TABLE I

Solvent System	R_f Value
1. *n*-BuOH, HCl, H_2O (100:20:36)	0.33
2. *sec*-BuOH, HCl, H_2O (100:20:36)	0.41
3. *tert*-BuOH, HCl, H_2O (100:10:20)	0.22
4. *n*-PrOH, 1N NH_4OH (5:1)	0.83

Isolation of N-methylcytisine. The ground seeds (240 g.) were extracted with methanol in a Soxhlet extractor. The extract was evaporated and the residue was treated with 10% hydrochloric acid. The acid solution was shaken with methylene chloride to remove lipids; it was then made basic by the addition of solid potassium carbonate and ammonia, and extracted with chloroform until the aqueous layer gave negative alkaloid tests. The chloroform extract was dried and the solvent was removed *in vacuo*. There was obtained 4.5 g. (1.9%) of colorless crystalline material, m.p. 137–139.5°. After recrystallization from ethyl acetate–cyclohexane a sample melted at 140–141°, $[\alpha]^{25}_{589}$ −223°, $[\alpha]^{25}_{436}$ −690° (*c*, 0.905, water).

Anal. Calcd. for $C_{12}H_{16}ON_2$: C, 70.56; H, 7.90; N, 13.72; NCH_3, 7.36. Found: C, 70.54; H, 7.87; N, 13.81; NCH_3, 7.19.

The hydrochloride, picrate, and perchlorate were prepared by standard methods. The melting points are given in Table II.

TABLE II

N-METHYLCYTISINE DATA

			Lit. Values
Base	m.p.	140–141°	138°[2,4]
	$[\alpha]^{25}_{589}$ (water)	−223°	−221.6°[2]
Hydrochloride	m.p.	255–258°	250–255°[2]
Picrate	m.p.	232°(dec.)	234°[4]
Perchlorate	m.p.	277–281°	282°[4]

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(4) L. Marion and J. Ouellet, *J. Am. Chem. Soc.*, **70**, 691 (1948).

11-Alkylated Steroids. II. 11-Methyl-3,11,20-trioxygenated Pregnanes

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Despite the fact that 11-oxosteroids have, on a number of occasions,[1] been treated with organometallic reagents that effected transformations elsewhere in the molecule, reaction at the 11-oxo group has been reported only recently.[2]

We wished to extend our knowledge of 11-methylsteroids, particularly of the pregnane series, and accordingly have prepared several new members of this group.

5β-Pregnane-3,11,20-trione 3,20-bis(ethylene acetal)[3] (IIa) underwent addition of methyllithium smoothly in good yield to give the bisketal IIIa, which, being somewhat difficult to crystallize, was usually not isolated but was hydrolyzed directly to 11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (Va), obtained in 65% yield from IIa. Similarly the hitherto unknown 5α-pregnane-3,11,20-trione 3,20-bis(ethylene acetal) (IIb) was treated with methyllithium to give the crystalline bisketal IIIb in 82% yield. Hydrolysis of IIIb afforded 11β-hydroxy-11-methyl-5α-pregnane-3,20-dione (Vb) in 80% yield. Apparently the configuration of the molecule at C-5 has little or no effect on the addition reaction at the 11-oxo group.

In the first paper in this series,[2] it was pointed out that although 21-triphenylmethoxypregna-5,-17(20)-[cis]-diene-3,11-dione 3-ethylene acetal underwent addition of methyllithium to the 11-oxo group, neither 21-hydroxypregna-5,17(20)-[cis]-diene-3,11-dione 3-ethylene acetal nor its acetate could be converted to the 11-methylated derivative. This was felt to be caused by initial formation of the 21-alcohol lithium salt, which might then be expected to be resistant to further attack by methyllithium. The adverse effect of the hydroxyl group (or of a group readily converted to hydroxyl by methyllithium) seemed clear. However, we have now found that in at least one case where the molecule contains a free hydroxyl group, namely 3α-hydroxy-5β-pregnane-11,20-dione 20-ethylene acetal[3] (VII), addition of methyllithium to the 11-oxo group does take place. Subsequent acid hydrolysis of the product gave 3α,11β-dihydroxy-11-methyl-5β-pregnan-20-one (VIIIa), which was also prepared by selective sodium borohydride reduction[4] of 11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (Va).

