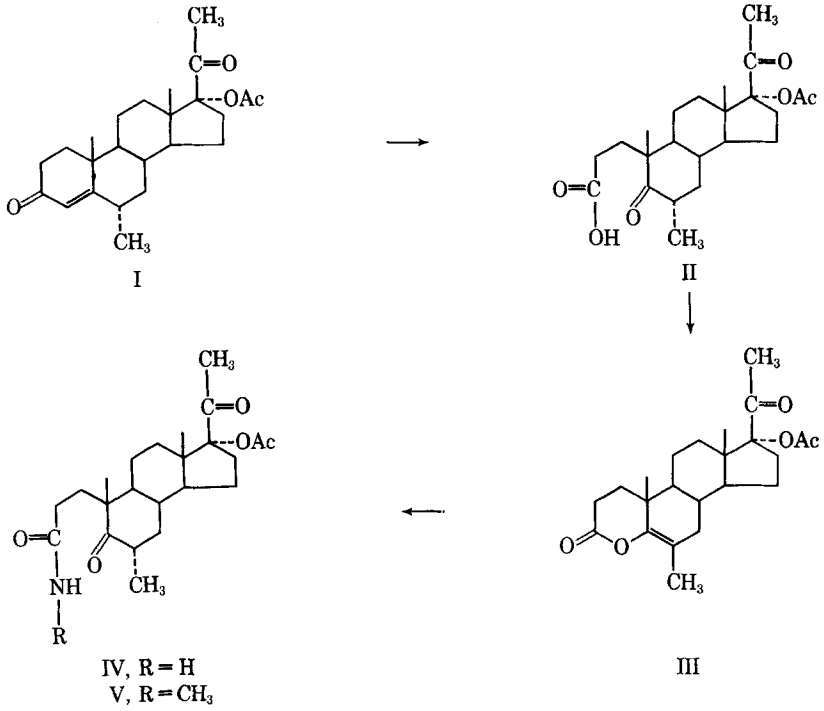
Secosteroids as Progestational Agents

By ARVIN P. SHROFF

This paper describes the synthesis of a few secosteroids. Their proton magnetic resonance spectra in $CDCl_3$ and C_6H_6 were investigated to evaluate the Δ values of the C-18, C-19, and C-6 methyl groups. The progestational activity of these compounds as evaluated in the Clauberg test is also described.

PROGESTATIONAL AGENTS have come into prominence in the last decade because of greatly increased potency. This has been accomplished through alteration of the basic structure of the progesterone or testosterone molecule. These include dehydrogenation, demethylation, or introduction of a methyl group, hydroxyl group, acetoxy group, and/or halogen atoms. At first interest was in the replacement of a carbon atom of the cyclopentanoperhydrophenanthrene system by nitrogen. A number of compounds resulting from these types of modification have been reported to be of potential biological interest (1).



Scheme I

Ozonization of the α,β-unsaturated ketone, 17α-acetoxy-6α-methylpregn-4-ene-3,20-dione (I), followed by oxidative decomposition of the ozonide with hydrogen peroxide gave 17α - acetoxy - 6α-methyl-3,5-seco-4-norpregna-5,20- dion - 3 - oic acid (II). (Scheme I.) The configuration of C-6 methyl was confirmed by PMR. The resonance peaks for C-6 methyl in deuterochloroform and benzene (Table 1) did not show any shift ($\Delta = 0$) and this indicates equatorial (α) conformation (2). The C-19 axial methyl, on the other hand, shows a significant shift ($\Delta = 0.38$) as observed by Williams and Baccha (2). The keto acid (II) was refluxed in a mixture of acetic anhydride and acetyl chloride (3) to give the lactone, 4 - oxa - 17α - acetoxy - 6 - methylpregn - 5 - ene-3,20-dione (III). The C-6 methyl group was deshielded, as expected by 0.70 p.p.m. (in $CDCl_3$). Shielding of C-19 methyl to the extent of 0.33 p.p.m. indicates that the benzene–solute complex formation occurred to the same extent as in keto acid (II). Treatment of lactone (III) with ammonia and methylamine gave the open chain amides (IV and V). The Δ values for C-19 and C-6 methyl groups suggest that the C-6 methyl group is equatorial. The infrared and ultraviolet data, along with PMR, confirm the assigned structures for IV and V.

Biological Data—Progestational activity of these compounds (II–V) was quantitatively evaluated in the Clauberg test as described earlier (4). The dose and the McPhail index are recorded in Table II.

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TABLE I—Δ VALUES ($CDCl_3$–C_6H_6)[a] OF SECOSTEROIDS

Compd.	C_{18} $CDCl_3$	C_{18} C_6H_6	Δ	C_{19} $CDCl_3$	C_{19} C_6H_6	Δ	C_6 $CDCl_3$	C_6 C_6H_6	Δ
II	0.72	0.55	0.17	1.10	0.72	0.38	0.97	0.97	0
III	0.67	0.53	0.14	1.08	0.76	0.32	1.67	1.65	0.02
IV	0.63	0.56	0.07	1.05	0.77	0.28	0.97	0.95	0.02
V	0.62	0.60	0.02	1.03	0.70	0.33	0.84	0.91	0.13

[a] Values are in p.p.m. units.

