Anal. Calcd. for $C_{25}H_{25}PO$: C, 80.62; H, 6.77. Found: C, 80.40; H, 6.68.

A 3.75-g. sample of the ylid **6c** gave 4.95 g. (98%) of the iodide **8c** as yellow prisms from methanol, m.p. 206–208°, dec., with infrared absorption at 1695 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{25}H_{26}IPO$: C, 60.01; H, 5.24; I, 25.36. Found: C, 59.72; H, 5.11; I, 25.63.

From the reaction of 7.410 g. (0.02 mole) of the ylid **6c** with 2.12 g. (0.02 mole) of benzaldehyde in 50 ml. of benzene was isolated 4.10 g. (74%) of triphenylphosphine oxide, m.p. 154–156°, and 3.08 g. (82.5%) of benzalcycloheptanone (**7c**), b.p. 200° (0.5 mm.), in a short-path still. Recrystallization gave 2.66 g. (71%) of the pure benzylidene derivative **7c**, m.p. 37–39°, identified with an authentic sample[20] by comparison of infrared spectra.

Hydrolysis of 3.7052 g. (0.01 mole) of the ylid **6c** in the presence of 1.265 g. of *o*-chlorotoluene (as an internal standard) and 12 ml. of 2:1 ethanol–water at 160° for 3 days produced 2.48 g. (84%) of triphenylphosphine oxide, m.p. 154.5–156°. The calculated yield of cycloheptanone (**1c**) was 90%; a portion of the volatile product was converted to cycloheptanone 2,4-dinitrophenylhydrazone, m.p. 147.5–148°, identified by a mixed melting-point determination.

Reaction of the Ylid 6b with Peracetic Acid.—To a cold (0°) solution of 3.44 g. (0.01 mole) of the ylid **6b** in 50 ml. of methanol was added, dropwise and with stirring, a solution containing from 0.01 to 0.04 mole of peracetic acid in a mixture (1:1 by volume) of methanol and methylene chloride. The resulting mixture was stirred for 1.5 hr. at 0° and then concentrated under reduced pressure and partitioned between methylene chloride and sodium bicarbonate. The adipic acid, recovered from the bicarbonate solution in the usual way, was recrystallized from an acetone–methylene chloride mixture to give the pure acid (**9**), m.p. 151–153°, identified by a mixed melting-point determination. Concentration of the methylene chloride solution followed by extraction with ether separated the unchanged ylid **6b** (recrystallized from an ethyl acetate–methylene chloride mixture, m.p. 243–245° dec.) and triphenylphosphine oxide (recrystallized from an acetone–pentane mixture, m.p. 152–156°). The yields as a function of quantity of peracid used are summarized in Table I.

TABLE I

REACTION OF 0.01 MOLE OF THE YLID 6b WITH PERACETIC ACID

Peracetic acid, mole	Ylid **6b**, %	Ph_3PO, %	Acid **9**, %
0.01	54	..	20
0.02	35	36	33.5
0.03	..	75	66
0.04	..	88	71

C-6 Hydroxylated Steroids. IV.[1] 6-Hydroxylated 17α-Acetoxyprogesterone, 17α-Acetoxy-6-methylprogesterone, and Related Compounds

JOHN P. DUSZA, J. P. JOSEPH, AND SEYMOUR BERNSTEIN

Organic Chemical Research Section, Lederle Laboratories, a Division of American Cyanamid Company, Pearl River, New York

Received September 4, 1962

The preparation of the 6α- and 6β-hydroxy derivatives of 17α-acetoxyprogesterone and 17α-acetoxy-6-methylprogesterone by a variety of methods is described. Certain transformations (dehydrogenation, elimination, and isomerization) of these C-6 oxygenated steroids have been studied.

Our interest in the various methods for the synthesis of steroids containing a 6-hydroxyl group has been centered about the study of the conversion of Δ^4-3-ones to the corresponding 6-hydroxy-Δ^4-3-ones.[2-4] In this paper we wish to report on the preparation of a number of 6-hydroxy compounds related to 17α-acetoxyprogesterone and 17α-acetoxy-6-methylprogesterone.

