To remove any doubts concerning its composition, the cardenolide IX was recrystallized from absolute ether–methanol and was dried at 150° for 4 hr. (0.1 mm.), giving anhydrous material[15] melting at 265–269°.

Anal. Calcd. for $C_{29}H_{42}O_{11}$: C, 61.46; H, 7.47. Found: C, 61.72; H, 7.76.

Tetra-O-acetyl-6′-hydroxyconvallatoxin (IXa).—To a solution of 1 ml. of acetic anhydride in 1.2 ml. of pyridine was added 50 mg. (0.085 mmole) of 6′-hydroxyconvallatoxin monohydrate (IX). After standing for 24 hr. at 0°, the mixture was poured into ice water, and was extracted with chloroform–ether (1:3). The extract thus obtained was washed successively with 5% aqueous sulfuric acid, 5% aqueous sodium bicarbonate, and water. After drying over sodium sulfate, the extract was filtered and evaporated *in vacuo*, giving 35 mg. (56%) of the tetraacetate IXa as amorphous powder. The material was further purified by chromatography on silicic acid (Fisher Reagent Grade, activated) and from the chloroform–ether (1:1), methanol–chloroform–ether (1:49.5:49.5), and methanol–chloroform–ether (5:47.5:47.5) eluates there was obtained pure IXa as amorphous powder, m.p. 128–133°. For analytical purposes the material was dried for 5 hr. at 80° (0.1 mm.).

Anal. Calcd. for $C_{37}H_{50}O_{15}$: C, 60.50; H, 6.86. Found: C, 60.42; H, 7.17.

(15) The desolvation was attended with considerable difficulty. When the monohydrate IX was heated at lower temperatures, even for long periods of time, no desolvation took place. Drying at 150° for periods longer than that prescribed (6–8 hr., for example) brought about some decomposition as evidenced in the analytical results which were high with respect to carbon.

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New Synthesis and Structure Activity Relationship in the 17-Alkylated Progesterone Series

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A new synthesis for 17α-alkylated pregnane derivatives, by reductive alkylation of 16-dehydro-20-keto-pregnanes, is described. Structure–activity relationships in the 17α-alkylprogesterone series are presented and compared with that of known substances. The probable biological role of substituents capable of imparting oral activity to these substances is discussed. The ability of blocking metabolic transformations or inactivation following oral administration is considered a major factor for activity in this series of steroid hormone analogs.

Progesterone is the least polar of all steroids of biological sources.[1] Besides its importance in pregnancy, it is an intermediate in the biosynthetic pathway of corticoids, androgens and estrogens.[2] Perhaps for this reason of biological economy all hydroxylated progesterones[3] are less active than their precursor; probably polarity and metabolic factors are more important than stereochemical ones in destroying the "progestational" activity. Molecules with drastically different stereochemistry like retroprogesterone[7] and Ehrenstein's 14-iso-17-iso-19-norprogesterone[8] are known to be active, but introduction of a single hydroxyl function in position 11, for instance, of progesterone is sufficient to greatly reduce its activity.[9]

Metabolic studies with radioactive progesterone have shown[11] that the steroid is cleared from blood plasma at an extremely fast rate and that degradation of the side chain (as determined from analysis of labeled carbon dioxide in the expired air) plays an important role in the metabolic fate of the hormone.

Other metabolic "inactivations" include hydroxylation at position 16α,[12,13] 17α,[14] reduction of the 20-ketone and inversion of the acetyl side chain to the thermodynamically less stable α configuration.[15]

Protection of the side chain is therefore an essential prerequisite for oral activity or absence of side effects due to metabolites, and 17α substituents meet at least partly this requirement. Halogens,[16] alkyl groups,[17] and acyloxy groups[18] have been found to increase the oral activity of the molecule; of these however, 17-halogenated progesterones were disappointing in humans,[19] and 17α-acetoxyprogesterones, known to

(1) R. V. Short, in "Hormones in Blood," Academic Press, London and New York, 1961, p. 379 ff.

