TABLE I

No.	Benzalmalononitrile	Formula	Solvent	Recryst. Solvent	M.P.	Anal. N Calcd.	Anal. N Found
I	3,4-Diethoxy	$C_{14}H_{14}N_2O_2$	None	Ethanol	104–4.5°	11.57	11.40
II	3-Ethoxy-4-hydroxy	$C_{12}H_{10}N_2O_2$	Ethanol	Ethanol	161.5°	13.08	13.04
III	3-Ethoxy-4-acetoxy	$C_{14}H_{12}N_2O_3$	None	Benzene–heptane	84.5°	10.93	10.91
IV	4-Acetoxy	$C_{12}H_8N_2O_2$	None	Benzene-heptane	111.0°	13.20	13.04
V	3-Acetoxy	$C_{12}H_8N_2O_2$	None	Benzene-heptane	71.0°	13.20	12.92
VI	3-Methoxy-4-acetoxy	$C_{13}H_{10}N_2O_3$	None	Benzene-heptane	122.0°	11.57	11.58
VII	3-Ethoxy-4-hydroxy-5-bromo	$C_{12}H_9BrN_2O_2$	Ethanol	Benzene-heptane	175.0°	9.56	9.32
VIII	3-Methoxy-4-acetoxy-5-bromo	$C_{13}H_9BrN_2O_3$	Ethanol	Benzene-heptane	156.5°	8.72	8.56
IX	3-Ethoxy-4-acetoxy-5-bromo	$C_{14}H_{11}BrN_2O_3$	Ethanol	Benzene-heptane	128.0°	8.36	8.43
X	3-Methoxy-4-hydroxy-5-bromo	$C_{11}H_7BrN_2O_2$	Dioxane	Benzene-heptane	176.5°	10.04	9.77

cipitate was formed, 9.4 g. (80% yield). This was recrystallized from a benzene-hexane solvent, m.p. 83.5–84.0°.

Anal. Calcd. for $C_{11}H_{13}BrO_4$: C, 46.00; H, 3.88. Found: C, 46.32; H, 4.12.

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Attempts to Prepare New Progestational Agents: Synthesis and Biological Activity of 11β-Acyloxyprogesterones

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Received June 20, 1957

Although 17α-hydroxyprogesterone is essentially devoid of progestational activity, esterification of the hydroxyl group at C-17 produces compounds with long-acting progestational properties both in animals and in man.[1] In an attempt to synthesize new progestational agents, derivatives of 11β-hydroxyprogesterone were prepared and tested. Although 11β-hydroxyprogesterone itself has no activity,[2] it was hoped that esterification of the free hydroxyl group would produce results similar to those obtained with 17α-hydroxyprogesterone.

The compounds prepared for testing were: 11β-formyloxyprogesterone (XIV), 11β-acetoxyprogesterone (XV), 11β,17α-diformyloxyprogesterone (XIX), 11β,17α-diacetoxyprogesterone (XX), 11β-acetoxy-17α-caproyloxyprogesterone (XVII), and 11β-acetoxy-17α-formyloxyprogesterone (XVIII).

Compounds XIV, XIX, and XX were prepared by acylation of the corresponding 4,5-dihydro compound [11β-hydroxypregnane-3,20-dione (IV) or 11β,17α-dihydroxypregnane-3,20-dione (V)], followed by bromination at C-4, and dehydrobromination in the usual fashion. Attempted acetylation of IV gave an oil which could not be crystallized. 11β-Acetoxypregnane-3,20-dione (VII) could be prepared by acetylation of 3α,11β-dihydroxypregnane-20-one to give the diacetate, partial hydrolysis to the 11-monoacetate, followed by oxidation at C-3 to give VII. However, 11β-acetoxyprogesterone (XV) prepared from this could not be obtained crystalline.

The mixed esters (XVII and XVIII) were prepared by direct acylation of 11β-acetoxy-17α-hydroxyprogesterone (XVI).

