

was dissolved in a large excess of absolute ethanol (10 ml.) and the reaction mixture was allowed to stand at room temperature for 3 hours after a clear solution was obtained. Triethylamine in an equivalent amount to the hydrogen bromide was then added to the reaction mixture. The ethanol-insoluble α -ethyl L-aspartate crystallized from the solution, which after filtration was washed with absolute ethanol giving crude ester, m.p. 179–181°. After recrystallization from water-ethanol, 1.3 g. (86.5%) of pure ester was obtained, m.p. 181–183°, $[\alpha]^{25}_D$ 24.2° (*c* 2.1 in water).²⁷

Anal. Calcd. for $C_8H_{11}O_4N$: N, 8.74. Found: N, 8.87.

α -Ethyl D-aspartate was obtained in 75% yield, m.p. 181–183°, $[\alpha]^{25}_D$ –23.6° (*c* 2 in water). Found: N, 8.99.

α -Methyl Aspartate. L-Isomer.—The crude ester was obtained in 83% yield, m.p. 169–172°. After two recrystallizations from water-alcohol, 67% pure α -ester was obtained, m.p. 181–182°, $[\alpha]^{25}_D$ 43.3° (*c* 0.44 in water).

Anal. Calcd. for $C_5H_9O_4N$: N, 9.58. Found: N, 9.32.

D-Isomer.—The yield after two recrystallizations was 58%, m.p. 183–184°, $[\alpha]^{25}_D$ –42.6° (*c* 0.5 in water). Found: N, 9.29.

α -Benzyl Aspartate. L-Isomer.—Preparation of this ester required 12 hours reaction time. After recrystallization from water, 63% pure α -ester was obtained, m.p. 174–175°, $[\alpha]^{25}_D$ –15.5° (*c* 5.1 in 1 *N* hydrochloric acid). It gave no depression on admixture with an authentic sample¹⁹ and with a sample which was prepared in 79% yield from α -benzyl-N-carbobenzoxy-L-aspartate²⁸ through the hydrobromic acid-acetic acid cleavage²⁹ followed by triethylamine treatment of the hydrobromide of α -benzyl-L-aspartate in methanol solution.

D-Isomer was obtained in 80% yield, m.p. 175–176°, $[\alpha]^{25}_D$ +16.0° (*c* 4.1 in *N* hydrochloric acid).

Anal. Calcd. for $C_{11}H_{15}O_4N$: N, 6.23. Found: N, 6.12.

Hydrobromic Acid Cleavage of Dibenzyl Aspartate.—Dibenzyl L-aspartate hydrochloride³⁰ (8.0 g., 0.023 mole) was dissolved in 12 ml. of 35% hydrobromic acid-acetic acid and was allowed to stand at room temperature for 24 hours. The solvent was evaporated *in vacuo*, the oily residue was covered with 5 ml. of methanol at –10°, and the pH of the stirred reaction mixture was adjusted to 7 with triethylamine. The precipitate was filtered and washed with methanol and ether. After recrystallization from water, 1.36 g. (25%) of α -benzyl L-aspartate was obtained, m.p. 174–175°, which gave no depression on admixture with an authentic sample; $[\alpha]^{25}_D$ –15.6° (*c* 4.2 in 1 *N* hydrochloric acid).

(27) The α -ethyl L-aspartate was also prepared through N-carbobenzoxy-L-aspartic anhydride by the method of LeQuesne and Young.²² They reported a m.p. of 181–183°; no specific rotation was given.

(28) M. Bergmann, L. Zervas and L. Salzmann, *Ber.*, **66**, 1288 (1933).

(29) D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

(30) A. Miller, A. Neidle and H. Waelsch, *Arch. Biochem. Bio phys.*, **56**, 11 (1955).

When the above experiment was carried out in the presence of 10 ml. of water, only 20% of the α -benzyl ester was obtained.

Dibenzyl aspartate *p*-toluenesulfonate³¹ can also be used in place of the hydrochloride, yielding 29% of α -benzyl aspartate, m.p. 174–175°.

Isoasparagine. L-Isomer.— α -Methyl L-aspartate (0.8 g., 0.0054 mole) was dissolved in liquid ammonia. The ammonia was allowed to evaporate at room temperature and the last traces were removed *in vacuo*. The residue was crystallized from water-alcohol; yield 87.5%, m.p. 212–214° dec., $[\alpha]^{25}_D$ 15.4° (*c* 1.8 in 0.1 *N* hydrochloric acid).³ When it was examined by paper electrophoresis¹⁷ and paper chromatography, only one spot was obtained.

D-Isomer was obtained in 67% yield, m.p. 212–214° dec., $[\alpha]^{25}_D$ –15.0° (*c* 1.8 in 0.1 *N* hydrochloric acid). When aqueous ammonia was used instead of liquid ammonia, chromatographically pure isoasparagine was obtained in 64% yield.

Anal. Calcd. for $C_4H_8O_3N_2 \cdot H_2O$: N, 18.66. Found: N, 18.55.

N-Acetyl-L-aspartic Anhydride from Aspartic Acid Hydrobromide and Acetic Anhydride.—L-Aspartic acid (4 g., 0.03 mole) was allowed to stand in 4 ml. of 35% hydrobromic acid-acetic acid for 0.5 hour. Then, 28 ml. of acetic anhydride was added to the reaction mixture and heated at 60° until a clear solution was obtained. The solution was concentrated to dryness and the crystalline residue triturated with dry ether and recrystallized from acetic anhydride giving flat plates, yield 2.9 g. (61%), m.p. 174–176°³²; $[\alpha]^{25}_D$ –37.1° (*c* 1.4 in acetic acid). The infrared spectrum had strong peaks at 5.37 and 5.59 μ .

Anal. Calcd. for $C_6H_7O_4N$: C, 45.85; H, 4.49; N, 8.94. Found: C, 45.95; H, 4.58; N, 9.21.

N-Acetyl-L-aspartic anhydride was hydrolyzed with water in the usual manner to an oily residue, which yielded upon standing 97% crystalline N-acetyl-L-aspartic acid, m.p. 139–141°³² $[\alpha]^{25}_D$ 5.65° (*c* 2.39 in water).

The optical purity of the anhydride was investigated by hydrolyzing a 0.148-g. sample with 5 ml. of 6 *N* hydrochloric acid for 24 hours. The hydrolysate was evaporated to dryness and then the specific rotation of the resulting aspartic acid was compared with that of a sample of aspartic acid, treated with hydrochloric acid as above; the values, 24.3 and 25.7, respectively, indicated that practically no racemization occurred during the acetic anhydride treatment.³²

Acknowledgment.—This work was supported by grants from the National Institutes of Health, Public Health Service (RG 6579 and RG 8795). We wish to thank Miss Dolores Johnson for the infrared spectra.

(31) L. Zervas, M. Winitz and J. P. Greenstein, *J. Org. Chem.*, **22**, 1515 (1957).

(32) C. C. Barker, *J. Chem. Soc.*, 450 (1953); specific rotation is not reported.

[CONTRIBUTION FROM THE NATURAL PRODUCTS LABORATORY, RESEARCH TRIANGLE INSTITUTE, DURHAM, N. C., AND THE EASTERN REGIONAL RESEARCH LABORATORY, PHILADELPHIA 18, PENNA.]

Steroids. LXIX.^{1,2a,b} A Novel Michael Addition–Aldol Condensation Reaction between Acetone and Δ^{16} -12,20-Diketopregnenes

BY MONROE E. WALL,³ SAMUEL SEROTA,⁴ HAROLD E. KENNEY⁴ AND G. SHUFORD ABERNETHY³

RECEIVED DECEMBER 1, 1962

The base-catalyzed reaction of acetone and 16-dehydro-12,20-ketopregnenes is described. Evidence is presented to show that the reaction path involves a typical Michael reaction between the carbanion derived from acetone and the steroid 16-carbon atom, followed by an intramolecular aldol condensation to produce a new ring E. The stereochemistry of this reaction sequence is discussed in detail, and it is shown that the substituents at C₁₆ and C₁₇ have, respectively, the 16 α - and 17 β -configurations.