(2) J. K. Grant, *Brit. Med. Bull.*, **18**, 99 (1962).

(3) One notable exception is 17α-hydroxyprogesterone, devoid of activity in the rabbit and humans, but 60 times as potent as progesterone in the Rockland–Swiss mouse (Hooker–Forbes assay) even by systemic injection.[4,5] The fact that enzymes responsible for 17α-hydroxylation are missing from rat and mouse adrenal cortex[2] is perhaps not coincidental. For a critical evaluation of the test *cf.* ref. 6.

(4) H. A. Salhanick, E. G. Holstrom, and M. X. Zarrow, *J. Clin. Endocrin. Metab.*, **17**, 667 (1957).

(5) T. R. Forbes, "Brook Lodge Symposium on Progesterone," Brook Lodge Press, Augusta, Michigan, 1961, p. 71.

(6) H. Weifenbach, *Endokrinologie*, **40**, 13 (1960).

(7) A. Bompiani and E. Moneta, *Ann. Ostet. Ginecol.*, **84**, 607 (1962).

(8) M. Ehrenstein, G. W. Barber, and R. Hertz, *Endocrinology*, **60**, 681 (1957).

(9) The high activity of Δ^{11}-progesterone[10] is possibly due to impeded metabolic hydroxylation at position 11.

(10) Ch. Meystre, E. Tschopp, and A. Wettstein, *Helv. Chim. Acta*, **31**, 1463 (1948).

(11) E. J. Plotz, "Brook Lodge Symposium on Progesterone," Brook Lodge Press, Augusta, Michigan, 1961, p. 91.

(12) H. I. Calvin and S. Lieberman, *Biochemistry*, **1**, 639 (1962).

(13) J. Zander, J. Thijssen, and A. M. von Münstermann, *J. Clin. Endocrin. Metab.*, **22**, 891 (1962).

(14) B. Little and A. Shaw, *Acta Endocrin.*, **36**, 455 (1961).

(15) L. R. Axelrod and J. W. Goldzieher, *J. Clin. Endocrin. Metab.*, **20**, 238 (1960).

(16) C. I. Chappel, C. Revesz, and R. Gaudry, *Acta Endocrin.*, **35**, (Suppl. 51), 915 (1960).

(17) R. Deghenghi, Y. Lefebvre, P. Mitchell, P. F. Morand, and R. Gaudry, *Tetrahedron*, **19**, 289 (1963).

(18) J. C. Stucki and E. M. Glenn, "Brook Lodge Symposium on Progesterone," Brook Lodge Press, Augusta, Michigan, 1961, p. 25.

(19) D. J. Marshall, private communication.

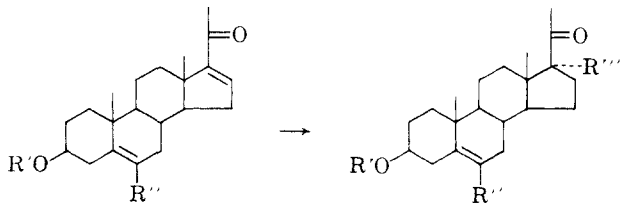
lose the ester group *in vivo*[20-22] may give rise to corticoid-like metabolites.

We have prepared and compared a series of 17α-alkylated progesterones and found that the oral activity (rabbit, Clauberg–McPhail test) increases in the order methyl < ethyl ≤ *n*-propyl and that the latter is as active as 17α-acetoxyprogesterone. The stability of our alkylated derivatives was shown by the fact that no degradation of the side chain was observed following *in vitro* incubation with several microorganisms, like *Septomyxa affinis* and *Streptomyces lavendulae* known to degrade 17-unsubstituted or hydroxylated progesterones.[23]

In Table I, we compare the endometrial proliferating activity of some 17α-alkylated progesterones as evidenced by the McPhail–Clauberg test in the rabbit, with other mono- or disubstituted compounds. The effect of substitutions in position 6 followed the observed pattern as in the 17α-acetoxy series[24] with increasing activity in the order: halogens (α), CH_3 (α), Δ^6-CH_3 and Δ^6-Cl.[25]

The most potent derivatives in the oral Clauberg test are 17α-methyl-6-chloro-6-dehydroprogesterone[17] and 17α-ethyl-6-methyl-6-dehydroprogesterone.