Bioassays for progestational activity were done according to the method of McPhail.[3] Immature virgin female rabbits were primed with 3.3 micrograms of estradiol benzoate on alternate days for six days, followed by daily injections of the test compound for five days. The compounds were dissolved in sesame oil, and injected subcutaneously.

The animals were killed on the day following the last injection. The uterus was dissected out, trimmed of fat and connective tissue, and weighed. Pieces of both uterine horns were removed and fixed in 10% formalin. Sections were cut at 5 microns and stained with hematoxylin-eosin.

Sections were scored for the degree of endometrial proliferation from 1+ to 4+ by comparison with standard slides of progesterone treated rabbits at high, medium, and low dose. Animals receiving estradiol benzoate alone were used as controls.

Three compounds exhibited progestational ac-

(1) K. Junkmann, *Arch. exp. Pathol. Pharmakol.*, **223**, 244 (1954); M. Davies and G. Wied, *J. Clin. Endocrinol. and Metabolism*, **15**, 923 (1955).

(2) *Cf.* E. Mardones, R. Iglesias, and A. Lipschutz, *Nature*, **174**, 839 (1954).

(3) M. K. McPhail, *J. Physiol.*, **83**, 145 (1934).

tivity, but of a much lower order than progesterone. The 11β,17α-diacetoxyprogesterone (XX) had one-fifth the activity of progesterone, and both 11β,17α-diformyloxyprogesterone (XIX) and 11β-acetoxy-17α-caproyloxyprogesterone (XVII) had one-thirteenth the activity of progesterone. Compounds XIV, XV, XVI, and XVIII did not possess progestational activity.

It can be concluded that the introduction of an 11β-acyloxy group into active progestins results in a marked decrease in activity.

EXPERIMENTAL[4]

11β-Acetoxy-17α-formyloxyprogesterone (XVIII). A solution of 0.25 g. of 11β-acetoxy-17α-hydroxyprogesterone (XVI)[5] in 5 ml. of anhydrous formic acid containing 25 mg. of *p*-toluenesulfonic acid was allowed to stand at room temperature for 23 hr., then poured into water. The precipitated solid was removed by filtration, dried, and crystallized from acetone-hexane to yield 0.16 g. of XVIII, m.p. 240–246°. The analytical sample, crystallized once more, melted at 242–246°, $[\alpha]_D$ +116.2° (dioxane), λ_{max}^{MeOH} 238 mμ (ϵ 17,200).

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.17; H, 7.65.

11β-Acetoxy-17α-caproyloxyprogesterone (XVII). A mixture of 0.50 g. of XVI, 20 ml. of benzene, 0.69 ml. of caproic anhydride, and 0.10 g. of *p*-toluenesulfonic acid was refluxed for 15 min., then allowed to stand at room temperature for 48 hr. and finally poured into water, stirred one hour, and extracted with methylene chloride. The organic extracts were washed with dilute sodium hydroxide solution, water, and dried. Evaporation of the solvent left 0.55 g. of a resin which was chromatographed on Florisil. Material eluted with 50% benzene-hexane was crystallized from hexane to give 0.10 g., m.p. 134.0–136.0°, $[\alpha]_D$ +73.8° (dioxane), λ_{max}^{MeOH} 239 mμ (ϵ 16,100).

Anal. Calcd. for $C_{29}H_{42}O_6$: C, 71.57; H, 8.70. Found: C, 71.50; H, 8.65.

11β-Formyloxypregnane-3,20-dione (VI). A solution of 1.00 g. of 11β-hydroxypregnane-3,20-dione (IV)[6] in 10 ml. of anhydrous formic acid containing 10 mg. of *p*-toluenesulfonic acid was allowed to stand overnight at room temperature, then poured into water and extracted with methylene chloride. The organic extracts were washed with dilute sodium bicarbonate solution and water, dried, and evaporated to 1.07 g. of a resin. Addition of ether gave 0.79 g. of crystals, which was crystallized from acetone-hexane to yield 0.52 g., m.p. 131–133°. The analytical sample, crystallized from aqueous methanol, melted at 134.6–136.0°, $[\alpha]_D$ +131.4° (dioxane).

