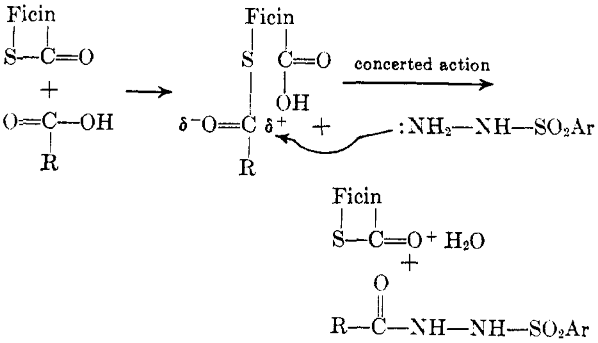
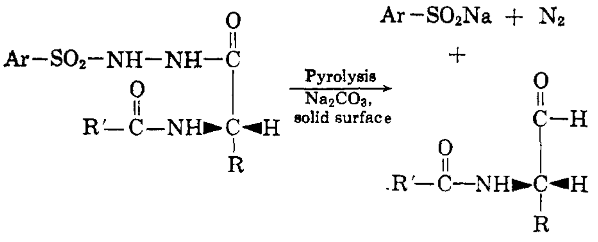


by using 1-hippuryl-2-*p*-tolylsulfonylhydrazine under the improved conditions of Newman and Caflish[9] for such an aldehyde synthesis. Pyrolytic conditions were employed with a finely divided, insoluble, solid for surface contact. If the experiment had worked, it would have provided a general method for the synthesis of *N*-acylamino aldehydes. A route to L-*N*-acylamino aldehydes might have



been established. Even if the reaction had worked, it might not have been possible to isolate separate antipodes. The basic conditions and high temperature might have caused racemization, although the short time of a few minutes for the reaction might have prevented this.

Acknowledgment.—This research was made possible by NSF-G13287 grant from the National Science Foundation and grants from the Fresno County Heart Association. Indebtedness is expressed to Professor R. J. Krantz of the University of Redlands for assistance during a period of relocation. Professor Robert B. Henderson of Long Beach State College permitted his research laboratory to be used during one summer session for certain phases of the research. The high precision Rudolph polarimeter of Pomona College was made available by Professors R. Nelson Smith and Corwin Hansch for the determination of some of the specific rotations. These agricultural attachés of the American embassies in South America were instrumental in providing information about ficin and supplying the dried enzyme, as well as fresh latex from the Higueron tree: Mr. Jerome M. Kuhl and Mr. George H. Day of Caracas, Venezuela, Mr. Henry Hopp of Bogotá, Colombia, and Mr. Jerome M. Kuhl more recently of Rio de Janeiro, Brazil. Mr. John Kreyssler contributed to many phases of this work. Dr. Clell Gray, Dr. Kendall B. Holmes, and Mrs. Joyce Richardson were instrumental in securing funds from the Fresno County Heart Association.

6,16-Dimethylated Steroids. I. Studies on the Synthesis of 6,16α-Dimethylprogesterones[1a]

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Intermediates leading to 6,16α-dimethylprogesterones have been prepared by three different routes. Two of these involve conjugate addition of a methyl group to a Δ^{16}-20-ketone followed *in situ* by a forced attack on a 5α,6α-epoxide or 6-ketone. Also described is a method for the stereospecific synthesis of 5α,6α-epoxides in high yield. The most potent compound of the series, Δ^{6}-dehydro-6,16α-dimethylprogesterone (*8a*), has an oral progestational activity 1.5 times greater than ethinyltestosterone.

The enhancement of progestational activity by substitution of a methyl group at the 6α-position has been known for some time; later it was shown that further enhancement could be achieved by dehydrogenation to the corresponding Δ^{6}-dehydro derivative.[2] Recent reports[3] have indicated that a great increase in anti-inflammatory activity occurs on substitution of corticoids with methyl groups at both the 6α- and 16-positions. We have now found that this enhancement of activity is also observed in

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[1a] Preliminary communication, R. P. Graber and M. B. Meyers, *Chem. Ind.* (London), 1478 (1960).

[1b] Present address: Department of Organic Chemistry, The University, Glasgow, W. 2, Scotland.

[1c] Present address: Department of Chemistry, University of Rochester, Rochester, New York.

(2) A. David, F. Hartley, D. R. Millson, and V. Petrow, *J. Pharm. Pharmacology*, **9**, 929 (1957); H. J. Ringold, E. Batres, and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, and W. E. Dulin, *J. Am. Chem. Soc.*, **80**, 2904 (1958); H. J. Ringold, J. P. Ruelas, E. Batres, and C. Djerassi, *ibid.*, **81**, 3712 (1959).

(3) M. Sletzinger and W. A. Gaines, U. S. Patent 2,940,968 (1960); W. P. Schneider and H. C. Murray, *Chem. Ind.* (London), 1163 (1960).

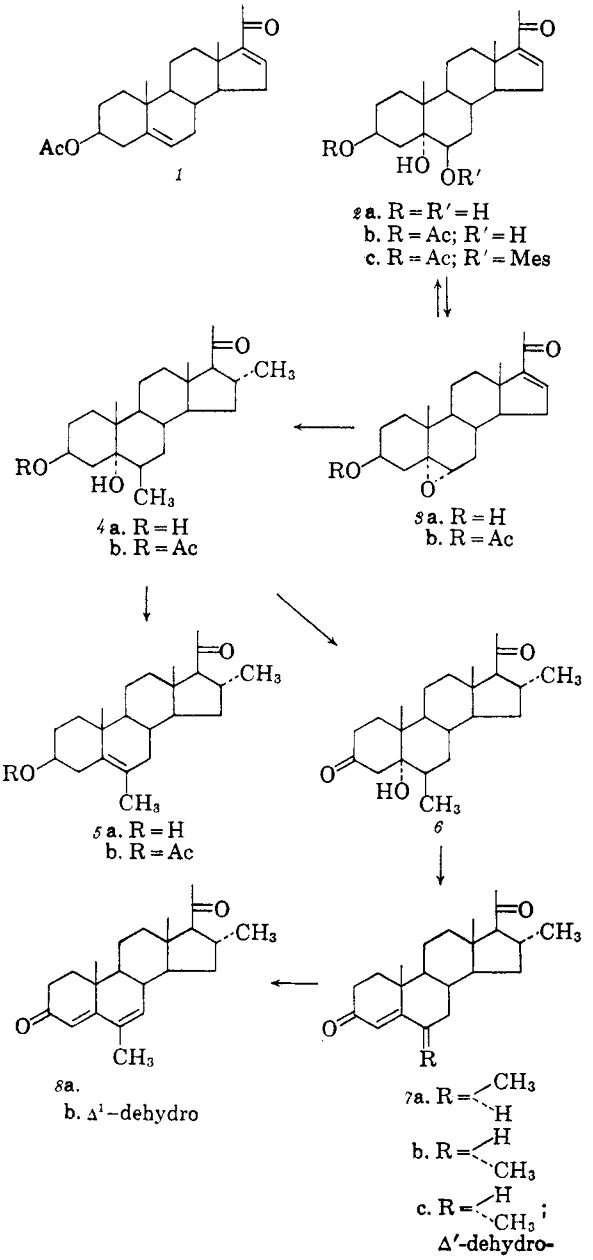
the progestational series[4] and in this and subsequent communications we wish to report our investigations on the facile synthesis of these systems.

