refluxing solution of 5 g. of the above hydrobromide in 25 ml. of acetic acid. The solution was allowed to cool to room temperature under a stream of nitrogen and diluted with 350 ml. of ether. The precipitated oil solidified after storage overnight at −5°; the yield of hydrobromide was 3.9 g., m.p. 147–148°. By evaporating the filtrate and crystallizing the residue from ethanol–ether, a further 1.5 g. was obtained as feathery plates from methanol–acetone, m.p. 157–158°.

Anal. Calcd. for $C_{17}H_{23}Br_2NO$: C, 48.7; H, 6.0; Br, 38.3. Found: C, 48.8; H, 5.9; Br, 38.1.

2-Methyl-9-oxo-5-propyl-6,7-benzomorphan Methobromide (II).—The above, finely divided bromo ketone hydrobromide (2.0 g.), 18 ml. of water, and 7 ml. of concentrated NH_4OH were shaken vigorously with three 50-ml. portions of ether, and the extracts were separated quickly. The combined ethereal solutions were evaporated at the water pump; the residue was crystallized from ethanol–ether to give 1.0 g. of II, m.p. 175–176°; feathery plates, m.p. 191–192° (sinters 186°), from methanol–acetone.

Anal. Calcd. for $C_{17}H_{24}BrNO$: C, 59.8; H, 7.2; N, 4.2. Found: C, 60.1; H, 7.0; N, 4.2.

α-2,9-Dimethyl-9-hydroxy-5-propyl-6,7-benzomorphan (III) Methiodide.—To a stirred suspension of 11.7 g. of II in 100 ml. of dry ether was added dropwise, 100 ml. of methylmagnesium iodide (from 24.5 g. of methyl iodide and 4.2 g. of magnesium). The mixture was stirred and refluxed for 48 hr., then poured onto a mixture of 50 g. of ice, 15 g. of potassium iodide, and 25 ml. of concentrated HCl. The solid which separated (while stirring for 2 hr.) was filtered, washed with ether, and recrystallized from methanol–acetone; yield of III methiodide, m.p. 200–202°, 10 g. The analytical sample (from methanol–acetone) melted at 223–224°.

Anal. Calcd. for $C_{18}H_{28}INO$: C, 54.0; H, 7.0; N, 3.5. Found: C, 54.6; H, 7.1; N, 3.7.

The **base III** was obtained in a yield of 1.9 g. by dry distillation (0.6 mm., bath temperature 210°) of 3.0 g. of III methiodide; prisms from ligroin (60–80°), m.p. 94.5–95.5°, $\nu_{max}^{CCl_4}$ 3445 cm.$^{-1}$ (OH–N bonding).[1-4]

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.7; H, 9.7; N, 5.4. Found: C, 78.4; H, 9.5; N, 5.4.

The **hydrochloride** of III crystallized from ethanol–ether as prisms, m.p. 221–222°.

Anal. Calcd. for $C_{17}H_{26}ClNO$: C, 69.1; H, 8.9; N, 4.8. Found: C, 69.0; H, 8.9; N, 5.0.

2-Methyl-9-methylene-5-propyl-6,7-benzomorphan (IV) Hydrochloride.—Thionyl chloride (60 ml.), 1 ml. of pyridine, and 10 g. of III were kept at 40° for 2 hr. (stirring). Solvents were removed at the water pump. To the residue was added ice and concentrated NH_4OH in excess. Drying (Na_2SO_4) of the liberated bases in three 100-ml. portions of ether gave 6.1 g. of an oil which, in ligroin (66–75°), was placed on an alumina column (Woelm grade III, neutral, 150 g.) and eluted with benzene–ligroin (66–75°). The fractions eluted by 10–55% benzene were combined to give 3.5 g. of crude IV, λ_{max}^{Nujol} 6.05 and 10.6 μ (=CH_2). The hydrochloride, prepared in acetone by addition of dry HCl and ether, crystallized as the monohydrate; yield 1.6 g.; m.p. 180–182°; λ_{max}^{Nujol} 2.80, 2.95 (H_2O), and 6.05, 10.6 μ (=CH_2).

