turnings in 350 ml. of anhydrous ether. A solution of 5 g. of 3β,17α,21-trihydroxy-Δ⁵-pregnen-20-one 3,21-diacetate (VIa) was then added dropwise and the resulting reaction mixture was allowed to reflux overnight. The suspension was cooled, and 500 ml. of 5% sulfuric acid was added. After 2 hr. of agitation, the two phases were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic fractions were washed with sodium bicarbonate and water to neutrality and dried over sodium sulfate. Vacuum concentration gave a crude product which was acetylated immediately. (In another experiment, methylation of 2.18 g. of VIa gave a crude which was crystallized from ethyl acetate to give 790 mg. with m.p. 214–248°. This material, in spite of the great discrepancy of the melting point, possessed an infrared spectrum very like that of the lithium aluminum hydride reduction product of VIIa. However, like the latter, it could not be purified by conventional techniques.) The entire residue was dissolved in 50 ml. of pyridine, and 50 ml. of acetic anhydride was added. The solution was allowed to stand at room temperature overnight and then poured into ice-water. The resulting solid was filtered and recrystallized from methanol to give 1.12 g., m.p. 185–202°. Three recrystallizations from ethyl acetate followed by two from methanol gave an analytical sample, 250 mg., m.p. 225–232°, no depression upon admixture of the diacetate from the lithium aluminum hydride reduction of VIIa, infrared spectrum identical with that of the latter, $[\alpha]^{25}_{D}$ −64.9°.

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

The Synthesis of Some 14-Iso-11-ketosteroids. Stereochemical Course of Chemical and Catalytic Reduction of a 14β-Δ⁸-11-Ketosteroid[1,2]

BY CARL DJERASSI AND G. H. THOMAS[3]

RECEIVED JANUARY 17, 1957

The lithium–ammonia reduction product of Δ⁸-22a,25a,5α,14β-spirosten-3β-ol-11-one (IVa) was shown to be 22a,25a,5α,-14β-spirostan-3β-ol-11-one (VIa) by converting the latter to the known 14β,17α-allopregnan-3β-ol-20-one acetate (XIb). With a reference compound (VI) of known stereochemistry now being available, application of conformational analysis leads to the assignment of the 8α,9α-orientation (V) to the *catalytic hydrogenation* product of IV. The elucidation of the stereochemistry of the *chemical reduction* product (VI) has a bearing on the evaluation of conformational factors involved in the metal–ammonia reduction of unsaturated ketones.

Recently, there has been undertaken in these laboratories a program aimed at the synthesis of steroid hormones with an abnormal configuration at C-8[4] and/or C-14 in order to evaluate the consequences of such a minor stereochemical change upon biological activity. The starting material for all the projected syntheses was Δ⁸-22a,25a,5α-spirosten-3β-ol-11-one (I)[5] since it is readily available[6] from diosgenin and can be transformed into the various C-8 and C-14 isomers.

Treatment of the unsaturated ketone I with base effects isomerization at C-14[6] and the resulting 14β-Δ⁸-11-ketone (IV) yields two different saturated 14-iso(β)-11-ketones depending upon whether chemical or catalytic reduction methods are employed. It already has been pointed out[6] that in the absence of a reference compound (as is the case with II in the 14α-series), a stereochemical assignment in the 14β-series is difficult since of the four possible isomers (V–VIII), all but one (VIII) can exist in an all-chair conformation.[7] Since precise information about the stereochemistry of these reduction products was necessary in order that the subsequent transformation to steroid hormone isomers be of stereochemical value, correlation of one of the reduction products of IV with a steroid of known configuration was attempted. The results of this work and its bearing upon certain aspects of carbanion reduction processes[8] form the subject of this paper.

The lithium–ammonia reduction product of Δ⁸-22a,25a,5α,14β-spirosten-3β-ol-11-one (IVa), now shown to be 22a,25a,5α,14β-spirostan-3β-ol-11-one (VIa), was transformed by a modified Wolff–Kishner reduction[9] and subsequent acetylation to 22a,-25a,5α,14β-spirostan-3β-ol acetate (IXb).[10] Con-

(1) We are indebted to the American Cancer Society through the Committee on Growth of the National Research Council for a research grant.

(2) A portion of this material has been described in a preliminary communication (C. Djerassi and G. H. Thomas, *Chemistry & Industry*, 1228 (1954).

(3) Postdoctorate research fellow, 1953–1955.