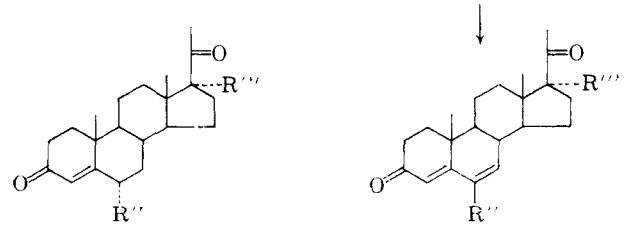
Somewhat surprising was the decrease in oral activity following introduction of a fluorine atom in position 21. These 21-fluorinated derivatives were, however, more active than their parent compounds upon



I II

a, R′ = Ac, R″ = H
b, R′ = Ac, R″ = CH_3

a, R′ = Ac, R″ = H, R‴ = C_2H_5
b, R′ = H, R″ = H, R‴ = C_2H_5
c, R′ = Ac, R″ = CH_3, R‴ = C_2H_5
d, R′ = Ac, R″ = H, R‴ = *n*-C_3H_7
e, R′ = H, R″ = CH_3, R‴ = CH_3
f, R′ = Ac, R″ = H, R‴ = CH_3
g, R′ = Ac, R″ = CH_3, R‴ = CH_3
h, R′ = H, R″ = CH_3, R‴ = C_2H_5



III IV

a, R″ = H, R‴ = C_2H_5
b, R″ = CH_3, R‴ = C_2H_5
c, R″ = H, R‴ = *n*-C_3H_7

a, R″ = CH_3, R‴ = C_2H_5
b, R″ = H, R‴ = C_2H_5
c, R″ = Cl, R‴ = C_2H_5
d, R″ = CH_3, R‴ = CH_3

(20) E. Castegnaro and C. Sala, *J. Endocrinol.*, **24**, 445 (1962).
(21) R. Sciaky, *Gazz. Chim. Ital.*, **92**, 539 (1962).
(22) M. L. Hellmreich and R. A. Hoseby, *J. Clin. Endocrin. Metab.*, **22**, 1018 (1962).
(23) C. Vézina, private communication.
(24) H. J. Ringold, in "Mechanism of Action of Steroid Hormones," Pergamon Press, New York, N. Y., 1961, p. 200 ff.
(25) The fact that introduction of a 6,7-double bond increases the activity may be correlated with the observed *in vivo* metabolic hydroxylation in position 6β of 6α-methylprogesterones.[26]

TABLE I

DERIVATIVES OF PROGESTERONE

No.	6	17α	21	Δ	Clauberg oral[a] relative potency: s.c. (Progesterone = 1)	Clauberg oral (Norethindrone = 1)	Reference
1		OAc			>2	0.1	26
2	α-CH_3	OAc			20	10	27
3		Br			2	0.04	28
4		CH_3			2	.05	29
5		C_2H_5			>2	1	31
6		*n*-C_3H_7			<2	.1	31
7	α-CH_3	CH_3			5	1	32
8	α-CH_3	H			..	<0.1	33
9	CH_3	Br		6	<1	<1	34
10	CH_3	CH_3		6	5	10	32
11	CH_3	H		6	..	<1	35
12	α-CH_3	C_2H_5			<10	<5	31
13	CH_3	C_2H_5		6	5	20	31
14		H	F		2	<0.05	36
15		CH_3	F		>10	<0.1	17
16		CH_3	F	1	<5	<1	17
17	α-CH_3	CH_3	F		10	<1	17
18	CH_3	CH_3	F	6	10	<10	17
19	α-F	H			5	<0.3	37
20	α-F	Br			4	0.3	38
21	α-F	CH_3			>5	3	17
22	α-F	CH_3		1	<5	3	17
23	α-F	CH_3	F		10	<10	17
24	α-F	H		1	<10	<0.3	37
25	α-Cl	CH_3			<5	<1	17
26	Cl	CH_3		6	10	20	17
27	Cl	CH_3	F	6	5	10	17
28	Cl	C_2H_5		6	<10	<20	31