We have discovered that 16-dehydro-12,20-diketopregnenes react with acetone in the presence of aqueous

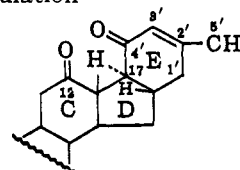
(1) Paper LXVIII: M. E. Wall, B. J. Warnock and J. J. Willaman, *Econ. Botany*, in press.

(2) (a) The research reported in this paper was initiated at the Eastern Regional Research Laboratory and completed at the Research Triangle Institute. Research at the latter institution was carried out under contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Institutes of Health. (b) Presented in part at the American Chemical Society Southwest–Southeast Regional Meeting, December 7–9, 1961, and IInd International Symposium on the Chemistry of Natural Products, Prague, Czechoslovakia, August 27–September 2, 1962.

(3) Research Triangle Institute.

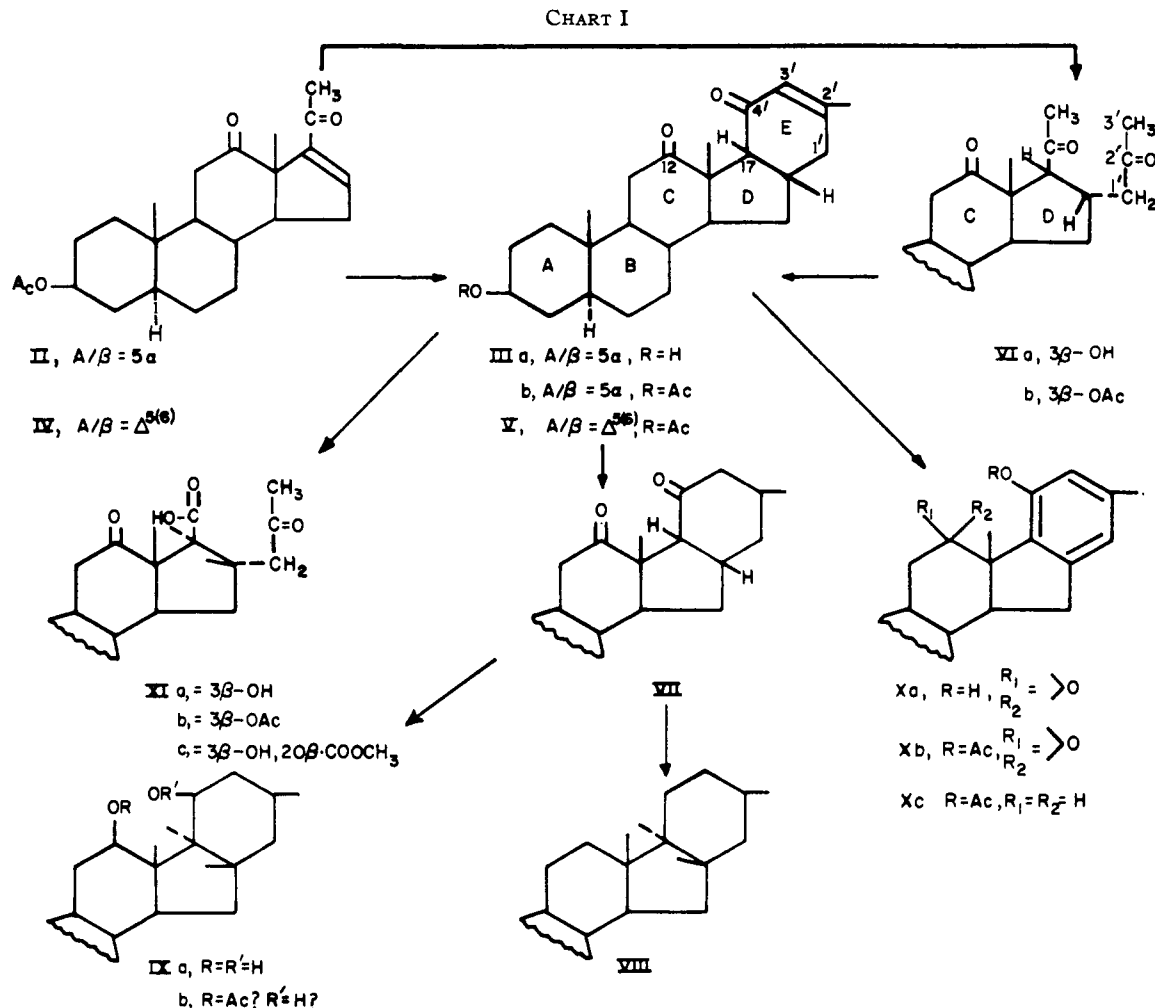
(4) Eastern Regional Research Laboratory.⁵

potassium hydroxide to give a novel cyclization product. The reaction does not occur with 12-desoxy- or 11-keto-16-dehydropregnenes. In this paper we shall present evidence to show that the best expression for the structure and stereochemistry of this cyclization product is the partial formulation



Our study of this reaction commenced with the observation that refluxing "hecone" (I) with acetone containing potassium hydroxide⁶ followed by acetylation did not result in the isolation of the expected hydrolysis product, 3 β -acetoxy-5 α , Δ^{16} -pregnene-12,20-dione (II). Instead, a compound with rather different physical properties, subsequently shown to be the cyclic product

of water. The resultant product would again contain a conjugated carbonyl group. The ultraviolet and infrared spectra of the cyclization product IIIb were in accord with the above hypothesis, the infrared spectrum showing three carbonyl bands of equal intensity at 1735 (3 β -acetate), 1710 (12-carbonyl) and 1675 cm^{-1} (conjugated carbonyl). The ultraviolet spectrum



IIIb, was obtained. Direct treatment of the pregnene II with acetone-potassium hydroxide followed by acetylation gave the cyclic product IIIb in 50% yield. Similar treatment of 3 β -acetoxy- $\Delta^{5,16}$ -pregnadiene-12,20-dione (IV) gave the corresponding cyclic compound V. On the other hand, no reaction other than hydrolysis of the 3 β -acetoxy moiety was observed when a variety of 12-desoxy-16-dehydropregnenes were subjected to the same reaction conditions. The analytical carbon and hydrogen values obtained for the cyclization product IIIb were in excellent agreement with the formula $\text{C}_{26}\text{H}_{38}\text{O}_4$. A compound with this formulation could be obtained by a base-catalyzed Michael reaction^{7a} of the carbanion derived from acetone with carbon 16 of II followed by an aldol condensation^{7b} with elimi-

showed one absorption band at 233 $\text{m}\mu$, ϵ 12,200. Both the ultraviolet and infrared spectra of IIIb show interesting differences from that of the starting material II which may be due to a change in the degree of the interaction between the C₁₂- and C₂₀-ketone groups.⁸

(8) The ultraviolet absorption spectra of a variety of 12-desoxy- Δ^{16} -20-keto pregnenes show an absorption maximum of 239 $\text{m}\mu$ with molecular extinction coefficients averaging about 10,000 (cf. for example M. E. Wall, H. E. Kenney and E. S. Rothman, *J. Am. Chem. Soc.*, **77**, 5665 (1955)). G. P. Mueller, R. E. Stobaugh and R. S. Winniford, *ibid.*, **75**, 4888 (1953), noted that Δ^{16} -12,20-diketopregnenes exhibit a hypsochromic shift to 227–229 $\text{m}\mu$ (cf. also Wall, *et al.*, above ref.) with molecular extinction values between 8000 and 9000. Similar effects are shown in the infrared. Mueller, *et al.*, have rationalized that hypsochromic shifts and lowered intensities are due to electrostatic repulsion between the C₁₂- and C₂₀-carbonyl groups, which are in close proximity in the stereochemically favored *s-trans* form (the *s-cisoid* form would involve unfavorable C₁₈, C₂₁-methyl interactions). The conjugated ketone in the cyclized compound IIIb has an absorption maximum at 233 $\text{m}\mu$, ϵ 12,200. According to Woodward's rules an absorption maximum at 239 $\text{m}\mu$ would be predicted. The infrared absorption spectrum of IIIb in the conjugated ketone region shows effects similar to those noted in the ultraviolet. A strong band is found at 1675 cm^{-1} , a position which lies between the values 1685 cm^{-1} (Δ^{16} -12,20-dione) and 1665 cm^{-1} (Δ^{16} -20-one). The intensity of this band is considerably greater than the band found in the 12-ketone series and equal or slightly stronger than that of the 12-desoxy series. The ultraviolet and infrared properties of IIIb can be rationalized on the basis that the interaction between the 12- and 4'-carbonyl groups is less than that found with Δ^{16} -12,20-diones but still of enough significance to cause a deviation from normal 12-desoxy wave lengths. Dreiding models demonstrate this point. The strong intensities found for the conjugated carbonyl group of III in both the ultraviolet

(5) The Eastern Regional Research Laboratory is a Laboratory of Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture.

