17α-diol-20-one 3-formate 17-acetate[6b] (Ia) which readily underwent preferential partial hydrolysis with methanolic potassium hydroxide to afford the 3β-alcohol Ib.[18] Peracid oxidation of Ib at 0° and direct crystallization of the product gave the 5α,-6α-epoxide II in good yield. This product then underwent diaxial cleavage of the epoxide ring upon treatment with boron trifluoride etherate[1,11,13–16,19] to afford the 6β-fluoro-5α-hydroxyfluorohydrin (III). Oxidation of III with 8 *N* chromic acid[20] led smoothly to the 3-ketone IV. In accord with previous experience[11,13–16] treatment of IV with anhydrous hydrogen chloride in acetic acid for four hours at 15–20° led to elimination of the 5α-hydroxyl group and concomitant inversion of the fluorine atom at C-6 to afford 6α-fluoro-17α-acetoxyprogesterone (V), λ_{max}^{EtOH} 236 mμ, ε 16,500. The stereochemistry of the fluorine atom followed from its stability to further treatment with acid[21] and the intensity of its maximum absorption at 236 mμ. 6β-Fluoro-Δ⁴-3-ketones have maximum ε values from 10,000 to 13,000.[22]

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(12) 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).

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

(15) A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron*, **5**, in press (1959).

(16) A. Bowers, E. Denot, M. Blanca Sánchez and H. J. Ringold, *ibid.*, **5**, in press (1959).

(17) For the activity of the 6-chloro progestational agents see ref. 1.

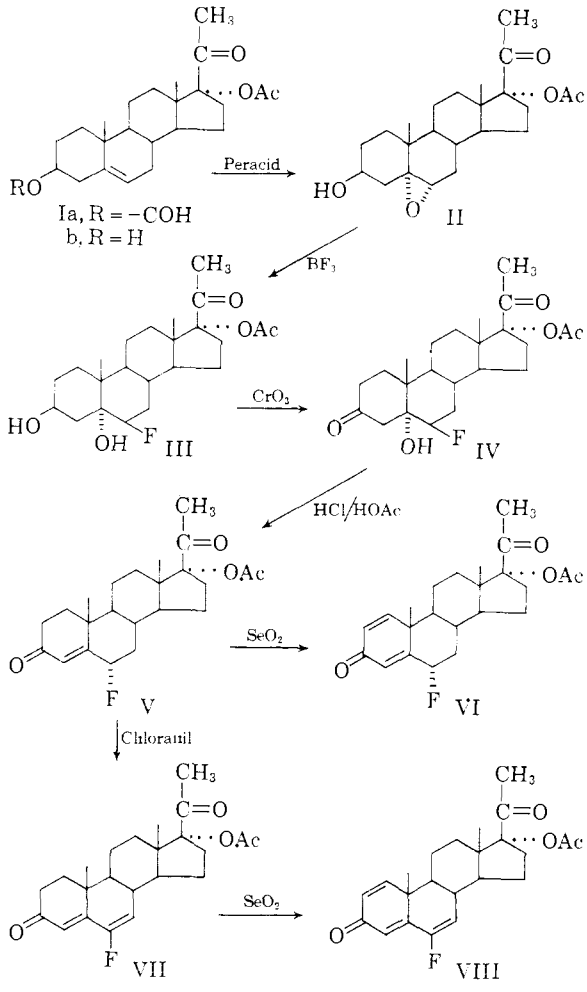
(18) H. J. Ringold, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **78**, 820 (1956).

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

(20) (a) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *ibid.*, 39 (1946); (b) A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *ibid.*, 2548 (1953).

(21) These conditions are known to epimerize 6β-fluoro-Δ⁴-3-ketones to their 6α-epimers; *cf.* refs. 11, 15 and 16.

(22) For a full discussion of the differences in ultraviolet light absorption properties and rotatory dispersion curves between 6α- and 6β-Δ⁴-3-ketone, *cf.* ref. 15.