We have previously demonstrated a general utility for the preparation of 6-hydroxy-Δ^4-3-ones through the reaction of $\Delta^{3,5}$-enol ethers with peracid.[1] Accordingly, when 17α-acetoxy-3-methoxypregna-3,5-dien-20-one (II) was oxidized with monoperphthalic acid there were isolated by chromatography two crystalline fractions. The less polar material was readily identified as 17α-acetoxy-6β-hydroxypregn-4-ene-3,20-dione (III). The second fraction isolated in much smaller yield proved to be 17α-acetoxy-6α-hydroxypregn-4-ene-3,20-dione (IV).[5] As in other series we have studied, a mixture of the 6-hydroxylated compounds is encountered with the β-epimer predominating.[1]

When the 6β,17α-diacetate V was dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone,[6] there was obtained 6β,17α-diacetoxypregna-1,4-diene-3,20-dione (VI). Under the vigorous reaction conditions required for 1,2-dehydrogenation, protection of the 6-hydroxyl group was mandatory.[7] Selective hydrolysis of VI afforded 17α-acetoxy-6β-hydroxypregna-1,4-diene-3,20-dione (VII). The latter was converted into its crude 6-mesylate, which on attempted recrystallization led to the formation of the $\Delta^{1,4,6}$-trienone VIII.[8] Chromic acid oxidation of VII yielded the $\Delta^{1,4}$-3,6-dione IX with an ultraviolet absorption maximum at 250 mμ (ε 14,800). Under basic conditions it exhibited a more intense maximum at 253 mμ (ε 18,000) and a second broad maximum centered at 393 mμ (ε 9650).[9]

The preparation of 6-hydroxy-6-methyl compounds was also undertaken and was approached through a number of pathways. Peracid attack on 3,17α-diacetoxy-6-methylpregna-3,5-dien-20-one (X)[10] was selected for one study. When an ethereal solution of the latter

(1) Previous paper in this series, *J. Org. Chem.*, **27**, 4046 (1962).

(2) S. Bernstein, W. S. Allen, C. E. Linden, and J. Clemente, *J. Am. Chem. Soc.*, **77**, 6612 (1955).

(3) S. Bernstein and R. Littell, *J. Org. Chem.*, **25**, 313 (1960).

(4) L. L. Smith, J. J. Goodman, H. Mendelsohn, J. P. Dusza, and S. Bernstein, *ibid.*, **26**, 974 (1961).

(5) (a) The 6β-hydroxy compound III has been previously prepared by acetic acid opening of the appropriate 5α,6α-epoxide and subsequent hydrolysis [R. Sciaky, *Gazz. chim. ital.*, **91**, 545 (1961)]; and (b) through the reaction of peracid on the corresponding $\Delta^{3,5}$-enol acetate [H. Mori, *Chem. Pharm. Bull. Japan*, **9**, 328 (1961)]. The 6α-hydroxy compound IV has been obtained by epimerization of the 6β-acetoxy derivative IV followed by 6-deacetylation (ref. 5a).

