dish orange colored solution was added in portions to a mixture of sodium bicarbonate–ice–water and swirled until gas evolution had ceased. The product was extracted into methylene chloride (twice) and the combined extracts were washed with water and dried. Evaporation of the solvent gave a yellow oil. A solution of the oil in 6 ml. of 10% potassium hydroxide–methanol was warmed on the hot plate for a few minutes, acidified with 2 *N* hydrochloric acid, and extracted twice with methylene chloride. The organic extracts were washed with water, dried, and evaporated to yield semicrystalline material which was crystallized from methanol to give 84 mg. (44%) of IV, m.p. 120.5–122°. Recrystallization from methanol gave 56 mg. of yellow plates, m.p. 123.5–125°. The infrared spectrum [λ_{max} 5.91 (s) μ] of this material was identical to that of authentic IV and no depression in melting point was noted upon admixture with the enedione prepared as reported.[10]

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GETTYSBURG, PA.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. CXCI.[1] Some Reactions of a 6-Methyl-Δ⁵-3β-hydroxy Steroid System

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Dehydration of 6β,16α-dimethylpregnane-3β,5α-diol-20-one acetate (Ib) gives the corresponding Δ⁵-olefin (III), which upon Jones oxidation yields directly 6α,16α-dimethyl-6β-hydroxyprogesterone (VI). The reaction apparently proceeds through an intermediate oxide and such oxides were actually isolated (XIV, XVII) in related chromium trioxide oxidations of 6-methyl-Δ⁵ (XII) and Δ⁶ (XI) olefins. Epoxidation of the 6-methyl-Δ⁵-3β-ol system (III) with peracid furnishes the 5α,-6α-oxide, which leads to both C-6 epimeric 6-methyl-6-hydroxy-Δ⁴-3-ketones (VI, VII) upon Jones oxidation. 6α- and 6β,16α-Dimethylprogesterones have been prepared from 6β,16α-dimethylpregnane-3β,5α-diol-20-one (Ia). Several structures are based largely on nuclear magnetic resonance measurements, which were performed on nearly all of the steroids recorded in this article and summarized in tabular form.

In connection with work in our laboratory on the synthesis of 6α,16α-dimethyl corticosteroids[3] there were also carried out investigations directed towards 6,16-dimethylated analogs of progesterone.[4] The present paper describes the successful synthesis of these progesterone derivatives and in particular a number of unexpected oxidation reactions, where nuclear magnetic resonance measurements[5] have proved very useful in settling the structures of some of the products.

The starting material for all of the present work was 6β,16α-dimethylpregnane-3β,5α-diol-20-one (Ia),[3] which was oxidized with chromium trioxide to the corresponding 3-ketone and then dehydrated by exposure to dilute base to 6β,16α-dimethylprogesterone. Warming with somewhat stronger alkali or treatment with acid caused inversion with formation of the desired 6α,16α-dimethylprogesterone (II).[3] The substance exhibited the expected ultraviolet and infrared spectral properties and the NMR spectrum was completely consistent with structure II. In particular, all five methyl groups could be located as follows: C-21 (δ,[6] 2.12), C-19 (1.27), C-6 (doublet at 70 and 77 cps (δ = 1.22)), C-16 (doublet at 54 and 61 cps (δ = 0.96) and C-18 (0.72)), while the single olefinic proton at C-4 was responsible for the signal at 5.76.

Acid-catalyzed dehydration of 6β,16α-dimethylpregnane-3β,5α-diol-20-one acetate (Ib) proceeded unidirectionally to give 6,16α-dimethyl-Δ⁵-pregnen-3β-ol-20-one acetate (IIIb), the absence of any Δ⁴-olefinic isomer being demonstrated by the NMR spectrum. This did not contain any signals corresponding to an olefinic proton but again showed complete separation of all methyl peaks

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(1) Paper CXC, P. Crabbé, M. J. Durazo, R. M. Saloma, and P. G. Holton, *Bull. soc. chim. Belge, in press.*

(2) (a) Syntex, S. A., Mexico, D. F.; (b) Varian Associates, Palo Alto, Calif.; (c) Department of Chemistry, Stanford University, Stanford, Calif.

(3) J. Iriarte and M. L. Franco, *J. Org. Chem.*, **26**, 2047 (1961).

(4) One such compound, 6α,16α-dimethylprogesterone (II) has since been synthesized (S. Bernstein, E. W. Cantrall, and J. P. Dusza, *J. Org. Chem.*, **26**, 269 (1961) and R. P. Graber and M. B. Meyers, *Chem. and Ind.*, 1478 (1960)) by methods different from the one described in the present article.

(5) For general references see (a) L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, London, 1959; (b) J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1959; (c) J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High-Resolution Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1959.

(6) For reasons discussed elsewhere [C. Djerassi, T. Nakano, A. N. James, L. H. Zalkow, E. J. Eisenbraun, and J. N. Shoolery, *J. Org. Chem.*, **26**, 1192 (1961)] all peak positions are reported in δ units (c.p.s./60 p.p.m. for a 60 megacycle instrument) rather than as τ(τ = 10 − δ), tetramethylsilane serving as an internal standard. A summary of the shifts observed for methyl groups and olefinic protons appears in Table I.

TABLE I

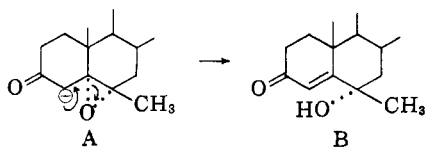
CHEMICAL SHIFTS IN P.P.M. RELATIVE TO $SiMe_4$ (δ = 0.0) FOR METHYL GROUPS AND OLEFINIC PROTONS

Compound	C_{18}[a]	C_{19}[a]	C_{21}[a]	Me-C_{16}[b]	C_6-Me	Olefinic
II	0.72	1.27	2.12	0.96	1.22[b]	C-4 (5.76)
III[a,b]	0.65	1.00	2.12	0.96	1.60[c]	—
IV[a]	0.58	1.03	2.12	0.94	1.27[a]	—
VI	0.68	1.37 or 1.40	2.10	0.88	1.37 or 1.40	C-4 (5.98)
VII	0.70	1.18	2.10	0.97	1.35[a]	C-4 (6.43)
VIII	0.73	1.10	2.12	0.99	1.87[c]	C-4 (5.86); C-7 (5.93)
IX	0.62	0.93	2.12	0.96	—	6-Methylene (4.84)
XI[a,b]	0.65	0.92	2.12	0.97	1.72[c]	C-7 (5.30)
XII[c]	0.63	1.01	2.12	0.90	1.63[c]	—
XIII	0.65	0.97	2.12	0.95	—	C-4 (5.46); 6-Methylene 4.70 and 4.85
XVI	0.70	1.26	2.12	0.97	1.40[a]	C-4 (6.45)
XVII[a,b]	0.67	0.85	2.12	0.97	1.33[a]	—
XVIII[a,b]	0.65	0.95	2.12	0.98	1.79[c]	—

[a] Singlet. [b] Doublet (J = ca. 7 c.p.s.). [c] Slightly broadened due to unresolved long-range spin-coupling.

(C-21 at 2.12, C-19 at 1.00, C-16 doublet at 0.96, and C-18 at 0.65), that associated with the 6-methyl group showing the expected downfield shift to 1.60 (no splitting) because of the attachment to the doubly bonded carbon atom. Saponification provided the corresponding free alcohol (IIIa), whose NMR spectrum was essentially identical with that of IIIb, except for the absence of the 2.03 acetate peak and the signal at 4.60 due to the 3α-hydrogen of the acetate IIIb, which was shifted upfield to 3.44. The hydroxyl proton of IIIa was found at 1.87 (concentration and temperature dependent).

Epoxidation of 6,16α-dimethyl-Δ^5-pregnen-3β-ol-20-one acetate (IIIb) with monoperphthalic acid yielded largely one isomer, which is assigned the anticipated 5α,6α-configuration (IVb) and which upon saponification led to 6β,16α-dimethyl-5α,6α-oxidopregnan-3β-ol-20-one (IVa).[7] The most significant difference between the NMR spectrum of the oxide IVa and its precursor IIIa is the particularly large upfield shift of the C-6 methyl signal from 1.60 in IIIa to 1.27 in IVa due to replacement of the double bond by the epoxide ring. Of interest is the course of the Jones oxidation[8] (chromium trioxide-sulfuric acid-acetone) of the epoxide IVa leading to a crude product, which was treated with alkali in order to perform the expected[9] base-catalyzed opening of the intermediate α-oxido ketone (A → B). Chromatography provided two isomeric α,β-unsaturated ketones (VI and VII), whose structures were proved as follows.