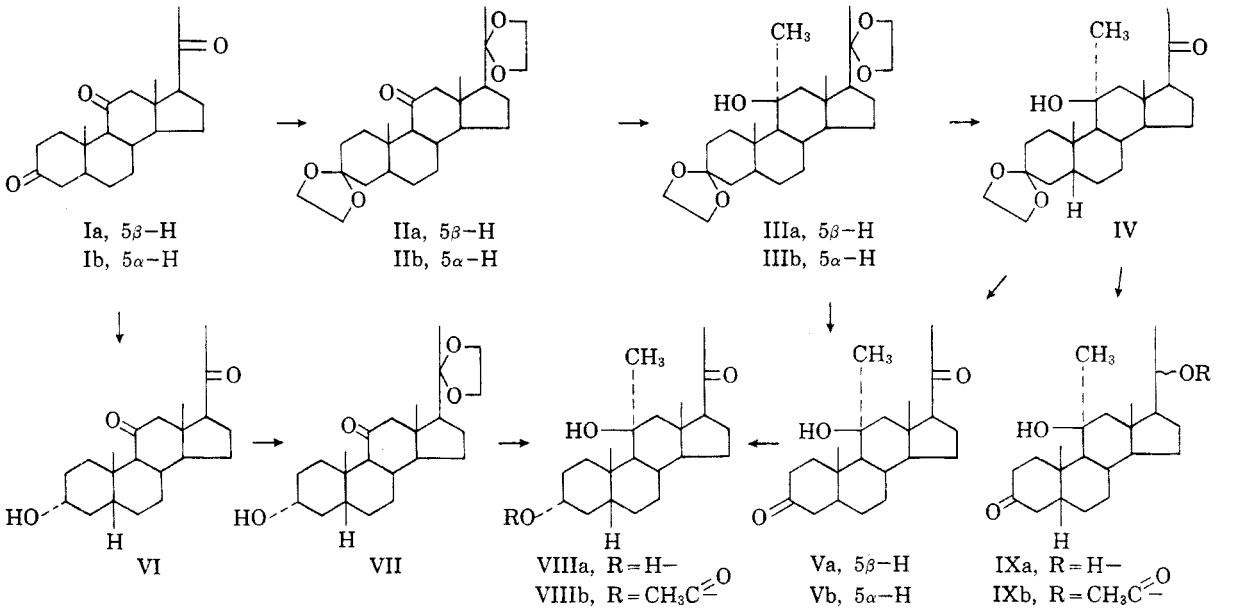
In connection with the preparation of Va, it was possible to isolate a second substance by chromatography of the total crude acid hydrolysis product. This material appeared, in the basis of analytical data, to be a monoacetal. In order to determine which ketone group was protected, the material was reduced with sodium borohydride and then subjected to acid hydrolysis. The resultant diol IXa could not be crystallized but was converted to the crystalline acetate IXb, which was not identical with the acetate (VIIIb) of 3α,11β-dihydroxy-11-methyl-5β-pregnan-20-one (VIIIa). Accordingly, IXb must have been a 20-acetoxy compound, de-

(1) See, for example: R. B. Turner, V. R. Mattox, L. L. Engel, B. F. McKenzie, and E. C. Kendall, *J. Biol. Chem.*, **166**, 345 (1946); A. Wettstein and C. Meystre, *Helv. Chim. Acta*, **30**, 1262 (1947); V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **185**, 589 (1950).

(2) G. S. Fonken and J. A. Hogg, *Tetrahedron*, **2**, 365, (1958).

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

(4) E. R. Garrett and D. A. Lyttle, *J. Am. Chem. Soc.*, **75**, 6051 (1953).



rived from 11β-hydroxy-11-methyl-5β-pregnane-3,20-dione 3-ethylene acetal (IV).