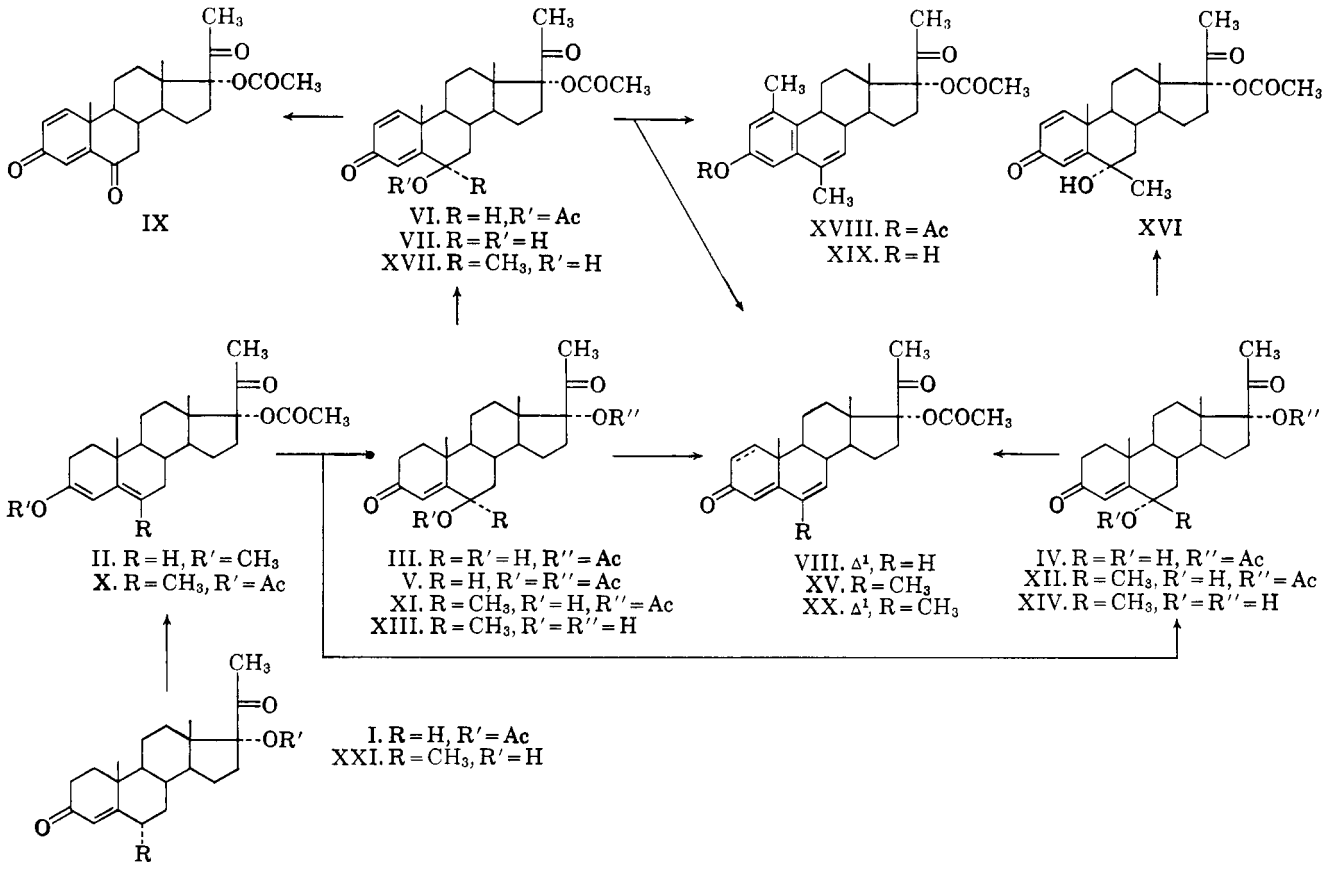
(6) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(7) Although the selective oxidation of Δ^4-3β,6β-diols to 6β-hydroxy-Δ^4-3-one by the quinone reagent has been successfully executed [D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Letters*, No. **9**, 14 (1960)] the conditions used were considerably milder than those employed here for 1,2-dehydrogenation.

(8) W. Hiersemann, E. Kaspar, and U. Kerb, U.S. Patent 2,962,510 (November 29, 1961).

(9) In the cholesterol series, this chromophore [λ_{max} 251 mμ (ε 14,800)] has been generated by quinone oxidation of the Δ^4-3,6-dione; D. Burn, V. Petrow, and G. Weston, *J. Chem. Soc.*, 29 (1962).

(10) H. J. Ringold, J. P. Ruelas, E. Batres, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3712 (1959).



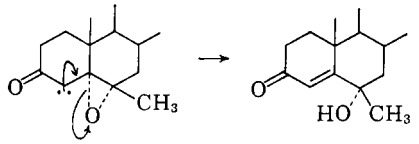
was refluxed with monoperphthalic acid, subsequent chromatography provided two crystalline fractions. The less polar component was identified as 17α-acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XI) because it exhibited an ultraviolet absorption maximum at 238 mμ (ϵ 13,300) and a characteristically broad and irregular absorption maximum near 1660 cm.$^{-1}$ in the infrared. In addition, the infrared spectrum showed diminished absorption for the double bond in the 1615-cm.$^{-1}$ region, also encountered with other 6β-hydroxy-Δ^4-3-ones.[11] The second more polar fraction eluted was 17α-acetoxy-6α-hydroxy-6β-methylpregn-4-ene-3,20-dione (XII).[12,13] This epimer exhibited an absorption maximum at 243 mμ (ϵ 14,100) which could be attributed to the 6α-hydroxy-Δ^4-3-one system and showed a sharp Δ^4-3-one infrared absorption band at 1667 cm.$^{-1}$. Although these compounds possess an additional methyl group at C-6, their ultraviolet spectra paralleled the desmethyl series except for a small bathochromic effect probably attributable to the 6-methyl group. Hydrolysis of the 17-acetate function in XI and XII was accomplished with refluxing potassium hydroxide giving rise to the respective diols XIII and XIV. The presence of the 6-methyl group in each case prevents formation of the 3,5-enolate which would effect isomerization of the 6-hydroxy-Δ^4-3-one to the 3,6-dione.[14]

