6-SUBSTITUTED-6-DEHYDRO-17-ALKYLPROGESTERONES: HIGHLY ACTIVE ORAL PROGESTINS

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The preparation of a series of 6-chloro-6-dehydro-17-alkylprogesterones, of the 6-fluoro and 6-methyl derivatives of 6-dehydro-17-ethylprogesterone and of 6-chloro-1,6-bisdehydroprogesterone is described. The oral progestational activity of these and other 17-alkylprogesterone derivatives is discussed.

We have recently reported a general procedure for the preparation of 17-alkylpregn-20-ones and the application of this method to the synthesis of a series of 17-alkylprogesterones.[1,2] These progesterone derivatives are orally active progestins, and we have already noted that 17-ethylprogesterone is about two-three times as active as 17-methylprogesterone, being approximately equal to 17-acetoxyprogesterone.[1] In addition we reported the introduction into 17-ethylprogesterone of certain groups which are known to enhance progestational activity. Since the incorporation of the 6-chloro-6-dehydro moiety into 17-acetoxyprogesterone has resulted in a pronounced enhancement of activity,[5] it was of immediate interest to prepare the corresponding 17-alkyl derivatives. We now wish to describe in detail the oral progestational activity of our previously reported derivatives and the preparation and biological activity of a series of 6-

Table I. 17-Alkylpregna-4,6-diene-3,20-diones (I)

17-Alkyl	Yield, %[a]	M.P., °C[b,c]	$[\alpha]_D$, °	HBV[d]	Molecular Formula	C Calcd.	C Found	H Calcd.	H Found
Ethyl	70	161-163 (A-PE)	+52		$C_{23}H_{32}O_2$	81.13	80.89	9.47	9.43
Propyl	30	147-152 (A)	+35		$C_{24}H_{34}O_2$	81.31	80.88	9.67	9.53
Hexyl	46	Syrup	+11	2.32	$C_{27}H_{40}O_2$	81.76	81.40	10.17	9.94
Octyl	33	Syrup		1.50	$C_{29}H_{44}O_2$	82.02	80.71	10.44	10.57
Decyl	80	Syrup							
Ethyl (6-methyl)	51	182-183[e] (H)	+47	2.14	$C_{24}H_{34}O_2$	81.31	81.31	9.67	9.84

[a]Material with sufficient purity for further transformations. [b]Analytical m.p.; λ_{max} 283-285 mμ (ε 20,900-26,200). [c]Recrystallization solvent: A=acetone; PE=petroleum ether (b.p. 60-70°); H=hexane. [d]Center of product-containing fraction from partition chromatogram. [e]λ_{max} 290 mμ (ε 23,600).

Table II. 17-Alkyl-6-chloropregna-4,6-diene-3,20-diones (III)

17-Alkyl	Yield, %	M.P., °C[a,b]	$[\alpha]_D$, °	Molecular Formula	C Calcd.	C Found	H Calcd.	H Found	Cl Calcd.	Cl Found
Ethyl	39	166-170[c]	+28.0	$C_{23}H_{31}ClO_2$	73.68	73.42	8.33	8.55	9.46	9.48
Propyl	18	144-146[c] (3.74)	+29.6	$C_{24}H_{33}ClO_2$	74.10	73.96	8.55	8.41	9.11	8.95
Hexyl	36	Syrup (2.09)	+3.9	$C_{27}H_{39}ClO_2$	75.24	74.50	9.12	8.42	8.23	7.95
Octyl	52	Syrup (1.54)	+3.6	$C_{29}H_{43}ClO_2$	75.86	75.62	9.44	9.65	7.72	8.04
Decyl	14	Syrup (1.39)	+1.1	$C_{31}H_{47}ClO_2$	76.03	74.68	9.73	9.76	7.28	7.98