Selenium dioxide oxidation[23] of V readily gave the $\Delta^{1,4}$-3-ketone VI, but the formation of the Δ^{6}-dehydro compound VII by treatment of V with chloranil[24] in boiling ethyl acetate containing 20% acetic acid proceeded only in poor yield. These conditions have been shown to convert testosterone acetate to 6-dehydrotestosterone acetate in 65% yield. However, when the ethyl acetate was replaced by *n*-amyl acetate, a reasonable yield of VII was obtained. Selenium dioxide oxidation of VII then led to the 6-fluoro-$\Delta^{1,4,6}$-3-ketone VIII.

Biological Activities.—The 6-fluoro-17-acetoxyprogesterone derivatives were compared to 19-nor-17α-ethynyltestosterone (activity = 1) in multi-dose Clauberg assays.[25] The activities recorded in Table I demonstrate that the progestational potency of 6α-fluoro-17α-acetoxyprogesterone is increased by double bond introduction at C-1 or at C-6 with the latter modification inducing the more pronounced effect.

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(24) E. J. Agnello and G. D. Laubach, THIS JOURNAL, **79**, 1257 (1957).

(25) Bioassays by the Endocrine Laboratories, Madison, Wisc.

TABLE I

Compound	Oral progestational activity[25]
19-Nor-17α-ethynyltestosterone[3]	1
6α-Fluoro-17α-acetoxyprogesterone	1
1-Dehydro-6α-fluoro-17α-acetoxyprogesterone	6
6-Dehydro-6α-fluoro-17α-acetoxyprogesterone	15
1,6-Bisdehydro-6α-fluoro-17α-acetoxyprogesterone	8

Experimental[25a]

Δ^5-Pregnene-3β,17α-diol-20-one 17-Acetate (Ib).—A solution of Δ^5-pregnene-3β,17α-diol-20-one 3-formate 17-acetate (Ia) (100 g.) in methanol (4 l.) was cooled to 8° (a portion crystallized out of solution). Potassium hydroxide (85 g.) in methanol (600 cc.) was then added and the suspension was stirred in an atmosphere of nitrogen for 1.5 hours at room temperature. After acidification with acetic acid the solution was concentrated *in vacuo* to approximately 300 cc.; addition of ice-water and filtraton afforded Δ^5-pregnene-3β,17α-diol-20-one 17-acetate (Ib) (90.5 g.), m.p. 215–220°. This material was used for the next step without further purification. A sample after several crystallizations from acetone–hexane had m.p. 225–227°, undepressed upon admixture with an authentic sample[18]; $[\alpha]_D$ −62°; lit.[18] records m.p. 227–229°, $[\alpha]_D$ −59°.

5α,6α-Oxidopregnane-3β,17β-diol-20-one 17-Acetate (II).—Monoperphthalic acid (15 g.)[26] in ether (400 cc.) was added over 15 minutes with stirring to a solution of Δ^5-pregnene-3β,17β-diol-20-one-17-acetate (Ib) (20 g.) in chloroform (400 cc.) at −10°. After keeping at 0° for 18 hours the solution was washed free of acid with 5% sodium carbonate solution and then to neutrality with water. Removal of the solvent from the dry solution (Na_2SO_4) afforded a residue (19.2 g.), m.p. 218–229°. One crystallization from acetone afforded (5α,6α-oxidopregnane-3β,17β-diol-20-one-17-acetate (II) 10.6 g.), m.p. 240–243°, raised by crystallizations from acetone to 244–246°, $[\alpha]_D$ −71°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.62; H, 8.83.

6β-Fluoropregnane-3β,5α,17α-triol-20-one 17-Acetate (III).—Freshly distilled boron trifluoride etherate (13.5 cc.) was added to a solution of the α-epoxide II (9.8 g.) in dry benzene–ether (1:1, 1600 cc.). After 12 hours at room temperature the solution was washed with water (4 × 200 cc.), dried (Na_2SO_4), concentrated to 500 cc. and adsorbed onto alumina (500 g.). Elution with benzene–ether (70:30, 2.7 l.) afforded slightly impure starting material (2.1 g.), m.p. 225–242°. Further elution with ether–acetone (50:50, 900 cc.) and one crystallization from acetone–hexane gave 6β-fluoropregnane-3β,5α,17α-triol-20-one 17-acetate (III) (2.6 g.), m.p. 222–225°, raised by several crystallizations from acetone–hexane to 224–225°, $[\alpha]_D$ −29°.