A direct structural assignment of the 6-hydroxy-6-methyl epimers was accomplished by chemical means. Refluxing the 6β-hydroxy-6α-methyl epimer XI in acetic acid led to the formation of 17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione (XV),[10] while similar treatment of the 6α-hydroxy-6β-methyl compound resulted in recovery of starting material. Since the 6β-hydroxyl group possesses the axial conformation, elimination tends to proceed under milder conditions than for the equatorial 6α-epimers.[15] The 6-methyl-$\Delta^{4,6}$-3-one XV was obtained from both epimers by employing acetic acid-*p*-toluenesulfonic acid.

The reaction of XII with 2,3-dichloro-5,6-dicyanobenzoquinone gave 17α-acetoxy-6α-hydroxy-6β-methylpregna-1,4-diene-3,20-dione (XVI) in approximately 50% yield. A similar reaction with XIII afforded 17α-acetoxy-6β-hydroxy-6α-methylpregna-1,4-diene-3,20-dione (XVII) in 75% yield. The tertiary nature of the C-6 hydroxyl group presented no complications during quinone oxidation. When the dienone XVII was allowed to stand at room temperature with acetic anhydride–*p*-toluenesulfonic acid, two compounds were obtained on chromatography of the reaction mixture. The initial material eluted was assigned the structure

(11) These observations are based on the experience of this laboratory with related compounds.

(12) Attack of peracid on a 6-methyl-$\Delta^{3,5}$-enol acetate system has recently been reported [B. Ellis, S. P. Hall, V. Petrow, and D. M. Williamson, *J. Chem. Soc.*, 22 (1962)]. They report only the isolation of the 6β-hydroxy epimer in their series. These authors have observed the formation of the 6α-hydIoxy-6β-methyl epimer as arising from base treatment of a 5α,6α-epoxy-6β-methyl-3-one system. A similar finding as illustrated below has recently been made [J. Iriate, J. N. Shoolery, and C. Djerassi, *J. Org. Chem.*, **27**, 1139 (1962)]



(13) Of interest is the 6β/6α ratio (1.25) observed in this experiment. Whereas ratios of 5 to 10 are normally encountered in oxidation of $\Delta^{3,5}$-enol ethers or enol acetates, the effect of the 6-methyl group and/or more vigorous reaction conditions have raised the yield of the 6α-hydroxy epimer appreciably.

(14) P. T. Herzig and M. Ehrenstein, *J. Org. Chem.*, **16**, 1050 (1951).

(15) This selectivity has been observed recently in this laboratory.

3,17α-diacetoxy-1,6-dimethyl-19-norpregna-1,3,5(10),6-tetraen-20-one (XVIII). Spectral data were in agreement with the proposed structure and quite similar to those reported for the 1,6-dimethylestra-1,3,5(10),6-tetraene system.[9] Selective hydrolysis of the 3-acetate was achieved thus affording 17α-acetoxy-3-hydroxy-1,6-dimethyl-19-norpregna-1,3,5(10),6-tetraen-20-one (XIX). The second fraction eluted was easily identified through its ultraviolet absorption spectrum as 17α-acetoxy-6-methylpregna-1,4,6-triene-3,20-dione (XX).[10]