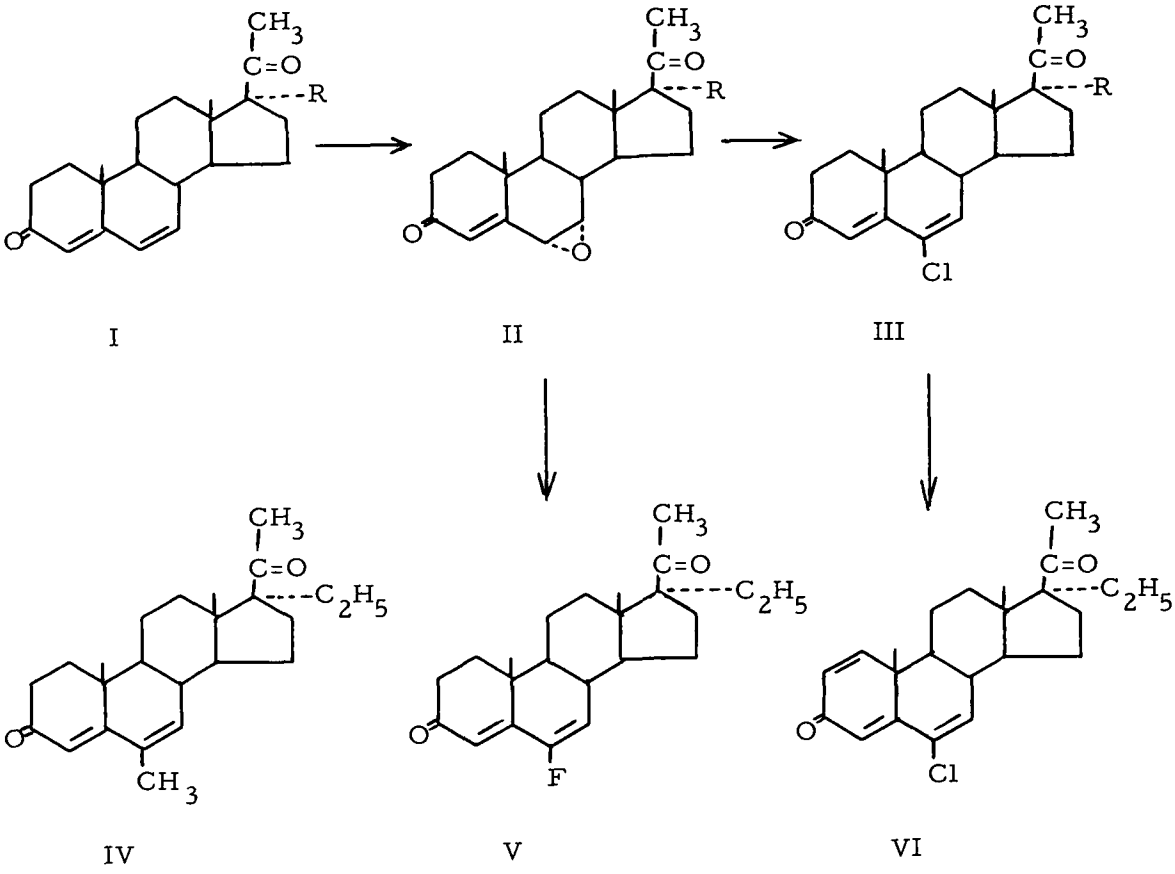
[a]Analytical m.p.; λ_{max} 285 mμ (ϵ 14,000-21,400). [b]Parentheses indicate center position as HBV of product-containing fraction from partition chromatogram. [c]Recrystallized from methylene chloride-petroleum ether.

chloro-6-dehydro-17-alkylprogesterones (III, 17-alkyl-6-chloropregna-4,6-diene-3,20-diones) and of the 6-fluoro and 6-methyl derivatives of 6-dehydro-17-ethylprogesterone (17-ethylpregna-4,6-diene-3,20-dione).

Introduction of the 6-chloro-6-dehydro-moiety was accomplished best by a three-step procedure analogous to that reported by Knox and co-workers.[6] Thus, dehydrogenation of the 17-alkylprogesterone[1] with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in the presence of hydrogen chloride[7] gave the corresponding 6-dehydro derivative I (Table I), which on treatment with monoperphthalic acid[8] afforded the 6α,7α-oxide II. Reaction of II with hydrogen chloride in acetic acid then furnished the desired 6-chloro-6-dehydro-17-alkylprogesterone (III). In this manner the 17-ethyl, propyl, hexyl, octyl and decyl[9] derivatives were obtained (Table II). An earlier preparation of the 17-ethyl derivative via chloranil dehydrogenation of 6α-chloro-17-ethylprogesterone[1] was not as satisfactory.