Anal. Calcd. for $C_{17}H_{26}ClN \cdot H_2O$: C, 68.9; H, 9.0; Cl, 12.0; N, 4.7. Found: C, 68.4; H, 9.0; Cl, 11.9; N, 4.5.

The molecule showed 2.6 active hydrogens based on a molecular weight of 295.8.

α-2,9-Dimethyl-5-propyl-6,7-benzomorphan (V) Hydrochloride.—The hydrochloride of IV (0.32 g.), 25 ml. of ethanol, and 0.15 g. of platinum oxide absorbed the calculated amount of hydrogen during 30 min. The residue from filtration and evaporation of the filtrate to dryness crystallized from acetone–ether in a yield of 0.27 g., m.p. 194° (sinters 176°). The analytical sample melted at 199–200°.

Anal. Calcd. for $C_{16}H_{26}ClN$: C, 72.9; H, 9.4; N, 5.0. Found: C, 72.8; H, 9.3; N, 5.0.

β-Isomer (VI) Hydrochloride.—The hydrochloride of IV (1.1 g.), 20 ml. of concentrated hydrochloric acid, 0.5 g. of platinum oxide, and 10 ml. of ethanol absorbed 1 molar equiv. of hydrogen during 2.5 hr. Filtration, evaporation to dryness *in vacuo*, addition of excess NH_4OH, and extraction with ether gave a mixture of V and VI (1:1.5) which was successfully separated by preparative, thin layer chromatography (silica gel G; ethanol, dioxane, benzene, concentrated NH_4OH, 5:40:50:5) in 85% recovery. The crude β-isomer (VI) in acetone was acidified with dry HCl. Addition of ether to turbidity and storage at −5° overnight gave a solid which was recrystallized from acetone–ether; yield 0.4 g., m.p. 248–249°.

Anal. Calcd. for $C_{16}H_{26}ClN$: C, 72.9; H, 9.4; N, 5.0. Found: C, 72.8; N, 9.3; N, 5.0.

Stereochemistry of V and VI.—By a method described before,[5] compound V was shown to form the methiodide five times more rapidly than did VI. Thus the 9-methyl substituent of V is oriented away from nitrogen (axial for the hydroaromatic ring). The β-structure[6] can therefore be assigned to VI.

Synthesis of 17-Acetoxy-6-chloro-21-fluoropregna-4,6-diene-3,20-dione, a Highly Active Oral Progestin

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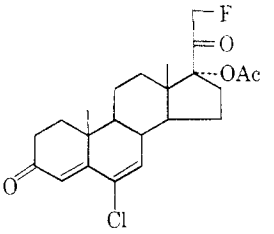
Among the groups which afford enhanced progestational activity when introduced into progesterone-type molecules are the 21-fluoro[1] and the Δ^6-6-chloro[2] functions. We wish to report here the synthesis of I, a highly active progestational agent resulting from the introduction of both of these functions into 17-acetoxyprogesterone.

Compound I was prepared by established procedures from 17-acetoxy-21-fluoroprogesterone[3] by 6-dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone,[4] and 6α,7α-epoxidation with monoperphthalic acid,[5] followed by treatment with HCl[6] to effect oxide ring opening and concomitant dehydration.



1

When assayed for progestational activity by the oral Clauberg procedure[7] compound I had a relative potency approximately 300 times that of 17-acetoxyprogesterone. Thus, introduction of the 21-fluoro group into 17α-acetoxy-6-chloropregna-4,6-diene-3,20-dione moderately enhances the activity of the latter compound, which we find to have a potency of 190 relative to 17-acetoxyprogesterone.

Experimental

General.—Melting points were taken on a Mel-Temp apparatus in open capillary tubes and are corrected. Optical rotations

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were determined at 25° in chloroform solution at 0.2–1.0% concentrations. Ultraviolet spectra were measured in methanol solution on a Cary recording spectrophotometer, and infrared spectra were determined in pressed KBr disks on a Perkin-Elmer spectrophotometer (Model 21). Solutions were dried with Na_2SO_4 and evaporations were carried out at reduced pressure. The petroleum ether used was that fraction boiling at 30–60°.