In this series of compounds, the carbonyl absorption maxima in the infrared spectra of Nujol mulls showed consistently different frequencies for 3- or 20-ketones. Compounds IV, VIIIa, and VIIIb, having a 20-ketone, showed a carbonyl absorption at 1682–1687 cm.$^{-1}$, whereas compound IXb, with a 3-ketone, absorbed at 1707 cm.$^{-1}$ Compounds Va and Vb, having both 3- and 20-ketones, showed two maxima, the former at 1715 and 1687 cm.$^{-1}$, and the latter at 1706 and 1681 cm.$^{-1}$ These facts serve as additional evidence of the structure of the monoketal IV.

EXPERIMENTAL[5]

5α-Pregnane-3,11,20-trione 3,20-bis(ethylene acetal) (IIb). A mixture of 22 g. of 5α-pregnane-3,11,20-trione (Ib), 100 ml. of ethylene glycol, 5 g. of *p*-toluenesulfonic acid monohydrate, and 500 ml. of toluene was stirred and refluxed through a Dean-Stark water trap for about 24 hr. and then cooled to 25°. A solution of 5 g. of potassium hydroxide in 50 ml. of methanol was added, and the mixture was washed with four 1-l. portions of water. The organic solution was filtered through a short column (5.5 × 15 cm.) of Florisil topped with sodium sulfate, "elution" being effected with 3 l. of benzene. Evaporation of the "eluate" gave a solid which was recrystallized from about 2 l. of Skellysolve B to give 14.99 g. of 5α-pregnane-3,11,20-trione 3,20-bis(ethylene acetal) (IIb), m.p. 207–210°, $[\alpha]_D$ + 48° (acetone), γ_{max}^{Nujol} 1693 (C=O), 1127, 1094, 1067, 1052, 1030 (C—O).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.53; H, 9.26.

11β-Hydroxy-11-methyl-5α-pregnane-3,20-dione (Vb). A solution of 10 g. of 5α-pregnane-3,11,20-trione 3,20-bis-(ethylene acetal) (IIb) in 150 ml. of benzene and 100 ml. of ether was treated with a threefold molar excess of approximately molar ethereal methyllithium and allowed to stand at room temperature overnight. The mixture was washed twice with water, the organic phase filtered through sodium sulfate, and evaporated to dryness. The residue was crystallized from Skellysolve B to give 8.5 g. of *11β-hydroxy-11-methyl-5α-pregnane-3,20-dione bis(ethylene acetal)* (IIIb) m.p. 131–133°. For analysis a 150 mg. sample was recrystallized again from Skellysolve B to m.p. 135–136°, $[\alpha]_D$ + 27° (acetone), γ_{max}^{Nujol} 3610 (OH; very weak), 1183, 1164, 1126, 1096, 1076, 1054, 1031 (C—O).

Anal. Calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 71.74; H, 9.89.

The remaining IIIb was dissolved in 150 ml. of hot methanol, cooled to room temperature, and treated with 10 ml. of 3*N* sulfuric acid overnight. Crystallization of the product began spontaneously and was increased by addition of 10 ml. of water. Filtration, with washing of the precipitate successively with water, aqueous 4% sodium bicarbonate, and water, gave 6.51 g. of crude Vb, m.p. 198–212°. Addition of 100 ml. of water to the filtrate gave an additional 1.3 g., m.p. 190–205°. The two crops were combined and recrystallized from acetone, giving 5.1 g. of Vb, m.p. 218–222°. A sample for analysis was recrystallized from acetone to m.p. 223–225°, $[\alpha]_D$ + 101° (acetone), γ_{max}^{Nujol} 3440 (OH), 1706, 1681 (C=O).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.02; H, 10.12.