In the three previously reported syntheses[4,5] of 6α,16α-dimethylprogesterone (*7b*), the methyl groups are introduced in a stepwise manner in which the 6-methyl group is added by opening a 5α,6α-epoxide with methyl Grignard reagent. The routes to the 6,16-dimethyl corticoids also follow the same approach.[3] The 20-ketone must be protected during this operation, either as a bismethylenedioxy derivative,[3] as an ethylene ketal[5a,b] (*cf.* below and ref. 14) or by reduction to an alcohol.[5a] Alternately, a sapogenin 5α,6α-epoxide may be opened with Grignard reagent followed by degradation of the spiroketal side chain to the Δ^{16}-20-ketone system.[3,4] In three of the approaches the 16-methyl group is in place before the epoxide opening whereas in others, the 16-methyl group is added subsequent to the establishment of the 6-methyl.

It is apparent that there are definite advantages to be gained if both methyl groups could be placed in position simultaneously, not only in the simplification of the reaction sequence but in allowing the employment of a readily available inexpensive starting material, 5α,6α-epoxy-Δ^{16}-dehydropregnenolone acetate (*3b*).[6]

Wettstein and co-workers[7] have shown that the conjugate addition of a methyl group to a Δ^{16}-20-ketone can be effected in essentially quantitative yield in the presence of cuprous chloride with as little as 1.4 moles of the Grignard reagent per mole of steroid. In contrast, the Grignard opening of a 5α,6α-epoxide requires a large excess of the Grignard reagent together with elevated temperatures and extended reaction times.[8] Therefore in attempting the simultaneous addition to the 6- and 16α-positions, it seemed desirable to separate the reaction into two parts, a first stage in which the 16α-methyl group would be added at room temperature with cuprous chloride catalysis and then a vigorous second stage to open the 5α,6α-epoxide. In experimental trials on *3b* it was observed that an insoluble complex formed at the first step which underwent further reaction with difficulty. Tetrahydrofuran, recommended as the solvent for conjugate addition at C-16[7], proved unusable since the magnesium enolate complex produced as a result of the conjugate addition was inert toward further reaction in this medium. Much more satisfactory results were obtained with toluene–ether mixtures[8b] combined with strong mechanical agitation and a 20-fold excess of the Grignard reagent. Under these conditions, the yield of crude 6β,16α-dimethylpregnane-3β,5α-diol-20-one (*4a*) was 95% or greater as indicated by infrared. For facility in purification, the crude Grignard product was acetylated and the 3β-monoacetate (*4b*) isolated in 76% yield on trituration with ether. To establish the structure, *4b* was dehydrated with *p*-toluenesulfonic acid in acetic anhydride and subsequent saponification gave the known 6,16α-dimethyl-5-pregnen-3β-ol-20-one[3,4] (*5a*).

CHART 1



Although 5α,6α-epoxy-Δ^{16}-dehydropregnenolone acetate (*3b*) can be isolated by fractional crystallization of the mixed epoxides obtained on treatment of Δ^{16}-dehydropregnenolone acetate (*1*) with peracids,

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(4) British Drug Houses, Ltd., Belgian Patent 576,418 (1959); D. N. Kirk, V. Petrow, and D. M. Williamson, *J. Chem. Soc.*, 2821 (1961).

(5a) S. Bernstein, E. W. Cantrall, and J. P. Dusza, *J. Org. Chem.*, **26**, 269 (1961); (b) J. Iriarte and M. L. Franco, *ibid.*, **26**, 2043 (1961).

(6) G. Slomp, U.S. Patent 2,751,381 (1956).

(7) K. Heusler, J. Kebrle, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **42**, 2043 (1959).

(8) *Cf.* (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, 1959, p. 199; (b) L. E. Miramontes, M. A. Romero, and F. A. Farjat, U. S. Patent 2,878,246 (1959).

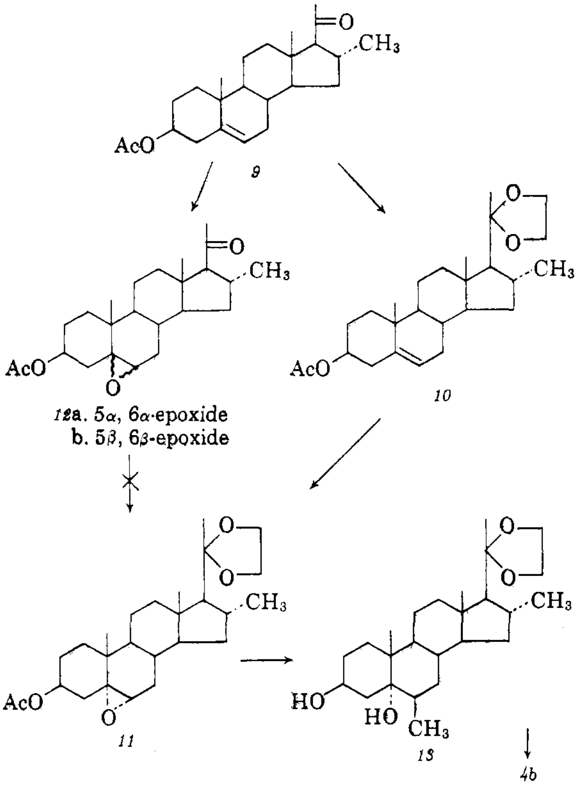
the method is unsatisfactory, since the highest yield of *3b* separated in this manner was 42%. The desired 5α,6α-epoxide (*3b*) could be prepared in excellent yield by perchloric acid-catalyzed opening of the isomeric 5,6-epoxides to give a single *trans* axial diol, 16-pregnene-3β,5α,6β-triol-20-one 3-acetate (*2b*), followed by formation of the 6β-mesylate (*2c*) and basic reclosure to the 5α,6α-epoxide.[9] The conditions given in the literature for this closure, refluxing methanolic potassium hydroxide, could not be employed in our case due to rapid Michael addition of methoxide ion at carbon 16.[10] However, investigation showed that the desired elimination and reclosure could be brought about under very mild alkaline conditions and, in fact, by refluxing a solution of the mesylate (*2c*) in aqueous pyridine with sodium bicarbonate, the epoxide was formed without saponification of the 3-acetate. Predictably, substitution of sodium hydroxide for the bicarbonate led to the 5α,6α-epoxy-3β-alcohol (*3a*).

In practice it was found that although the 3-monoacetate (*4b*) could be readily hydrolyzed back to the parent 3-hydroxy compound (*4a*) and then oxidized to 6β,16α-dimethylpregnan-5α-ol-3,20-dione (*6*), it was preferable to oxidize the crude Grignard product, without intermediate purification, with sodium dichromate in acetic acid to give *6* in 45–55% over-all yield from *3b*.