A B

The less soluble isomer was shown to be 6β-hydroxy-6α,16α-dimethylprogesterone (VI), since it was also obtained by acid-catalyzed opening of the 5,6-oxide ring of IVa to the 3β,5α,6β-triol (Va),[10] followed by chromium trioxide–pyridine oxidation[11] of the secondary alcoholic function and base-promoted dehydration of the intermediate crystalline 5α,6β-dihydroxy-3-ketone. This sequence is stereochemically unambiguous and shows that the production of the 6β-hydroxy-6α-methyl isomer VI in the Jones oxidation of IVa must have involved acid-catalyzed opening of the oxide ring to a glycol either before or after oxidation of the C-3 hydroxyl group. The more soluble isomer in the Jones oxidation of IVa must, therefore, be the 6α-hydroxy-6β-methyl derivative VII arising from the originally anticipated path (A → B) and this could be confirmed by oxidizing the 5α,6α-oxido 3β-alcohol IVa with chromium trioxide in pyridine solution[11] whereupon 6α-hydroxy-6β,16α-dimethylprogesterone (VII) was produced directly without any intermediate base treatment.

A third and by far the simplest path to 6β-hydroxy-6α,16α-dimethylprogesterone (VI) was discovered when it was observed that Jones oxidation[8] of 6,16α-dimethyl-Δ^5-pregnen-3β-ol-20-one (IIIa) produced the hydroxylated progesterone directly. This was quite unexpected as we had shown earlier[12] that Jones oxidation of Δ^5-3β-hydroxy steroids proceeds normally to provide the Δ^5-3-ketone, which can then be rearranged with acid or base to the conjugated isomer. Two possible explanations come to mind in rationalizing the direct formation

(7) This substance has already been mentioned briefly by W. P. Schneider and H. C. Murray, *Chem. and Ind.*, 1163 (1960).

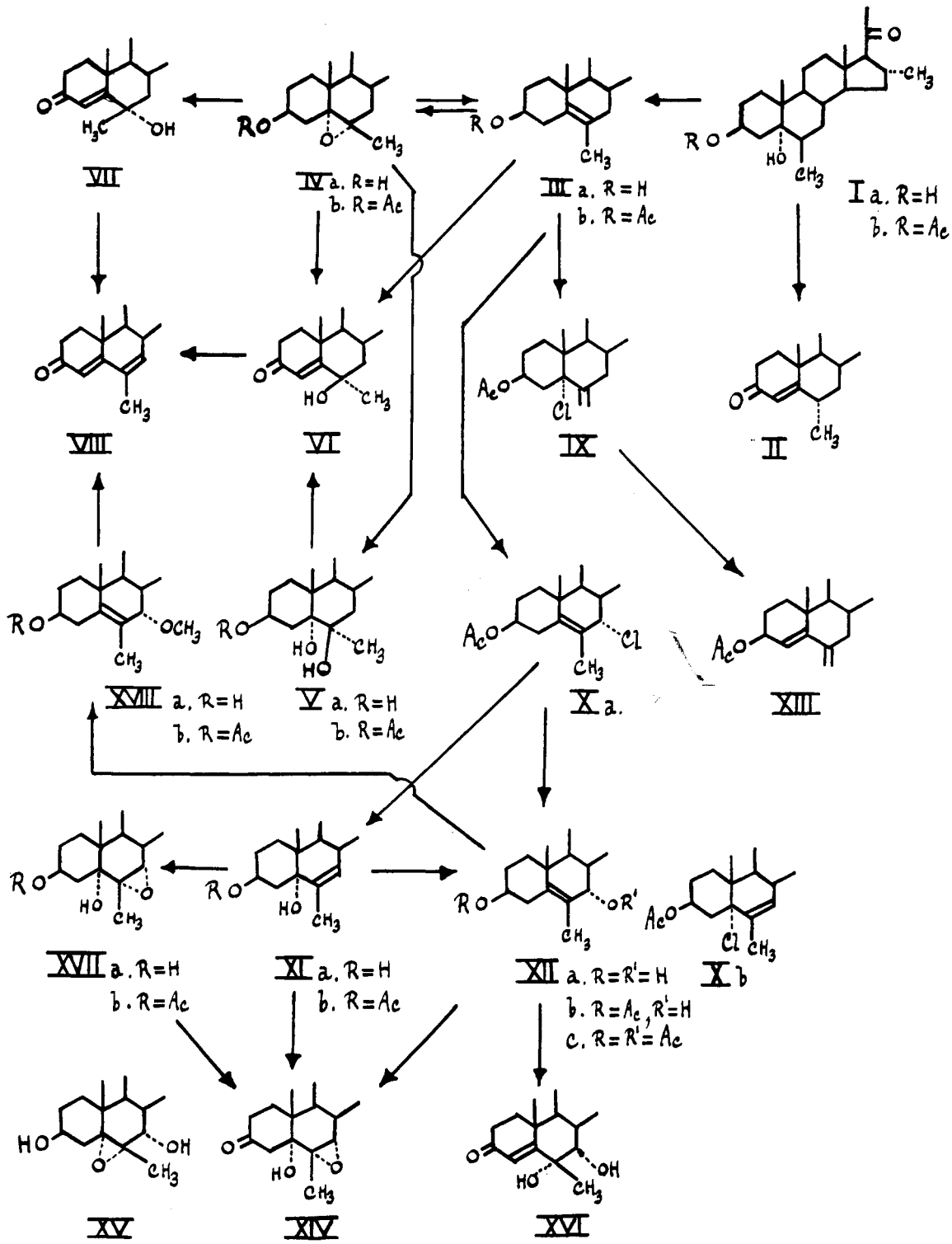
(8) See K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946) and later papers

(9) See C. Djerassi, O. Mancera, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 3505 (1953).

(10) For a full discussion of diaxial opening of 5,6-oxides, see L. F. Fieser and M. Fieser, *Steroids*, Reinhold, New York, 1959, chapter 6.

(11) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(12) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).



of VI from the olefin IIIa. The simplest explanation would be allylic oxidation of 6α,16α-dimethylprogesterone (II), but this possibility was excluded when it was observed that II was stable to the conditions of the Jones oxidation. It appears, therefore, that formation of an intermediate 5,6-oxide must be postulated, either before or after[13] oxidation of the 3β-hydroxyl group, which is then cleaved by the acid medium to the 5α,6β-glycol and thence dehydrated to VI. Strong support for the possible intervention of an oxide intermediate is presented

(13) Δ^5-3-Ketones are particularly labile to oxidation at C-6 [see L. F. Fieser, T. W. Greene, F. Bischoff, G. Lopez, and J. J. Rupp, *J. Am. Chem. Soc.*, **77**, 3928 (1955)] and Δ^4-3,6-diones are occasionally encountered as by-products in the Jones oxidation of Δ^4-3β-ols [see P. Crabbe, E. A. Azpeitia, and C. Djerassi, *Bull. Soc. Chim. Belg.*, **70**, 168 (1961)].

below, where oxides (XIV, XVII) were actually isolated during similar Jones oxidations.

The NMR spectra of the isomeric 6-hydroxy-6,16α-dimethylprogesterones (VI, VII) were completely consistent with the structural assignments. All five methyl groups could be observed separately, but only the C-16, C-18, and C-21 substituents were found in the usual positions (as in II discussed above). In VI, both the C-6 and the C-19 methyl groups fall practically into the same location (1.37, 1.40), while in VII they appear well separated (C-6 being assigned at 1.35 and C-19 at 1.18). The downfield shift of C-19 in VI relative to VII is attributed to the diaxial interaction between the C-19 methyl function and the 6β-hydroxyl group. These conclusions are consistent with the occurrence of the olefinic proton at 5.98 in VI, comparable to the 5.76 value in the spectrum of the simple 6α-methyl-Δ^4-3-ketone II. The equatorial hydroxyl group in VII produces a strong downfield effect on this signal, which is now observed at 6.43.