Anal. Calcd. for $C_{23}H_{35}O_5F \cdot 0.5H_2O$: C, 65.85; H, 8.55; F, 4.53. Found: C, 66.05; H, 8.63; F, 4.78.

6β-Fluoropregnane-5α,17α-diol-3,20-dione 17-Acetate (IV).—A solution of 6β-fluoropregnane-3β,5α,17α-triol-20-one (III) (1.96 g.) in acetone (150 cc.) at 0° was treated in the usual way with an excess of 8 *N* chromic acid[20] (permanent orange color). After two minutes at 0° addition of ice-water and filtration afforded 6β-fluoropregnane-5α,17α-diol-3,20-dione 17-acetate (IV) (1.74 g.), m.p. 250–255° raised by crystallizations from acetone–hexane to 259–261°, $[\alpha]_D$ ±0°, λ_{max}^{EtOH} 280–286 mμ, ϵ 72.

Anal. Calcd. for $C_{23}H_{33}O_5F$: C, 67.62; H, 8.14; F, 4.65. Found: C, 67.85; H, 8.34; F, 4.50.

(25a) Melting points are uncorrected. Rotations were measured in chloroform and ultraviolet light absorption spectra in 95% ethanol solution. The rotatory dispersion measurements were obtained with a Rudolph Spectropolarimeter in dioxane solution using a xenon arc lamp (250–350 mμ) and a zirconium arc lamp (350–700 mμ). We are grateful to Dr. L. J. Throop and his staff for these measurements and for the infrared spectra which were obtained with a Perkin–Elmer model 21 spectrophotometer with a sodium chloride prism. The alumina used in this work had previously been suspended in boiling ethyl acetate for 6 hours and redried at 100° *in vacuo*. The elemental analyses were carried out by Dr. A. Bernhardt, Mulheim, Ruhr, Germany.

(26) Prepared according to the method of E. A. Royals and L. L. Harrell, Jr., THIS JOURNAL, **77**, 3405 (1955).

6α-Fluoro-17α-acetoxyprogesterone (V).—Anhydrous hydrogen chloride was bubbled steadily through a suspension of the fluoro-hydrin IV (1.6 g.) in acetic acid (350 cc.) at 15–18° for 2 hours. The flask was then stoppered and kept at room temperature for a further 3 hours. The solution was then poured onto an excess of ice-water and the product was isolated with ether. The ether solution was washed with a saturated salt solution (4 × 150 cc.), an excess of 5% sodium bicarbonate solution and finally water. Removal of the ether and crystallization of the product from benzene–hexane afforded 6α-fluoro-17α-acetoxyprogesterone (V) (1.2 g.), m.p. 243–246°, raised by several crystallizations from benzene–hexane to 255–257°, $[\alpha]_D$ +54°, λ_{max}^{EtOH} 236 mμ, ε 15,900; λ_{max}^{KBr} 1745, 1720, 1670, 1630 cm.$^{-1}$; rotatory dispersion curve (*c* 0.067, dioxane): $[\alpha]_{700}$ +54°, $[\alpha]_{589}$ +63°, $[\alpha]_{397.5}$ +167.5°, $[\alpha]_{370}$ +16°, $[\alpha]_{307.5}$ +3220, $[\alpha]_{300}$ +2560.

Anal. Calcd. for $C_{23}H_{31}O_4F$: C, 70.74; H, 8.00; F, 4.86. Found: C, 70.82; H, 8.16; F, 4.76.

Compound V was recovered unchanged after treatment with dry hydrogen chloride in acetic acid for 3 hours at 15°.