(4) *Cf.* C. Djerassi, A. J. Manson and A. Segaloff, *J. Org. Chem.*, **21**, 490 (1956); C. Djerassi, H. Bendas and A. Segaloff, *ibid.*, **21**, 1056 (1956); C. Djerassi, A. J. Manson and H. Bendas, *Tetrahedron*, **1**, 22 (1957).

(5) For nomenclature see C. Djerassi, T. T. Grossnickle and L. B. High, THIS JOURNAL, **78**, 3166, ref. 10 (1956).

(6) C. Djerassi, W. Frick, G. Rosenkranz and F. Sondheimer, *ibid.*, **78**, 3496 (1953).

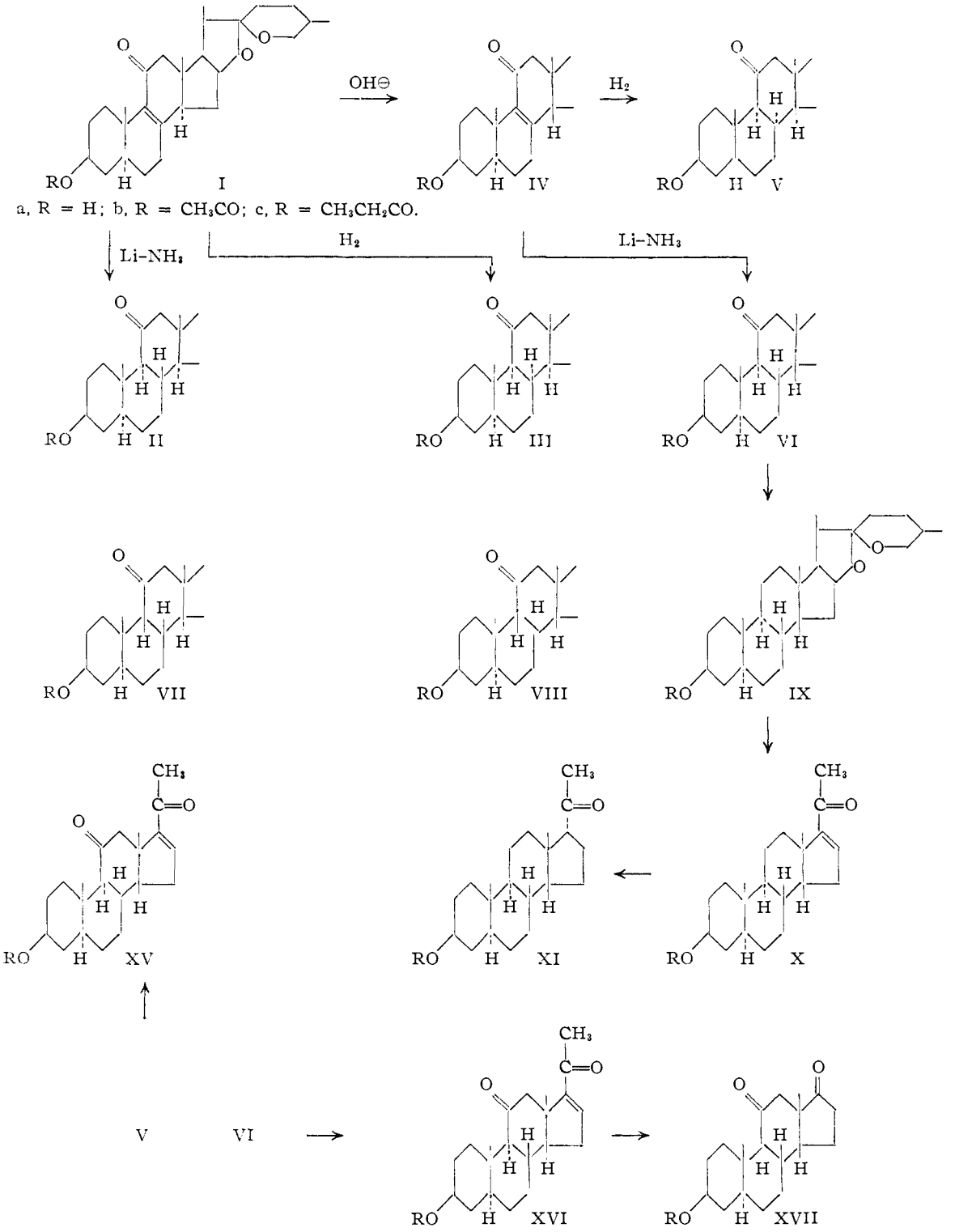
(7) See Table I in ref. 6.