Dehydration of the 3,20-diketone (*6*) with thionyl chloride in pyridine[11] gave 6β,16α-dimethylprogesterone (*7a*) while treatment of *6* in refluxing absolute ethanol containing a catalytic amount of concentrated hydrochloric acid[12] effected both dehydration and epimerization producing 6α,16α-dimethylprogesterone (*7b*). The configurations of the 6-methyl group were assigned by analogy and rotational comparisons.[13]

As an independent proof of structure of *4b*, the compound was synthesized by the procedure outlined in Chart 2 using 16α-methylpregnenolone acetate (*9*)[7] as the starting material. Ketalization with ethylene glycol in the usual manner gave the 20-ketal (*10*)[14] which was then treated with peracetic acid and the 5α,6α-epoxide (*11*) obtained by fractional crystallization in 42% yield. The mild acid conditions required for the peroxidation did not hydrolyze the 20-ketal (*10*), but attempted ketalization of 5α,6α-epoxy-16α-methylpregnenolone acetate (*12a*)[5a,15,16] failed presumably because of acid cleavage of the oxirane. Treatment of the 5α,6α-epoxy-20-ketal (*11*) with methyl Grignard went smoothly to give 6β,16α-dimethylpregnane-3β,5α-diol-20-one 20-ethylene ketal (*13*) which could not be satisfactorily crystallized and was therefore acetylated. Work-up of the acetylation mixture partially hydrolyzed the 20-ketal and as a consequence the diolone acetate (*4b*) was isolated at this point and found to be identical with the compound prepared by the reactions shown in Chart 1. Further amounts of *4b* were provided by heating a solution of the mother liquor residues in dilute methanolic sulfuric acid.

CHART 2



The sequence in Chart 3 was studied in an effort to determine whether milder conditions could be employed for the introduction of the 6-methyl

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[9] A. Fürst and F. Kollar, *Helv. Chim. Acta*, **30**, 1454 (1947).

[10] D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951).

[11] L. F. Fieser and J. Rigaudy, *ibid.*, **73**, 4660 (1951).

[12] D. Burn, G. Cooley, V. Petrow, and G. O. Weston, *J. Chem. Soc.*, 3808 (1959).

[13] *Cf.*, C. G. Bergstrom, P. B. Sollman, R. T. Nicholson, and R. M. Dodson, *J. Am. Chem. Soc.*, **82**, 2322 (1960).

[14] Bernstein, *et al.*,[5a] in attempting the synthesis of 6α,16α-dimethylprogesterone (*7b*) by this route reported the ketalization of 16α-methylpregnenolone acetate (*9*) to be nonreproducible. We did not encounter this problem in the course of three runs. However, yields of the ketal (*10*) were increased by lengthening reaction times up to 72 hours and use of a 50-fold molar excess of ethylene glycol.

[15] J. A. Edwards, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 2318 (1960).

[16] Peroxidation of *9* gave the isomeric 5,6-epoxides in a ratio of approximately α:β = 7:1, from which *12a* could be separated by crystallization in 57.5% yield. Our physical constants are notably different from those reported by Edwards, *et al.*[15] On the basis of molecular rotational differences the constants found in this paper would seem to be closer to what might be expected for this oxide pair:

Compound	MD 5α,6α	MD 5β,6β	ΔMD 5α,6α– 5β,6β
5,6-Epoxy-16α-methylpregnenolone acetate[a]	−45 (−39)[c]	+127	−172
5,6-Epoxy-16α-methylpregnenolone acetate[b]	+31	+155	−124
5,6-Epoxypregnenolone acetate[d]	+18	+192	−174

[a] This paper. [b] Ref. 15. [c] Ref. 5a. [d] B. Ellis and V. Petrow, *J. Chem. Soc.*, 4417 (1956) and confirmed in those laboratories.

group.[17] Oxidation of the triol monoacetate (*2b*) with sodium dichromate in acetic acid produced the corresponding 6-ketone (*14*) in excellent yield. Reaction of a benzene solution of *14* with ethereal methylmagnesium bromide containing cuprous chloride led to an insoluble complex after the addition of the 16-methyl group. Because of the unreactivity of this complex, substances arising from 16α-methylpregnane-3β,5α-diol-6,20-dione could occasionally be isolated in later steps. Fortunately the amount of material containing an unchanged 6-keto group could be greatly reduced, as in the 5α,6α-epoxide case above, by vigorous mechanical agitation. The crude Grignard product, 6α,16α-dimethylpregnane-3β,5α,6β-triol-20-one (*15a*) was difficult to crystallize because of gel formation and ordinarily was oxidized directly to the 3-ketone (*16*). At this point any of the highly insoluble 16α-methylpregnan-5α-ol-3,6,20-trione (*17*) present could be readily separated. Dehydration of *16* with hydrochloric acid in ethanol afforded Δ^6-dehydro-6,16α-dimethylprogesterone (*8a*) identical to the compound obtained on treating 6α,16α-dimethylprogesterone (*7b*) with chloranil in xylene in the presence of *p*-toluenesulfonic acid.[18] In one instance a crude sample of *16* was treated with hot acetic acid containing a trace of sulfuric acid and the oily product chromatographed. 16α-Methyl-4-pregnene-3,6,20-trione (*18a*) was isolated identical to the product obtained on dehydration of *17* above. In addition a small amount of a compound was obtained which was identified as 6-methylene-16α-methylprogesterone (*18b*) on the basis of its ultraviolet [$\lambda_{\max}$ 263 mμ (11,550)] and infrared spectrum [$\lambda_{\max}^{\text{KBr}}$ 3.21, 5.38, and 11.27 μ (vinyl absorption bands[19])]. In a repetition of the acetic–sulfuric acid dehydration on pure *16*, the $\Delta^{4,6}$-3-ketone (*8b*) was the only detectable product. Treatment of *16* with dilute ethanolic sodium hydroxide gave exclusively the expected monodehydration product, 6β-hydroxy-6α,16α-dimethylprogesterone (*19*).

The Δ^1-dehydro derivatives of *7b* and *8a*, respectively *7c* and *8b*, were prepared in poor yield[20] by selenium dioxide oxidation of the parent compounds in refluxing xylene containing a small amount of acetic acid.

Table I summarizes the approximate oral pro-progestational activities of the 6,16α-dimethylprogesterones as estimated by the Clauberg method on immature estrogen primed rabbits.[21] Progesterone and 6α-methylprogesterone in spot tests involving only two rabbits at each dose level have been shown to have low activities in the oral Clauberg test. The values are approximately 0.1 and 0.4 relative to ethinyltestosterone, respectively.[22] In general screening tests by subcutaneous injection of 2 mg./day for 14 days on intact 21 day old male rats, all of the 6,16α-dimethylprogesterones exhibited marked adrenal suppression and thymus involution with the exception of 6β-hydroxy-6α,16α-dimethylprogesterone (*19*) which proved to be completely inactive in both the general screen and Clauberg assays.