6α-Fluoro-Δ^{1,4}-pregnadiene-17α-ol-3,20-dione 17-Acetate (VI).—Selenium dioxide (0.52 g.) was added to a solution of 6α-fluoro-17α-acetoxyprogesterone (V) (1.0 g.) in *t*-butyl alcohol (45 cc.) containing pyridine (0.143 cc.) and heated under reflux for 18 hours in an atmosphere of nitrogen. The solution was then filtered through Celite to remove the precipitated selenium and evaporated to dryness on the steam-bath. The residue was triturated with water, filtered, dissolved in acetone and boiled with a little carbon and then crystallized from acetone–hexane to afford 6α-fluoro-Δ^{1,4}-pregnadiene-17α-ol-3,20-dione 17-acetate (VI) (460 mg.), m.p. 255–260°, raised by several crystallizations from acetone–hexane to 258–261°, $[\alpha]_D$ +19°, λ_{max}^{EtOH} 240–242 mμ, ε 15,900; λ_{max}^{KBr} 1735, 1718, 1660, 1625, 1605 and 1250 cm.$^{-1}$; rotatory dispersion curve (*c* 0.055, dioxane); $[\alpha]_{700}$ −7°, $[\alpha]_{589}$ −25°, $[\alpha]_{310}$ +1885°, $[\alpha]_{300}$ +1192°.

Anal. Calcd. for $C_{23}H_{29}O_4F$: C, 71.08; H, 7.52; F, 4.89. Found: C, 71.34; H, 7.50; F, 4.77.

Δ^{4,6}-Androstadiene-17β-ol-3-one Acetate.—Chloranil (10.0 g.) was added to a solution of testosterone acetate (5.0 g.) in ethyl acetate (250 cc.) containing acetic acid (50 cc.) and heated under reflux for 8 hours in an atmosphere of nitrogen. After cooling to room temperature the excess of reagent was removed by filtration and washed with a little cold ethyl acetate. The filtrate was diluted with ethyl acetate (500 cc.) and washed with sodium hydroxide solution (5%) until the alkaline wash was no longer highly colored. It was then washed with water and dried over sodium sulfate. Removal of the solvent afforded a product which was chromatographed over alumina to afford Δ^{4,6}-androstadiene-17β-ol-3-one acetate (3.24 g.), m.p. 136–142°, raised by one crystallization from acetone–hexane to 141–143° undepressed on admixture with an authentic sample[27]; λ_{max}^{EtOH} 284 mμ, ε 27,600. The infrared spectra were identical.

6-Fluoro-Δ^{4,6}-pregnadiene-17β-ol-3,20-dione 17-Acetate (VII).—Chloranil (8.0 g.) was added to a solution of 6α-fluoro-17α-acetoxy-progesterone (V) (4.0 g.) in *n*-amyl acetate (110 cc.) containing glacial acetic acid (22 cc.) and heated under reflux in an atmosphere of nitrogen for 9 hours. After cooling to room temperature the solution was filtered from the excess of reagent. The filtrate was then diluted with ethyl acetate (250 cc.), washed with 5% sodium hydroxide solution (4 × 500 cc.) and then with water until the washings were neutral. Removal of the solvent *in vacuo* afforded a product which was adsorbed from benzene onto alumina (200 g.). Elution with benzene–ether (90:10, 1.25 l.) afforded 6-fluoro-Δ^{4,6}-pregnadiene-17β-ol-3,20-dione 17-acetate (VII) (1.51 g.), m.p. 222–225°, raised by several crystallizations from acetone–hexane to 226–228°, $[\alpha]_D$ −53°, λ_{max}^{EtOH} 282-284 mμ, ε 24,500; λ_{max}^{KBr} 1740, 1720, 1660, 1650, 1620 and 1600 cm.$^{-1}$; rotatory dispersion curve (*c* 0.054, dioxane): $[\alpha]_{700}$ −57°, $[\alpha]_{589}$ −54°, $[\alpha]_{392.5}$ +832, $[\alpha]_{332.5}$ −2300, $[\alpha]_{315}$ −1490.