(8) *Cf.* D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954), and references cited.

(9) D. H. R. Barton, A. A. J. Ives and B. R. Thomas, *ibid.*, 2056 (1955). We are indebted to Prof. Barton for providing us with the experimental details prior to publication.

(10) The argument might be raised that even though the saturated 11-ketone was found to be stable to base, it could still have been represented by the 8β,9β-11-ketone VII and that IX (8β,9α) is produced in the Wolff–Kishner reduction by a "kinetic inversion" *via* the 8β,9α-ketone VI similar to the observed (ref. 5) reduction of the alkali-stable 14-iso(β)-digitogenone to gitogenin (14α). Such a kinetic inversion would require a considerable difference in the reactivity of the carbonyl groups in VI and VII which cannot be determined experimentally since only one isomer is known. However, two arguments can be offered against such an assumption: (a) the good yield in the Wolff–Kishner reduction (VI → IX) in contrast to the poor one observed in the digitogenin series (ref. 5); (b) conformational analysis which would suggest that VI should be more stable than VII in spite of the fact that both can exist in all-chair conformations. Not only is the 9–11 bond axial in VII, but there exists also a 1,3-diaxial interaction between the 7–8 and 13–17 bonds which is not found in VI. In any event, none of the other stereochemical assignments made in this paper are affected by this question since the 8β-orientation has been proved rigorously by conversion to XI.

It should be noted that in the 14α-series the 8β,9β-isomer can be isomerized with base to the natural 8β,9α-derivative (P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. W. Wood, J. Elks, R. M. Evans, E. E. Hathway, J. F. Oughton and G. H. Thomas, *J. Chem. Soc.*, 2921 (1953)), but on the other hand the conformational difference between the two isomers is a much more striking one (see Table I in ref. 6 and A. Crawshaw, H. B. Henbest, E. R. H. Jones and A. A. Wagland, *ibid.*, 3420 (1955)) as compared to the 14β-series.



ventional side chain degradation yielded Δ^{16}-14β-allopregnen-3β-ol-20-one acetate (Xb), and catalytic hydrogenation led in good yield to 14β,17α-allopregnan-3β-ol-20-one acetate (XIb), which had been obtained[11] previously by catalytic hydrogenation of $\Delta^{14,16}$-allopregnadien-3β-ol-20-one acetate.[12]

The above correlation with a 14β-steroid (XI) of

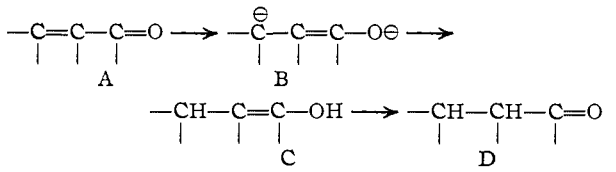
(11) P. A. Plattner, L. Ruzicka, H. Heusser and E. Angliker, *Helv. Chim. Acta*, **30**, 385 (1947); P. A. Plattner, H. Heusser and A. Segre, *ibid.*, **31**, 249 (1948).

(12) While C-8 and possibly even C-9 could have been involved (*via* the enol) in the preparation and reduction of the $\Delta^{14,16}$-dien-20-one, this has been excluded by a correlation with a 14β-androstane derivative where participation of C-8 and C-9 need not be considered (A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica and C. R. Scholz, THIS JOURNAL, **74**, 5506 (1952)).

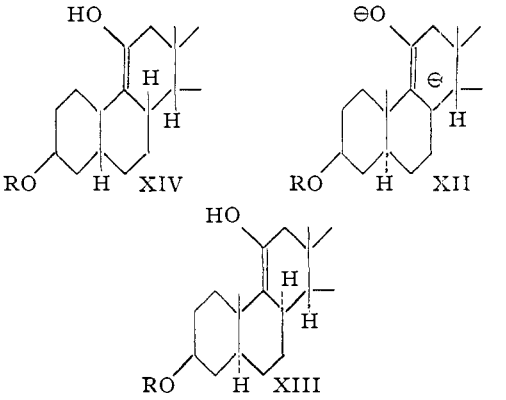
known configuration at C-8 and C-9 establishes[10] the stereochemistry of the *chemical reduction product* (VI) of the 14β-Δ⁸-11-ketone IV and thus offers an important reference compound. The plausible criterion[8,13] that chemical reduction of an α,β-unsaturated ketone (under equilibration conditions) gives the thermodynamically more stable product could, *a priori*, not have been applied easily to the present case (IV) since the energy differences are probably small. While VIII is surely the least favored (ring B present as boat),[7] analysis by Johnson's method[14] —determination of number of equatorial and axial bonds by which the central ring is joined to its two neighbors—shows only a difference of one axial bond in favor of the all-chair 8β,9α-isomer VI over the all-chair 8α,9α-isomer V.[15]