Chart 3

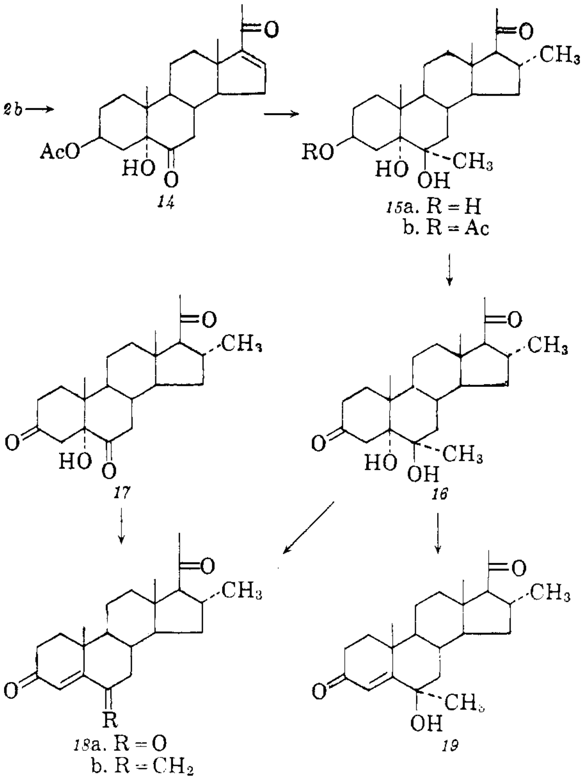

Table I

Oral Progestational Activities of 6,16α-Dimethylprogesterones

Compound	Potency[a]
16α-Methylprogesterone	<0.25
6α,16α-Dimethylprogesterone (*7b*)	1.0
Δ^6-Dehydro-6,16α-dimethylprogesterone (*8a*)	1.5
Δ^1-Dehydro-6α,16α-dimethylprogesterone (*7c*)	0.5
$\Delta^{1,6}$-Bisdehydro-6,16α-dimethylprogesterone (*8b*)	1.0

[a] Ethinyltestosterone = 1.0.

Experimental[23]

5α,6α-Epoxy-Δ^{16}-dehydropregnenolone Acetate (**5α,6α-Epoxy-16-pregnen-3β-ol-20-one Acetate**) (*3b*).—A. A well stirred mixture of 1.5 g. of anhydrous sodium acetate and

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[17] Compare B. Ellis, D. N. Kirk, V. Petrow, and B. Waterhouse, *J. Chem. Soc.*, 2828 (1960).

[18] R. M. Dodson and P. B. Sollman, U.S. Patent 2,891,079 (1959).

[19] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 2nd ed., 1958, p. 34.

[20] C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956) have noted that the yields in this reaction are dependent on the degree of substitution by oxygen in the side chain of the starting steroid.

[21] All bioassays by Endocrine Laboratories, Madison 1, Wisconsin.

[22] Private communication from Dr. Robert W. Heinle of the Upjohn Co., Kalamazoo, Michigan.

[23] Unless otherwise noted: (1) melting points determined on a micro hot stage; (2) rotations determined in an approximately 1% chloroform solution; (3) ultraviolet spectra taken in 95% ethanol; (4) comparison of compounds by usual methods, *e.g.*, mixed melting points, rotations, and infrared spectra.

15 ml. of 40% peracetic acid was cooled to −4° and a solution of 15 g. of Δ^{16}-dehydropregnenolone acetate (*1*) in 30 ml. of chloroform added dropwise in 1 hr. The mixture was stirred for an additional 135 min. allowing the temperature to rise slowly to +5°. Water was added, the organic layer separated and washed twice with 5% aqueous sodium bicarbonate solution, then dried and evaporated to give 15.35 g. of the mixed oxides. Crystallization from 400 ml. of methanol afforded 5.80 g. (37%) of the 5α,6α-epoxide (*3b*), m.p. 188–190°. Chromatography on neutral alumina followed by recrystallization from methanol gave the pure material, m.p. 194–195.5°, $[\alpha]^{26}\mathrm{D}$ −37.9°, $\lambda_{\max}$ 238 mμ (10,800) (lit.,[6] m.p. 196–197.5°, $[\alpha]\mathrm{D}$ +37°).

B. Seventy-five milliliters of a pyridine solution of mesylate *2c* (prepared as shown below from 10.0 g. of *2b*) was added to a slurry of 22 g. of sodium bicarbonate in 75 ml. of water. The mixture was heated to reflux for 30 min. and the hot solution slowly diluted with water until precipitation was complete. Filtration gave 8.94 g. (94%) of the α-oxide as crystalline material, m.p. 190–195°. Recrystallization from methanol gave needles, m.p. 192.5–195.5°, identical with material prepared by direct crystallization of the crude mixed epoxides shown above in A.

5α,6α-Epoxy-Δ^{16}-dehydropregnenolone (*3a*).—A. A solution of 3.0 g. of 5α,6α-epoxy-Δ^{16}-dehydropregnenolone acetate (*3b*) and 2.0 g. of potassium bicarbonate in 150 ml. of methanol and 15 ml. of water was heated under reflux for 1 hr., cooled, and 1 ml. of glacial acetic acid added. The mixture was partially evaporated, diluted with 250 ml. of water, and filtered. After drying, the residue weighed 2.4 g. (71%), m.p. 198–206°. The sample for analysis was prepared by recrystallization from acetone–petroleum ether (b.p. 60–70°), m.p. 206.5–208°, $[\alpha]^{29}\mathrm{D}$ −42.8°, $\lambda_{\max}$ 240 mμ (9420).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.24; H, 9.26.

B. A solution of 195 mg. of 16-pregnene-3β,5α,6β-triol-20-one 3-acetate (*2b*) in 1.5 ml. of ice-cold pyridine was treated with 0.132 ml. of methanesulfonyl chloride and the mixture stored at 0–5° for 16 hr. The pale brown solution of the 6-mesylate (*2c*) was then added to a solution of 439 mg. of potassium hydroxide in 3.0 ml. of water and the flask rinsed with 5.0 ml. of pyridine. After heating under reflux for 30 min., the mixture was cooled and diluted slowly with about 30 ml. of water. Buff-colored crystals separated which were removed by filtration, washed thoroughly with water, and dried to give 105 mg. of microplates, m.p. 195–198.5°, $\lambda^{\mathrm{KBr}}_{\max}$ 6.02, 6.06, 6.32, and 12.57 μ. This material exhibited an infrared spectrum substantially identical to that prepared in section A. above and the melting point was not depressed on admixture.

A 78-mg. sample was acetylated in 1.0 ml. of pyridine with 0.5 ml. of acetic anhydride at room temperature overnight. Dilution with water gave needles which were removed by filtration, washed with water, and dried; 87.2 mg., m.p. 194.5–196.5°. The melting point was not depressed on admixture with the α-oxide acetate (*3b*) prepared above and the infrared spectra in potassium bro mide were identical.

16-Pregnene-3β,5α,6β-triol-20-one 3-Acetate (*2b*).—To a solution of 3.20 g. of the mixed 5,6-epoxides of Δ^{16}-dehydropregnenolone acetate in 66 ml. of acetone was added with stirring 33 ml. of a 1.5 *N* aqueous perchloric acid solution. After standing for 3 hr., filtration gave 2.65 g. of crystalline material. Partial evaporation of the mother liquors gave an additional 0.47 g. Recrystallization of the combined crude products from methanol gave 1.87 g. (56%) of needles, m.p. 252–256°, $[\alpha]^{26}\mathrm{D}$ −7.0° (dioxane), $\lambda_{\max}$ 240 mμ (9560) (lit.,[6] m.p. 245–253°).