[a] Progesterone: s.c. daily dose 0.1 mg. (+4) per rabbit; norethindrone: oral daily dose 0.5 mg. (+4) per rabbit. The notation < indicates that the end point (+4) was not reached at the dose level tested.

subcutaneous administration. From our comparison, it is evident that "both" 6 and 17 substituents have to be present in our series for high oral activity; their main function is probably a block of metabolic inactivation. Subcutaneously, 17α-*n*-propylprogesterone is less active than its lower homolog. The relationship between structure and other types of activity, like the maintenance of pregnancy and ovulation inhibition, in this class of compounds will be discussed in successive papers.

The 17α-alkyl substituents (other than methyl) in our progesterone derivatives were introduced by reductive alkylation[30,39,39a] of a Δ^{16}-20-ketone function as in I.

(26) R. B. Turner, *J. Am. Chem. Soc.*, **75**, 3489 (1953).
(27) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stoeckl, L. E. Barnes, and W. E. Dulin, *ibid.*, **80**, 2904 (1958).
(28) C. R. Engel and H. Jahke, *Can. J. Biochem. Physiol.*, **35**, 1017 (1957).
(29) Pl. A. Plattner, H. Heusser, and P. Th. Herzig, *Helv. Chim. Acta*, **32**, 270 (1949).
(30) R. Deghenghi and R. Gaudry, *Tetrahedron Letters*, 489 (1962).
(31) This work, see Experimental.
(32) R. Deghenghi and R. Gaudry, *J. Am. Chem. Soc.*, **83**, 4068 (1961).
(33) D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4092 (1957).
(34) P. Mitchell, unpublished results from these Laboratories.
(35) P. de Raggieri, *Ann. Chim.*, **49**, 1371 (1959).
(36) P. Tamburini, R. J. Pratt, and E. V. Jensen, *J. Am. Chem. Soc.*, **78**, 2658 (1958).
(37) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958).
(38) Ch. R. Engel and R. Deghenghi, *Can. J. Chem.*, **38**, 452 (1960).
(39) G. Stork, P. Rosen, and N. L. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961).
(39a) NOTE ADDED IN PROOF.—After submission of this paper to the Editor, a preliminary communication by M. J. Weiss, *et al.* [*Chem. Ind.* (London), 118 (1963)], describing essentially the same alkylation procedure appeared.

Conventional Oppenauer oxidation gave the progesterones III, whereas addition of chloranil to the Oppenauer mixture afforded smoothly the dienones IV.

Experimental

Optical rotations were determined as 1% solutions in chloroform at 23°; ultraviolet spectra were determined in ethanolic solution. Melting points are corrected.

17α-Methylpregnenolone Acetate (IIf).—Lithium wire (1.3 g.) was dissolved (30 min.) in 250 ml. of liquid ammonia and cooled in a Dry Ice–acetone bath. A solution of 5.0 g. of 16-dehydropregnenolone acetate (16-DPA) (Ia) in 100 ml. of tetrahydrofuran freshly distilled from lithium aluminum hydride was added dropwise while stirring, followed by a solution of 20 ml. of methyl iodide in 60 ml. of anhydrous ether also added dropwise to the still blue mixture. The blue color disappeared during this addition. The cold bath was removed and liquid ammonia was slowly replaced by additional ether while stirring. The mixture was diluted with ether and washed with water to neutrality. An oil (4.82 g.) was obtained, representing crude 17α-methylpregnenolone. This substance was acetylated with 5 ml. of acetic anhydride and 20 ml. of pyridine on a steam bath for 1 hr., or alternatively overnight at room temperature. Usual working up gave 5.2 g. of crude acetate which was chromatographed on neutral alumina (Woelm III). Petroleum ether–benzene (4:1) eluted crystalline fractions (ca. 1.0 g.) m.p. 179–180° which were combined after thin layer chromatography (t.l.c.) checking for homogeneity. This product was identical with an authentic sample.[29]