The present chemical proof that the lithium–ammonia reduction product is represented by the 8β,9α-11-ketone VI offers also a means of establishing the stereochemistry of the *catalytic hydrogenation* product of the 14β-Δ⁸-11-ketone IV. Since the hydrogenation product was stable to heating with alkali,[6] the 8β,9β-isomer VII is excluded since it would have led to the chemical reduction product VI, which was also unaffected by base. This leaves only 22a,25a,5α,8α,14β-spirostan-3β-ol-11-one (Va) as the appropriate structure for the hydrogenation product since it (all-chair conformation) would not be expected to be isomerized to the *trans*-isomer VIII (requiring ring B as a boat).[7]

It has been suggested[8] that reduction of α,β-unsaturated ketones A by metals in liquid ammonia proceeds *via* the dianion B which is protonated to the enol C and then furnishes the saturated ketone D. This implies that the controlling factor for the eventual stereochemistry of the saturated ketone D is the protonation step of the β-carbon atom, since the more stable orientation at the enolizable α-position (*cf.* C) will be governed by it.[16]



The above course of the reaction (A → D) is in accordance with all the reductions reported so far[8,13] for unsaturated alicyclic ketones and in each instance protonation of the β-position resulted in a *trans* or *anti* relationship with respect to hydrogen or methyl at the γ-carbon atom. The presently investigated reduction of the 14β-Δ⁸-11-ketone IV demonstrates clearly that this need not be the case. Rather than indicating that protonation at the β-carbon atom does not occur first, the *syn* configuration for the present case provides good support for the conclusion that metal–ammonia reduction will give the more stable stereoisomer insofar as the β-position is concerned.[16,17] Conformational analysis suggests that the same factor[15] favoring the ketone VI (8β,9α) over V (8α,9α) also applies to the enols XIV (8β) and XIII (8α) and that consequently the *syn*-stereochemistry (XIV) is produced.



With the stereochemistry of the 11-oxygenated sapogenins (V and VI) established, these compounds can now serve as standard starting materials for the synthesis of 11-oxygenated steroids with abnormal configuration. Side chain degradation of V and VI led respectively to Δ¹⁶-8α-14β-allopregnene-11,20-dione-3β-ol acetate (XVb) and Δ¹⁶-14β-allopregnene-11,20-dione-3β-ol acetate (XVIb), which could represent key intermediates for the synthesis of 14-iso and 8-iso-14-iso 11-oxygenated cortical hormones. In the case of Δ¹⁶-14β-allopregnene-11,20-dione-3β-ol acetate (XVI) it was also attempted to synthesize the corresponding 17-ketone XVIIb by Beckmann rearrangement of its oxime,[18] and while it was possible to isolate the desired substance, the yield was sufficiently poor to discourage further transformations.[19]

Experimental[20]

Δ⁸-22a,25a,5α,14β-Spirosten-3β-ol-11-one Acetate (IVb). —Since only the propionate IVc had been described earlier,[6] a sample of the alcohol IVa[6] was acetylated with acetic anhydride–pyridine overnight and recrystallized from ether–hexane, m.p. 188–190°, $[\alpha]_D$ +86°; $\lambda_{max}^{CHCl_3}$ 5.76, 5.98, 6.18 (weak) and 8.0 μ.

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 74.33; H, 9.29.

(13) Leading references are given by H. Heusser, M. Roth, O. Rohr and R. Anliker, *Helv. Chim. Acta*, **38**, 1178 (1955).

(14) W. S. Johnson, *Experientia*, **7**, 315 (1951); THIS JOURNAL, **75**, 1498 (1953).

(15) The important factor to be considered is the nature of the non-bonded interaction produced by the additional axial linkage. In point of fact, this is rather serious in the 8α,9α-11-ketone V since ring C is now present in a different chair conformation (not possible in the 14α-series because of the *trans* C/D ring juncture) with an equatorial C-13 angular methyl group, whereby there is produced a 1,3-diaxial interaction between the C-10 angular methyl group and the 8–14 bond. No such interaction is present in the 8β,9α-isomer.