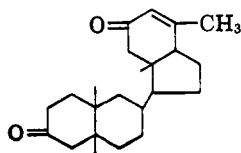
(6) These reaction conditions were used by O. Halpern and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 4391 (1959), to cleave 11 α -hydroxy-"diosone" to the corresponding 16-dehydropregne.

(7) For a review of this subject cf. (a) E. D. Bergmann, D. Ginsburg and R. Pappo, "Organic Reactions," Vol. X, ed. by R. Adams, John Wiley and Sons, New York, N. Y., 1959, p. 179; (b) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp. 389–394.

The n.m.r. spectrum of III was consistent with the assigned structure. The three methyl groups C₁₈, C₁₉ and C₂' of the cyclization product IIIa gave rise to signals at 9.00, 8.73 and 7.97 τ , respectively; the Δ^3 -olefinic proton appeared at 4.25 τ . The corresponding acetate IIIb gave similar signals including that for the acetate methyl (*cf.* Experimental).⁹ The belief that the reaction indeed follows the previously postulated path was greatly strengthened by the formation of the Michael adduct VIa,b, a = 3 β -OH, b = 3 β -OAc, *via* the reaction of acetone with the pregnene II in the presence of catalytic amounts of tetrabutylammonium hydroxide and the subsequent smooth cyclization of VI to IIIa and IIIb when treated, respectively, with refluxing acetone-aqueous potassium hydroxide or a suspension of sodium methoxide in dry benzene at room temperature. The conversion of VI to III is not reversible, at least in the final step (*cf.* footnote 22). The cyclic product III is recovered unchanged after treatment with strong base. On treatment of VI with base in the presence of C¹⁴-labeled acetone, non-labeled III is obtained. The carbon and hydrogen analysis of VIb was in accord with the assigned structure. The infrared spectrum shows one band in the carbonyl region at 1735 cm.⁻¹ (3 β -acetate) and a broad, stronger band at 1700-1720 cm.⁻¹ (12-carbonyl and 16 α -(propanone-2')-carbonyl). The n.m.r. spectrum of VIa satisfactorily accounts for all the methyl groups with signals at 9.21 (C₁₈), 9.14 (C₁₉), 8.05 (C₃') and 7.87 (C₂'). The stereochemistry of the C₁₆ and C₁₇ side chains of compound VI is of considerable interest since undoubtedly VI is the direct precursor of the cyclization product III. A number of base-catalyzed 1,4-additions of a variety of anions (oxygen, nitrogen, carbon) to 12-desoxy- Δ^{16} -20-ketopregnenes have been reported.^{10a-10i} In all cases the 16 α -configuration has been assigned to the bulky substituent on the reasonable assumption that approach of the anion would occur from the least hindered side. The 17 β -configuration was assigned to the acetyl side chain because of the well known fact that the 17 β -acetyl side chain is more stable under alkaline equilibrating conditions than the 17 α -analog and from considerations of optical rotation or rotatory dispersion data. Thus, Mazur and Cella^{10h} have stressed the fact that the presence of a 17 α -acetyl side chain is associated with an enormous negative shift¹¹ which was not shown in any

and infrared are undoubtedly due to the fact that the carbonyl and double bond in this compound are in a ring and are coplanar.

(9) According to L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, a methyl group attached to the β -carbon of an α,β -conjugated system should exhibit a doublet near 8.0 τ ($J \sim 1.0$ c.p.s.);

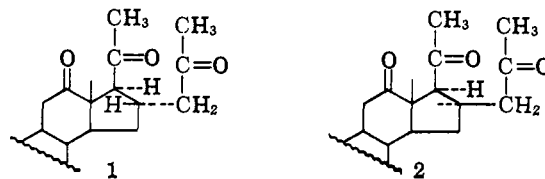


cf. pp. 124-125. Recently Wechter and Slomp in the compound shown noted a doublet ($J \sim 1.5$ c.p.s.) at 8.02 ascribed to the methyl and a quartet at 4.00 ascribed to the olefinic proton. Under our experimental conditions we did not obtain sufficient resolution to demonstrate positively either the methyl doublet or proton quartet. However, the reasonably close correspondence of our signals with the data obtained by Wechter and Slomp for a similar structure leave little doubt that the observed signals are due to the

H—C—
—C— moiety in III.

(10) (a) D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951); (b) J. Romo, M. Romero, C. Djerassi and G. Rosenberg, *ibid.*, **73**, 1528 (1951); (c) H. Hirschmann, E. B. Hirschmann and M. A. Daus, *ibid.*, **74**, 539 (1952); (d) D. Gould, F. Gruen and E. B. Hershberg, *ibid.*, **75**, 2510 (1953); (e) G. P. Mueller and B. Riegel, *ibid.*, **76**, 3686 (1954); (f) D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen and E. B. Hershberg, *ibid.*, **78**, 3158 (1956); (g) J. Romo, *Tetrahedron*, **3**, 37 (1958); (h) R. H. Mazur and J. H. Cella, *ibid.*, **7**, 130 (1959); (i) P. F. Beal and J. E. Pike, *J. Org. Chem.*, **26**, 3887 (1961).

of the compounds prepared by anionic addition to 16-dehydropregnenolone acetate. In this connection it is of interest to compare the molecular rotations of 3 β -acetoxy-5 α -pregnane-12,20-dione with compound VIb. The values are, respectively, +503° and +482°. In addition, the rotatory dispersion curve of VIb gives the strong positive Cotton effect (maximum at 360 μ , $[\alpha]_{360} +680^\circ$) associated with the 17 β -acetyl side chain.^{12,13} On the basis we assign the 17 β -configuration to the acetyl side chain in VI. We assign the 16 α -configuration to the C₁₆ side chain of VI from considerations based largely on analogy with the additions of anions to 12-desoxy-16 dehydro-20-ketopregnenes.^{10a-10i} Approach of the bulky acetone anion from the β -side would be greatly hindered as compared with α -approach. There is in addition certain experimental evidence for this assignment. Mazur and Cella^{10h} have shown that under alkaline equilibrating conditions 16 α -cyano-17 β -acetyl adducts are converted to 17 α -acetyl-16 β -carboxylic acids, an observation confirmed by Beal and Pike.¹⁰ⁱ Even more pertinent is the repeatedly confirmed observation that 16 β -methylpregnan-20-one derivatives are easily isomerized under alkaline conditions to the 16 β -methyl-17 α -pregnan-20-one series.^{14a,b,c} Presumably, the driving force for the epimerization at C₁₇ is the greater stabilization obtained as a result of the relief of the non-bonded interactions between the bulky C₁₆ β - and C₁₇ β substituents. If the two alternative C₁₆-configurations of compound VI are considered, one would expect that the C₁₇-side chain of a compound with formulation 1 would be stable toward alkaline equilibration whereas the 17 β -side chain of formulation 2 would be expected to



epimerize. We have obtained experimental verification of this hypothesis. Although a steroid with the exact configuration shown in formulation 2 was not available, we were able to show that a 16 β -methyl steroid, 3 β -hydroxy-16 β -methylpregnan-20-one was rapidly converted to the 17 α -epimer when treated under the identical experimental conditions used to prepare VIb from II; VIb was not affected by prolonged refluxing under these conditions (1% concentration of tetraethylammonium hydroxide). The propanone side chain of VI is obviously bulkier than the 16-methyl side chain. Hence, in conjunction with data previously presented, the failure of VI to epimerize under alkaline conditions which rapidly isomerize the 17-acetyl side chain of a 16 β -methyl steroid is convincing proof that the propanone side chain of VI possesses the 16 α -configuration.