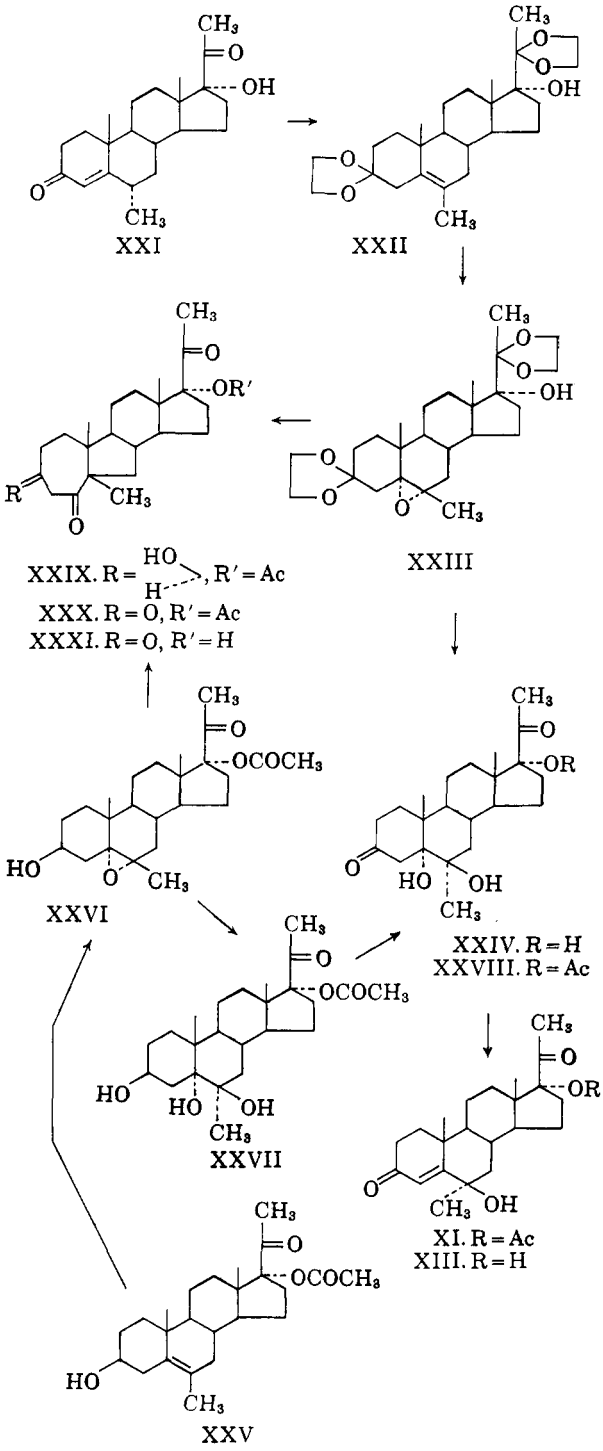
The conditions employed in this reaction were less severe than those normally used to effect dienone–phenol rearrangements. In simple $\Delta^{1,4}$-3-ones, the rearranged products have been shown to be 1-hydroxy-4-methyl and 3-hydroxy-1-methyl aromatic ring A compounds.[9,16] When the rearrangement conditions were applied to $\Delta^{1,4,6}$-3-ones, the products have been characterized as the 3-hydroxy-1-methyl-6-dehydro aromatic ring A compounds. In the 6-methyl series, a report confirmed the rearrangement to the corresponding 1,6-dimethyl compound.[9] The isolation of both XVIII and XX suggested that the initial step is an elimination reaction leading to the trienone, which was then partially rearranged to the aromatic product.[17]

A more general approach for the introduction of a second substituent into the 6-position of a 6-methyl steroid was formulated on the preparation of the 5α,6α-epoxy-6β-methyl unit. At the time, literature information from the 6-methylcholesterol series confirmed the possibility of the proposed epoxidation of the Δ^5-6-methyl grouping and demonstrated a normal *trans* opening of the epoxide.[18] Since both the 6α-methyl-Δ^4-3-one and 3β-hydroxy-Δ^5-6-methyl steroids were available, a sequence of reactions from each substrate was pursued.

The ketalization of 17α-hydroxy-6α-methylpregn-4-ene-3,20-dione (XXI) afforded the bisketal XXII in excellent yield. Epoxidation of this material with monoperphthalic acid under refluxing conditions gave the desired 5α,6α-epoxy-6β-methyl unit. Assignment of configuration to the epoxide was based solely on the 6-methylcholesterol series mentioned above.[19] The reaction of the bisketal epoxide XXIII with aqueous perchloric acid led to 5α,6β,17α-trihydroxy-6α-methylpregnane-3,20-dione (XXIV). Epoxide opening was accompanied by removal of the two ketal groupings.[8] Base treatment to effect β-elimination yielded the desired diol XIII identical in all respects to the compound prepared by the hydrolysis of XI reported above.

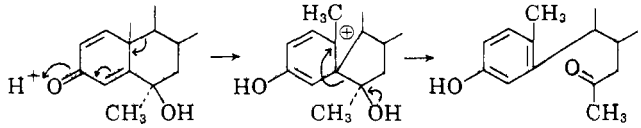
The epoxidation of 17α-acetoxy-3β-hydroxy-6-methylpregn-5-en-20-one (XXV) with monoperphthalic acid under reflux gave a compound assigned the structure 17α-acetoxy-5α,6α-epoxy-3β-hydroxy-6β-methylpregnan-20-one (XXVI) on the basis of the evidence cited previously. Aqueous perchloric acid treatment led to the expected *trans* opening of the epoxide and compound XXVII. Chromic acid oxidation of the triol produced XXVIII which on treatment with anhydrous hydrogen chloride gave 17α-acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XI), identical to one of the compounds isolated from peracid treatment of the enol acetate X and which had been assigned the 6β-hydroxy confirmation.