(16) Provided the reaction mixture is worked up under equilibration conditions. H. E. Zimmerman (THIS JOURNAL, **78**, 1168 (1956)) and A. J. Birch, H. Smith and R. E. Thornton (*J. Chem. Soc.*, 1339 (1957)) have called attention to the fact that under non-equilibrium conditions the unstable isomer (at the α-position) may be formed.

(17) An exception to this statement has been presented recently in the decahydrochrysene series in the reduction of a styrene double bond by W. S. Johnson, J. Ackerman, J. F. Eastham and H. A. De Walt (THIS JOURNAL, **78**, 6302 (1956)). However, a complicating factor was the presence of a hydroxyl group at the ring juncture which may have directed attack to the opposite side of the molecule because of electrostatic repulsion.

(18) G. Rosenkranz, O. Mancera, F. Sondheimer and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956).

(19) Originally, it had been planned to prove the stereochemistry of 22a,25a,5α,14β-spirostan-3β-ol-11-one (VIa) *via* XVI and XVII followed by Clemmensen reduction to 14β-androstan-3β-ol.

(20) Melting points are uncorrected. Rotations were measured in chloroform solution in 1-dcm. tubes. The microanalyses were performed by Geller Laboratories, Hackensack, N. J.

22a,25a,5α,14β-Spirostan-3β-ol-11-one (VIa).—The earlier reported reduction[6] (of the propionate IVc) was carried out in slightly modified form (with the acetate IVb) on a larger scale. A solution of 6.0 g. of the above acetate IVb in 50 cc. of dry ether was added with stirring at −40° to a solution of 400 mg. of lithium in 500 cc. of liquid ammonia. After stirring for 4 min., the excess metal was decomposed by the addition of ammonium chloride, the ammonia was allowed to evaporate and the residue was treated with 5% methanolic potassium hydroxide for 1 hr. with occasional warming. Isolation with ether yielded 5.2 g. of solid (m.p. 216–220°) which was chromatographed on 200 g. of alumina. Elution with benzene–ether and recrystallization from ether–hexane furnished 3.01 g. of the saturated ketone VIa[6] as needles, m.p. 236–239°. The substance was recovered unchanged after being heated under reflux for 20 hr. with 5% ethanolic potassium hydroxide solution.

22a,25a,5α,14β-Spirostan-3β-ol Acetate (IXb).—Sodium (2.0 g.) was dissolved in 200 cc. of diethylene glycol, the saturated 11-ketone VIa (1.5 g.) was added and the solution heated to 180°. Freshly prepared anhydrous hydrazine (obtained by heating 50 cc. of hydrazine hydrate under reflux for 3 hr. with 50 g. of sodium hydroxide) was distilled into the reaction mixture until it boiled gently at 180°. After the solution had been heated at that temperature for 18 hr., sufficient hydrazine was distilled out to raise the reflux temperature to 210°, and the mixture was maintained at that temperature for 24 hr. The crude product was acetylated with acetic anhydride–pyridine and filtered in benzene solution through alumina. Crystallization from methanol–methylene chloride gave 1.25 g. of the acetate IXb (m.p. 155–161°) while the analytical sample (85% recovery) was obtained from the same solvent pair as colorless needles, m.p. 165–167°, $[\alpha]_D$ −38°, $\lambda_{max}^{CHCl_3}$ 5.79 and 8.0 μ.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 76.11; H, 10.05.

Δ16-14β-Allopregnen-3β-ol-20-one Acetate (Xb).—The above sapogenin IXb (1.5 g.) was heated in 10 cc. of acetic anhydride in a sealed tube for 9 hr. at 195°. The cooled reaction mixture was poured onto ice and the product was isolated with ether. Chromium trioxide (0.9 g.) in 10 cc. of 90% acetic acid was added dropwise to a solution of the furosten in 35 cc. of 80% acetic acid and 24 cc. of ethylene dichloride, the solution then being stirred for 2 hr. at room temperature. Extraction with ether yielded a gum which was adsorbed on 60 g. of basic alumina in benzene solution. After standing for 1 hr., the product was eluted with benzene and 1:1 benzene–ether and recrystallized from methanol; yield 0.33 g., m.p. 167–170°. Further recrystallization from methanol gave the analytical sample with the following constants: m.p. 170–172°, $[\alpha]_D$ +74°; λ_{max}^{EtOH} 242 mμ, log ε 3.95; $\lambda_{max}^{CHCl_3}$ 5.79, 5.99, 6.21 (weak) and 8.0 μ.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.16; H, 9.71.