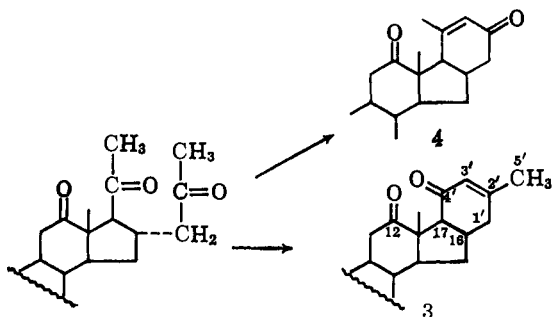
The formation of the cyclization product III from II or VI involves reversible reactions.^{7a,b} Consequently, the C₁₆, C₁₇-configurations of III need not be identical with those of its precursors. In addition, the cyclization of the 16 α side chain can take place theoretically in two ways to give 3, 4 or possibly a mixture.

(11) D. H. R. Barton and W. Klyne, *Chem. Ind.* (London), 755 (1948).

(12) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 51.

(13) W. A. Struck and R. L. Houtman, *J. Org. Chem.*, **26**, 3883 (1961), have shown that a number of progesterone and 17-isoprogestosterone derivatives with a variety of 16 α - or 16 β -substituents invariably show the positive or negative Cotton effects associated, respectively, with 17 β - or 17 α -acetyl side chains.

(14) (a) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944); (b) J. Attenburrow, *et al.*, *J. Chem. Soc.*, 4547 (1961); (c) G. G. Nathansohn, F. Donadelli, E. Testa and G. F. Odasso, *J. Org. Chem.*, **27**, 3677 (1962).



Several distinctly different lines of evidence show clearly that III has formulation 3. Catalytic hydrogenation of IIIb in the presence of palladium-on-charcoal resulted in the uptake of 1 mole of hydrogen to give VII, a product with an infrared spectrum which shows only non-conjugated carbonyl bands. Wolff-Kishner reduction of VII removed all the carbonyl groups, giving VIII, a product with the basic ABCDE ring structure of this new steroid series. Reduction of VII with lithium aluminum hydride or lithium in liquid ammonia followed by mild acetylation gave a monohydroxydiacetate, formulated as IXb. The infrared spectrum of IXb displayed the interesting type of intramolecular hydrogen bonding of the hydroxyl group to the alcoholic oxygen of the ester first noted by Henbest and Lovell.^{15,16} The infrared spectrum showed a strong sharp band at 3580 and strong bands at 1750, 1730, 1243 and 1225 cm^{-1} . The 1730 and 1243 cm^{-1} bands are

normal for the $\text{C}=\text{O}$ stretching and $\text{C}-\text{O}-$ stretching of a 3β -acetate in a 5α -A/B fused system.¹⁷ The bands at 1750 and 1225 occur in positions similar to those found by Henbest and Lovell.¹⁵ Another reaction provided an even stronger instance of hydrogen bonding. Treatment of IIIb with N-bromosuccinimide in refluxing carbon tetrachloride in the presence of azobisisobutyronitrile gave the phenol Xa in 40–50% yield. The reaction presumably proceeds *via* allylic bromination followed by spontaneous dehydrobromination, copious evolution of HBr being noted during the course of the reaction. The infrared spectrum of Xa showed a very strong hydroxyl band at 3220 cm^{-1} and strong carbonyl bands at 1733 and 1685 cm^{-1} . Since the 1733 band is clearly attributable to the 3β -acetate group, the 1685 band must be due to the 12-carbonyl. The latter has shifted from the normal 1710 cm^{-1} position because of intramolecular hydrogen bonding by the 4'-phenolic hydroxyl.^{18a,b} The phenol Xa could not be acetylated under normal conditions but under forcing conditions (perchloric acid catalysis) gave the diacetate Xb.¹⁹ The infrared spectrum of Xb indicated that the 12-carbonyl was no longer hydrogen bonded (1765 cm^{-1} , phenol acetate; 1730 cm^{-1} , 3β -acetate; 1715 cm^{-1} , 12-ketone). Inspection of formulations 3 and 4 and examination of molecular models shows clearly that the hydrogen bonding discussed above can be accommo-

(15) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957).

(16) Although the evidence available does not precisely locate the hydrogen bonded acetoxy and hydroxyl groups, they must be either at C_{12} or $\text{C}_{4'}$. The important feature is not the precise location but the fact that the ether oxygen of the acetate is strongly hydrogen bonded by an appropriately located hydroxyl group.

(17) R. N. Jones and F. Herling, *J. Am. Chem. Soc.*, **78**, 1152 (1956).

(18) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 2nd Ed., 1958, pp. 103–106; (b) For a similar shift due to hydrogen bonding of a 12 β -hydroxyl to a Δ^{16-20} -ketone *cf.* M. E. Wall and S. Serota, *Tetrahedron*, **10**, 238 (1960).

(19) In compound Xa the hydrogen bonding of the phenolic $\text{C}_{4'}$ hydroxyl to the C_{12} carbonyl is so strong that the phenol now exists largely in the hydrogen bonded form. This may account for the difficulty in acetylating this group. Removal of the C_{12} -carbonyl *via* Wolff-Kishner reduction of Xa gives a product in which the phenolic hydroxyl is easily converted to the acetate Xc.

dated only by 3. The structures of Xa, Xb and the 12-desoxy-4'-acetate Xc were confirmed by carbon and hydrogen analyses and by n.m.r. spectra. In the latter case signals were obtained for each compound at locations appropriate for hydrogen or methyl groups attached to an aromatic nucleus; *cf.* Experimental section. Evidence obtained by another route confirms formulation 3. Oxidation of IIIa or IIIb with permanganate-metaperiodate reagent^{20a,b} resulted in smooth cleavage of the $\Delta^{2'}$ -double bond with elimination of one carbon atom to give the acid XIa or XIb. The carbon and hydrogen analyses for the acid XIb or the methyl ester XIc were in excellent agreement with the formulations $\text{C}_{25}\text{H}_{36}\text{O}_6$ and $\text{C}_{26}\text{H}_{38}\text{O}_6$, required for loss of one carbon atom. The infrared spectrum of XIb showed unusually strong hydrogen bonding between the C_{12} -carbonyl and the C_{20} -carboxyl group.²¹ The preparation of C^{14} -labeled XIb permitted an unequivocal decision between formulations 3 and 4.



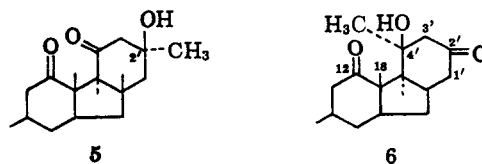
Reaction of II with CH_3CCH_3 in the presence of aqueous potassium hydroxide followed by acetylation gave labeled IIIb. The possibilities for labeling and the results obtained by permanganate-metaperiodate oxidation of labeled IIIb are shown below. It will be noted that in either of the possible formulations 3 or 4 the same 3'-carbon atom is lost during oxidative cleavage. However, in formulation 3, this carbon is derived from the steroid and is unlabeled, whereas in 4 it is derived from the tagged acetone carbons. As shown by the data given below, the acid XI retains full activity in accordance with formulation 3.²²

We believe that the acid XIb has identical C_{16} - and C_{17} -stereochemistry as the parent substance IIIb. We offer the following evidence for this statement: The acid is obtained in high yield under very mild conditions (room temperature, pH 7.8). Moreover, it has long been known that carboxyl groups attached to C_{17} are resistant to epimerization under strongly alkaline conditions,²³ and as we have discussed previously the C_{16} and C_{17} side chains of the potentially more reactive product VI are unchanged under more rigorous conditions of alkalinity and temperature than were used in

(20) (a) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1710 (1955); (b) M. E. Wall and S. Serota, *J. Org. Chem.*, **24**, 741 (1959).