In an attempt to elaborate the 6-chloro-6-methyl-Δ^4-3-keto grouping in this series,[14] there was studied the chlorination of the 6-methyl-Δ^5-3β-ol acetate IIIb. Even in carbon tetrachloride at 0°, chlorination was accompanied by spontaneous loss of hydrogen chloride with formation of a relatively unstable allylic chloride. A decision between the two possible alternatives, namely the 7α-chloro-Δ^5 (Xa) or 5α-chloro-Δ^6 (Xb) 6,16α-dimethylpregnen-3β-ol-20-one acetate structures could be reached very simply by NMR spectroscopy. The C-6 methyl group of Xa exhibited a signal at 1.80 (because of its location on a doubly bonded carbon atom), but no evidence of an olefinic proton (required by Xb) could be found. On the other hand, there existed a slightly broadened single peak, corresponding in area to one hydrogen, at 4.23 which can be assigned quite unambiguously to the 7β-proton, the downfield shift being due to the combined effects of the chlorine atom and the adjacent double bond. The probable equatorial nature of this hydrogen atom can already be suggested on the basis of the NMR spectrum in view of the absence of large spin coupling (as would be observed between adjacent axial hydrogens) and this stereochemical point could be settled unambiguously in favor of a 7α-oriented chlorine substituent by considering the rotation of this substance (Xa). Introduction of a 7α-chlorine atom into a Δ^5-3β-ol (*e.g.* cholesterol acetate or benzoate) produces a large levorotatory shift,[15a] while a 7β-chloride causes a moderate change in a positive direction. The large negative rotation increment in going from IIIb to Xa is, therefore, only compatible with the 7α-chloro stereochemistry.

Chromatography of the 7α-chloro-Δ^5-3β-acetate Xa on neutral alumina provided three products of which the least polar was the isomeric 5α-chloro-6-methylene-16α-methylpregnan-3β-ol-20-one acetate (IX). The presence of the terminal methylene function follows from the infrared bands at 1640 and 905 cm.$^{-1}$ and the NMR doublet with intensity corresponding to two protons in the vicinity of 4.84. The location of the chlorine atom at C-5 rather than at C-7 can be deduced from the NMR spectrum since the hydrogen atom at C-7 in a 6-methylene-7-chloro derivative would have been shifted downfield (see Xa) into an extremely easily recognizable position, which was not the case. Dehydrochlorination of the 6-methylene 5α-chloride IX with collidine provided the crystalline 6-methylene-16α-methyl-Δ^4-pregnen-3β-ol-20-one acetate (XIII), which contained strong ultraviolet absorption maxima at 236 and 242 mμ. The NMR spectrum of this diene XIII shows the 5.46 signal attributable to the C-4 olefinic proton as well as the methylenic protons which are observed separately at 4.70 and 4.85 (see also IX).

The more polar substances arising from chromatography of the initial chlorination product [6,16α-dimethyl-7α-chloro-Δ^5-pregnen-3β-ol-20-one acetate (Xa)] proved to be a pair of isomeric allylic alcohols, the net effect in the chromatogram having been replacement of chlorine by hydroxyl. The easier eluted member of this pair was 6,16α-dimethyl-Δ^6-pregnene-3β,5α-diol-20-one 3-acetate (XIb), the tertiary nature of the hydroxyl group being established by the resistance of this substance towards acetylation. The location of the double bond between carbon atoms 6 and 7 was shown unambiguously by the NMR spectra of the acetate XIb and the corresponding saponification product XIa, both of them containing a single peak at 5.30 associated with the olefinic proton at C-7 and a methyl peak at 1.72 due to the C-6 methyl group located on a doubly bonded carbon.

The third and most polar product was assigned the 6,16α-dimethyl-Δ^5-pregnene-3β,7α-diol-20-one 3-acetate (XIIb) structure on the following evidence. The secondary nature of the newly introduced hydroxyl group followed from the acetylation to a diacetate (XIIc), while the Δ^5-location of the double bond was established by the NMR spectrum which contained no olefinic proton signals, but did show the presence of a methyl group (at 1.63) situated on a double bond. This leaves only two possible locations for the hydroxyl function—C-4 or C-7—and the former appears to be excluded by the NMR spectra of the 3β-monoacetate XIIb and diacetate XIIc, as the splitting pattern of the C-3 hydrogen atom is of

(14) For other 6-chloro derivatives of progesterone and their biological properties see H. J. Ringold, E. Batres, A. Bowers, J. Edwards, and J. A. Zderic, *J. Am. Chem. Soc.*, **81**, 3485 (1959); J. S. Mills, O. Candiani, and C. Djerassi, *J. Org. Chem.*, **25**, 1056 (1960).

(15) (a) See J. P. Mathieu and A. Petit, *Pouvoir Rotatoire Naturel. I. Steroides*, Masson, Paris 1956; (b) ref. 10, p. 156 (note that on p. 100 of ref. 10, the rotations of C-7 isomeric Δ^5-cholestene-3β,7-diol diacetates have been reversed).

the usual type observed in 3β-acetoxy-Δ^5-steroids (*e.g.* IIIb) and occurs within 4 c.p.s. (0.067 p.p.m.) from that found in IIIb.

We conclude, therefore, that the hydroxyl group is attached to C-7 and the α-orientation at that center can be deduced readily by molecular rotation arguments, notably by the characteristic levorotatory shift[15a,b] in going from the alcohols XIIa and XIIb to the diacetate XIIc.

When the initial chlorination product (Xa) was treated with potassium acetate in aqueous acetone followed by saponification with methanolic potassium hydroxide, there was again isolated the Δ^5-3β,7α-diol XIIa as well as a new substance, which could be shown to be the corresponding methyl ether XVIIIa, further characterized as the 3β-acetate XVIIIb. The NMR spectra of XVIIIa and XVIIIb lacked signals of any olefinic proton, thus confirming the Δ^5-double bond location, but showed peaks at 1.79 (C-6 methyl group on double bond) and 3.55 (methoxyl group).

Chemical proof for the correctness of structure XVIIIa could be adduced by Zeisel determination (one methoxyl group) and by Jones oxidation[8,12] which led directly to 6,16α-dimethyl-$\Delta^{4,6}$-pregnadiene-3,10-dione (VIII) with its characteristic ultraviolet absorption maximum at 290 mμ. The same dienone VIII could also be obtained by acid-catalyzed dehydration of either 6β-hydroxy-6α- (VI) or 6α-hydroxy-6β- (VII) 16α-dimethylprogesterone, the latter's equatorial 6α-hydroxy group being more resistant to such treatment.

The stereochemistry of the 7-methoxyl function of XVIII could be established as 7α in view of the levorotatory shift in going from XII to XVIII (a dextrorotatory change accompanying methylation of a Δ^5-7β-ol).[16] The mode of formation of XVIIIa became apparent when it was found that methanolic alkali treatment of the 7α-hydroxy derivative XIIb resulted only in saponification of the 3β-acetoxy function provided acetic acid was not used during the work-up. Neutralization of the alkaline hydrolysis reaction mixture with an excess of acetic acid followed by distillation to reduce the volume of solvent or treatment of XIIa directly with acetic acid in methanol afforded the Δ^5-7α-methoxy-3β-ol (XVIIIa).

It was interesting to note that alkaline hydrolysis of XIb and work-up of the product in the absence of acid led to the corresponding diol XIa. However treatment of XIa under reflux with acetic acid in anhydrous methanol afforded XIIa, the product of an allylic rearrangement, together with a small amount of the corresponding methyl ether XVIIIa. Turning now to the isomeric allylic alcohols XIb and XIIb, a definite decision with respect to the mechanism of their formation can only be made after undertaking a kinetic investigation. The 7α-hydroxy derivative XIIb is almost certainly produced by a SN1 mechanism, but it is not clear whether the 5α-isomer XIb results from S_N2' attack or via the allylic carbonium ion.

Finally, we should like to record the course of the Jones oxidation of the allylic alcohols XI and XII, which proved to be much more complicated than is usually encountered in such oxidations.[8,12,17] Thus, oxidation of 6,16α-methyl-Δ^6-pregnene-3β,-5α-diol-20-one 3-acetate (XIb)—in spite of the absence of any secondary hydroxyl function—rapidly consumed chromium trioxide in acetone solution[8] to produce the3β- acetoxy-5α-hydroxy-6,7-oxide XVIIb, which could be saponified to the 3β,5α-diol XVIIa. The structures of these two substances follow largely from their NMR spectra: the C-16 and C-18 methyl groups occur in the usual positions indicated above (*e.g.* II), while the C-19 methyl can now be found at 0.85, a typical position for a C-19 methyl group in a steroid without keto groups or double bonds in rings A and B. The position of the C-6 methyl substituent at 1.33 is compatible with the termination of an oxide at C-6. As far as differentiating XVIIa from XV is concerned, this can be done readily on the basis of the signal at 3.14 associated with the C-7 proton attached to the same carbon atom as one terminus of the oxide ring. This same peak is observed at the identical position in the spectra of XVIIb and XIV. If the alternate structure XV had obtained (involving allylic rearrangement during oxidation of XI), then this C-7 proton should have exhibited a signal in the vicinity of 3.5 as was the case in XVI.