11β-Hydroxy-11-methyl-5β-pregnane-3,20-dione bis(ethylene acetal) (IIIa). A solution of 50.9 g. of 5β-pregnane-3,11,-20-trione 3,20-bis(ethylene acetal) (IIa)[3] in 1 l. of 1:1 benzene-ether was treated with 400 ml. of 0.6*M* ethereal methyllithium at room temperature overnight. The reaction mixture was washed thrice with water and the organic phase dried over sodium sulfate and evaporated to dryness. Drying the residue *in vacuo* at 60° gave a colorless glass that crystallized after standing at room temperature for one month. Recrystallization from Skellysolve B afforded 33.5 g. of IIIa, m.p. 95–106°. For analysis a sample was recrystallized four times from Skellysolve B to m.p. 79–83°, $[\alpha]_D$ + 40° (acetone), γ_{max}^{Nujol} 3480 (OH), 1247, 1218, 1183, 1087, 1062, 1052 (C—O).

Anal. Calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 72.18; H, 9.77.

The erratic change in melting point on recrystallization, and the poor analysis, suggest that partial ketal cleavage may have taken place during recrystallization of IIIa.

11β-Hydroxy-11-methyl-5β-pregnane-3,20-dione (Va) was prepared as described above from 12.7 g. of IIa. The total crude bisketal IIIa thus obtained was dissolved in 200 ml.

(5) Infrared spectra were measured using a Perkin-Elmer Model 21 Spectrophotometer. Maxima are expressed in cm.$^{-1}$ Rotations were determined in acetone (c ~1%). Melting points, determined on a Fisher-Johns block, are uncorrected.

of hot methanol and treated with 10 ml. of 3*N* sulfuric acid at room temperature for 20 hr. Slow addition of 190 ml. of water, and cooling, precipitated the crude product, which was recovered by filtration, washed with water, and dried. One recrystallization from acetone–Skellysolve B afforded 6.75 g. of Va, m.p. 162–165.5°. A sample for analysis was repeatedly recrystallized from the same solvents to m.p. 171–173°, $[\alpha]_D$ + 106° (acetone), γ_{max}^{Nujol} 3420 (OH), 1715, 1687 (C=O).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.58; H, 9.98.

Another experiment, carried out as described above, was worked up by extraction with methylene chloride, following dilution of the acid hydrolysis mixture with water. The crude material thus obtained was chromatographed over 350 g. of Florisil. Elution with 5% acetone–methylene chloride afforded about 2.5 g. of crude oil, recrystallized from acetone–Skellysolve B to give 1.18 g. of *11β-hydroxy-11-methyl-5β-pregnane-3,20-dione 3-ethylene acetal* (IV), m.p. 139–142°, γ_{max}^{Nujol} 3420 (OH), 1682 (C=O), 1100, 1087, 1048 (C—O).

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.62; H, 10.33

Hydrolysis of 100 mg. of IV in 5 ml. of methanol containing 5 ml. of 0.1*N* sulfuric acid at room temperature overnight afforded, following addition of 4 ml of water, 85 mg. of the dione Va, m.p. 167–168°.

3α,11β-Dihydroxy-11-methyl-5β-pregnan-20-one (VIIIa). *A. By selective reduction*[4] *of* Va. To a solution of 1.9 g. of Va in 10 ml. of purified[6] dioxane, cooled in an ice bath, was added 62 mg. of sodium borohydride in 1 ml. of 0.1*N* sodium hydroxide. The mixture was stirred for 2 min. with cooling, and then diluted slowly (5 min.) with 12 ml. of water, followed by 0.65 ml. of concentrated hydrochloric acid. Further dilution with water and extraction with methylene chloride gave a crude product that was chromatographed over Florisil. Elution with, at first 2% acetone–methylene chloride, and finally, 25% acetone–methylene chloride gave crude VIIIa, recrystallized first from acetone–Skellysolve B and then from ethyl acetate to give 0.93 g. of pure VIIIa, m.p. 181–183°, identical to VIIIa prepared as described below.

B. From 3α-hydroxy-5β-pregnane-11,20-dione (VI). 3α-Hydroxy-5β-pregnane-11,20-dione (VI) was converted to the 20-ethylene acetal (VII),[2] m.p. 139–141°, $[\alpha]_D$ + 55° (acetone).