6-Dehydro-6-fluoro-17-ethylprogesterone (V, 17-ethyl-6-fluoropregna-4,6-diene-3,20-dione) was obtained, albeit in poor yield, by hydrogen fluoride treatment of the corresponding 6α,7α-oxide II. 6-Dehydro-6-methyl-17-ethylprogesterone (IV, 17-ethyl-6-methylpregna-4,6-diene-3,20-dione) was prepared by DDQ dehydrogenation of 17-ethyl-6α-methyl-progesterone.[1] Finally, 1,2-dehydrogenation with DDQ[11] of 6-chloro-6-dehydro-17-ethylprogesterone (6-chloro-17-ethylpregna-4,6-diene-3,20-dione) afforded the 1,6-bisdehydro derivative VI.

Those compounds of this study wherein the 17-alkyl group is hexyl or higher could not be crystallized despite intensive efforts at purification. Nevertheless, on the basis of combustion and spectral analyses, we consider these products to be of relatively good quality.



I II III

IV V VI

Biological Evaluation

All steroid assays for oral progestational activity were carried out by the Clauberg procedure as conducted by Dr. Elva G. Shipley at the Endocrine Laboratories, Madison, Wisconsin.

As we reported in our preliminary communication,[1,2] the introduction of a 17-alkyl group confers oral activity on the progesterone molecule. In the unsubstituted 17-alkylprogesterone series maximum activity occurs with the 17-ethyl and 17-propyl derivatives, the latter being somewhat more active. The 17-butyl, hexyl, octyl, nonyl,[10] decyl[9] and allyl members of this series were also active, but less so than the ethyl and propyl mem-

bers. In the 6-dehydro series (the first five compounds of Table I and the 17-methyl derivative[1]), a similar trend was observed. The relationship of side-chain length to activity was also studied in the 6-chloro-6-dehydro series, as described below.

Various 6-substituents and dehydro functions are known to enhance the oral activity of 17-acetoxyprogesterone.[12] Introduction of certain of these moieties into 17-ethylprogesterone also results in an enhancement of activity (Table A). The most potent compounds of those containing only one activity principle were the 6α-methyl and 6-dehydro derivatives.[1] In contrast to the considerable effect of the 6-dehydro function, 1-dehydrogenation had little if any effect. Introduction of the 6α-chloro, 6α-bromo, 6α-nitro and the 1,6-bisdehydro functions[1] and removal of the 19-methyl group[13] gave compounds which, with the exception of the 6α-chloro derivative, were not fully evaluated, but appeared to have a similar level of activity; however, all were somewhat less active than the 6α-methyl and 6-dehydro compounds.

As observed in the 17-acetoxy series,[12b] the most active 17-alkyl derivatives included a combination of the 6-dehydro function with a 6-methyl, chloro or fluoro group (Table A).[2] In the 6-chloro-6-dehydro series (Table II) the ethyl derivative was distinctly the most active, and the decyl derivative the least active. The hexyl and octyl members were not fully evaluated so that their exact relative position in this series remains undetermined. However, they appear to be less active than the ethyl derivative and more active than the decyl derivative. The relationship of the ethyl and propyl members of this series stands in contrast to that observed in the unsubstituted Δ^4-3-ketone series. The 1,6-bisdehydro derivative VI of 6-chloro-17-ethylprogesterone was not fully evaluated, but, at best, it did not appear to be more active than 6-chloro-6-dehydro-17-ethylprogesterone.

Finally, a comparison of the 17-alkyl to the 17-acetoxy series was of interest. Although 17-ethyl, 17-propyl and 17-acetoxyprogesterone are essentially equivalent in activity, the degree of enhancement noted on introduction of the 6α-methyl group or the 6-chloro-6-dehydro moiety into 17-acetoxyprogesterone is greater than that observed in the 17-alkyl series (see Table A).