When the 3β,5α-dihydroxy 6,7-oxide (XVIIa) was again exposed to the Jones reagent, oxidation of the 3β-hydroxy group was effected with formation of 6α,7α-oxido-6β,16α-dimethylpregnan-5α-ol-3,20-dione (XIV), a substance which was also obtained by Jones oxidation of 6,16α-dimethyl-Δ^6-pregnene-3β,5α-diol-20-one (XIa) or 6,16α-dimethyl-Δ^5-pregnene-3β,7α-diol-20-one (XIIa). In the last oxidation, there was isolated a second product possessing a strong ultraviolet absorption maximum at 244 mμ to which we assign the 6β,-16α-dimethyl-6α,7α-dihydroxyprogesterone (XVI) structure for the following reasons. The NMR signal for the C-4 hydrogen of XVI occurs at the unusually low position 6.45, which is also found (6.43) in the 6α-hydroxy derivative VII, while the 6β-hydroxy isomer VI shows this peak at the expected 5.98 p.p.m., typical of Δ^4-3-keto steroids. We believe that this shift to lower field in VII and XVI can be attributed directly (see p. 408 in ref. 5c) to the effect of the equatorial 6α-hydroxyl group upon the C-4 hydrogen atom and that we are justified, therefore, in assigning the α-orientation

(16) See ref. 15a, p. 221 as well as H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1798 (1948).

(17) *Inter al.*, P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *J. Chem. Soc.*, 2402 (1951); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

to the C-6 hydroxyl function of XVI. The only logical way in which such a 6α-orientation can be generated is by opening of a 5α,6α-oxide by the process A→B (*vide supra*), since the usual acid-catalyzed diaxial opening[10] of a 5,6- or 6,7-oxide would produce the 6β-hydroxy stereochemistry. If this reasoning is correct, then no reaction has occurred at C-7 and this hydroxyl group must still bear the original 7α-orientation of its precursor XIIa. The other noteworthy feature of the NMR spectrum of XVI is the above mentioned signal at 3.50 due to the 7β-hydrogen.

There remains to be considered only the structure of the oxido ketone XIV and its formation from XIa, XIIa, and XVIIa. If structure XIV is correct, then the production of this ketone from XI involves epoxidation of the Δ^6 double bond (similar to the formation of XVIIb from XIb) and oxidation of the 3β-hydroxy group, the chronological sequence of these two steps not having been established. Oxidation of XVIIa to the ketone XIV is, of course, unexceptional. However, in order to rationalize the isolation of XIV in the oxidation of XIIa, it is necessary to postulate an allylic rearrangement of the Δ^5-7α-hydroxy system.

The structure of the ketone XIV is based on the absence of strong ultraviolet absorption and the presence of infrared bands corresponding to a hydroxyl group and carbonyl groups at C-3 (or its structural equivalent) and C-20. The NMR spectrum is consistent with such a formulation, since the peak at 3.14 assigned in XVIIa and XVIIb to the 7β-hydrogen on the same carbon atom as the epoxide termination point can also be found here. However, the intensity of this peak now corresponds to two protons, which we attribute to the accidental overlap by the 5α-hydroxyl proton. In the precursors XVIIa and XVIIb, this hydroxyl proton, though occurring in the same neighborhood, could be separately distinguished at 3.02 (XVIIa) and 3.05 (XVIIb).

EXPERIMENTAL[18]

6,16α-Dimethyl-Δ^5-pregnen-3β-ol-20-one acetate (IIIb). The dehydration of 6β,16α-dimethylpregnane-3β,5α-diol-20-one 3-acetate (Ib) was effected by addition of concentrated sulfuric acid (5 drops) to a suspension of the steroid (10 g.) in acetic anhydride (800 cc.) at room temperature with stirring. A pink to green changing discoloration took place immediately. The mixture was kept three days at room temperature and shaken occasionally. Slow, but progressive dissolution of the steroid took place. The homogeneous solution was then poured into water and the product isolated by extraction with ethyl acetate. The oily residue was purified by dissolving it in benzene-hexane (1:1) and filtering the solution through a column of alumina (600 g.). Evaporation of the solvent and crystallization of the residue from hexane gave material with m.p. 138–139° (7 g.) which showed a yellow color reaction with tetranitromethane. The oily mother liquors were chromatographed on alumina and in this way additional crystalline material (0.5 g., m.p. 135–137°) could be recovered. An analytical sample of IIIb was prepared by crystallization from hexane: prisms, m.p. 142–144°, $[\alpha]_D$ −12.5°, ν_{max} 1740, 1700, 1240 cm.$^{-1}$.

This compound was also obtained by heating 6β,16α-dimethylpregnane-3β-5α-diol-20-one 3-acetate (Ib) (2 g.) with acetic anhydride (200 cc.) and *p*-toluenesulfonic acid (0.2 g.) under reflux for 2 hr. and isolating the product (1.1 g., m.p. 135–137°) through a procedure identical to that described.

Anal. Calcd. for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91; O, 12.42. Found: C, 77.62; H, 9.74; O, 12.80.

The substance was recovered unchanged after attempted hydrogenation in ethyl acetate in the presence of 10% palladium charcoal even after shaking for 3 hr. at 50° and 40 p.s.i.

6,16α-Dimethyl-Δ^5-pregnen-3β-ol-20-one (IIIa). The hydrolysis of 6,16α-dimethyl-Δ^5-pregnen-3β-ol-20-one 3-acetate (IIIb) (2 g.) was accomplished by refluxing with 1% methanolic potassium hydroxide (100 cc.) for 0.5 hrs. The solution was then neutralized with acetic acid and the product was isolated by extraction with ethyl acetate. A crystalline residue was thus obtained (1.5 g., m.p. 171–173°) which was purified by recrystallization from acetone–ether. An analytical specimen showed m.p. 180–181°, $[\alpha]_D$ −10°, ν_{max} 3600, 1685 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53; O, 9.29. Found: C, 79.97; H, 10.50; O, 9.38.

6β,16α-Dimethyl-5α,6α-oxidopregnan-3β-ol-20-one acetate (IVb). The oxidation of 6,16α-dimethyl-Δ^5-pregnen-3β-ol-20-one acetate (IIIb) (7 g.) was carried out in ether (400 cc.) solution with 1.2 molecular equivalents of monoperphthalic acid (30.2 cc. of a 1.2*N* solution in ether) at 10° for 20 hr. The reaction mixture was then pouredin to sodium bicarbonate solution and extracted with ether. Evaporation of the neutral ether solution gave a crude residue with m.p. 125–140° which was recrystallized from acetone-ether or from ether-hexane to yield material (5.2 g.) with m.p. 150–153°. An analytical sample prepared by recrystallization from the same solvents showed m.p. 157–158° (prisms), $[\alpha]_D$ +3.4°, ν_{max} 1750, 1700, 1235 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51; O, 15.90. Found: C, 74.96; H, 9.43; O, 15.93.

6β,16α-Dimethyl-5α,6α-oxidopregnan-3β-ol-20-one (IVa). The hydrolysis of 6β,16α-dimethyl-5α,6α-oxidopregnan-3β-ol-20-one acetate (IVb) was carried out by dissolving this steroid (5 g.) in methanol (100 cc.), adding a solution of potassium hydroxide (8 g.) in water (12 cc.) and methanol (120 cc.) and keeping the mixture at room temperature for 1 hr. It was then acidified with acetic acid, water was added and the crystalline precipitate formed was collected by filtration. The filtrate was extracted with ethyl acetate. The crude material had m.p. 170–185°. It was purified by crystallization from acetone-ether and by chromatography of the mother liquors on neutral alumina (elution with benzene-ether 9:1) whereby it was obtained as needles (3.5 g.) with m.p. 197–198°, $[\alpha]_D$ +4.9°,[7] ν_{max} 3700, 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07; O, 13.31. Found: C, 77.08; H, 10.04; O, 13.16.