TABLE II—PROGESTATIONAL POTENCY OF SECOSTEROIDS

Compd.	Total Dose, mg.	McPhail Index
II	5.0	0
III	5.0	0.3
IV	5.0	3.17
V	5.0	0.1

EXPERIMENTAL

All melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected. The ultraviolet and infrared data were obtained on Cary model 11 and Beckman IR-5 spectrophotometers, respectively. The proton magnetic resonance spectra were determined on a Varian A-60 spectrometer, in deuterochloroform and benzene, using tetramethylsilane as an internal standard (0 p.p.m.). All p.p.m. values are the centers of the signals. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

17α - Acetoxy - 6α - methyl - 3,5 - seco - 4 - norpregna-5,20-dion-3-oic Acid—A solution of 5.0 Gm. (0.013 mole) of 17α-acetoxy-6α-methylpregn-4-ene-3,20-dione in 30 ml. of ethyl acetate and 100 ml. of glacial acetic acid was cooled in an ice-water bath and ozonized for 1.5 hr. To this 5 ml. of 30% hydrogen peroxide was added, followed by 2000 ml. of water. The mixture was refrigerated for 2 hr. before adding an additional 100 ml. of water. The white semisolid was collected by filtration and dissolved in ether. The ethereal solution was extracted several times with 5% sodium hydroxide. The extracts were combined and acidified with concentrated hydrochloric acid. The cloudy solution was once again extracted with ether and the ether layer was washed several times with water until neutral to litmus. It was dried over sodium sulfate and evaporated to give a semisolid which could be recrystallized from ether–hexane to give 4.5 Gm. (79%) of 17α-acetoxy-6α-methyl-3,5-seco-4-norpregna-5,20-dion-3-oic acid, m.p. 216–218°. $[\alpha]_D$ +8.6° (1.0 c $CHCl_3$). $\lambda_{max.}^{CHCl_3}$ 2.81 μ, 5.77 μ, 5.85 μ. PMR in $CDCl_3$, 0.72 p.p.m. (C-18); 1.10 p.p.m. (C-19); 0.97 p.p.m. (C-6).

Anal.—Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.13; H, 8.44.

4 - Oxa - 17α - acetoxy - 6 - methylpregn - 5 - ene-3,20-dione—A solution of 1.0 Gm. (0.0025 mole) of 17α-acetoxy-6α-methyl - 3,5 - seco - 4 - norpregna-5,20-dion-3-oic acid in 12 ml. of acetic anhydride and 6 ml. of acetyl chloride was refluxed for 64 hr. The solvent was removed under reduced pressure and the solid residue was dissolved in ether. The ethereal solution was washed several times with 5% potassium hydroxide solution followed by water until neutral to litmus. It was then dried over sodium sulfate and evaporated. The solid residue was recrystallized from ether to give 800 mg. (84%) of 4-oxa-17α-acetoxy-6-methylpregn-5-ene-3,20-dione, m.p. 204–206°. $[\alpha]_D$ −77.9° (1.0 c $CHCl_3$) $\lambda_{max.}^{KBr}$ 5.75 μ, 5.82 μ. PMR in $CDCl_3$, 0.67 p.p.m. (C-18); 1.08 p.p.m. (C-19); 1.67 p.p.m. (C-6).

Anal.—Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.83; H, 8.37.

17α - Acetoxy - 6α - methyl - 3,5 - seco - 4 - norpregna - 5,20 - dione - 3 - carboxamide — 4 - Oxa-17α - acetoxy - 6α - methylpregn - 5 - ene - 3,20-dione (1.0 Gm., 0.0025 mole) was dissolved in 10 ml. of absolute alcohol saturated with ammonia and allowed to remain in the icebox for 3 days. The solution was added to a large amount of ice and water and extracted with ethyl acetate. The ethyl acetate layer was washed several times with water, dried over sodium sulfate, and evaporated to give a semisolid which was recrystallized from ethyl acetate–hexane. Analytically pure 17α-acetoxy-6α-methyl-3,5 - seco - 4 - norpregna - 5,20 - dione - 3-carboxamide (650 mg., 63%), m.p. 120–123°, was obtained by recrystallization from hexane–acetone. $[\alpha]_D$ +41.5° (1.0 c $CHCl_3$), $\lambda_{max.}^{KBr}$ 2.95 μ, 5.78 μ, 5.84 μ, 5.03 μ. PMR in $CDCl_3$, 0.63 p.p.m. (C-18); 1.05 p.p.m. (C-19); 0.97 p.p.m. (C-6).

Anal.—Calcd. for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.45. Found: C, 68.08; H, 9.03; N, 3.18.

17α - Acetoxy - 6α - methyl - 3,5 - seco - 4 - norpregna - 5,20 - dione - 3 - carboxmethylamide—4 - Oxa - 17α - acetoxy - 6 - methylpregn - 5 - ene-3,20-dione (600 mg., 0.0015 mole) was dissolved in 10 ml. of absolute alcohol saturated with methylamine and allowed to stand in the icebox for 3 days. The solution was poured into ice and water and extracted with methylene chloride. The organic layer was washed with dilute hydrochloric acid, followed by water, dried over sodium sulfate, and evaporated to give an oil. This was recrystallized from ethyl acetate–pentane to give 394 mg. (61%) of 17α - acetoxy - 6α-methyl-3,5-seco-4-norpregna- 3,20-dione-3-carboxymethylamide, m.p. 90–92°. $[\alpha]_D$ +29.7° (1.0 c $CHCl_3$). $\lambda_{max.}^{KBr}$ 2.95 μ, 5.76 μ, 5.86 μ, 6.05 μ. PMR in $CDCl_3$, 0.62 p.p.m. (C-18); 1.03 p.p.m. (C-19); 0.91 p.p.m. (C-6); 2.80 p.p.m. (N-CH_3); 5.95 p.p.m. (NH). No absorption in the ultraviolet.

Anal.—Calcd. for $C_{24}H_{37}NO_5$: C, 68.70; H, 8.89; N, 3.34. Found: C, 68.92; H, 8.83; N, 3.76.

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