17α-Acetoxy-21-fluoropregna-4,6-diene-3,20-dione.—Hydrogen chloride was bubbled vigorously over a 3–4 min. period (to saturation) into a well-stirred solution of 2.227 g. (5.71 mmoles) of 17-acetoxy-21-fluoroprogesterone[3] and 1.480 g. (6.52 mmoles) of recrystallized 2,3-dichloro-5,6-dicyanobenzoquinone[4] in 75 ml. of dioxane (purified according to Fieser[5]). Precipitation of hydroquinone began in about 1 min. (exothermic). The mixture was stirred 30 min. and filtered. The precipitate of hydroquinone was washed well with benzene, the entire filtrate was further diluted with benzene (200 ml. total), and the resulting solution was washed with two 50-ml. portions of water, two 75-ml. portions of 1% aqueous NaOH, and two 50-ml. portions of saturated aqueous NaCl. The solution was dried, the solvent was evaporated, and the residue crystallized on trituration in ether. Recrystallization from acetone–petroleum ether afforded 1.684 g. (76%) of product. The analytical sample (from acetone–hexane) had m.p. 205.5–206.5°; $[\alpha]D$ −10°; λ_{max} 5.78, 6.02, 6.19, 6.31, 7.93, 9.52 μ; λ_{max} 282 mμ (ε 25,200).

Anal. Calcd. for $C_{23}H_{29}FO_4$: C, 71.10; H, 7.53; F, 4.89. Found: C, 70.85; H, 7.45; F, 5.22.

17α-Acetoxy-6α,7α-epoxy-21-fluoropregn-4-ene-3,20-dione.—To a solution of 776 mg. (2 mmoles) of 17α-acetoxy-21-fluoropregna-4,6-diene-3,20-dione in 190 ml. of methylene chloride was added 53 ml. of an ethereal solution of monoperphthalic acid[5] in ether(containing 48 mg./ml., 14 mmoles of perphthalic acid), and the solution was stirred well and allowed to stand at room temperature for 68 hr. protected from atmospheric moisture. The solution was decanted from precipitated phthalic acid, washed with two 50-ml. portions of saturated aqueous Na_2CO_3, two 50-ml. portions of water, and two 50-ml. portions of saturated aqueous NaCl, and dried. The solvent was evaporated and the oily residue (711 mg.) crystallized on trituration with ether. The precipitate was washed several times with cold ether to afford 477 mg. of product, m.p. 228–232° dec. Recrystallization from methylene chloride–ether afforded 227 mg. of product, m.p. 240–243° dec. containing approximately 1% of 4,6-diene starting material (as estimated from the ultraviolet spectrum). The analytical sample (from ethyl acetate–petroleum ether) had m.p. 242–245° dec.; $[\alpha]D$ +3°; λ_{max} 5.80, 6.03, 7.92, 8.08, 11.56 μ; λ_{max} 240 mμ (ε 14,900).

Anal. Calcd. for $C_{23}H_{29}FO_5$: C, 68.29; H, 7.24; F, 4.70. Found: C, 68.48; H, 7.50; F, 5.21.

17α-Acetoxy-6-chloro-21-fluoropregna-4,6-diene-3,20-dione (I).—Hydrogen chloride was bubbled into a stirred solution of 195 mg. of 17α-acetoxy-6α,7α-epoxy-21-fluoropregn-4-ene-3,20-dione in 10 ml. of glacial acetic acid over a 10-min. period and the orange solution was allowed to stand 2 hr. loosely capped at room temperature. After resaturation with HCl, the solution was allowed to stand an additional 2 hr., and then was poured slowly with stirring into 100 ml. of ice–water. The aqueous mixture was extracted with CH_2Cl_2 and the extracts were combined, washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, and dried. The solvent was evaporated and the residue crystallized on trituration with methanol. Chromatography on silica gel using 5% ether–benzene as eluent afforded the product (150 mg., m.p. 210–214°). Recrystallization from methanol gave the analytical sample: m.p. 217–219°; $[\alpha]D$ −8°; λ_{max} 5.76, 6.00, 6.23, 6.30, 7.94, 8.11, 11.42 μ; λ_{max} 284 mμ (ε 21,200).