Reacetylation of this material (900 mg.) by warming on the steam bath with pyridine (5 cc.) and acetic anhydride (10 cc.) followed by the usual isolation procedure by extraction with ethyl acetate and chromatography on neutral

(18) All melting points are uncorrected and were determined on the Fisher-Johns block. Unless noted otherwise, all rotations were measured in chloroform solution, while ethanol was used for the ultraviolet spectra and potassium bromide disks for the infrared spectra. We are indebted to Dr. J. Matthews and staff for all of these determinations and to Dr. A. Bernhardt (Mülheim, Germany) for the microanalyses. All NMR measurements were conducted by Dr. A. Melera in deuterochloroform solution (tetramethylsilane added as internal reference) with a Varian HR-60 High Resolution Spectrometer, peak positions (in c.p.s. relative to tetramethylsilane) being obtained by the usual audio side-band technique using a Hewlett-Packard 200 CD audio oscillator.

alumina (30 g.) (elution with hexane-benzene 2:1) gave the starting acetate IVb (460 mg.), crystallized from hexane, and whose melting point, 153–155° was undepressed on admixture with an authentic sample.

Regeneration of 6,16α-dimethyl-Δ^5-pregnen-3β-ol-20-one (IIIa) from 6β,16α-dimethyl-5α,6α-oxidopregnan-3β-ol-20-one (IVa) was accomplished by stirring a mixture of the latter (0.5 g.), acetic acid (8 cc.), water (0.2 cc.), sodium iodide, (0.85 g.), sodium acetate (0.28 g.) and zinc dust (0.85 g.) at room temperature for 3 hr. Addition of water, extraction with ethyl acetate and chromatography on alumina (30 g.) furnished crystalline material in the hexane–benzene 1:1 eluates (200 mg., m.p. 170–176°), which were purified by crystallization from acetone–ether. The compound obtained had m.p. 175–176°, which was undepressed on admixture with 6,16α-dimethyl-Δ^5-pregnen-3β-ol-20-one (IIIa). The infrared spectra of both compounds were identical.

6α,16α-Dimethylpregnane-3β,5α,6β-triol-20-one (Va). The acid-catalyzed opening of 6β,16α-dimethyl-5α,6α-oxidopregnan-3β-ol-20-one (IVa) was effected by heating a solution of the steroid (0.5 g.), acetone (50 cc.), water (20 cc.) and *p*-toluenesulfonic acid (300 mg.) under reflux for 0.5 hr. Addition of water, extraction with ethyl acetate and evaporation of the solvent gave a residue which was crystallized from ethyl acetate–ether. The purified 5α,6β-glycol Va (200 mg.) crystallized as needles with m.p. 180–182°, $[\alpha]_D$ +31.5°, ν_{max} 3500, 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12; O, 16.91. Found: C, 72.70; H, 10.01; O, 17.62.

6α,16α-Dimethylpregnane-3β,5α,6β-triol-20-one 3-acetate (Vb). This compound was prepared by acetylation of Va by warming with acetic anhydride and pyridine. It was isolated as usual and purified by chromatography on alumina and crystallization from acetone-ether: prisms with m.p. 200–202°, ν_{max} 3550, 1710, 1260 cm.$^{-1}$, $[\alpha]_D$ +18.1°.

Anal. Calcd. for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.45; H, 9.68; O, 19.63.

6α,16α-Dimethyl-6β-hydroxyprogesterone (VI). (*a*) *From 6α,16α-dimethylpregnane-3β,5α,6β-triol-20-one* (Va). 6α,16α-Dimethylpregnane-3β,5α,6β-triol-20-one (Va) (300 mg.) dissolved in anhydrous pyridine (40 cc.), reacted with 300 mg. of chromium trioxide in 40 cc. of pyridine[11] at room temperature for 20 hr. Ethyl acetate (about 800 cc.) was added to the mixture, the solids were removed by filtration through Celite and the filtrate was washed with dilute hydrochloric acid, sodium bicarbonate solution and water, dried and evaporated. The colored residue (220 mg., m.p. 226–228°) was adsorbed onto a column of neutral alumina (30 g.), whence elution with benzene-ether (9:1) afforded a crystalline material with m.p. 223–235°, and after three crystallizations from ethyl acetate the analytical specimen of 6α,16α-dimethylpregnane-5α,6β-diol-3,20-dione as needles with m.p. 237–239°, $[\alpha]_D$ +53°. It showed no significant absorption in the ultraviolet; ν_{max} 3550, 1720 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64; O, 17.00. Found: C, 73.33; H, 9.27; O, 17.15.

The above ketone (100 mg.) in methanol (30 cc.) was heated under reflux for 1 hr. (nitrogen atmosphere) with potassium hydroxide (1.5 cc. of a 5% aqueous solution). The solution was then neutralized with acetic acid, diluted with water and extracted with ethyl acetate. Evaporation of the solvent furnished a crude product (78 mg.) with m.p. 240–250°. It was purified by chromatography on neutral alumina (5 g.) whereby elution with benzene and with benzene-ether (4:1) followed by crystallization from acetone-ether afforded fine needles of *6α,16α-dimethyl-6β-hydroxyprogesterone* (VI) with m.p. 255–256°, $[\alpha]_D$ +83°, λ_{max} 238–240 mμ, log ϵ 4.12, ν_{max} 3550, 1695, 1668, 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 76.80; H, 9.47; O, 13.91.

(*b*) *By oxidation of 6,16α-dimethyl-Δ^5-pregnen-3β-ol-20-one* (IIIa). The steroid (4.0 g.) dissolved in acetone (100 cc.) was oxidized (3–5 min.) by titration at 5° with 8 *N* chromic acid in 8*N* sulfuric acid.[8] The usual isolation procedure by extraction with ethyl acetate furnished a crude product (3.4 g.) with m.p. 235–238° which after two crystallizations from acetone–ether gave material with m.p. 252–255° (2.6 g., fine needles), $[\alpha]_D$ +81.1°, λ_{max} 238 mμ, log ϵ 4.10, ν_{max} 3550, 1710, 1670, 1610 cm.$^{-1}$. This compound was found to be identical with 6α,16α-dimethyl-6β-hydroxyprogesterone obtained as described in (a) by mixture melting point and infrared comparisons.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 77.70; H, 9.50; O, 12.98.

(*c*) *By oxidation of 6β,16α-dimethyl-5α,6α-oxidopregnan-3β-ol-20-one* (IVa). This reaction was accomplished by dropwise addition of 8*N* chromic acid in 8*N* sulfuric acid[8] to a solution of the steroid (1.6 g., m.p. 196–197°, purified by chromatography and recrystallization) in acetone (200 cc.) at 0 to 5°. After 3 min., the reaction mixture was diluted with water and the product isolated by extraction with ethyl acetate. Crystallization from ethyl acetate–ether provided 1.3 g. of solid, m.p. 178–185°, λ_{max} 240 mμ, log ϵ 3.52.

This total material was then heated under reflux for 1 hr. (nitrogen) with potassium hydroxide (1.5 cc. of a 5% aqueous solution) in methanol (30 cc.). Neutralization with acetic acid, dilution with water and isolation by extraction with ethyl acetate gave a residue which crystallized from ethyl acetate-ether to yield a crude product with m.p. 190–195°, $[\alpha]_D$ +101.6° and λ_{max} 240–242 mμ, log ϵ 4.17. This material proved to be a binary mixture which was separated into its components by fractional crystallization and chromatography as follows: The less soluble component was obtained by recrystallization from several solvents, acetone-ether, methanol-ether, ethyl acetate-ether, as needles with m.p. 248–250°, $[\alpha]_D$ +84° and λ_{max} 238–239 mμ log ϵ 4.09. It was found to be identical with *6α,16α-dimethyl-6β-hydroxyprogesterone* (VI) prepared as described above in (a) and (b), by comparison of their infrared spectra and by mixture melting point. Chromatography of an aliquot of the mother liquors on silica gel afforded additional amounts of that compound by elution with ether and crystallization from the same solvent (m.p. 250–255°, λ_{max} 238 mμ, log ϵ 3.99), together with the more soluble and, also, more polar component of the mixture, obtained, by elution with ether, as plates with m.p. 202–205°, λ_{max} 242–244 mμ, log ϵ 4.16.