17α-Ethylpregnenolone Acetate (IIa).—To a solution of 3.9 g. of lithium in 750 ml. of liquid ammonia was added 15.0 g. of 16-DPA (Ia) in 270 ml. of tetrahydrofuran followed by 43 ml. of ethyl iodide in 180 ml. ether. The usual working up gave 14.52 g. of a foam which was reacetylated with 15 ml. of acetic anhydride in 60 ml. of pyridine to give 15.87 g. of crude acetate. This was chromatographed on 450 g. of alumina (Woelm III). Petroleum ether–benzene (5:1) eluted 6.6 g. of crystalline fractions combined after t.l.c. proof of homogeneity. A sample was recrystallized to m.p. 178–180°, $[\alpha]^{23}D$ −61° (1%, $CHCl_3$).

Anal. Calcd. for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91. Found: C, 77.71; H, 9.88.

17α-Ethylpregnenolone (IIb).—The acetate (IIa) was hydrolyzed to the corresponding 17α-ethylpregnenolone by alkaline treatment in the usual manner, m.p. 199–202° (from acetone).

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.05; H, 10.33. $[\alpha]^{23}D$ −65.4° (1%, $CHCl_3$). Nuclear magnetic resonance spectra confirmed the proposed structure. The optical rotatory dispersion curve was superimposable to that of 17α-methylpregnenolone acetate.

17α-Ethylprogesterone (IIIa).—A quantity of 2.1 g. of IIb was oxidized according to Oppenauer (100 ml. of toluene, 24 ml. of cyclohexanone, 2.0 g. of aluminum isopropoxide) in the usual manner to give 2.1 g. of yellow crystals, filtered over 40 g. of alumina (Woelm III). Petroleum ether–benzene (4:1) and benzene eluted the product (2.0 g.) which was recrystallized from ether to m.p. 148–150°, $[\alpha]^{23}D$ +93.3° (1% $CHCl_3$); λ_{max} 241 mμ ε 19,000.
Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.58; H, 10.14.

17α-Propylpregnenolone Acetate (IId).—Lithium wire (3.9 g.) was dissolved in 750 ml. of liquid ammonia. A solution of 15.0 g. of 16-dehydropregnenolone acetate in 275 ml. of tetrahydrofuran was added dropwise, followed by a solution of 50 ml. of *n*-propyl iodide in 180 ml. of anhydrous ether. The usual work up gave a residue which was acetylated overnight at room temperature with 15 ml. of acetic anhydride in 60 ml. of pyridine to give 16.31 g. of crude acetate. This product was chromatographed on 450 g. of alumina (Woelm III), the column being filled with a petroleum ether–benzene (9:1) mixture. Twenty-three fractions were eluted with petroleum ether–benzene (9:1). Fractions 24 to 37 were eluted with petroleum ether–benzene (4:1), fractions 38 to 44 with a 1:1 mixture, fractions 45–50 with pure benzene. Fractions 8 to 16 were combined and recrystallized from ether and provided the analytical sample, m.p. 168–171°, $[\alpha]^{23}D$ −66.7° (1%, $CHCl_3$).

Anal. Calcd. for $C_{26}H_{40}O_3$: C, 77.95; H, 10.07. Found: C, 77.73; H, 10.00. The mother liquors of the analytical sample were combined with fractions 5, 6, 7 (t.l.c.) to give a total of 2.06 g. of IId.

17α-Propylprogesterone (IIIc).—A quantity of IId (2.06 g.) was refluxed on a steam bath under nitrogen with 25 ml. of a 4% methanolic sodium hydroxide solution for 30 min. The usual work up gave 1.738 g. of crude 17α-propylpregnenolone as a yellow oil. Without purification this was oxidized according to Oppenauer, with 130 ml. of toluene, 25 ml. of cyclohexanone and 1.8 g. of aluminum isopropoxide. Part of the toluene (60 ml.) was distilled and refluxing was maintained for 1 hr. The usual work up gave 1.740 g. of crude IIIc. This was chromatographed over 55 g. of alumina. Petroleum ether–benzene (9:1) and 4:1 fractions were combined and recrystallized for analysis (from ether), m.p. 153–155°, $[\alpha]^{23}D$ +88.9° (1%, $CHCl_3$); λ_{max} 240 mμ, ε 17,200.