Saponification was effected by refluxing with sodium hydroxide in aqueous pyridine. Dilution with water precipitated the triol (*2a*) which was purified by crystallization from methanol–ethyl acetate, m.p. 246–253°, $[\alpha]^{30}\mathrm{D}$ +16.9° (CH_3OH).

Anal. Calcd. for $C_{21}H_{32}O_4 \cdot {}^1/_2CH_3OH$: C, 70.85; H, 9.40. Found: C, 71.07, 71.28; H, 9.21, 9.22.

16-Pregnene-3β,5α,6β-triol-20-one 3-Acetate 6-Mesylate (*2c*).—A solution of 2.0 g. of 16-pregnene-3β,5α,6β-triol-20-one 3-acetate (*2b*) in 15 ml. of pyridine was cooled to 0° and 1.4 ml. of methanesulfonyl chloride added dropwise. After standing at 7° overnight, followed by 2 hr. at room temperature, the mixture was poured onto crushed ice and extracted with cold ether. The extracts were washed in the cold with water, 1 *N* aqueous hydrochloric acid, water, 5% aqueous sodium bicarbonate, twice with water, and finally with saturated salt solution giving 2.25 g. (93.3%) of an amorphous solid after evaporation. Two recrystallizations from cold ether gave the pure mesylate as needles, m.p. 113–118° dec., $[\alpha]^{24}\mathrm{D}$ −32.3°, $\lambda_{\max}$ 239 mμ (9700); on storage at room temperature, the mesylate slowly decomposed.

Anal. Calcd. for $C_{24}H_{36}O_7S$: C, 61.51; H, 7.74. Found: C, 61.22; H, 7.70.

6β,16α-Dimethylpregnane-3β,5α-diol-20-one 3-Acetate (*4b*).—To a well stirred mixture (Morton flask) of 670 ml. of 3 *M* methylmagnesium bromide in ether (Arapahoe Chemicals, Inc.) and 6.6 g. of powdered cuprous chloride was added a solution of 37.3 g. of 5α,6α-epoxy-Δ^{16}-dehydropregnenolone acetate (*3b*) in 1750 ml. of toluene in 20 min. The mixture was brought to reflux with continued stirring for 135 min., then cooled in ice and 750 ml. of saturated aqueous ammonium chloride added. The toluene was removed by steam distillation and the residue extracted with ethyl acetate. The extracts were filtered through Celite, washed twice with water, and then with saturated salt solution. Evaporation gave a solid, 38 g., which was dissolved in 50 ml. of pyridine and treated with 25 ml. of acetic anhyride overnight. The solid which precipitated on dilution with water was removed by filtration and washed successively with water and methanol giving 31.3 g. (76%) of platelets, m.p. 215–238°. The sample for analysis was prepared by successive recrystallizations from methanol–methylene chloride and acetone–methylene chloride, m.p. 243.5–248°, $[\alpha]^{26}\mathrm{D}$ +23.7° (lit.,[5b] m.p. 253–255°, $[\alpha]\mathrm{D}$ +22.2°).

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.05; H, 9.85.

6β,16α-Dimethylpregnane-3β,5α-diol-20-one (*4a*).—A solution of 1.32 g. of 6β,16α-dimethylpregnane-3β,5α-diol-20-one 3-acetate (*4b*) in 150 ml. of methanol containing 3 ml. of 70% perchloric acid was allowed to stand at room temperature for 18 hr. The solution was then filtered through glass wool into 300 ml. of water. The precipitate which formed was removed by filtration and washed thoroughly with 2:1 water–methanol giving 1.02 g. (87%) of microcrystalline material, m.p. 160–165°. Two recrystallizations from acetone–petroleum ether gave the sample for analysis as fine needles, m.p. 205–209° $[\alpha]^{24}\mathrm{D}$ +37.6°, $\lambda^{\mathrm{KBr}}_{\max}$ 5.86 μ (lit.,[5b] m.p. 213–214°, $[\alpha]\mathrm{D}$ +29.2°).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.02; H, 10.45.

6β,16α-Dimethylpregnan-5α-ol-3,20-dione (*6*).—A. To a solution of 0.85 g. of 6β,16α-dimethylpregnane-3β,5α-diol-20-one (*4a*) in 20 ml. of glacial acetic acid was added a solution of 0.5 g. of sodium dichromate dihydrate in 20 ml. of glacial acetic acid with stirring in 5 min. The mixture was stirred for 19 hr., then 25 ml. of methanol was added and after stirring for an additional 10 min., the suspension was filtered giving 0.45 g. (53%) of microcrystalline material, m.p. 227–238°. The sample for analysis was obtained after two recrystallizations from methanol–methylene chloride, m.p. 257–260.5°, $[\alpha]^{25}\mathrm{D}$ +56.4° (lit., m.p. 262.5–265°, $[\alpha]\mathrm{D}$ +54°[6a]; m.p. 270–273°, $[\alpha]\mathrm{D}$ +57°[6b]).

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.81; H, 10.30.

B. Twenty grams of crude *4a* (obtained directly from the Grignard reaction on *3b*) was dissolved in 150 ml. of glacial acetic acid and a solution of 10 g. of sodium dichromate dihydrate in 100 ml. of acetic acid added in 5 min. with stirring. After 4 hr. the precipitated product was removed by filtration, washed several times with methanol, and dried; 7.4 g. An additional 2.1 g. was obtained by evaporation of the combined mother liquors and washes followed by trituration of the residue with methanol. Crystallization of the combined crude products from methanol gave 7.8 g. (40%), m.p. 243–253°, identical with the material prepared in A above by infrared comparison.

6,16α-Dimethyl-5-pregnen-3β-ol-20-one Acetate (*5b*).—A solution of 1.0 g. of 6β,16α-dimethylpregnane-3β,5α-diol-20-one 3-acetate (*4b*) and 0.05 g. of *p*-toluenesulfonic acid in 30 ml. of acetic anhydride was heated for 15 min. at 100° and then allowed to stand at room temperature overnight. After diluting with 300 ml. of water, the mixture was extracted with ethyl acetate. The extracts were washed twice with water, once with 5% aqueous sodium bicarbonate solution, and once with saturated salt solution. Evaporation of the dried extracts gave an oil which deposited crystals after standing in methanol for 2 days. The crude solid was recrystallized twice from aqueous methanol giving 0.232 g. (24%) of needles, m.p. 135–138.5°, $[\alpha]^{29}\text{D}$ −14.4°.

Anal. Calcd. for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91. Found: C, 77.70; H, 10.11.

6,16α-Dimethyl-5-pregnen-3β-ol-20-one (*5a*).—A mixture of 0.14 g. of 6,16α-dimethyl-5-pregnen-3β-ol-20-one acetate (*5b*) and 0.1 g. of potassium carbonate in 15 ml. of methanol and 3 ml. of water was heated under reflux for 50 min. Evaporation *in vacuo* to a small volume and dilution with water gave 0.12 g. of solid, m.p. 168–171°, which on recrystallization from acetone–petroleum ether had m.p. 168.5–171°, $[\alpha]^{28}\text{D}$ −1.6° (lit., m.p. 170–172°, [α]D −5° [3]; m.p. 170–172°, [α]D −20° [4]).