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.31, 73.47; H, 9.14, 9.04.

11β-Formyloxyprogesterone (XIV). A solution of 0.50 g. of VI in 15 ml. of acetic acid was brominated by the addition of 0.23 g. of bromine in 5 ml. of acetic acid; decolorization was complete in less than two minutes. The solution was then poured into water and the precipitated solid removed by filtration and dried: weight 0.55 g. This was dissolved in 40 ml. of *tert*-butyl alcohol and 15 ml. of methylene chloride, then 0.31 g. of semicarbazide was added and the mixture stirred overnight at room temperature. The solvents were removed under reduced pressure, water added, and the solids removed by filtration: weight 0.56 g. This was dissolved in 12 ml. of acetic acid and 3 ml. of water containing 3 ml. of 85% pyruvic acid and the mixture allowed to react for 72 hours at room temperature, then poured into water and extracted with methylene chloride. The organic extracts were washed with dilute sodium bicarbonate solution and water, then dried and evaporated to yield 0.40 g. of a resin. This was dissolved in benzene and chromatographed on Florisil. Material eluted with 50% benzene–methylene chloride, 100% methylene chloride and 1% methanol–methylene chloride was crystallized from ether to give 90 mg. of XIV, m.p. 157–161°, λ_{max}^{MeOH} 239 mμ (ϵ 15,900).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 74.00; H, 8.61.

11β,17α-Diformyloxyprogesterone (XIX). A solution of 1.00 g. of 11β,17α-diformyloxypregnane-3,20-dione[7] in 1.5 ml. of methylene chloride and 15 ml. of *tert*-butyl alcohol was brominated by the addition of a solution of 0.41 g. of bromine in 10 ml. of methylene chloride; the bromine color was discharged in 4 hr. About half of the organic solvent was removed under reduced pressure and the remainder poured into water to give 1.13 g. of crude 4-bromide (XII). This material was dissolved in 23 ml. of *tert*-butyl alcohol and 17 ml. of C.P. chloroform, 0.52 g. of semicarbazide was added and the mixture stirred under nitrogen for 2.5 hr. The solution was distilled under reduced pressure to *ca.* 0.5 volume and water added to precipitate 1.16 g. of crude semicarbazone. This was dissolved in 20 ml. of acetic acid containing 2 ml. of water, and 2.15 g. of 85% pyruvic acid was added under a CO_2 atmosphere. The resulting solution was allowed to stand at room temperature for 72 hr., then poured into water to precipitate 0.93 g. This was chromatographed on Florisil and the fractions eluted with 50% benzene–methylene chloride, 100% methylene chloride and 1% methanol–methylene chloride were combined and crystallized from acetone-hexane to give 0.20 g. of XIX. The analytical sample, crystallized from aqueous methanol, melted at 228–234°, λ_{max}^{MeOH} 238 mμ (ϵ 12,900).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 68.63; H, 7.51. Found: C, 68.35; H, 7.73.

11β,17α-Diacetoxypregnane-3,20-dione (IX). A solution of 1.0 g. of 11β,17α-dihydroxypregnane-3,20-dione (V) in 10 ml. of acetic acid and 2 ml. of acetic anhydride containing 0.1 g. of *p*-toluenesulfonic acid was allowed to stand at room temperature overnight, then poured into water. The precipitated solid was removed by filtration, dried, and crystallized from ether to yield 0.71 g. of IX, m.p. 241.5–244°. The analytical sample, crystallized twice from ether-hexane, melted at 245.0–246.5°, $[\alpha]_D$ +29.7° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.32; H, 8.36.