Table A. ORAL PROGESTATIONAL ACTIVITY

Compound	Activity
17-Acetoxyprogesterone	1
17-Propylprogesterone	2
6α-Chloro-17-ethylprogesterone	2-4
6α-Methyl-17-ethylprogesterone	9
6-Dehydro-17-ethylprogesterone	5
1-Dehydro-17-ethylprogesterone	1
6-Methyl-6-dehydro-17-ethylprogesterone	130
6-Fluoro-6-dehydro-17-ethylprogesterone	48
6-Chloro-6-dehydro-17-ethylprogesterone	65
6-Chloro-6-dehydro-17-propylprogesterone	14
6α-Methyl-17-acetoxyprogesterone[a]	60[b]
6-Chloro-6-dehydro-17-acetoxyprogesterone[c]	190[b]

[a]Babcock, J. C., Gutsell, E. S., Herr, M. E., Hogg, J. A., Stucki, J. C., Barnes, L. E., and Dulin, W. E., J. AM. CHEM. SOC., 80, 2905(1958). [b]Based on data obtained by present authors. [c]Ref. 5.

EXPERIMENTAL

General. - Melting points were determined in open capillary tubes and are uncorrected. Optical rotations were measured at 25° in chloroform solution at concentrations of 0.6-1.0%. Ultraviolet spectra were determined in methanol solution on a Cary recording spectrophotometer. Infrared spectra were determined in pressed potassium bromide discs on a Perkin-Elmer spectrophotometer (Model 21). All evaporations were carried out at reduced pressure. Partition chromatograms were carried out on Celite[14] diatomaceous earth with the heptane-2-methoxyethanol system according to the procedure developed by one of us (C. C. P.).[10,15] Hold back volume (HBV) is defined as the volume of solvent necessary to fill the column.

Preparation of 17-Alkylpregna-4,6-diene-3,20-diones (I) (Table I). The following preparation of 17-ethylpregna-4,6-diene-3,20-dione illustrates this procedure.[7] Hydrogen chloride gas was bubbled into a solution containing 20.94 g. of 17-ethylprogesterone and 15.3 g. of recrystallized 2,3-dichloro-5,6-dicyanobenzoquinone in 650 ml. of purified dioxane until crystallization began. After standing for 30 min., the precipitated hydroquinone was collected and the filtrate diluted with methylene chloride, washed with water, 1% aqueous alkali and finally with water. Upon drying over anhydrous magnesium sulfate and evaporation of solvent, the crude product was recrystallized from acetone-petroleum ether to give 14.6 g. (70%) of crystals with m.p. 158-161°. Further characterization of this substance is given in Table I.

Preparation of 17-Alkyl-6α,7α-epoxypregn-4-ene-3,20-diones (II). The following preparation of 6α,7α-epoxy-17-ethylpregn-4-ene-3,20-dione exemplifies this procedure.[8] To a solution of 17-ethylpregna-4,6-diene-

3,20-dione (2 g.) in 260 ml. of methylene chloride was added a solution of monoperphthalic acid (6.43 g.) in 134 ml. of ether. The resulting solution was kept at room temperature, protected from moisture, for 72 hr. The phthalic acid which had precipitated was filtered and the filtrate was diluted with 300 ml. of methylene chloride, washed with saturated sodium carbonate solution, saline and then with water, dried with anhydrous magnesium sulfate and evaporated. Trituration of the residue with ether followed by filtration furnished 818 mg. (40%) of product, m.p. 218-222°. Two recrystallizations from methylene chloride-ether gave white crystals, m.p. 226-230°; $[\alpha]_D$ +49°; λ_{max} 5.86, 5.95, 6.11 μ; 241 mμ (ϵ14,650).

Anal. Calcd. for $C_{23}H_{32}O_3$ (356.49): C, 77.49; H, 9.05. Found: C, 76.99; H, 9.29.

The other oxides required as intermediates for the compounds of Table II were not obtained pure. However, the ultraviolet spectra of these oxides showed little, if any, $\Delta^{4,6}$-3-ketone present, and they were suitable for the subsequent step.

Preparation of 17-Alkyl-6-chloropregna-4,6-diene-3,20-diones (III) (Table II). The following preparation of 6-chloro-17-ethylpregna-4,6-diene-3,20-dione illustrates this procedure.[6] To 30 ml. of glacial acetic acid, saturated at room temperature with hydrogen chloride, was added 500 mg. of 6α,7α-epoxy-17-ethylpregn-4-ene-3,20-dione. After standing for 4 hr., the solution was poured into 60 ml. of ice water and stirred for 15 min. The precipitated amorphous material (512 mg.) was collected and crystallized from ether-petroleum ether to furnish 80 mg. (15%) of 6β-chloro-17-ethyl-7α-hydroxypregn-4-ene-3,20-dione, m.p. 225-226° dec. Recrystallization from methylene chloride-ether gave white crystals, m.p. 230-231° dec.; $[\alpha]_D$ +20°; λ_{max} 2.93, 5.89, 5.96, 6.18 μ; 240 mμ (ϵ15,000).