Chemical support for the assignment of the 5α,6α-orientation to the epoxide grouping in XXVI was obtained indirectly. In an attempt to introduce a fluorine



(16) (a) A. S. Dreiding, W. J. Pummer, and A. J. Tomasewski, *J. Am. Chem. Soc.*, **75**, 3159 (1953); (b) R. B. Woodward and T. Singh, *ibid.*, **72**, 494 (1950).

(17) Had the dienone–phenol rearrangement taken place prior to the elimination reaction, one might also expect the formation of seco products of the following type, suggestive of the acid cleavage of 1,3-glycols; H. E. Zimmerman and J. English, Jr., *ibid.*, **76**, 2294 (1954), and references cited therein.



(18) M. Shiota, *Nippon Kagaku Zasshi*, **75**, 1217 (1954); **76**, 1272 (1956); **77**, 778 (1956). *Chem. Abstr.*, **51**, 17969 (1957); **52**, 416, 417 (1958).

(19) A report on the reinvestigation of the 6-methylcholesterol work [M. Davis and G. H. R. Summers, *J. Chem. Soc.*, 4707 (1960)] has shown that the β-epoxide is also formed but only to a minor extent.

atom at C-6, the reaction of 17α-acetoxy-5α,6α-epoxy-3β-hydroxy-6β-methylpregnan-20-one (XXVI) with anhydrous hydrogen fluoride and boron trifluoride etherate was studied. In each case the same fluorine-free product was isolated. On the basis of the reported isomerization of 5α,6α-epoxy-6β-methyl steroids to A-homo-B-nor compounds,[20] the structure assigned to this material was 17α-acetoxy-3β-hydroxy-5β-methyl-A-homo-B-norpregnane-4a,20-dione (XXIX). Chromic acid oxidation provided the 3,4a,20-trione XXX. The intense ultraviolet absorption maximum [$\lambda_{max}^{MeOH + Base}$ 300 mμ (ε 18,000)] exhibited on addition of base, confirmed the positioning of both oxygen functions in ring-A and in a 1,3-relationship.[21] Further support for the structure of the trione XXX has been supplied by n.m.r. data. The five methyl groups could be located as follows: C-21 (δ 2.16), C-19 (δ 1.20), C-18 (δ 0.62), C-5 (δ 0.94),[22] C-17 acetyl methyl (δ 2.07). In addition, the only other prominent peak in the spectrum was found centered at 3.62 δ as a doublet having 2-c.p.s. splitting. This peak, intergrating for two hydrogens, has been assigned to the methylene hydrogens at C-4.

An identical ring expansion was observed in the 3,20-bisketal series. When 5α,6α-epoxy-3,20-bisethylenedioxy-6β-methylpregnan-17α-ol (XXIII) was treated with 72% perchloric acid in acetone, there was obtained 17α-hydroxy-5β-methyl-A-homo-B-norpregnane-3,4a,-20-trione (XXXI) in contrast to the normal epoxide opening observed with 1.5 *N* aqueous perchloric acid.

NOTE ADDED IN PROOF. R. Sciaky and A. Consonni [*Gazz. chim. ital.*, **92**, 547 (1962)] have recently reported the preparation of III and IV by a similar oxidation of the enol acetate X with monoperphthalic acid.

Experimental

Melting points are uncorrected. The ultraviolet spectra were determined as indicated in 2% Methyl Cellosolve–methanol and in basic methanol. The expression basic methanol refers to a solution of the steroid (20 γ/ml.) in 1 part of 20% Methyl Cellosolve–methanol and 9 parts of 0.1 *N* sodium hydroxide solution. The infrared absorption spectra were determined in potassium bromide disks. The authors are indebted to William Fulmor and associates for the infrared, ultraviolet absorption, optical rotation, and nuclear magnetic resonance data. We wish also to thank Louis M. Brancone and associate for the analyses. Petroleum ether refers to the fraction, b.p. 60–70°.