(21) The infrared spectrum of acid XIa merits special comment. Strong bands at 1750, 1715–1720 and 1675 cm^{-1} (CH_2Cl_2 solution) were noted. This spectrum was almost identical to that found for 3β -acetoxy-17 β -carboxy-5 α -pregnane-12,20-dione prepared by reaction of ethyl formate with 3β -acetoxy-5 α -pregnane-12,20-dione followed by permanganate-periodate oxidation. Hence, the band at 1750 cm^{-1} is assigned to the carbonyl band of the C_{20} -carboxyl group. This carbonyl exists almost entirely in the unbonded rather than the normally hydrogen bonded form which is found near 1700 cm^{-1} ; *cf.* Bellamy, reference 16a, pp. 165–167. The 12-carbonyl group in XIa is strongly hydrogen bonded by the hydroxyl of the carboxyl group and is shifted to 1675 cm^{-1} . The 3β -acetate and 16 α -[propanone-2'-]carbonyl are found in one broad band between 1715 and 1720 cm^{-1} .

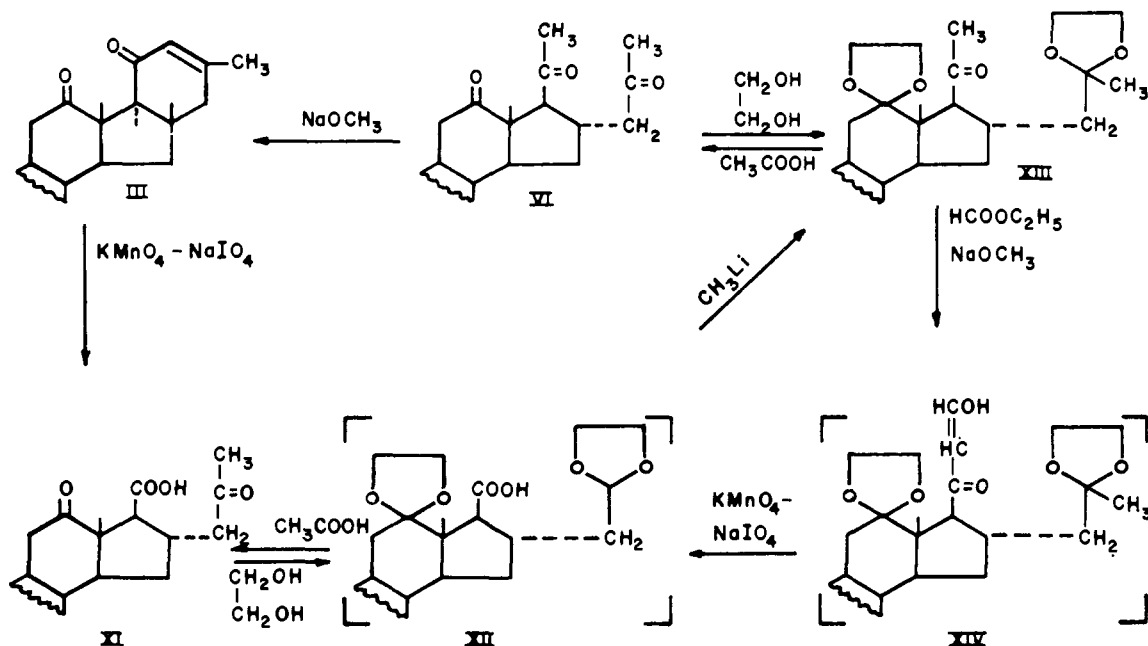
(22) The exclusive formation of a compound with formulation 3 in respect to the alternative 4 may be rationalized by considering the stereochemistry of their hypothetical precursors 5 and 6. As can be clearly demonstrated with molecular models, formulation 6 requires a number of serious non-



bonded interactions between substituents at C_{13} and C_{14} with the $\text{C}_{4'}$ -substituents, whereas formulation 5 involves much less severe interactions. Since the aldol condensation is reversible prior to elimination of water, formation of a compound with structure 3 derived from the sterically favored intermediate 5 occurs exclusively.

(23) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 628.

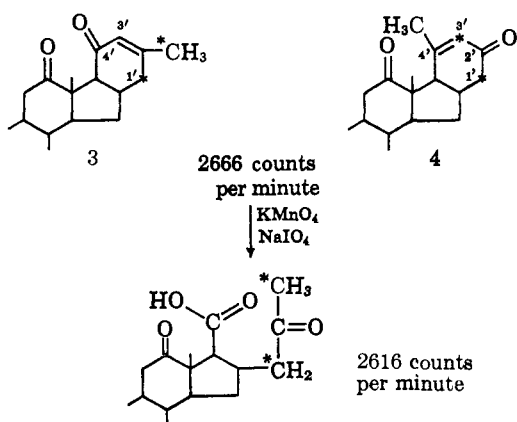
CHART II



the formation of XIb from IIIb. Hence, the C₁₆- and C₁₇-configurations of the acid XI should be identical with the configurations in the cyclic precursor III. We have interrelated XIb and VIb as shown in Chart II: Treatment of XIb with ethylene glycol in the presence of

of the aqueous layer, the crude diketal-acid XII was obtained in non-crystalline form. Acetic acid cleavage of the diketal gave a crystalline diketo-acid identical in all respects with XIb. The data which has been presented above thus shows that the cyclized product III, the Michael adduct VI and the acid XIb are identical in regard to the configurations of their respective side chains, which may be defined as 16 α , 17 β .

Finally, we wish to refer briefly to the fact mentioned previously that Michael addition of acetone does not occur with 12-desoxy- $\Delta^{16,20}$ -ketopregnenes under reaction conditions which are successful in the case of the 12-keto analogs. This statement is applicable not only to acetone but to a number of carbanions derived from even more acidic compounds such as acetylacetone, nitromethane and ethyl cyanoacetate. The driving force for the more facile reactions observed in the case of 16-dehydro-12,20-diketopregnenes may be due to relief of ring strain. Dreiding models indicate that the C/D ring system of the 12-keto-steroids is much more strained than that of the corresponding 12-desoxy-analogs.



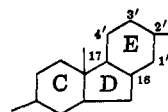
p-toluenesulfonic acid gave a non-crystalline diketal-acid XII. On treatment with acetic acid, XII is converted to XIb. Reaction of XII with a large excess of methyl lithium gave the crystalline diketal methyl ketone XIII. Removal of the protecting groups in refluxing acetic acid gave a crystalline product identical with VIb in all respects. The over-all conversion of XIb to VIb was 15%. About 60% of unreacted XIb was recovered. Treatment of VIb with ethylene glycol in the presence of *p*-toluenesulfonic acid gave XIII, previously prepared from XIb. The C₁₂-ketone is attacked preferentially to the C₂₀-ketone. Reaction of XIII with ethyl formate in the presence of sodium methoxide suspended in dry benzene gave the crude hydroxymethylene derivative XIV. The infrared spectrum of XIV showed a typical strong band at 1630 cm.⁻¹ characteristic of α,β -unsaturated β -hydroxyketones²⁴ and gave a strong red color with ferric chloride. Infrared examination of XIV indicated the presence of unreacted XIII. The crude mixture was oxidized with the permanganate-metaperiodate reagent. An acidic fraction remained in the slightly alkaline aqueous layer and was thus separated from unreacted XIII. On acidification

Experimental²⁵

3 β -Acetoxy-2'-methyl-16 β ,17 α ,5 α -[16,17-butanoandrost-2'-ene]-4',12-dione²⁶ (IIIb).—To 100 g. of the 16-dehydropregne II in 1500 ml. of acetone was added a solution of 152.5 g. of potassium hydroxide in 950 ml. of water. The resulting two-phase mixture was refluxed with vigorous stirring for 5 hours. The solution was cooled and the aqueous layer drawn off. Concentration of the acetone solution afforded 60 g. of tan crystals.

(25) Unless otherwise noted, all melting points were obtained on the Kofler hot-stage, optical rotations in chloroform solution, ultraviolet spectra in methanol, infrared spectra in carbon disulfide or methylene chloride and n.m.r. spectra in deuteriochloroform solution using a Varian spectrometer operating at 60 Mc. and calibrated against internal tetramethylsilane; chemical shifts are given by τ -values ($\tau = 10.0 - \text{p.p.m. from tetramethylsilane}$). We wish to thank Mrs. Ruth Kelley, Eastern Regional Research Laboratory, for some of the carbon and hydrogen analyses and Mr. Leon Pope, Camille Dreyfus Laboratory, RTI, for n.m.r. spectra.