Anal. Calcd. for $C_{23}H_{28}ClFO_4$: C, 65.36; H, 6.69; Cl, 8.31; F, 4.49. Found: C, 65.56; H, 6.95; Cl, 8.95; F, 4.32.

Acknowledgment.—We wish to thank Dr. I. Ringler for assistance in obtaining and interpreting the Clauberg assays, Mr. L. Brancone and staff for microanalytical data, and Mr. W. Fulmor and associates for the spectroscopic and polarimetric data.

(8) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed. (revised), D. C. Heath and Company, Boston, Mass., 1957, p. 285, method a.

2H-1,3,2-Oxazaphosphorine Derivatives[1]

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The widespread interest in Cytoxan, which may be considered as a nitrogen mustard derivative of 2H-1,3,2-oxazaphosphorine (I),[2] led us to prepare other derivatives of I, with a stilbene or benzylideneindene group. One compound showed marked antitumor activity against the Walker 256 tumor in rats (Table I).

TABLE I

BIOLOGICAL ACTIVITY

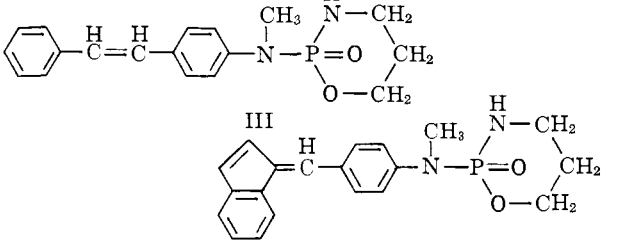
Compd.	KB cell test[a] ED_{50}, mg./kg.	Tumor wt.[b] *T/C* @ mg./kg.		Killed @ mg./kg.	
II		0.9	12	1/3	25
III	33	0.13	250	3/3	500
		0.8	100	0/3	250
V	29	0.8	320	3/3	640

[a] Results of the standard *in vitro* KB tumor cell inhibition tests carried out under sponsorship of the Cancer Chemotherapy National Service Center at the University of Miami Cell Culture Laboratory and Southern Research Institute. [b] We are grateful to Professor Alexander Haddow, Mr. J. E. Everett, and Mr. B. C. V. Mitchley of the Chester Beatty Research Institute for data on toxicity and activity against the Walker 256 tumor in rats weighing 200–250 g. Each compound was administered as a single i.p. injection in Arachis oil on the day following tumor implantation or on the first day of the toxicity observation. Tumor bearing animals were sacrificed approximately 8 days later and the average weights of tumors in treated and untreated hosts are reported as the ratio *T/C*.

Experimental

***p*-Styrylphenylmethylphosphoramidic Dichloride (II).**—A mixture of 13.6 g. of 4-N-methylaminostilbene[3] and 120 ml. of $POCl_3$ was refluxed 16 hr., then most of the $POCl_3$ was removed by distillation. Recrystallization of the solid product produced almost colorless crystals, m.p. 126–127° (cor.), yield 71%.

Anal.[4] Calcd. for $C_{15}H_{14}Cl_2NOP$: C, 55.24; H, 4.38. Found: C, 55.05; H, 4.39.



III

V

2-(Styryl-N-methylanilino)tetrahydro-2H-1,3,2-oxazaphosphorine 2-Oxide Monohydrate (III).—A mixture of 9.06 g. of II, 2.06 g. of 3-amino-1-propanol, 5.61 g. of triethylamine, and 300 ml. of anhydrous dioxane was allowed to stand for 12 hr. at room temperature then filtered to remove the triethylamine hydrochloride formed. (The 96% yield of triethylamine hydro-

(1) This investigation was supported by Public Health Service Research Grants No. CA 03717-05-7 from the National Cancer Institute.

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