17α-Acetoxy-3-methoxypregna-3,5-dien-20-one (II).—Concentrated sulfuric acid (0.1 ml.) was added to the suspension resulting from the addition of 17α-acetoxypregn-4-ene-3,20-dione (I, 2.0 g.) to a solution consisting of dioxane (15 ml.), trimethyl orthoformate (15 ml.) and absolute methanol (0.1 ml.). The reaction mixture became homogeneous in 5 min. and was allowed to stand an additional 15 min. at room temperature when pyridine (2.0 ml.) was added and the solution was poured into water. The collected solid was crystallized from aqueous methanol to give the desired enol ether II (2.1 g.). A portion of the material was crystallized several times from methanol, m.p. 195–198°, $[\alpha]^{25}D$ −135° (1% pyridine in chloroform); λ_{max} 239 mμ (ε 21,000); ν_{max} 1745, 1720, 1660, 1637, 1252, and 1172 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_4$ (386.51): C, 74.57; H, 8.87. Found: C, 74.19; H, 8.96.

17α-Acetoxy-6β-hydroxypregn-4-ene-3,20-dione and 17α-Acetoxy-6α-hydroxypregn-4-ene-3,20-dione (III and IV).—A solution of 17α-acetoxy-3-methoxypregna-3,5-dien-20-one (II, 2.0 g.) in ether (130 ml.) was treated with 0.684 *N* monoperphthalic acid in ether solution (15.2 ml.). After standing at room temperature in the dark for 18 hr., the precipitated crystalline solid was separated to yield 0.745 g., m.p. 238–243°. This material was dissolved in methylene chloride and chromatographed on a synthetic magnesium silicate. After an initial small quantity of 17α-acetoxypregn-4-ene-3,20-dione (I), there was obtained two crystalline fractions. The material eluted with 3% acetone–methylene chloride (3 × 50 ml.), 4% acetone–methylene chloride (4 × 50 ml.), and 5% acetone–methylene chloride (4 × 50 ml.) proved to be the 6β-hydroxy epimer III, which after crystallization from acetone–petroleum ether afforded the product (0.327 g.), m.p. 245–246°, $[\alpha]^{25}D$ +14° (chloroform); λ_{max} 236 mμ (ε 15,500); ν_{max} 3440, 1740, 1680 (sh), 1658, 1260, 1250, and 1227 cm.$^{-1}$; lit.,[5b] m.p. 239–243°, $[\alpha]^{20}D$ +7°; λ_{max}^{EtOH} 238 mμ.

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 71.20; H, 8.62.

The second fraction eluted with the later 7% acetone–methylene chloride (3 × 50 ml.), 10% acetone–methylene chloride (4 × 50 ml.), and the early 15% acetone–methylene chloride (3 × 50 ml.) fractions was crystallized from acetone–petroleum ether and was shown to be the 6α-hydroxy epimer IV, m.p. 254–255°, $[\alpha]^{25}D$ +55° (chloroform): λ_{max} 239 mμ (ε 15,400); ν_{max} 3520, 3450 (sh), 1712, 1664, 1282, 1267, and 1250 cm.$^{-1}$; lit.,[5a] m.p. 244–246°, $[\alpha]D$ +75°; λ_{max} 241 mμ (ε 14,700).

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 71.40; H, 8.69.

The initial reaction mixture (crystalline phase removed) was diluted with methylene chloride and washed with a saturated aqueous sodium bicarbonate solution followed by a saturated saline solution. The evaporation of this dried solution provided a glass which was chromatographed in a manner similar to that described above. An additional quantity of the 6β-hydroxy epimer III (0.325 g.) was obtained with the 3, 4, and 5% acetone fractions. No subsequent fractions containing the pure 6α-hydroxy epimer could be isolated, although paper strip chromatography indicated these fractions contained a mixture of the α- and β-hydroxy epimers.

6β,17α-Diacetoxypregn-4-ene-3,20-dione (V).—17α-Acetoxy-6β-hydroxypregn-4-ene-3,20-dione (III, 0.5 g.) was dissolved in a solution of acetic anhydride (2.0 ml.) and pyridine (4.0 ml.). After standing at room temperature for approximately 24 hr., the reaction mixture was poured into water. The collected solid was crystallized from acetone–petroleum ether and provided the diacetate (0.47 g., m.p. 245–248°); $[\alpha]^{25}D$ +28° (chloroform); λ_{max} 235 mμ (ε 14,800); ν_{max} 1740, 1714, 1693, 1252, and 1238 cm.$^{-1}$; lit.,[5b] m.p. 243–245°, $[\alpha]^{20}D$ +22°; λ_{max}^{EtOH} 236 mμ.