(26) We wish to thank Dr. Leonard T. Capell, Nomenclature Director of Chemical Abstracts, for advising us on the nomenclature to be used in this series. As indicated below, the series is given the butanoandrostane stem,



fusion at C₁₆ and C₁₇ is noted and the remaining 4 carbon atoms of ring E designated 1', 2', 3', 4'.

(24) Reference 18, pp. 143-144.

IIIa, m.p. 214–221°; recrystallized from methylene chloride-acetone, m.p. 220–223°; n.m.r.: 9.00 (18-H), 8.73 (19-H), 7.97 (2'-CH₃), 6.30 broad (3 α -H), 4.25 τ (3'-vinyl-H).

The crystalline product was acetylated by refluxing in 150 ml. of acetic anhydride for 0.5 hour. The solution was diluted with water and extracted with methylene chloride. The extracts were washed with water and bicarbonate solution. Skellysolve C was added and the methylene chloride distilled. After standing in the refrigerator overnight, 35 g. of crystals was obtained, m.p. 243–246°. Concentration of the mother liquors yielded 19.8 g. of crystals, m.p. 241–245°.

The analytical sample was crystallized from methanol; m.p. 246–248°, $[\alpha]^{25}_D + 197^\circ$, λ_{max} 223 m μ (ϵ 12,200); ν_{max} (CS₂) 1735, 1710 and 1675 cm.⁻¹; n.m.r.: 9.09 (18-H), 8.81 (19-H), 8.08 (methyl of 3 β -acetate), 7.98 (2'-methyl), 5.45 broad (3 α -H) and 4.40 τ (3'-vinyl-H).

Anal. Calcd. for C₂₈H₃₆O₄: C, 75.69; H, 8.80. Found: C, 75.87; H, 8.77.

3 β -Acetoxy-2'-methyl-16 β ,17 α -[16,17-butanoandrostane-2',5-diene]-4',12-dione (V).—A solution of 10 g. of 3 β -acetoxy-5,16-pregnadiene-12,20-dione²⁷ in 200 ml. of acetone was added to a solution of 16 g. of potassium hydroxide in 10 ml. of water. The resulting two-phase solution was refluxed with vigorous stirring for 5.5 hours. The solution was diluted with water, cooled, and the precipitate filtered, yielding 7.78 g. of a granular solid. Crystallization from methanol afforded 6.4 g. of material, m.p. 262–265°, $[\alpha]^{25}_D + 147^\circ$. The adduct (1.0 g.) was acetylated by standing in 25 ml. of 50% acetic anhydride-pyridine solution overnight at room temperature. Dilution with water and filtration of the precipitate yielded 1.05 g. of solid. The analytical sample was crystallized from methanol; m.p. 234–236°, $[\alpha]^{25}_D + 104^\circ$; ν_{max} (CH₂Cl₂) 1727, 1711, 1683, 1652, 1620 cm.⁻¹.

Anal. Calcd. for C₂₈H₃₄O₄: C, 76.06; H, 8.34. Found: C, 75.68; H, 8.40.

3 β -Acetoxy-5 α ,16 α -[propanone-2']-pregnane-12,20-dione (VIb).—To a solution of 10.0 g. of II in 50 ml. of acetone was added 2 ml. of a 25% aqueous solution of tetraethylammonium hydroxide. The solution was refluxed for 4 hours and concentrated to a small volume *in vacuo*. The residual mixture was extracted with ether and the extracts washed with water. After drying over magnesium sulfate and removal of the ether *in vacuo*, 11.7 g. of brown glass was obtained. Chromatography on Florisil (80 g.) afforded 8.4 g. of crystals, m.p. 142–149°. The analytical sample crystallized from methylene chloride-methanol as plates, m.p. 153–154°, $[\alpha]^{25}_D + 112.4^\circ$; ν_{max} (CS₂) 1735, 1720–1700 cm.⁻¹; n.m.r.: 9.20 (18-H), 9.15 (19-H), 8.12 (methyl of 3 β -acetate), 8.04 (3'-H), 7.87 (21-H), 7.08 doublet (1'-H?), 5.31 broad (3 α -H). O.R.D.: $[\alpha]^{589} + 114.7^\circ$, $[\alpha]^{600} + 190^\circ$, $[\alpha]^{460} + 275^\circ$, $[\alpha]^{400} + 440^\circ$, $[\alpha]^{362} + 680^\circ$ (maximum), $[\alpha]^{350} + 425^\circ$.

Anal. Calcd. for C₂₈H₃₆O₅: C, 72.52; H, 8.89. Found: C, 72.56; H, 8.68.

Preparation of VIa.—Compound VIb (0.5 g.) in 25 ml. of a 1% solution (v./v.) of hydrochloric acid in methanol was allowed to stand overnight at room temperature. The mixture was then poured into excess water and the solids filtered, giving 0.44 g. of product. Crystallization from aqueous ethanol gave 0.4 g., m.p. 126–128°; ν_{max} (CH₂Cl₂) 3605, 1710–1700 cm.⁻¹; n.m.r.: 9.21 (18-H), 9.14 (19-H), 8.05 (3'-H), 7.87 (21-H), 6.49 (3 α -H), a doublet 7.11, 7.06 (*J* ~ 2.8 c.p.s.) may be 1'-H.

Conversion of VIb to IIIa. (a) With Potassium Hydroxide.—The acetone adduct VIb (1.0 g.) was dissolved in 15 ml. of acetone in which the methyl carbons were C¹⁴-labeled (specific activity, 0.001 millicurie/millimole). To this solution was added 1.5 g. of potassium hydroxide in 9.5 ml. of water. The resulting two-phase solution was refluxed with stirring for 5 hours; 10 ml. of ethylene glycol was added and the acetone distilled off. The residual suspension was extracted with methylene chloride. The extracts were concentrated to a small volume, acetone was added and the methylene chloride boiled off. On standing in the refrigerator, 0.40 g. of crystals was obtained, m.p. 220–222°. The infrared spectrum was identical to that of authentic IIIa. The sample exhibited no radioactivity above normal background.

(b) With Sodium Methoxide in Benzene.—Compound VIb (0.215 g.) was dissolved in 30 ml. of benzene. Benzene was distilled off until the volume was reduced to 5 ml. The solution was cooled and 0.03 g. of sodium methoxide was added. The flask was tightly stoppered and the suspension stirred at room temperature overnight. The mixture was washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*, yielding 0.20 g. of a glassy product. The infrared spectrum was identical to that of IIIa. Acetylation was accomplished by refluxing in acetic anhydride for 0.5 hour. The liquid was removed *in vacuo* and the residue crystallized from methanol; 0.10 g. of crystals, m.p. 243–245°, was obtained. The infrared spectrum was identical to that of authentic IIIb.

(27) H. A. Walens, S. Serota and M. E. Wall, *J. Org. Chem.*, **22**, 182 (1957).

3 β -Hydroxy-2'-methyl-16 β ,17 α ,5 α -[16,17-butanoandrostane]-4',12-dione (VII).—The cyclized product IIIa (0.2 g.) was dissolved in 50 ml. of methanol and 0.1 g. of 5% palladium-on-charcoal added. The mixture was hydrogenated at room temperature. The residue was washed with methanol. Evaporation of the filtrate yielded a mixture of crystals and glass. Chromatography on Florisil and recrystallization from methanol yielded 0.1 g. of crystals melting at 224–228°. Crystallization from acetone afforded crystals melting at 228–230.5°, $[\alpha]^{25}_D + 240^\circ$; ν_{max} CS₂ 3600, 1710 cm.⁻¹.

3 β -Hydroxy-2'-methyl-16 β ,17 α ,5 α -[16,17-butanoandrostane] (VIII).—A solution of 1.0 g. of VII in 27 ml. of ethylene glycol was added to a solution of 1.35 g. of sodium hydroxide in 27 ml. of ethanol and 1.35 ml. of hydrazine hydrate. The resulting solution was heated under reflux for 0.5 hour and the volatiles boiling below 190° distilled. Ethylene glycol (27.0 ml.) was added and the solution refluxed for 2 hours. The solution was poured into water and the granular precipitate filtered, giving 0.92 g. of semicrystalline material. Recrystallization from methanol yielded 0.4 g. of crystals, m.p. 167–177°. The infrared spectrum showed no bands in the carbonyl region. Chromatography on Florisil (5 g.) and crystallization from methanol afforded an analytical sample, m.p. 177–178°, $[\alpha]^{25}_D - 26^\circ$.