Anal. Calcd. for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 81.16; H, 10.26.

6,17-Dimethylpregnenolone Acetate (IIg).—A quantity of 5.0 g. of 6-methyl-16-dehydropregnenolone acetate[33] in 100 ml. of dry tetrahydrofuran was added dropwise to a stirred solution of 1.3 g. of lithium in 250 ml. liquid ammonia. A solution of 10 ml. of methyl iodide in 60 ml. of ether was added during 5 min. and stirring was continued for 15 min. The usual work up gave 5.0 g. of colorless foam which was reacetylated on a steam bath with 5 ml. of acetic anhydride in 25 ml. of pyridine for a period of 1 hr. The isolated crude acetate weighed 5.14 g. This was chromatographed on 150 g. of alumina (Woelm III). Petroleum ether–benzene (4:1) fractions eluted 2.142 g. of crystalline material, recrystallized from ether–hexane for analysis, m.p. 137–138°, $[\alpha]^{23}D$ −65.0° (1%, $CHCl_3$).

Anal. Calcd. for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91. Found: C, 78.03; H, 10.01.

6,17-Dimethylpregnenolone (IIe).—A quantity of 2.142 g. of acetate IIg was hydrolyzed with methanolic potassium hydroxide (0.5 g. in 10 ml.) at room temperature for 3.5 hr. The usual work up gave 1.876 g. of crystalline product, m.p. 185–187°, $[\alpha]^{23}D$ −61.5° (1%, $CHCl_3$).

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.84; H, 10.24.

6-Methyl-17-ethylpregnenolone Acetate (IIa).—6-Methyl-16-dehydropregnenolone acetate[33] (15.0 g.), dissolved in 300 ml. of tetrahydrofuran, was added dropwise during 10 min. to a solution of 3.9 g. of lithium in 750 ml. of liquid ammonia (Dry Ice–acetone bath), followed by a dropwise addition of 50 ml. of ethyl iodide in 180 ml. of dry ether. The organic layer was washed to neutrality with water, dried and evaporated to give 15.155 g. of a yellowish foam, which was acetylated overnight with 15 ml. of acetic anhydride in 60 ml. of pyridine at room temperature. The usual work up gave 15.77 g. of crude acetate which was chromatographed on 400 g. of alumina (Woelm III). Petroleum ether–benzene (6:1) eluted 5 g. of crystalline product. A sample was recrystallized for analysis from acetone-water, m.p. 141–144° $[\alpha]^{23}D$ −72.6° (1%, $CHCl_3$).

Anal. Calcd. for $C_{26}H_{40}O_3$: C, 77.95; H, 10.07. Found: C, 77.62; H, 10.24.

6-Methyl-17α-ethylpregnenolone (IIh).—A quantity of 4.832 g. of IIc was hydrolyzed with 50 ml. of methanol containing 1.5 g. of sodium hydroxide in 2 ml. of water at reflux under nitrogen for 30 min. Usual work up gave 4.2 g. of crystalline product. The analytical sample melted at 233–237° (from acetone), $[\alpha]^{23}D$ −67.5° (1%, $CHCl_3$).

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.67; H, 10.72.