This second component of the mixture obtained in this oxidation could also, and more easily, be isolated by treatment of the mother liquors of 6α,16α-dimethyl-6β-hydroxyprogesterone with acetic acid (15 cc.) and concentrated hydrochloric acid (3 cc.) at room temperature for 12 hr., which converted VI into the less polar dienone VIII, while VII was largely unchanged. Addition of water and isolation by extraction, with ethyl acetate, washing with sodium bicarbonate, furnished a partially crystalline residue. By washing the crystals with ether (m.p. 195–197°) and by recrystallizing them from methanol–ether and acetone–ether, prisms of *6β,16α-dimethyl-6α-hydroxyprogesterone* (VII) were obtained with m.p. 209–210°, $[\alpha]_D$ +121°, λ_{max} 243–244 mμ, ν_{max} 3600, 1715, 1665, 1610 cm.$^{-1}$. This compound was found to be identical with the specimen described below.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 77.16; H, 9.54; O, 13.51.

6β,16α-Dimethyl-6α-hydroxyprogesterone (VII). The oxidation of highly purified 6β,16α-dimethyl-5α,6α-oxidopregnan-3β-ol-20-one (IVa) (2 g., m.p. 197–198°, chromatographically pure) was carried out in pyridine (60 cc.) with pyridinium chromate[11] (from 1 g. of chromium trioxide which was slowly added into 50 cc. of anhydrous pyridine) at room temperature for 20 hours. Ethyl acetate was then added to the reaction mixture, the solids were removed by filtration, the solution was washed, dried and the solvents eliminated under vacuum. The colored residue thus obtained had λ_{max} 244 mμ, log ϵ 3.88. Chromatography of this crude material (1.4 g.) on neutral alumina (50 g.), elution with benzene-ether (1:1) and crystallization from acetone-ether

provided the pure ketone VII (0.9 g.) with m.p. 212–213°, $[\alpha]D$ +113.8°, λ_{max} 242–244 mμ, log ε 4.15, ν_{max} 3600, 1715, 1665, 1610 cm.$^{-1}$. This substance was identical (by mixture melting point and infrared comparisons) with the isomer of 6α,16α-dimethyl-6β-hydroxyprogesterone described in the preceding experiment. When it was heated under reflux in methanol (30 cc.) with potassium hydroxide (1.5 cc. of an aqueous 5% solution) for 1 hr. under nitrogen, and the product isolated by neutralization with acetic acid, addition of water and collection of the crystals, the compound was recovered unchanged.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 77.06; H, 9.49; O, 13.70.

6,16α-Dimethyl-Δ^{4,6}-pregnadiene-3,20-dione (VIII). (*a*) *From 6α,16α-dimethyl-6β-hydroxyprogesterone* (VI). The acid-catalyzed dehydration of 6α,16α-dimethyl-6β-hydroxyprogesterone (VI) (1 g., m.p. 257–258°) was effected in acetic acid (20 cc.) with concentrated hydrochloric acid (4 cc.) at room temperature for 12 hr. The product was then isolated by adding ice water to the mixture, extracting with ethyl acetate and washing the solution with sodium bicarbonate. The crude material (0.85 g.), crystallized from ether, had m.p. 155–157°, raised to 163–164° by recrystallization. The compound was, however, purified best by chromatography of the total material on neutral alumina (40 g.) whereby elution with benzene-ether (9:1) and recrystallization from acetone-ether afforded an analytical specimen with m.p. 163–165°, $[\alpha]D$ +136.5°, λ_{max} 288–290 mμ, log ε 4.42, ν_{max} 1700, 1665, 1580, 895 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47; O, 9.40. Found: C, 81.66; H, 9.07; O, 9.70.

(*b*) *From 6β,16α-dimethyl-6α-hydroxyprogesterone* (VII). The acid dehydration of pure 6β,16α-dimethyl-6α-hydroxyprogesterone (VII) (1.5 g., m.p. 209–211°) was carried out in acetic acid (15 cc.) with concentrated hydrochloric acid (3 cc.) at room temperature for 12 hr. Ice and water were then added to the reaction mixture and the product was isolated by extraction with ethyl acetate. The crude residue was partially crystalline. This impure crystalline material had m.p. 195–203°. Chromatography of the total product on neutral alumina (50 g.) led to the isolation of two compounds:

Elution with hexane–benzene (9:1) afforded 6,16α-dimethyl-Δ^{4,6}-pregnadiene-3,20-dione (VIII) (0.95 g., 63%) which was crystallized from acetone-ether (m.p. 160–163°) and found to be identical with the authentic compound, described in the preceding experiment, by comparison of their infrared spectra and by mixture melting point.

Elution with benzene-ether (9:1) and with ether furnished unchanged starting material (0.36 g., 24%) which was crystallized from acetone-ether (m.p. 208–210°) and identified by infrared comparison.

(*c*) *By dehydration of 6α,16α-dimethylpregnane-5α,6β-diol-3,20-dione.* A solution of 6α,16α-dimethylpregnane-5α,6β-diol-3,20-dione (200 mg.), glacial acetic acid (15 cc.) and hydrochloric acid (3 cc.) was kept 4 hr. at room temperature. It was then poured into ice water and the product extracted with ethyl acetate washing the solution with sodium bicarbonate. Evaporation of the solvent gave an oily residue which was dissolved in hexane and adsorbed onto a column of alumina (30 g.). Elution with hexane-benzene (1:1) afforded crude 6,16α-dimethyl-Δ^{4,6}-pregnadiene-3,20-dione (150 mg., m.p. 155–165°) and recrystallization from ether-hexane furnished the pure dienone VIII, m.p. 163–165°, λ_{max} 290 mμ, log ε 4.42.

6α,16α-Dimethylprogesterone (II). The dehydration of 6β,16α-dimethylpregnan-5α-ol-3,20-dione[8] (3 g.) dissolved in methanol (250 cc.) was accomplished by heating under reflux with dilute potassium hydroxide (12.5 cc. of a 5% aqueous solution) for 20 min. in an atmosphere of nitrogen. The solution was immediately poured into water and the product isolated by extraction with ethyl acetate. The crude material (2.6 g.) had m.p. 160–170°, $[\alpha]D$ +117°. It was crystallized three times from acetone-ether; in this manner the pure *6β,16α-dimethylprogesterone* was obtained as needles with m.p. 179–182°, $[\alpha]D$ +112.7°, λ_{max} 242 mμ, log ε 4.21, ν_{max} 1715, 1675, 1610 cm.$^{-1}$ (R_f 0.58 in paper partition chromatography with the solvent system formamide–hexane).

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01; O, 9.34. Found: C, 80.62; H, 9.95; O, 9.39.

When this 6β-methyl isomer was heated (nitrogen atmosphere) with 1% potassium hydroxide in aqueous methanol for 1 hr., or else, when it was treated at room temperature with a mixture of acetic acid and concentrated hydrochloric acid (5:1) for 20 hr., there was obtained, after the usual isolation procedure by extraction with ethyl acetate, the epimeric *6α,16α-dimethylprogesterone* (II)[8] as needles (from ether-hexane) with m.p. 126–128°, $[\alpha]D$ +146.9°, λ_{max} 240–242 mμ, log ε 4.19, ν_{max} 1720, 1690, 1610 cm.$^{-1}$ (R_f 0.68 in paper partition chromatography with the solvent system formamide-hexane).[19]

The substance remained unchanged upon exposure to chromium trioxide–sulfuric acid in acetone solution.

Chlorination of 6,16α-dimethyl-Δ^5-pregnen-3β-ol-20-one acetate (IIIb). By chlorination of 6,16α-dimethyl-Δ^5-pregnen-3β-ol-20-one acetate (10 g.) in carbon tetrachloride (100 cc.) with a solution of chlorine in the same solvent (60 cc. 1.1 *N*) at 0° (immediate evolution of hydrogen chloride), there was obtained after isolation by extraction with methylene chloride a crude crystalline chloride (10.5 g.) with m.p. 145–148°, $[\alpha]D$ −112.6°. By recrystallization from ether an analytical sample was obtained as needles with m.p. 140–143° (decomposition with gas evolution), $[\alpha]D$ −112.3°, ν_{max} 1740, 1690, 1650, 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{37}O_3Cl$: C, 71.32; H, 8.86; O, 11.40; Cl, 8.42. Found: C, 71.06; H, 8.86; O, 11.48; Cl, 8.45.