Anal. Calcd. for C₂₈H₄₀O: C, 83.65; H, 11.70. Found: C, 83.70; H, 11.86.

3 β ,4',12 β -Trihydroxy-2'-methyl-16 β ,17 α ,5 α -[16,17-butanoandrostane] (IXa). (a) **By Reduction of VII with Li-NH₃.**—A solution of 1.0 g. of VII in 25 ml. of methanol was added to 100 ml. of liquid ammonia in a Dry Ice bath; 1.75 g. of lithium wire was added in small pieces. The resulting mixture was stirred for 1.5 hours, 17.5 g. of ammonium chloride added, and the ammonia allowed to evaporate. The residue was extracted with ether and the extracts washed successively with dilute hydrochloric acid, sodium carbonate solution, and water. After drying and evaporation of the solvent, 0.81 g. of solid was obtained. Chromatography on Florisil (16 g.) afforded 0.3 g. of crystals. Recrystallization from methanol provided an analytical sample, m.p. 234–238°, $[\alpha]^{25}_D - 30^\circ$.

Anal. Calcd. for C₂₈H₄₀O₃: C, 76.55; H, 10.71. Found: C, 76.99; H, 10.72.

3 β ,12 β -Diacetoxy-4'-hydroxy-2'-methyl-16 β ,17 α ,5 α -[16,17-butanoandrostane] (IXb).—A sample of IXa was acetylated by standing in a 50% acetic anhydride pyridine solution overnight. The solution was diluted with water and the precipitate filtered. Two crystallizations from methanol provided the analytical sample IXb, m.p. 205–207°, $[\alpha]^{25}_D - 54^\circ$; ν_{max} (CS₂) 3530, 1750, 1730, 1242, 1222 cm.⁻¹.

Anal. Calcd. for C₂₈H₄₄O₅: C, 73.00; H, 9.63. Found: C, 72.89; H, 9.74.

(b) By LiAlH₄ Reduction of VII.—A solution of 1.0 g. of VII in 100 ml. of anhydrous ether was added to a stirred solution of 3.5 g. of lithium aluminum hydride in 100 ml. of ether. After refluxing 1.5 hours, excess LiAlH₄ was destroyed by cautious addition of water. The solution was acidified and extracted with ether. The product, 0.86 g., was acetylated at room temperature and worked up as described under section a. The acetylated product was identical to IXb in all respects.

3 β -Acetoxy-4'-hydroxy-2'-methyl-5 α -[16,17-butanoandrostane-1',3',16-triene]-12-one (Xa).—To a solution of 29 g. of IIIb in 580 ml. of carbon tetrachloride was added 1.25 g. of N-bromosuccinimide and 0.58 g. of azobisisobutyronitrile. The mixture was heated under reflux in a foil-covered flask. After 15 minutes white fumes of hydrogen bromide were observed escaping from the top of the condenser. The solution was refluxed for 1 hour, cooled and washed with water. After drying and removal of the solvent, 32.2 g. of foam was obtained. Trituration with ether afforded 16.5 g. of white crystals, m.p. 272–280°. Recrystallization from methylene chloride-ethyl acetate yielded 11.2 g. of crystals, m.p. 282–286°. The analytical sample was crystallized from ethanol; m.p. 285–287°, $[\alpha]^{25}_D + 150^\circ$, λ_{max} 268 m μ (ϵ 775), Beilstein test (-); ν_{max} (CS₂) 3235, 1735, 1685 cm.⁻¹; n.m.r.: 9.02 (18-H), 8.75 (19-H), 7.96 (CH₃ of 3 β -acetate), 7.71 (2'-CH₃), 5.48 broad (3 α -H), 3.71 (1',3'-H), 1.42 (4'-OH?).

3 β ,4'-Diacetoxy-2'-methyl-5 α -[16,17-butanoandrostane-1',3',16-triene]-12-one (Xb).—Attempted acetylation of Xa in acetic anhydride-pyridine gave unchanged Xa. The successful acetylation procedure required use of perchloric acid catalyst²⁸ as follows: 1.0 g. of the phenol Xa was dissolved in 10 ml. of acetic anhydride. The solution was cooled to 18° in an ice-bath and 0.1 ml. of 5 N perchloric acid was added. The resulting solution was stirred for 1 hour. The temperature was kept below 35°; 5 g. of ice was added and allowed to melt. Dilution with water and filtration of the precipitate yielded 1.1 g. of granular solid. Crystallization from methylene chloride-methanol afforded 0.88 g. of crystals, m.p. 202–206°. The analytical sample crystallized from methylene chloride-ethanol as needles, m.p. 210–212°, $[\alpha]^{25}_D + 132^\circ$; ν_{max} (CS₂) 1775, 1735, 1710, 1240 and 1200 cm.⁻¹;

(28) B. Whitman and E. Schwenk, *J. Am. Chem. Soc.*, **68**, 1865 (1946).

n.m.r.: 9.10 (18-H), 8.82 (19-H), 8.14 (CH₃ of 3 β -acetate), 7.92 (CH₃ of 4'-acetate), 7.80 (2'-CH₃), 5.50 broad, (3 α -H), 3.42 (1',3'-H).

Anal. Calcd. for C₂₈H₃₈O₅: C, 74.30; H, 8.02. Found: C, 74.46; H, 7.85.

3 β -4'-Diacetoxy-2'-methyl-5 α -[16,17-butanoandrosta-1',3'-16-triene] (Xc).—A mixture of 15.0 g. of Xa, 120 ml. of ethylene glycol, 60 ml. of anhydrous hydrazine, 750 ml. of absolute ethanol and 120 g. of sodium hydroxide was treated under the standard Huang-Minlon modification²⁹ of the Wolff-Kishner reduction. At the end of the reaction, the solution was made just acidic to litmus with dilute hydrochloric acid and the cloudy aqueous suspension extracted repeatedly with benzene containing 30% ether. Removal of solvent gave a residue (14.3 g.) insoluble in all common solvents. This product was refluxed with 50 ml. of acetic anhydride for 40 minutes. Dilution with water gave a granular precipitate (14.0 g.). The infrared spectrum of the crude product showed absence of hydroxyl bands. Chromatography on 70 g. of Florisil with benzene eluent gave 12.6 g. of crystalline product. Crystallization from methylene chloride-methanol (most of the methylene chloride boiled off) gave 10.9 g. of crystals, m.p. 179–181.5° (sublimed at 152–155°), $[\alpha]_D^{25} +2.5^\circ$; ν_{\max} (CS₂) 3015, 1765, 1730, 1230, 1195 cm.⁻¹; also in CH₂Cl₂, 1640 and 1560 cm.⁻¹; n.m.r.: 9.09 (18-H, 19-H), 8.08 (CH₃ of 3 β -OAc), 7.84 (CH₃ of 4'-acetate), 7.70 (2'-CH₃), 4.78 (3 α -H), 3.38, 3.17 (1',3'-H).

Anal. Calcd. for C₂₈H₃₈O₄: C, 76.67; H, 8.74. Found: C, 76.71; H, 8.91.

3 β -Hydroxy-17 β -carboxy-5 α ,16 α -[propanone-2']-pregnan-12-one (XIa).—To 1.0 g. of IIIa in 240 ml. of *tert*-butyl alcohol was added 110 ml. of an aqueous solution containing 4.05 g. of sodium metaperiodate, 0.12 g. of potassium permanganate and 1.0 g. of potassium carbonate. The resulting two-phase solution was shaken overnight at room temperature. The mixture was extracted with ether and the ethereal extracts discarded. Acidification of the aqueous fraction with dilute hydrochloric acid and extraction with ether yielded 0.69 g. of solid on evaporation of the ether. Crystallization from methanol afforded crystals melting at 188–191°, $[\alpha]_D^{25} +72^\circ$; ν_{\max} (CH₂Cl₂) 3580, 3120, 1753, 1710, 1675 cm.⁻¹.