6α-Methyl-17α-ethylprogesterone (IIIb).—The pregnenolone derivative IIh (4.01 g.) was oxidized according to Oppenauer with 40 ml. of cyclohexanone, 200 ml. of toluene and 4 g. of aluminum isopropoxide at the reflux temperature for 1 hr. The usual work up gave 4.146 g. of a yellow oil which was dissolved in 100 ml. of methanol containing 0.25 g. of sodium hydroxide in 0.5 ml. of water. It was refluxed for 1 hr. under nitrogen, and the cooled solution was acidified with acetic acid to pH 4.5. The solvent was evaporated, the residue extracted with ether, washed with water and dried to give 3.992 g. of a yellow oil. This was chromatographed on 120 g. of Al_2O_3 (Woelm III). Petroleum ether–benzene (1:1) eluted crystalline fractions (2.3 g.). A sample was recrystallized for analysis, m.p. 149–151° (from ether), $[\alpha]^{23}D$ +77.8° (1%, $CHCl_3$); λ_{max} 241 mμ, ε 16,250.

Anal. Calcd. for $C_{24}H_{36}O_2$: C, 80.85; H, 10.10. Found: C, 80.61; H, 10.16.

6-Methyl-17α-ethyl-6-dehydroprogesterone (IVa).—The progesterone derivative IIIb (2.212 g.) was dehydrogenated[40] with

(40) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **79**, 1257 (1957).

1.7 g. of chloranil in 65 ml. of refluxing isobutyl alcohol for 10 hr. Work up gave 2.3 g. of a yellow oil which was chromatographed on 200 g. of Florisil. Ethyl acetate–benzene (2% and 5%) fractions eluted the product as yellow crystals (1.358 g.), m.p. 181–184° (from ether). The analytical sample had m.p. 183–185°, $[\alpha]^{23}D$ +52° (1%, $CHCl_3$) λ_{max} 294 mμ ε 23,400.

17α-Ethyl-6-dehydroprogesterone (IVb).—A quantity of 3.985 g. of 17α-ethylpregnenolone (IIb) was dissolved in 160 ml. of toluene. Part of the solvent (35 ml.) was distilled and 35 ml. of cyclohexanone, 3.9 g. of aluminum isopropoxide and 3.9 g. of chloranil were added. The mixture was refluxed for 1 hr. Work up gave 3.768 g. of anamorphous material, which was chromatographed on 110 g. of alumina (Woelm III). The petroleum ether–benzene (1:1) fractions contained IVb. A sample was purified for analysis through thick layer chromatography (system: CCl_4–EtOAc, 4:1), m.p. 170–173°, $[\alpha]^{23}D$ +48.5° (1%, $CHCl_3$), λ_{max} 287 mμ ε 25,900.

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 81.10; H, 9.31.

6-Chloro-17α-ethyl-6-dehydroprogesterone (IVc).—To a quantity of 1.98 g. of the 6-dehydro compound IVb dissolved in 50 ml. of dry methylene chloride was added 95 ml. of a 0.364 *N* solution of monoperphthalic acid in ether. After 65 hr. the mixture was washed with sodium bicarbonate solution and water to give 1.945 g. of a partly crystalline residue. Some starting material was shown to be present by thin layer chromatography. Crystallization from ether gave 675 mg. of 6α,7α-epoxide, m.p. 215–228° dec. Without purification, this epoxide was dissolved in 25 ml. of acetic acid and the solution saturated with dry hydrochloric acid for 5 min., then left at room temperature for 16 hr.[41] Extraction with ether and washing to neutrality gave, after evaporation, 0.690 g. of a yellow oil which crystallized from ether to give 0.284 g. of IV as needles, m.p. 172–175°. A sample was recrystallized for analysis, m.p. 177–179°, $[\alpha]^{23}D$ +30.9° (1%, $CHCl_3$), λ_{max} 288 mμ ε 24,800.

Anal. Calcd. for $C_{23}H_{31}ClO_2$: C, 73.68; H, 8.33; Cl, 9.45. Found: C, 73.87; H, 8.67; Cl, 9.28.