6β,16α-Dimethyl-4-pregnene-3,20-dione (6β,16α-Dimethylprogesterone) (*7a*).—A solution of 0.58 g. of 6β,16α-dimethylpregnan-5α-ol-3,20-dione (*6*) in 10 ml. of pyridine was cooled to 0° and 0.5 ml. of freshly distilled thionyl chloride added dropwise. After 20 min. the mixture was diluted with water and filtered giving 0.34 g. (62%) of solid, m.p. 157–159°. Recrystallization from aqueous methanol followed by acetone–petroleum ether gave the sample for analysis, m.p. 157.5–161°, $[\alpha]^{25}\text{D}$ +113.4°, $\lambda_{\max}$ 242 mμ (16,300), $\lambda_{\max}^{\text{CCl}_4}$ 5.84, 5.93, and 6.21 μ.

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.46; H, 10.10.

6α,16α-Dimethyl-4-pregnene-3,20-dione (6α,16α-Dimethylprogesterone) (*7b*).—To a solution of 0.84 g. of 6β,16α-dimethylpregnan-5α-ol-3,20-dione (*6*) in 100 ml. of absolute ethanol was added 0.5 ml. of concentrated hydrochloric acid. The mixture was heated under reflux for 45 min. and then diluted with water. After standing at 6° for 22 hr., filtration gave 0.70 g. (88%) of crystalline material, m.p. 90–104°, which was recrystallized from acetone–petroleum ether producing 0.43 g. (54%), m.p. 104–116°. Two further recrystallizations from acetone–petroleum ether provided the anaytical sample, m.p. 122–126°, $[\alpha]^{24}\text{D}$ +144.2°, $\lambda_{\max}$ 241 mμ (15,450), $\lambda_{\max}^{\text{CCl}_4}$ 5.83, 5.93, and 6.19 μ (lit., m.p. 120–122°, [α]D +144°, $\lambda_{\max}^{\text{C}_2\text{H}_5\text{OH}}$ 241 mμ, ε 16,230[4]; m.p. 113–116.5°, [α]D +145°, $\lambda_{\max}^{\text{C}_2\text{H}_5\text{OH}}$ 242 mμ, ε 16,100[5a]; m.p. 126–128°, [α]D +147°, $\lambda_{\max}^{\text{C}_2\text{H}_5\text{OH}}$ 242 mμ, ε 15,500[5b]).

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.47; H, 10.19.

5α,6α- and 5β,6β-Epoxy-16α-methylpregnan-3β-ol-20-one Acetate (*12a* and *12b*).—Following the procedure described above for the epoxidation of *1*, 3.72 g. of 16α-methylpregnenolone acetate (*9*) gave 3.97 g. of the mixed epoxides. Crystallization from methanol gave 2.1 g. (53%) of the 5α,6α-epoxide (*12a*), m.p. 157–160° (cap.). Further recrystallizations from methanol and then acetone–petroleum ether gave the analytical sample, m.p. 165.7–166.8° (cap.), [α]D −11.6° (lit., m.p. 162–164°, [α]D +8°[15]; m.p. 167.5–168.5°, [α]D −10°[5a]).

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.19; H, 9.39.

The combined mother liquor residues were chromatographed on neutral alumina. Elution with 9:1 petroleum ether–benzene gave the 5β,6β-isomer (*12b*), m.p. 142.3–144° (cap.), after recrystallization from methanol. A further recrystallization from methanol furnished the sample for analysis, m.p. 143–144° (cap.), $[\alpha]^{24}\text{D}$ +32.8° (lit.,[15] m.p. 120–121°, [α]D +40°).

Anal. Found: C, 74.17; H, 9.32.

A benzene solution of the crude mixed epoxides was purified by passage through neutral alumina. Evaporation of the eluate gave material of [α]D −6.1°. The ratio of 5α,-6α- to 5β,6β-epoxides in the mixture was therefore 88:12.

16α-Methyl-5-pregnen-3β-ol-20-one 3-Acetate 20-Ethylene Ketal (10).—A mixture of 1.86 g. of 16α-methylpregnenolone acetate (*9*), 0.01 g. of *p*-toluenesulfonic acid, 13.9 ml. of ethylene glycol, and 50 ml. of benzene was heated under reflux with vigorous stirring; the water that evolved was collected in a Dean-Stark trap. After 17 hr., 0.5 g. of potassium carbonate and 1.0 ml. of pyridine were added. The mixture was diluted with 50 ml. of ethyl acetate and the solvent layer washed twice with 5% aqueous sodium bicarbonate, twice with water and then with saturated salt solution. Evaporation gave 2.08 g. of residue which on crystallization from methanol afforded 1.58 g. (76%) of the ketal (*10*), m.p. 140–143.8° (cap.). The sample for analysis was obtained after two further recrystallizations from methanol, m.p. 146.5–147.5° (cap.), $[\alpha]^{25}\text{D}$ −37.4° (lit.,[5a] m.p. 144.5–146°, [α]D −62.5°).

Anal. Calcd. for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 74.96; H, 9.68.

5α,6α-Epoxy-16α-methylpregnan-3β-ol-20-one 3-Acetate 20-Ethylene Ketal (*11*).—Following the procedure described above for the epoxidation of *1*, 8.32 g. of 16α-methyl-5-pregnen-3β-ol-20-one 3-acetate 20-ethylene ketal (*10*) gave 8.84 g. of the mixed epoxides. Crystallization from acetone–petroleum ether provided the 5α,6α-epoxide (*11*), m.p. 168.2–170.6° (42%). Two further recrystallizations from methanol gave the pure sample, m.p. 172.5–173.5° (cap.), $[\alpha]^{25}\text{D}$ −62.6° (lit.,[5a] m.p. 171.5–172.5°, [α]D −61°).

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.21; H, 9.36.

Methylmagnesium Bromide on 5α,6α-Epoxy-16α-methylpregnan-3β-ol-20-one 3-Acetate 20-Ethylene Ketal (*11*).—To a solution of 17.30 g. of *11* in 350 ml. of tetrahydrofuran was added 266 ml. of 3 *M* ethereal methylmagnesium bromide solution. The reaction mixture was distilled until the solution temperature reached 67°, then heated under reflux for 6 hr., and finally hydrolyzed with saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate and the extracts washed with water and saturated salt solution. Evaporation gave 16.5 g. of the crude ketal (*13*) as a resin. Crystallization from acetone–petroleum ether afforded 11.45 g. of partially purified ketal, m.p. 145–160°. This material was dissolved in 25 ml. of pyridine and treated overnight with 25 ml. of acetic anhydride. The mixture was diluted with 500 ml. of water and after the addition of 100 ml. of ethyl acetate, the precipitated gummy product partially crystallized. Filtration of the two phase mixture gave 6.4 g. of 6β,16α-dimethylpregnane-3β,5α-diol-20-one 3-acetate (*4b*), m.p. 238–244°, identical with the material prepared by direct dimethylation. The ethyl acetate layer of the filtrate was separated and worked up in the usual manner to give an amorphous residue. Trituration of the residue with methanol provided another 1.07 g. of *4b*, m.p. 241–243°. Finally, all mother liquors were combined and evaporated to a gummy residue which was taken up in 105 ml. of methanol containing 1.2 ml. of concentrated sulfuric acid. The solution was heated under reflux for 40 min. and the solid which separated on cooling was removed by filtration giving an additional 1.23 g. of *4b*, m.p. 230–235°.