Anal. Calcd. for $C_{23}H_{33}ClO_3$: C, 70.31; H, 8.46; Cl, 9.02. Found: C, 69.82; H, 8.64; Cl, 9.07.

Further concentration of the filtrate with the addition of petroleum ether afforded 203 mg. (39%) of 6-chloro-17-ethylpregna-4,6-diene-3,20-dione, m.p. 157-160°; for further characterization see Table II.

17-Ethyl-6-fluoropregna-4,6-diene-3,20-dione (V). A solution of 17-ethyl-6α,7α-epoxypregn-4-ene-3,20-dione (500 mg.) in 3 ml. of chloroform was added to 5 ml. of a solution prepared by mixing 4 ml. of hydrogen fluoride, 7 ml. of tetrahydrofuran and 4 ml. of chloroform at -70°. The resulting solution, after warming to room temperature, was allowed to stand for 19 hr. It then was added with stirring to 200 ml. of iced 5% potassium carbonate solution and extracted twice with chloroform. The combined extracts were washed with saline and then water, dried with anhydrous magnesium sulfate and evaporated to furnish 531 mg. of crude, amorphous fluorohydrin. This material was dissolved in 10 ml. of glacial acetic acid containing 1 ml. of 30% hydrogen bromide in acetic acid. The resulting solution was kept at room temperature for 7 hr., when it was diluted with ice water and the precipitated product was filtered to give 313 mg. of an amorphous solid. This solid was submitted to partition chromatography and the product (47 mg., m.p. 217-220°) was isolated in the fraction with peak at HBV 4.57. Recrystallization from methylene chloride-ether afforded white crystals, m.p. 221-222°; $[\alpha]_D$ +176°; λ_{max} 5.89, 6.00, 6.07, 6.26 μ; 285 mμ (ϵ 29,000).

Anal. Calcd. for $C_{23}H_{31}FO_2$: C, 77.05; H, 8.72; F, 5.30. Found: C, 78.15; H, 8.89; F, 5.24.

6-Chloro-17-ethylpregna-1,4,6-triene-3,20-dione (VI). 6-Chloro-17-

ethylpregna-4,6-diene-3,20-dione (400 mg.) was treated with 264 mg. of 2,3-dichloro-5,6-dicyanobenzoquinone[11] in 10 ml. of dioxane. The crude product (297 mg.) was chromatographed on Florisil[16] magnesia-silica gel, and the solids eluted by benzene (50 ml.), 10% methylene chloride-in-benzene (50 ml.) and methylene chloride (50 ml.) were combined and recrystallized from methylene chloride-ether to give 138 mg. (35%) of white crystals, m.p. 183-186°. A second recrystallization gave crystals, m.p. 185-187°; $[\alpha]_D$ -66°; λ_{max} 5.91, 6.05, 6.15, 6.24 μ; 229, 258, 299 mμ (ϵ 10,800; 10,000; 10,200).

Anal. Calcd. for $C_{23}H_{29}ClO_2$: C, 74.08; H, 7.84; Cl, 9.51.

Found: C, 74.19; H, 8.14; Cl, 9.72.

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13. The preparation of 17-ethyl-19-norprogesterone from 17-acetoxy-3-ethoxy-19-nor-17α-pregna-3,5-dien-20-one [Mills, J. S., Ringold, H. J., and Djerassi, C., J. AM. CHEM. SOC., 80, 6118(1958)] by the reductive alkylation procedure[1] will be described in a forthcoming publication.[10]

14. Celite is the trademark of Johns-Manville for diatomaceous silica products.

15. Kissman, H. M., Pidacks, C., and Baker, B. R., J. AM. CHEM. SOC., 77, 18(1955).

16. Florisil is the trademark of the Floridin Co. for a magnesia-silica gel adsorbent.