6,17-Dimethyl-6-dehydroprogesterone (IVd).—6,17-Dimethylpregnenolone (IIe) (2.35 g.) was dissolved in 120 ml. of toluene and 24 ml. of distilled cyclohexanone. Part of the solvent (30 ml.) was distilled to remove traces of water. Aluminum isopropoxide (2.4 g.) and 2.4 g. of chloranil were added, and the mixture was stirred and refluxed for 1 hr. It was diluted with ether and washed with 5% sodium hydroxide solution until colorless washings were obtained, then with water. The organic layer was evaporated, then steam distilled to remove the excess cyclohexanone. A slightly yellow residue (2 g.) was obtained which was purified on a column of alumina (Woelm III). Petroleum ether–benzene (4:1 and 1:1) eluted crystalline fractions (1.283 g.) which were recrystallized from ether to give 0.813 g. of IVd, m.p. 144–146°, identical with an authentic sample.[32]

(41) L. H. Knox, J. A. Zderic, J. P. Ruelas, C. Djerassi, and H. J. Ringold, *J. Am. Chem. Soc.*, **82**, 1230 (1960).

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Some 3-Phenyl Derivatives of Pregnane-11,20-dione

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The addition of phenylmagnesium bromide to pregnane-3,11,20-trione 20-ethylene ketal (III) yielded both epimeric alcohols, which were separated and characterized. After removal of the protective ketal, a series of 3-phenyl substituted pregnane-11,20-diones was prepared, none of which showed any aldosterone antagonist activity.

The observation that steroids possessing a spirolactone function at C-17 are able to inhibit competitively[1] the mineral-corticoid activity of aldosterone revealed an entirely new field of pharmacological interest. However, in the interval since the original disclosures,[2] no clinically useful activity-enhancing groups have been found although much work has been expended in that direction.[3] This disappointing phenomenon has provided the impetus for a search for other compounds also capable of exerting the same biological function.

The proposition that lactones are uniquely capable of inhibiting the action of aldosterone seems untenable, *e.g.*, this activity is also well documented for progesterone.[4] In addition a low order of activity has been claimed for numerous other steroids.[5] Accordingly, the possibility that the activity of a derivative other than a lactone might be enhanced by the application of classical antimetabolite concepts[6] was examined. In particular, it was felt that increasing the "back-side bulk" of progesterone might lead to an interesting aldosterone antagonist. The synthesis of such a compound, 3α-phenyl-3β-hydroxypregnane-11,20-dione (Va) is the subject of this paper.

The acid-catalyzed reaction of ethylene glycol with 3α-acetoxypregnane-11,20-dione resulted in hydrolysis of the acetate functionality as well as ketal formation to give the previously described II.[7] Oxidation readily afforded the desired substrate (III) for the addition of phenylmagnesium bromide. As expected, the

(1) C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1957).

(2) (a) J. A. Cella and C. M. Kagawa, *J. Am. Chem. Soc.*, **79**, 4808 (1957); (b) J. A. Cella and R. C. Tweit, *J. Org. Chem.*, **24**, 1109 (1959).

(3) (a) J. A. Cella, E. A. Brown, and R. R. Burtner, *ibid.*, **24**, 743 (1959); (b) E. A. Brown, R. D. Muir, and J. A. Cella, *ibid.*, **25**, 96 (1960); (c) S. Kaufmann, *ibid.*, **26**, 5197 (1961).

(4) (a) R. L. Landau and K. L. Lugibihl, *J. Clin. Endocrinol. Metab.*, **18**, 1237 (1958); (b) H. P. Jorgensen and P. Eilersen, *Acta Med. Scand.*, **168**, 55 (1960).

(5) (a) A. A. Patchett, F. Hoffman, F. F. Giarrusso, H. Schwam, and G. E. Arth, *J. Org. Chem.*, **27**, 3822 (1962); (b) R. Neher, Ch. Meystre, and A. Wettstein, *Helv. Chim. Acta*, **42**, 132 (1959); (c) T. Nakao, K. Hiraga, T. Saito, and Y. Muragama, Acta Endocrinol. Suppl. 51 (First International Congress of Endocrinology, Copenhagen), Session IIIb, No. 94 (1960).

(6) D. W. Wooley, "A Study of Antimetabolites," John Wiley & Sons, Inc., New York, N. Y., 1952.

(7) G. Rosenkranz, J. Pataki, and C. Djerassi, *J. Org. Chem.*, **17**, 230 (1952).