14β,17α-Allopregnan-3β-ol-20-one Acetate (XIb).—The Δ16-20-ketone Xb (250 mg.) in 50 cc. of ethyl acetate was shaken with 10% palladized charcoal (70 mg.) in an atmosphere of hydrogen for 1 hr. The uptake of hydrogen was rapid and the crude reduction product showed no significant ultraviolet absorption at 242 mμ. Crystallization from aqueous methanol yielded the saturated ketone (XIb) as laths (185 mg.), m.p. 109–110°, $[\alpha]_D$ +7°; $\lambda_{max}^{CHCl_3}$ 5.79, 5.85 and 8.0 μ. Identity with authentic specimens,[11,12] kindly provided by Dr. H. Heusser (E. T. H., Zurich) and Dr. H. B. MacPhillamy (Ciba Pharmaceutical Products, Summit, N. J.), was established by mixture melting point determination and by infrared comparison.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.71; H, 10.10.

Δ16-14β-Allopregnene-11,20-dione-3β-ol Acetate (XVIb).—The side chain degradation of 1.3 g. of 22a,25a,5α,14β-spirostan-3β-ol-11-one (VIa) was carried out exactly as described above for the 11-desoxo compound and yielded 470 mg. of crude, crystalline ketone (λ_{max}^{EtOH} 235 mμ, log ε 3.89). Recrystallization from aqueous acetone furnished 390 mg. of the analytical sample as needles, m.p. 182–184°, $[\alpha]_D$ +34°; λ_{max}^{EtOH} 235 mμ,[21] log ε 3.90; $\lambda_{max}^{CHCl_3}$ 5.80, 5.84, 5.98, 6.15 (weak) and 8.0 μ.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.57; H, 9.03.

14β-Androstane-11,17-dione-3β-ol Acetate (XVIIb).—The Δ16-11,20-diketone XVIb (390 mg.) in ethanol (2 cc.) and pyridine (0.5 cc.) was heated under reflux with 170 mg. of hydroxylamine hydrochloride for 30 min. No solid separated on leaving the solution at 20° for 18 hr. Accordingly, the oxime was precipitated with water, collected and dried *in vacuo* over phosphorus pentoxide.

The crude oxime was dissolved in 2 cc. of pyridine, cooled to 0° and a solution of *p*-acetamidobenzenesulfonyl chloride (0.5 g.) in 2 cc. of pyridine was added. The solution was kept at 20° for 2 hr. during which time a considerable amount of discoloration occurred. On addition of water a black gum separated which could not be induced to solidify. Sulfuric acid (5.5 cc. of 10%) was added and the reaction mixture was heated on the steam-bath for 2 hr. The residual solid was collected and extracted several times with benzene. Evaporation of the combined extracts afforded 90 mg. of a gummy solid which was crystallized from methanol to give 40 mg. of the 11,17-diketone XVIIb as needles, m.p. 248–253°. The analytical specimen was sublimed at 160° and 0.005 mm. and exhibited m.p. 251–255°; $\lambda_{max}^{CHCl_3}$ 5.75, 5.79–5.84 (broad) and 8.0 μ.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 73.02; H, 8.94.

It should be noted that no difficulty was encountered in duplicating the recorded yield[17] in a model experiment with Δ5,16-pregnadien-3β-ol-20-one acetate.

Δ16-8α,14β-Allopregnene-11,20-dione-3β-ol Acetate (XVb).—The degradation of 22a,25a,5α,8α,14β-spirostan-3β-ol-11-one (Va)[6] (1.2 g.) was performed in the above described manner and afforded 200 mg. of the Δ16-11,20-diketone XVb, m.p. 131–132°, $[\alpha]_D$ +99°; $\lambda_{max}^{CHCl_3}$ 5.81, 5.85, 5.98, 6.13 (weak) and 8.0 μ.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.74; H, 8.58.

DETROIT, MICHIGAN

(21) A similar bathochromic shift due to the 11-ketone has been observed in the 14α-series (E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **73**, 2396 (1951); C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, *ibid.*, **74**, 3634 (1952)).