16-Pregnene-3β,5α-diol-6,20-dione 3-Acetate (*14*).—To a well stirred solution of 1.0 g. of 16-pregnene-3β,5α,6β-triol-20-one 3-acetate (*2b*) in 20 ml. of glacial acetic acid was added a solution of 0.5 g. of sodium dichromate dihydrate in 10 ml. of glacial acetic acid. After standing for 4 hr. at room temperature, 15 ml. of methanol was added, and after 10 min. the mixture was diluted with water and extracted with chloroform. The extracts were washed with water, 5% aqueous sodium bicarbonate solution and saturated salt solution. Evaporation gave 0.81 g. (82%) of crystalline material, m.p. 227–237°. The sample for analysis was obtained after two recrystallizations from methanol, m.p. 241–244°, $[\alpha]^{25}\mathrm{D}$ −40.6°.

Anal. Calcd. for $C_{23}H_{32}O_5\cdot{}^1/_2CH_3OH$: C, 69.60; H, 8.70. Found: C, 69.75, 69.93; H, 8.43, 8.36.

6α,16α-Dimethylpregnane-3β,5α,6β-triol-20-one (*15a*).—To a well stirred mixture of 1.6 g. of cuprous chloride and 260 ml. of a 3 *M* ethereal methylmagnesium bromide solution was added a solution of 8.5 g. of 16-pregnene-3β,5α-diol-6,20-dione 3-acetate (*14*) in 300 ml. of benzene over a period of 15 min. The mixture was heated under reflux for 1 hr. and then hydrolyzed with 750 ml. of saturated aqueous ammonium chloride solution. The organic layer was diluted with ethyl acetate, washed several times with water and finally with saturated salt solution. Evaporation gave 7.2 g. of a solid residue, melting slowly between 120–135°, which was oxidized without further purification (see below). A portion recrystallized several times from acetone–petroleum ether provided the sample for analysis, m.p. 175–178°, after sintering at 125°, $[\alpha]^{24}\mathrm{D}$ +33.9°.

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 72.57; H, 10.19.

6α,16α-Dimethylpregnane-3β,5α,6β-triol-20-one 3-Acetate (*15b*).—A solution of 0.8 g. of crude 6α,16α-dimethylpregnane-3β,5α,6β-triol-20-one (*15a*) in 15 ml. of pyridine was treated overnight with 2.0 ml. of acetic anhydride. The mixture was diluted with water and the resulting oil extracted with ethyl acetate. The extracts, after washing with dilute hydrochloric acid, water, and saturated saline, were evaporated to a foam, 0.92 g., which was dissolved in benzene–petroleum ether and placed on 45 g. of neutral alumina. The fractions obtained by elution with 1:1 petroleum ether–benzene and benzene were combined and crystallized from petroleum ether giving needles, 0.33 g., m.p. 188–193.5°. Recrystallization from petroleum ether produced the sample for analysis, m.p. 191–195°, $[\alpha]^{29}\mathrm{D}$ +10.5°.

Anal. Calcd. for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.46, 71.20; H, 9.63, 9.49.

Saponification of the triol monoacetate (*15b*) with potassium bicarbonate in aqueous methanol under reflux regenerated the triol (15a), m.p. 174–179°, $[\alpha]^{27}\mathrm{D}$ +33.3°, identical with the purified Grignard product described above.

6α,16α-Dimethylpregnane-5α,6β-diol-3,20-dione (*16*).—To 1.97 g. of 6α,16α-dimethylpregnane-3β,5α,6β-triol (*15a*) in 40 ml. of glacial acetic acid was added a solution of 1.0 g. of sodium dichromate dihydrate in 20 ml. of acetic acid. After stirring for 5 hr. at room temperature, the mixture was treated with 50 ml. of methanol, diluted with water, and extracted with chloroform. The extracts were washed with water, 5% aqueous sodium bicarbonate solution, and saturated salt solution. Evaporation gave 1.38 g. (70%) of crystalline material, m.p. 215–221°. Recrystallization from aqueous methanol and then acetone–petroleum ether provided the sample for analysis, m.p. 218–224°, $[\alpha]^{25}\mathrm{D}$ +48.2°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.48; H, 9.55.

In another instance, an impure sample of the triol (*15a*), 31 g., on oxidation gave 25.4 g. (82%) of crude product. A solution of the material in acetone–petroleum ether deposited 1.0 g. of finely divided **16α-methylpregnan-5α-ol-3,6,20-trione** (*17*), m.p. 247–267° dec. Recrystallization from ethyl acetate gave microcrystalline *17*, m.p. 268–275°, $[\alpha]^{29}\mathrm{D}$ +19.9° (dimethyl formamide).

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.07; H, 8.96.

Further work up of the mother liquors as above eventually gave 12.9 g. (42%) of the dimethyldioldione (*16*), m.p. 220–226°.

6,16α-Dimethyl-4,6-pregnadiene-3,20-dione (**Δ^6-Dehydro-6,16α-dimethylprogesterone**) (*8a*). **A. From the Dimethyl dioldione** (*16*) **with Hydrochloric Acid in Ethanol.**—To a solution of 3.84 g. of 6α,16α-dimethylpregnane-5α,6β-diol-3,20-dione (*16*) in 250 ml. of absolute ethanol was added 1.0 ml. of concentrated hydrochloric acid. The mixture was heated under reflux for one hr., then cooled and 1.0 ml. of concentrated aqueous ammonium hydroxide added. The ethanol was evaporated *in vacuo*, the residue taken up in 125 ml. of acetone and the solution filtered to remove a small amount of insoluble material. The filtrate was concentrated, diluted with petroleum ether and stored at room temperature. The crystalline material which separated was removed by filtration giving 2.41 g. (69%) of thick yellow plates, m.p. 154–161°. The crude product was decolorized by passage through a short column of alumina and recrystallization of the eluted material from petroleum ether provided the pure compound, m.p. 158–162°, $[\alpha]^{28}\mathrm{D}$ +179°, $\lambda_{\max}$ 290 mμ (24,400).

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 81.10; H, 9.28.

B. From the Dimethyldioldione (*16*) **with Sulfuric Acid in Acetic Acid.**—A mixture of 1.50 g. of crude 6α,16α-dimethylpregnane-5α,6β-diol-3,20-dione (*16*) in 20 ml. of glacial acetic acid containing 2 drops of concentrated sulfuric acid was heated on the steam bath for 1 hr. The resulting deep red solution was poured into excess 5 *N* aqueous sodium hydroxide solution. The mixture was further diluted with water and extracted with chloroform. The chloroform extracts were washed with water until neutral and then evaporated to give 1.3 g. of oily product. The residue was dissolved in benzene and petroleum ether and placed on 50 g. of alumina and 17 fractions of 125 ml. each were taken. Fractions 3 through 13 (19:1 and 9:1 petroleum ether–benzene) were combined and crystallized from petroleum ether giving 0.46 g., m.p. 139–155°. This material was triturated with 10 ml. of acetone and the residue, 0.04 g., recrystallized from petroleum ether to produce 0.023 g. of **6-methylene-16α-methylprogesterone** (*18b*), m.p. 182.5–186°, $[\alpha]^{22}\mathrm{D}$ +328.4°, $\lambda_{\max}$ 263 mμ (11,550), $\lambda_{\max}^{\mathrm{KBr}}$ 3.21, 5.38, 5.83, 5.94, 6.13, 6.24, and 11.27 μ.