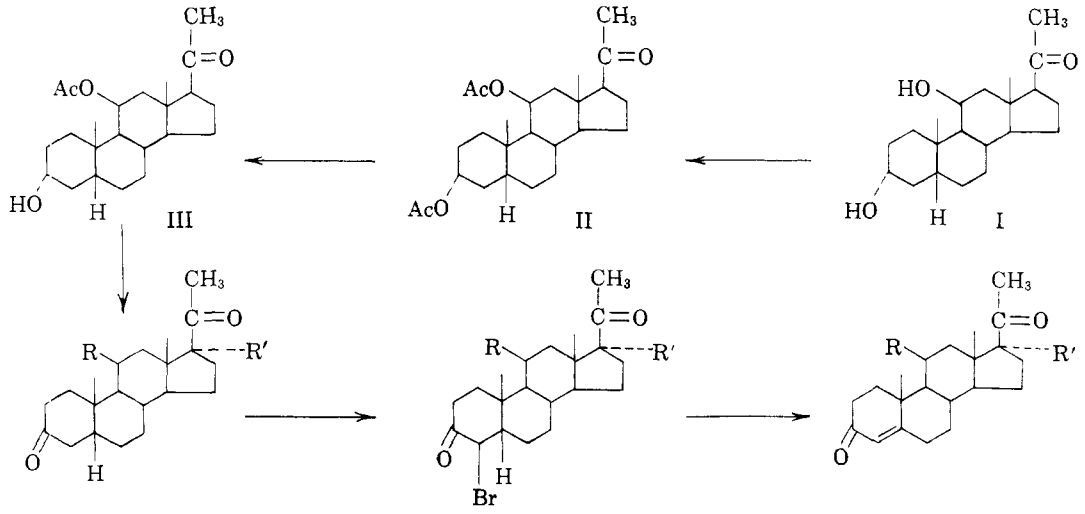
11β,17α-Diacetoxyprogesterone (XX). A solution of 0.865 g. of IX in 3 ml. of methylene chloride and 15 ml. of *tert*-butyl alcohol was brominated at room temperature by the addition of 0.33 g. of bromine in 5 ml. of *tert*-butyl alcohol; the mixture was decolorized in *ca.* 4 hr. It was then concentrated under reduced pressure to about 5 ml., then poured into water, and the precipitated solid removed by filtration and air dried. Trituration with ether, followed by crystallization from aqueous acetone, gave 0.70 g. of 4-bromide (XIII), m.p. 194–200° dec. A solution of 511 mg. of XIII in 5 ml. of methylene chloride and 15 ml. of *tert*-butyl alcohol was treated with 400 ml. of semicarbazide for 2 hr. Most of the solvent was removed under reduced pressure, water was added, and the precipitated solid removed by filtration. This was then dissolved in 15 ml. of acetic acid, 5 ml. of water, and 3 ml. of 92% pyruvic acid and allowed to stand at

(4) All melting points are corrected. All rotations were taken in a 1-dm. tube at a concentration of *ca.* 1%. Analyses and optical data were obtained by the Physical Chemistry and Microanalytical Departments of these laboratories.

(5) E. Oliveto, C. Gerold, L. Weber, H. Jorgensen, R. Rausser, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 5486 (1953).

(6) E. Oliveto, T. Clayton, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 486 (1953).

(7) E. Oliveto, C. Gerold, R. Rausser, and E. B. Hershberg, *J. Am. Chem. Soc.*, **77**, 3564 (1955).



IV, R = OH; R′ = H
V, R = R′ = OH
VI, R = OCHO; R′ = H
VII, R = $OCOCH_3$; R′ = H
VIII, R = R′ = OCHO
IX, R = R′ = $OCOCH_3$

X, R = OCHO; R′ = H
XI, R = $OCOCH_3$; R′ = H
XII, R = R′ = OCHO
XIII, R = R′ = $OCOCH_3$

XIV, R = OCHO; R′ = H
XV, R = $OCOCH_3$; R′ = H
XVI, R = $OCOCH_3$; R′ = OH
XVII, R = $OCOCH_3$; R′ = $OCOC_5H_{11}$
XVIII, R = $OCOCH_3$; R′ = OCHO
XIX, R = R′ = OCHO
XX, R = R′ = $OCOCH_3$

room temperature for 20 hr. Water was added and the mixture extracted with methylene chloride. The organic extracts were washed with dilute sodium hydroxide and water, dried and evaporated to a residue. Crystallization from ether-hexane gave 270 mg., m.p. 215–230°. The analytical sample, crystallized from acetone, melted at 250–255°, $[\alpha]_D$ +92.2° (dioxane), λ_{max}^{MeOH} 240 mμ (ε 16,000).