This substance, *6,16α-dimethyl-7α-chloro-Δ^5-pregnen-3β-ol-20-one acetate* (Xa) was stable at room temperature for several days but it decomposed in the solid state under the influence of light. When its solutions were warmed, formation of hydrogen chloride was noted. The total material was chromatographed on neutral alumina (200 g.). Elution with hexane-benzene (9:1) afforded an isomeric chloride (2.6 g.) which was purified by further chromatography and crystallization from acetone-hexane, whereupon it showed m.p. 163–165°, $[\alpha]D$ −8.3°, ν_{max} 1730, 1700, 1640, 1240, and 905 cm.$^{-1}$. This isomer was different from that (Xa) obtained by direct crystallization of the chlorination mixture and, as indicated in the discussion section, should be assigned the structure IX (6-methylene-16α-methyl-5α-chloropregnan-3β-ol-20-one acetate). It was found to be stable indefinitely at room temperature in the solid state.

Anal. Calcd. for $C_{25}H_{37}O_3Cl$: C, 71.32; H, 8.86; O, 11.40; Cl, 8.42. Found: C, 71.33; H, 8.86; O, 12.24; Cl, 8.38.

Elution with hexane-benzene (4:1) and hexane-benzene (3:2) furnished crystalline material (3.3 g., m.p. 155–183°, $[\alpha]D$ +26°) which was recrystallized from ether-hexane or from ether-methanol until an analytical sample was obtained with m.p. 179–182°, $[\alpha]D$ +40.2°, ν_{max} 3500, 1730, 1785, 1240 cm.$^{-1}$. This compound was recovered unchanged after attempted acetylation with acetic anhydride–pyridine (heating on the steam bath for 1 hr.) and on the basis of its NMR spectrum (see Discussion) should be represented as *6,16α-dimethyl-Δ^6-pregnene-3β,5α-diol-20-one 3-acetate* (XIb).

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51; O, 15.90. Found: C, 74.61; H, 9.51; O, 16.23.

Saponification of XIb (0.5 g.) was performed by heating under reflux for 1 hr. with 1% potassium hydroxide in aqueous methanol (50 cc.) and then isolating the product by extraction with ethyl acetate. The crude total material crystallized from ether as elongated prisms (410 mg.) with m.p. 169–170°, raised to 176–177° by recrystallization from acetone-hexane. The purified sample of *6,16α-dimethyl-Δ^6-*

(19) Bernstein and collaborators (ref. 4) report m.p. 113–116.5°, $[\alpha]D$ +145°. The difference in melting point may be due to polymorphism.

pregnene-3β,5α-diol-20-one (XIa) showed $[\alpha]D$ +49.9°, ν_{max} 3550, 1700, 1685 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 76.62; H, 10.07; O, 13.31. Found: C, 76.65; H, 9.85; O, 13.66.

Elution with benzene provided 3.0 g. of solid with m.p. 152–156°. An analytical sample of *6,16α-dimethyl-Δ^5-pregnene-3β,7α-diol-20-one 3-acetate* (XIIb) prepared by recrystallization from ether-hexane had m.p. 156–158°, $[\alpha]D$ −43°, ν_{max} 3560, 1735, 1685, 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51; O, 15.90. Found: C, 74.91; H, 9.68; O, 15.48.

Acetylation of XIIb (0.5 g.) by warming with acetic anhydride (10 cc.) and pyridine (5 cc.) for 30 min. followed by extraction with ethyl acetate, produced a crude acetate (0.46 g., m.p. 175–180°) which was chromatographed on neutral alumina (30 g.), eluted with hexane-benzene (9:1) (m.p. 190–197°) and crystallized from acetone-hexane or ether-hexane to give an analytical sample of *6,16α-dimethyl-Δ^5-pregnene-3β,7α-diol-20-one diacetate* (XIIc) with m.p. 195–197°, $[\alpha]D$ −135°, ν_{max} 1740, 1710, 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07; O, 17.99. Found: C, 73.35; H, 9.07; O, 17.75.

Isomerization of XIa *to* XIIa. A solution of XIa (300 mg., m.p. 172–175°, $[\alpha]D$ +53.3°) in anhydrous methanol (100 cc.) and glacial acetic acid (10 cc.) was refluxed for 2 hr. and then poured into water. The product was extracted with ethyl acetate and washed with sodium bicarbonate and water. Evaporation and chromatography of the residue on washed alumina (30 g.) furnished pure XIIa by elution with ethyl acetate and crystallization from acetone-ether (80 mg., m.p. 195–198°, $[\alpha]D$ −44°) identified by infrared and mixture melting point comparisons. Elution with benzene furnished a trace of XVIIIa, m.p. 145–150° after repeated crystallization from ether-hexane, identified by infrared comparison and by mixture melting point with an authentic sample.

Saponification of XIIb (300 mg.) was effected by heating under reflux with 1% methanolic potassium hydroxide (50 cc.) for 40 min. and the product was isolated by addition of water and extraction with ethyl acetate. The crude material (220 mg., m.p. 185–187°) was recrystallized twice from acetone-ether to afford an analytical sample of *6,16α-dimethyl-Δ^5*-pregnene-3β,7α-diol-20-one (XIIa) which showed m.p. 197–200°, $[\alpha]D$ −44°, ν_{max} 3600, 1685 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 77.62; H, 10.07. Found: C, 77.71; H, 10.08.

Acetylation of XIIa by the usual procedure with acetic anhydride in pyridine, and purification of the crude acetate by chromatography on neutral alumina, elution with benzene and crystallization from ether-hexane, gave a *diacetate* (m.p. 190–195°, $[\alpha]D$ −135°) identical by infrared and mixture melting point comparisons with the above described diacetate XIIc.

In another experiment, the total crude chloro compound Xa (3.15 g.) prepared by chlorination of 6,16α-dimethyl-Δ^5-pregnen-3β-ol-20-one acetate (IIIb) was heated under reflux in aqueous acetone[20] (360 cc. acetone, 40 cc. water) with potassium acetate (15 g.) for 10 hr. The product was isolated by concentrating to one third of the starting volume, addition of water and extraction with ethyl acetate. The crude displacement product thus obtained (2.8 g., $[\alpha]D$ −1.2°) was hydrolyzed by refluxing for 1 hr. with 1% potassium hydroxide in methanol (400 cc.). The total material, isolated by neutralization with an excess of acetic acid, concentration, addition of water and extraction with ethyl acetate, was amorphous (1.9 g.) and it was then chromatographed on neutral alumina (200 g.). Elution with benzene furnished a crude compound (0.8 g., m.p. 98–100°) which was purified by recrystallization from acetone-ether or from ether-hexane. The analytical sample of *6,16α-dimethyl-7α-methoxy-Δ^5-pregnen-3β-ol-20-one* (XVIIIa) crystallized as brilliant plates and exhibited m.p. 160–161°, $[\alpha]D$ −87°, no selective ultraviolet absorption, ν_{max} 3500, 1700, 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23; O, 12.81; 1 OMe, 8.28. Found: C, 76.50; H, 10.01; O, 12.37; OMe, 8.25.

By elution with ether, another compound (0.7 g.) was obtained, which was purified by crystallization from acetone-ether (m.p. 183–185°, $[\alpha]D$ −48.1°) and identified as 6,16α-dimethyl-Δ^5-pregnene-3β,7α-diol-20-one (XIIa). Acetylation in the usual manner with acetic anhydride in pyridine afforded the diacetate XIIc, m.p. 185–188° (from ether-hexane), $[\alpha]D$ −135°.

Acetylation of 300 mg. of 6,16α-dimethyl-7α-methoxy-Δ^5-pregnen-3β-ol-20-one (XVIIIa) with acetic anhydride (20 cc.) and pyridine (10 cc.) was accomplished by heating the mixture on the steam bath for 1 hr. Isolation by extraction with ethyl acetate afforded a crude product (270 mg.) with m.p. 108–110°. Ether–hexane crystallization provided an analytical sample of the *3β-acetate* XVIIIb with m.p. 135–136°, $[\alpha]D$ −88.6°, ν_{max} 1730, 1700, 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68; O, 15.36; 1 OMe, 7.45. Found: C, 74.85; H, 9.60; O, 15.32; OMe, 7.31.

Formation of XVIIIa *from* XIIa. A solution of XIIa (470 mg., m.p. 195–198°, $[\alpha]D$ −42°) in anhydrous methanol (95 cc.) and glacial acetic acid (5 cc.) was heated under reflux for 1 hr. It was then concentrated *in vacuo* to one third of its volume, water was added and the product was isolated by extraction with ethyl acetate, washing with sodium bicarbonate solution and finally with water. Drying and evaporation of the solution gave an amorphous residue which was chromatographed over neutral alumina (30 g.). By elution with benzene, crystalline material (208 mg., m.p. 140–145°) was obtained which after recrystallization from acetone ether and ether-hexane furnished pure XVIIIa (100 mg.) with m.p. 157–158° and $[\alpha]D$ −91°. A mixture melting point of this material with an authentic sample of XVIIIa was undepressed and their infrared spectra were identical.