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 81.11; H, 9.38.

The mother liquors contained further amounts of *18b* which could not be separated from the Δ^6-dehydro compound (*8a*) also present.

Fractions 15 and 16 (benzene) were combined and recrystallized from aqueous methanol giving 0.07 g. of crystals, m.p. 188–200°. A further recrystallization from acetone–petroleum ether provided **16α-methyl-4-pregnene-3,6,20-trione** (*18a*) as yellow platelets, 0.05 g., m.p. 199–203.5°, $[\alpha]^{24}\mathrm{D}$ +11.2°, $\lambda_{\max}$ 252 (11,500), $\lambda_{\max}^{\mathrm{KBr}}$ 5.86, 5.95 and 6.23 μ.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.95; H, 8.86.

A solution of 0.21 g. of 16α-methylpregnan-5α-ol-3,6,20-trione (*17*) in 30 ml. of glacial acetic acid containing 3 drops of concentrated sulfuric acid was heated on the steam bath for 75 min. After cooling, the mixture was evaporated *in vacuo* to a small volume and diluted with water. Filtration gave 0.159 g. of material which was recrystallized from acetone–petroleum ether to produce *18a*, m.p. 200.5–203.5°, identical with the compound prepared above.

C. From 6α,16α-Dimethylprogesterone (*7b*).—A mixture of 0.497 g. of 6α,16α-dimethylprogesterone (*7b*), 0.497 g. of chloranil and 0.014 g. of *p*-toluenesulfonic acid monohydrate in 45 ml. of xylene was heated under reflux for 4.5 hr. The reaction mixture was poured onto a column of 30 g. of silica gel. The material obtained by elution with 9:1 and 3:1 benzene–ethyl acetate mixtures was dissolved in benzene and placed on 25 g. of alumina. The fractions eluted with 1:1 benzene–petroleum ether and with benzene were combined, evaporated to dryness *in vacuo*, and the residue recrystallized from petroleum ether giving 0.275 g. of *8a*, m.p. 158–161.5°, identical with the material prepared in A above.

6α,16α-Dimethyl-4-pregnen-6β-ol-3,20-dione (**6β-Hydroxy-6α,16α-dimethylprogesterone**) (*19*).—To a degassed solution of 0.5 g. of 6α,16α-dimethylpregnane-5α,6β-diol-3,20-dione (*16*) in 100 ml. of absolute ethanol was added 4.0 ml. of 0.1 *N* aqueous sodium hydroxide which had also been degassed. The mixture was allowed to stand at room temperature for 3 days and then evaporated *in vacuo* to a small volume. Water was added and the organic material extracted with a mixture of ethyl acetate and ether. The extracts were washed once with water and then with saturated salt solution. Evaporation afforded 0.41 g. of a solid product which was recrystallized from acetone–petroleum ether to give 0.30 g. (63%), m.p. 248–255°. A further recrystallization from acetone–petroleum ether provided the sample for analysis, m.p. 256–260°, $[\alpha]^{24}\text{D}$ +77.3°, λ_{max} 239 mμ (13,300), λ_{max}^{KBr} 5.83, 5.93, 6.22, and 11.37 μ.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.92; H, 9.53.

6α,16α-Dimethyl-1,4-pregnadiene-3,20-dione (**Δ^1-Dehydro-6α,16α-dimethylprogesterone**) (*7c*).—A mixture of 3.0 g. of 6α,16α-dimethylprogesterone (*7b*), 3.0 g. of selenium dioxide, and 3.0 ml. of glacial acetic acid in 300 ml. of *t*-butyl alcohol was heated under reflux for 16 hr. The suspension was then filtered through Celite and the filtrate evaporated to a red oil. The oil was taken up in 250 ml. of ethyl acetate and washed with 5% aqueous sodium bicarbonate solution, water, 10% ammonium polysulfide solution, 10% ammonium hydroxide, and finally with saturated salt solution. Evaporation of the ethyl acetate solution *in vacuo* gave 2.5 g. of a yellow foam which was dissolved in benzene, diluted with petroleum ether and placed on 120 g. of alumina. The material obtained with the first 250 ml. of the 49:1 benzene–ether eluates was recrystallized from acetone–petroleum ether to give 0.334 g. (11%), m.p. 140–143°, $[\alpha]^{26}\text{D}$ +71.0°, λ_{max} 245 mμ (15,760), $\lambda_{max}^{CCl_4}$ 5.84, 5.98, 6.12, 6.21, and 11.22 μ.

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 80.79; H, 9.30.

6,16α-Dimethyl-1,4,6-pregnatriene-3,20-dione (**$\Delta^{1,6}$-Bisdehydro-6,16α-dimethylprogesterone**) (*8b*).—Following the same procedure as described in the preparation of *7c*, 2.13 g. of Δ^6-dehydro-6,16α-dimethylprogesterone (*8a*) was oxidized with 0.65 g. of selenium dioxide. After chromatography and recrystallization from acetone–petroleum ether, 0.626 g. (28%) of the trienedione was obtained as prisms, m.p. 139–141°, $[\alpha]^{30}\text{D}$ +65.2°, λ_{max} 228 mμ (13,400), 255 mμ (9060), 305 mμ (11,960), $\lambda_{max}^{CCl_4}$ 5.84, 6.00, 6.17, and 11.21 μ.

Anal. Calcd. for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.78, 81.63; H, 8.81, 8.62.

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Preparation and Reactions of Steroidal α-Aminonitriles

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The 17α-aminonitriles of estrone and dehydroepiandrosterone were prepared by the addition of cyanide to the appropriate ternary imminium salt. The reaction of the nitriles with methyl and ethynyl Grignard reagents was found to lead to the 17-methyl- and 17-ethynyl-17-dimethylamino compounds. Evidence is presented which indicates that the Grignard reagent enters the molecule on the same side as the departing cyano group.

In the continuing search for compounds which may show useful "splits" in their hormonal activities considerable attention has been devoted to steroids modified by the replacement of oxygen by nitrogen. While a sizeable number of 3-[1] and 17-[2] aminoandrostanes are known, relatively few reports of interesting properties have appeared. Since most of the compounds of this class contained a nitrogen fragment attached to a secondary center, the possibility was considered that facile metabolism at this site might account for the apparent lack of hormonal properties. We therefore undertook the preparation of some 17-alkyl-17-dimethylamino steroids incorporating nitrogen at the tertiary carbon atom of a series of compounds whose oxygenated parents are known to be potent hormonal agents.

The versatility of α-aminonitriles as intermediates in the preparation of highly substituted amines has been demonstrated previously.[3] These nitrogen analogs of cyanohydrins are readily obtained from aldehydes and simple ketones by reaction of the carbonyl compound with an amine salt and cyanide ion.[4] Though dehydroepiandrosterone (I) undergoes the cyanohydrin reaction,[5] this

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