A solution of 13.6 g. of VII in 150 ml. of benzene and 100 ml. of ether was treated with 144 ml. of *M* ethereal methyllithium at room temperature overnight. The reaction mixture was washed several times with water, the organic phase dried over sodium sulfate, and evaporated to dryness. Attempts to crystallize the resultant glass were unsuccessful, both before and after chromatography over Florisil (the major product was eluted with 5–10% acetone–Skellysolve B, and amounted to about 13 g.), so it was dissolved in 200 ml. of methanol and treated with 10 ml. of 3*N* sulfuric acid at room temperature for 28 hr. Addition of 200 ml. of water, and prolonged cooling at about 5° afforded 6.74 g. of crude crystals, m.p. 149–168°, consisting largely of VIIIa. A sample for analysis was recrystallized repeatedly from acetone–Skellysolve B to m.p. 184–186°, $[\alpha]_D$ + 111° (acetone), γ_{max}^{Nujol} 3540, 3440 (OH), 1687 (C=O).

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10 41. Found: C, 75.43; H, 10.25.

The *3-acetate* (VIIIb), prepared by treatment of 200 mg. of VIIIa with 2 ml. of pyridine and 2 ml. of acetic anhydride at room temperature overnight, was obtained in 93% yield, m.p. 169–171.5°. Recrystallization from acetone–Skellysolve B afforded an analytical sample, m.p. 171–172.5°, $[\alpha]_D$ + 112° (acetone), γ_{max}^{Nujol} 3440 (OH), 1725, 1240 (CH_3CO_2), 1684 (C=O).

(6) K. Hess and H. Frahm, *Ber.*, **71**, 2627 (1938).

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.50; H, 9.61.

11β,20ξ-Dihydroxy-11-methyl-5β-pregnan-3-one (IXa) was obtained by treatment of 500 mg. of the monoketal IV with 122 mg. of sodium borohydride in 10 ml. of methanol at room temperature overnight, followed by hydrolysis of the ketal by addition of 2 ml. of 3*N* sulfuric acid in 5 ml. of methanol. After a 4 hr. hydrolysis, dilution with water and extraction with methylene chloride and eventual evaporation of the solvent gave an oil (IXa) that failed to crystallize even after Florisil chromatography (elution with 10% acetone–Skellysolve B).

Acetylation of the oily IXa with acetic anhydride–pyridine at room temperature gave, after two recrystallizations from acetone–Skellysolve B, the 20ξ-acetate, m.p. 167–169°, $[\alpha]_D$ + 42° (acetone), γ_{max}^{Nujol} 3500 (OH), 1707 (C=O), 1262 (acetate C—O), not identical with VIIIb.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81 Found: C, 73.82; H, 9.77.

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2-Fluoro- and 2,2-Difluoroethylnitroguanidine

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The preparation of 2,2,2-trifluoroethylnitroguanidine has been reported.[1] 2-Fluoro- and 2,2-difluoroethylnitroguanidine have now been prepared in a similar manner by the reaction of the respective fluoroethylamines with 1-nitro-2-methyl-2-thiopseudourea. Efforts to nitrate the fluoroalkylnitroguanidines to dinitroguanidine by methods similar to those of McKay and Milks[2] and Meen and Wright[3] were not successful. The nitrate salts of the original fluoroalkylamines were isolated indicating that decomposition had occurred. 2-Fluoroethylnitroguanidine was cyclized to the tetrahydrofluoride salt of 2-imino-1,3-diazacyclopentane. The free base of this compound was identified as the picrate. A comparable cyclization procedure applied to the other fluoroalkylnitroguandiines gave negative results. The nitrate and picrate salts of 2-fluoro- and 2,2-difluoroethylguanidine were prepared from the corresponding fluoroethylnitroguanidines.

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(3) R. H. Meen and G. F Wright *J. Am. Chem. Soc.*, **74**, 2077 (1952).