Anal. Calcd. for $C_{23}H_{29}O_4F$: C, 71.03; H, 7.52; F, 4.89. Found: C, 71.09; H, 7.50, F, 4.36.

6-Fluoro-Δ^{1,4,6}-pregnatrien-17α-ol-3,20-dione Acetate (VIII).—Selenium dioxide (200 mg.) was added to a solution of 6-fluoro-Δ^{4,6}-pregnadien-17α-ol-3,20-dione acetate (VII) (400 mg.) in *t*-butyl alcohol (36 cc.) containing pyridine (0.055 cc.) and heated under reflux in an atmosphere of nitrogen for 36 hours. Ethyl acetate (50 cc.) was added and the solution filtered through a layer of Celite to remove the precipitated selenium. The solvent was then removed *in vacuo* and the semi-solid residue was triturated with water, filtered, dried and then adsorbed from benzene onto alumina (30 g.). Elution with benzene–ether (90:10, 400 cc.) afforded 6-fluoro-Δ^{1,4,6}-pregnatrien-17α-ol-3,20-dione (VIII) (170 mg.), m.p. 202–206° raised by crystallizations from acetone–hexane to 204–206°, $[\alpha]_D$ −123°; λ_{max}^{EtOH} 225, 254 and 298 mμ; ε 10,580, 10,000 and 10,230, respectively; λ_{max}^{KBr} 1745, 1720, 1665, 1620, 1585 and 1255 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{27}O_4F$: C, 71.52; H, 7.04; F, 4.91. Found: C, 71.28; H, 7.07; F, 4.81.

(27) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, THIS JOURNAL, **72**, 4534 (1950).

MEXICO, D. F., MEXICO

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

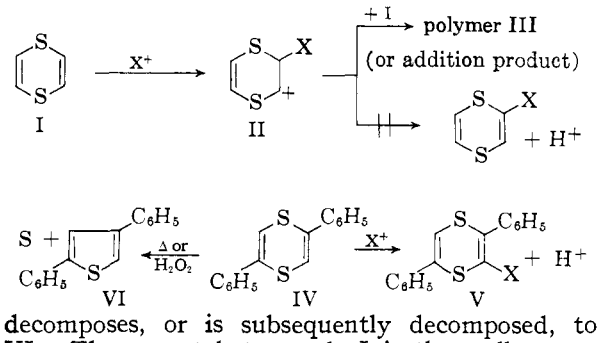
Heterocyclic Vinyl Ethers. XVI. 2,5-Dimethyl-1,4-dithiadiene[1]

BY WILLIAM E. PARHAM, GWENDOLYN L. O. MAYO[2] AND BRIAN GADSBY

RECEIVED MAY 6, 1959

2,5-Dimethyl-1,4-dithiadiene, the first example of an alkyl dithiadiene, has been prepared, and its chemical behavior compared with that of 1,4-dithiadiene and 2,5-diphenyl-1,4-dithiadiene.

A comparison of the chemical behavior of 1,4-dithiadiene (I) with that of 2,5-diphenyl-1,4-dithiadiene (IV) reveals rather marked dissimilarities.[3,4] The latter readily undergoes certain electrophilic substitution reactions (IV → V), decomposes at 180° to give the diphenylthiophene VI and sulfur, and is converted to a monosulfoxide which readily



decomposes, or is subsequently decomposed, to VI. The parent heterocycle I is thermally more

(1) This work was supported by the Office of Ordnance Research, Contract No. DA-11-022-Ord-2616.

(2) In part from the Ph.D. thesis of G. L. O. Mayo, University of Minnesota, 1958.

(3) W. E. Parham, B. Gadsby and R. A. Mikulec, *J. Org. Chem.*, **24**, in press (1959).

(4) "Organic Sulfur Compounds," editor N. Kharasch, Pergamon Press, Inc., New York 22, N. Y., in press, Vol. I, Ch. 8, W. E. Parham.