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.40; H, 7.78.

11β-Acetoxypregnane-3,20-dione (VII). A mixture of 3.68 g. of 3α,11β-dihydroxypregnane-20-one (I)[6] in 18.5 mg. of acetic acid, 11 ml. of acetic anhydride, and 0.74 g. of *p*-toluenesulfonic acid was allowed to stand at room temperature for 5 hr., then poured into water and extracted with methylene chloride. The organic extracts were washed with water, 5% sodium bicarbonate solution, and water, dried and concentrated to a residue. Crystallization from aqueous methanol gave 2.73 g. of the 3,11-diacetate (II), m.p. 129.5–132.0°. The analytical sample, crystallized from aqueous acetone, melted at 134.0–135.2°, $[\alpha]_D$ +134.1° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.76; H, 8.88.

A mixture of 8.36 g. of II, 50 ml. of methanol, 8 ml. of water, and 2.05 g. of potassium bicarbonate was refluxed for 2 hr., then neutralized with acetic acid, concentrated under reduced pressure, and extracted with methylene chloride. The organic extract was washed with water, dried, and evaporated to an oil which resisted crystallization. This was dissolved in 80 ml. of acetone and 20 ml. of water and treated with 8 g. of *N*-bromosuccinimide and 2 ml. of concd. hydrochloric acid for 2 hr. at 10°. Sodium sulfite solution was added to destroy excess oxidizing agent, and the acetone removed on the steam bath. The precipitated solid was removed by filtration, dried, and crystallized from ether to give 3.93 g. of VII, m.p. 130–135°, $[\alpha]_D$ +106.4° (dioxane).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.50; H, 9.31.

11β-Acetoxyprogesterone (XV). A solution of 3.74 g. of VII in 5 ml. of methylene chloride and 30 ml. of *tert*-butyl alcohol was brominated at room temperature by the addition of 1.68 g. of bromine; the color was discharged in 2.5 hr. The solution was concentrated under reduced pressure to *ca.* 10 ml., then poured into water. The precipitated solid was removed by filtration and air dried. Crystallization from aqueous acetone gave 2.94 g. of 4-bromide (XI), m.p. 150–157° dec. A solution of 0.50 g. of XI in 40 ml. of *tert*-butyl alcohol and 15 ml. of methylene chloride was treated with 0.28 g. of semicarbazide under a CO_2 atmosphere, and the resulting mixture stirred overnight. It was then concentrated under reduced pressure, and water was added to precipitate 0.50 g. of semicarbazone. This was dissolved in 10 ml. of acetic acid, 2 ml. of water, and 2 ml. of 85% pyruvic acid and allowed to stand at room temperature for 72 hr. The solution was poured into water and extracted with methylene chloride. The organic extracts were washed with dilute sodium bicarbonate solution and water, then evaporated to an oily residue (0.39 g.). This was chromatographed on Florisil and the fractions eluted with 50% benzene–methylene chloride, 100% methylene chloride, and 1% methanol–methylene chloride were combined to give 140 mg. of a resin which resisted crystallization, λ_{max}^{MeOH} 239 mμ (ε15,200).

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Synthesis of 2-Hydroxy(*p*-methoxyphenyl)-bicyclo[3.3.1]nonane-6,9-dione

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Received June 24, 1957

2-Hydroxy-8-(*p*-methoxyphenyl)bicyclo[3.3.1]-nonan-6,9-dione (III) has been synthesized by C-alkylation of 5-(*p*-methoxyphenyl)cyclohexane-dione-1,3 (I) with β-chloropropionaldehyde diethyl acetal in a hydrocarbon solvent and cyclization of the product.