3 β -Acetoxy-17 β -carboxy-5 α ,16 α -[propanone-2']-pregnan-12-one (XIb).—Permanganate-metaperiodate oxidation of 2.2 g. of IIIb as described under XIa gave 1.9 g. of crude acid. Crystallization from methanol gave the analytical sample, m.p. 222–224°, $[\alpha]_D^{25} +66^\circ$; ν_{\max} (CH₂Cl₂) 3120, 1750, 1720–1715 and 1675 cm.⁻¹; n.m.r.: 9.15 (18-H), 8.99 (19-H), 8.11 (CH₃ of 3 β -OAc), 8.01 (3'-CH₃), 5.50 (3 α -H).

Anal. Calcd. for C₂₈H₃₈O₆: C, 69.42; H, 8.39. Found: C, 69.23; H, 8.49.

3 β -Hydroxy-17 β -carboxymethoxy-5 α ,16 α -[propanone-2']-pregnan-12-one (XIc).—The acid XIa (0.5 g.) was added to a solution of 0.7 g. of diazomethane in 50 ml. of ether. After 15 minutes the acid had dissolved. Evaporation of the solvent yielded 0.53 g. of semicrystalline residue. Recrystallization from petroleum ether-acetone afforded an analytical sample, 0.22 g., m.p. 188–189°, $[\alpha]_D^{25} +56^\circ$; ν_{\max} (CH₂Cl₂) 3580, 1725–1700 cm.⁻¹.

Anal. Calcd. for C₂₄H₃₆O₆: C, 71.25; H, 8.97. Found: C, 71.21; H, 9.10.

Preparation of C¹⁴-Labeled IIIa and IIIb.—3 β -Acetoxy-, 5 α ,16-pregnen-12,20-dione (II) (2.53 g.) was dissolved in 38 ml. of acetone in which the methyl carbons were labeled with C¹⁴ (specific activity, 0.001 millicurie/millimole). To this solution was added 3.8 g. of potassium hydroxide in 24 ml. of water. The resulting two-phase solution was heated under reflux with stirring for 5 hours. Ethylene glycol, 10.0 ml., was added and the acetone distilled. The residual aqueous solution was extracted with ether. After drying, evaporation of the solvent *in vacuo* yielded 2.82 g. of foam. Crystallization from acetone-methylene chloride afforded 1.24 g. of crystals, m.p. 190–225°. The infrared spectrum was identical with that of an authentic sample of IIIa.

The crystalline radiocarbon-labeled IIIa was acetylated by refluxing for 0.5 hour in acetic anhydride. The anhydride was removed *in vacuo* and the residue crystallized from methanol yielding 1.11 g. of crystals of C¹⁴-labeled IIIb, m.p. 243–246°. The radioactivity of the compound is 2,666 counts/minute. The infrared spectrum of C¹⁴-labeled IIIb was identical to that of a non-labeled authentic specimen.

Preparation of C¹⁴-Labeled XIb.—A solution of 4.6 g. of sodium metaperiodate, 1.1 g. of potassium carbonate and 0.136 g. of potassium permanganate in 124 ml. of water was added to 1.1 g. of IIIb (radioactivity, 2,666 counts/minute) in 275 ml. of *tert*-butyl alcohol. The resulting mixture was vigorously stirred at room temperature overnight. The solution was diluted with water, extracted with ether, and the extracts discarded. The aqueous solution was then acidified with dilute hydrochloric acid

and extracted with ether. Drying and evaporation of the extracts afforded 1.048 g. of cream-colored solid. Crystallization from methylene chloride-methanol yielded 0.960 g. of crystals, m.p. 213–217°. Recrystallization from ethyl acetate afforded material, m.p. 222–224°; radioactivity, 2,616 counts/minute. The infrared spectrum is identical to that of the authentic non-labeled acid XIb.

Conversion of XIb to VI. (a) **3 β -Acetoxy-17 β -carboxy-5 α ,16 α -[propanone-2']-pregnane-12-one 2',12-Bis-(cyclic ethylene acetal) (XII).**—A 3.75-g. sample of acid XIb was refluxed 6 hours with 100 ml. of dry benzene containing 15 ml. of ethylene glycol and 0.090 g. of *p*-toluenesulfonic acid using a water removal trap. The warm solution was washed well with water and dried over magnesium sulfate. The product, 3.83 g. of XII, could not be crystallized. The infrared spectrum and solubility in sodium hydroxide indicated that both carbonyl groups had been converted to ketals and that a free carboxyl group was present. On heating a sample of XII in aqueous acetic acid on a steam-bath for 0.5 hour, a crystalline product identical in all physical properties to starting material XIb was obtained.

(b) **3 β -Acetoxy-5 α ,16 α -[propanone-2']-pregnane-12,20-dione 2',12-Bis-(cyclic ethylene acetal) (XIII).**—A solution of methyl-lithium in anhydrous ether was prepared from 2.0 g. of lithium wire and 3.25 ml. of methyl iodide. The resulting solution was added to 3.6 g. of XII in 100 ml. of ether and refluxed 9 hours. After the usual work-up, ether extraction gave 1.53 g. of a glassy product. The aqueous residue was acidified and extracted with ether, giving 2.0 g. of product which on acetylation was identical to starting material XII. The neutral fraction was acetylated. Thin-layer chromatography of the crude product indicated three well separated spots. Development with 2,4-dinitrophenylhydrazine indicated that only the fastest moving spot was ketonic. The entire sample was then chromatographed on 40 g. of Florisil. The benzene eluate afforded 0.45 g. of crystals, m.p. 160–163.5°. The analytical sample crystallized from methylene chloride-methanol; m.p. 163–164.5°, $[\alpha]_D^{25} +52^\circ$; ν_{\max} (CS₂) 1730, 1700, 1230, 1040, 1020, 965, 930 cm.⁻¹.

Anal. Calcd. for C₃₀H₄₆O₇: C, 69.47; H, 8.94. Found: C, 69.69; H, 9.14.

(c) **Conversion of XIII to VIb.**—To a solution of 2.5 ml. of acetic acid and 0.75 ml. of water was added 0.10 g. of XIII, and the mixture heated on the steam-bath for 0.5 hour. On cooling and addition of 10 ml. of water followed by scratching, 0.075 g. of fine needles, m.p. 152–153.5°, $[\alpha]_D^{25} +116^\circ$, was obtained. Mixture melting point with VIb gave no depression; the infrared spectrum was identical to that of VIb.

Conversion of VIb to XIb. (a) **Conversion of VIb to XIII.**—A 5.0-g. sample of VIb was treated with 20 ml. of ethylene glycol and 0.24 g. of *p*-toluenesulfonic acid in refluxing benzene for 7 hours. After the usual work-up, the residue, 5.2 g., was chromatographed on 50 g. of Florisil. The benzene eluate gave 3.3 g. of crystals, m.p. 156–160°, identical in every physical property to XIII.

(b) **Conversion of XIII to XIb.**—To a suspension of 0.21 g. of sodium methoxide in 6 ml. of dry benzene was added 0.285 g. of ethyl formate and 1.0 g. of XIII in 8 ml. of benzene. The suspension of methoxide and steroid-ethyl formate solution was stirred under nitrogen overnight at room temperature. The orange, gelatinous reaction mixture was diluted with water, acidified with dilute hydrochloric acid and extracted with ether. The product was a white foam, XIV, 1.06 g., with a strong infrared band at 1620 cm.⁻¹ and giving a strong ferric chloride reaction. The crude condensation product XIV was oxidized in the standard manner with potassium permanganate-metaperiodate reagent; cf. preparation of XIb. The water-*tert*-butyl alcohol mixture was further diluted with water and extracted with ether. Evaporation of solvent followed by acetylation gave 0.46 g. of unreacted XIII. The aqueous fraction was then acidified and re-extracted with ether, yielding 0.435 g. of a white foam. Acetylation with acetic anhydride-pyridine gave 0.450 g. of a non-crystalline acid. The infrared spectrum of this product appeared identical to that of the non-crystalline product XII prepared from XIb. Treatment with hot, aqueous acetic acid gave 0.305 g. of a glass which on methanol crystallization yielded 0.16 g. of crystals, m.p. 220–223°, identical in all respects with XIb. Further concentration of the mother liquors yielded 0.1 g. of crystals of slightly less pure XIb.

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(29) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946); **71**, 3301 (1949).