By elution with ethyl acetate, unchanged starting material (202 mg.) was recovered, which was purified by recrystallization from acetone-ether to give needles (120 mg.) with m.p. 197–199°, $[\alpha]D$ −48.3°, identified by infrared and mixture melting point comparisons.

6,16α-Dimethyl-7α-methoxy-Δ^5-pregnen-3β-ol-20-one (XVIIIa) (500 mg.) dissolved in acetone (40 cc.) was oxidized at 0° with 8 *N* chromic acid in 8 *N* sulfuric acid[8] by titration over a period of 3–5 min. Addition of water and extraction with ethyl acetate gave an amorphous residue which was chromatographed on neutral alumina (40 g.). By elution with benzene, crystals (320 mg.) were obtained with m.p. 144–145°. Recrystallization from ether provided the pure substance with m.p. 158–160°, $[\alpha]D$ +132.9°, λ_{max} 290 mμ, log ε 4.40, ν_{max} 1710, 1670, 1635, 1585 cm.$^{-1}$. Its infrared spectrum was identical to that of 6,16α-dimethyl-$\Delta^{4,6}$-pregnadiene-3,20-dione (VIII) and a mixture melting point was undepressed.

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47; O, 9.40. Found: C, 80.90; H, 9.45; O, 9.75.

6-Methylene-16α-methyl-Δ^4-pregnen-3β-ol-20-one acetate (XIII). The dehydrochlorination of the 6-methylene-5α-chloride IX was accomplished by heating 400 mg. of it under reflux with γ-collidine (40 cc.) for 0.5 hr. The product was isolated by extraction with ethyl acetate and washing the solution with dilute hydrochloric acid. The amorphous residue, obtained on evaporation of the solvent, was redissolved in hexane and the solution passed through a column of neutral alumina (30 g.). Evaporation of the solvent afforded a crude crystalline material (250 mg.) with m.p. 152–155°, raised by recrystallization from ether-hexane to 168–170°. The pure compound gave a strong orange color reaction with tetranitromethane and showed $[\alpha]D$

(20) When the reaction was carried out in anhydrous acetone and the reaction mixture processed by chromatography prior to alkaline saponification, approximately equal amounts of XIb and XIIb were isolated.

+50.3°, λ_{max} 236, 242 mμ, log ε 4.17, 4.19; ν_{max} 1740, 1690, 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44; O, 12.48. Found: C, 77.77; H, 9.03; O, 12.79.

6α,7α-Oxido-6β,16α-dimethylpregnan-5α-ol-3,20-dione (XIV). (a) *By oxidation of 6,16α-dimethyl-Δ⁵-pregnene-3β,-5α-diol-20-one* (XIa). A solution of compound XIa (0.6 g., m.p. 176–17[illegible] [α]D +50°) in acetone (60 cc.) was oxidized over a perio[illegible]-5 min. by titration with 8 *N* chromic acid in 8 *N* sulfuric acid[8] at 0 to 5°. Addition of water and extraction with ethyl acetate gave a semicrystalline residue. This material was chromatographed on neutral alumina (30 g.) whereby elution with benzene afforded a compound (350 mg.) with m.p. 235–245°. An analytical sample of the oxido ketone XIV was obtained by crystallization from acetone-ether: needles with m.p. 252–253°, [α]D +40.4°, ν_{max} 3650, 1720, 1700 cm.$^{-1}$. It showed no selective high ultraviolet absorption.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.97; H, 8.89; O, 17.51.

(b) *By oxidation of 6,16α-dimethyl-Δ⁵-pregnene-3β,7α-diol-20-one* (XIIa). A solution of XIIa (0.5 g., m.p. 183–185°, [α]D −48.1°) in acetone (60 cc.) was oxidized over a period of 3 min. by titration with 8 *N* chromic acid in 8 *N* sulfuric acid[8] at 0 to 5°. Isolation by addition of water and extraction with ethyl acetate furnished a crystalline crude product which was purified by chromatography on neutral alumina. By elution with benzene, crystals with m.p. 218–250° (200 mg.) were obtained. Further purification by crystallization from acetone-ether provided an analytical sample as fine needles with m.p. 248–250°, [α]D +45.8°, ν_{max} 3600, 1720, 1700 cm.$^{-1}$, and without characteristic ultraviolet absorption. This compound showed an infrared spectrum completely identical to that presented by the product isolated in the preceding experiment (a) and its melting point was not depressed on admixture of such a specimen.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.61; H, 9.27; O, 17.35.

Elution with ether and crystallization from acetone–ether gave needles (80 mg.) of *6β,16α-dimethyl-Δ⁴-pregnene-6α,7β-diol-3,20-dione* (XVI) with m.p. 250–252°, [α]D +111.8° (dioxane), λ_{max} 244, log ε 4.11, ν_{max} 3600, 3320, 1700, 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.67; H, 8.81; O, 17.39.

6α,7α-Oxido-6β,16α-dimethylpregnane-3β,5α-diol-20-one (XVIIa). 6,16β-Dimethyl-Δ⁶-pregnene-3β,5α-diol-20-one 3-acetate (XIb) (350 mg., m.p. 180–181°) dissolved in acetone (150 cc.) was oxidized at 5° by titration with 8 *N* chromic acid in 8 *N* sulfuric acid.[8] The oxidation product was isolated after 4 min. by addition of water and extraction with ethyl acetate. The crude material (270 mg.) had m.p. 175–178°, raised by two crystallizations from acetone-ether to 220–222° (150 mg.). An analytical sample of the *3-monoacetate* XVIIb prepared by further recrystallization had m.p. 230–232°, [α]D +23.8° (dioxane), ν_{max} 3650, 1720, 1690, 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15; O, 19.11. Found: C, 71.84; H, 9.09; O, 19.09.

The saponification of the acetate XVIIb (100 mg.) was carried out by heating under reflux for 1 hr. with a 1% methanolic potassium hydroxide solution (40 cc.). Neutralization with acetic acid, addition of water and extraction with ethyl acetate gave a crude crystalline material with m.p. 200–205°, raised to 233–237° (60 mg.) by two crystallizations from acetone-ether. Recrystallization from the same provided an analytical sample of the *oxidodiol* XVIIa with m.p. 248–250°, [α]D +27° (dioxane), ν_{max} 3500, 1685 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64; O, 17.00. Found: C, 73.29; H, 9.57; O, 17.03.

A solution of 6α,7α-oxido-6,16α-dimethylpregnane-3β,-5α-diol-20-one (XVIIa) (50 mg.) dissolved in acetone (30 cc.) was treated for 3 min. at 0 to 5° with 8 *N* chromic acid in 8 *N* sulfuric acid.[8] The reagent was added dropwise until a yellow color persisted in the acetone solution. The mixture was then poured into water and the product extracted with ethyl acetate. Evaporation of the extract gave a crystalline residue (43 mg.) with m.p. 174–175°. Purification by chromatography on neutral alumina (15 g.) afforded, by elution with benzene-ether (19:1), needles (32 mg.) with m.p. 253–255°. The analytical sample exhibited m.p. 256–257°, [α]D +61° (dioxane), no selective high ultraviolet absorption, ν_{max} 3640, 1730, 1700 cm.$^{-1}$. This compound was found to be identical by infrared and mixture melting point comparisons, with that obtained by oxidation of XIa and XIIa as described above.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.44; H, 8.97; O, 17.95.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Preparation of Some Steroidal Enamines[1]

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The preparation of some α-(aminomethylene)keto steroids is described. Observed ultraviolet spectral and optical rotatory relationships are discussed.

The discovery that steroidal [3,2-*c*]pyrazoles are effective anabolic agents while exhibiting minimal androgenic side effects[2] prompted us to prepare another series of nitrogen-containing steroids, some α-aminomethylene derivatives of keto steroids.

J. Meier[3] has reported 2-(1-pyrrolidylmethylene)testosterone as a crude intermediate in the preparation of 2-(1-pyrrolidylmethyl)testosterone.

(1) Steroidal Heterocycles. V. For preceding paper, see R. O. Clinton, R. L. Clarke, F. W. Stonner, D. K. Phillips, K. F. Jennings, and A. J. Manson, *Chem. & Ind.*, (London), 2099 (1961).

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