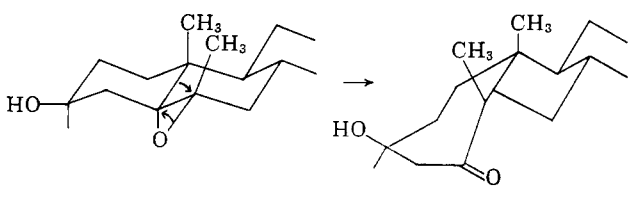
6β,17α-Diacetoxypregna-1,4-diene-3,20-dione (VI).—A solution of 6β,17α-diacetoxypregn-4-ene-3,20-dione (V, 0.82 g.) and 2,3-dichloro-4,6-dicyanobenzoquinone (0.65 g.) in dry dioxane (20 ml.) was refluxed for 20 hr. and then cooled. The precipitated hydroquinone was removed by filtration and the filtrate was evaporated. The resultant glass was dissolved in methylene chloride (250 ml.) and passed through a short magnesium silicate column to remove colored impurities. Additional methylene chloride (250 ml.) was then passed through the column. Evaporation and crystallization of the residue from acetone–petroleum ether afforded 0.371 g., m.p. 252–254°, $[\alpha]^{25}D$ −13° (chloroform); λ_{max} 243 mμ (ε 17,800); ν_{max} 1742, 1712, 1670, 1635, 1256, and 1229 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{32}O_6$ (428.51): C, 70.07; H, 7.53. Found: C, 69.75; H, 7.79.

17α-Acetoxy-6β-hydroxypregna-1,4-diene-3,20-dione (VII).—Nitrogen was bubbled through a solution of 6β,17α-diacetoxypregna-1,4-diene-3,20-dione (VI, 0.35 g.) in methanol (50 ml.). To the purged solution was added a 10% aqueous potassium carbonate solution (2.5 ml.) and the nitrogen stream was continued for 45 min. Acetic acid was added dropwise to neutralize the reaction mixture and then most of the methanol was evaporated at reduced pressure. The reaction mixture was poured into water and after filtration provided VII (0.30 g.), m.p. 194–195°. Crystallization from acetone–petroleum ether gave 0.243

(20) D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4657 (1960).

(21) The α-configuration assigned to the epoxide is thereby supported since only this epoxide is favorably oriented from 5,10-bond migration *trans* to the equatorially departing group at C-6 as illustrated.



(22) Assignment of the signals to the C-19 and C-5 methyl groups may well be reversed.

g., m.p. 224–225°, $[\alpha]^{25}D$ −45° (pyridine); λ_{max} 243 mμ (ε 17,200); ν_{max} 3330, 1740, 1634, 1618, 1262, and 1252 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.73; H, 8.20.

17α-Acetoxypregna-1,4,6-triene-3,20-dione (VIII).—A solution of 17α-acetoxy-6β-hydroxypregna-1,4-diene-3,20-dione (VII, 0.2 g.) dissolved in dry pyridine (1.5 ml.) at 5° was treated with methane–sulfonyl chloride (120 mg.), and the mixture was allowed to stand at room temperature for 20 hr. It was then poured into water and the precipitated material collected, 0.173 g., m.p. 105–130°. Because the material could not be recrystallized from acetone–petroleum ether or aqueous methanol, it was chromatographed on a synthetic magnesium silicate. The crystalline fractions obtained from the late 10% acetone–petroleum ether (4 × 20 ml.) and early 12% acetone–petroleum ether, (2 × 20 ml.) fractions were combined and crystallized from acetone–petroleum ether to give VIII (30 mg.); m.p. 195–196°, $[\alpha]^{25}D$ −33° (chloroform); λ_{max} 220, 255, and 298 mμ (ε 12,550, 9600, and 12,650); ν_{max} 1743, 1728, 1667, 1612, 1590, 1260, and 1250 cm.$^{-1}$; lit.,[8] m.p. 192–192.5°; λ_{max}221, 259, and 296 mμ (ε 11,025, 9790, and 12,830).

17α-Acetoxypregna-1,4-diene-3,6,20-trione (IX).—Dropwise addition of 8 *N* chromic acid in 8 *N* sulfuric acid to a solution of 17α-acetoxy-6β-hydroxypregna-1,4-diene-3,20-dione (VII, 150 mg.) was continued until the yellow color of the oxidizing agent persisted then methanol was added to decompose the excess reagent. The reaction mixture was filtered and the filtrate evaporated. The residue was dissolved in methylene chloride and chromatographed on a synthetic magnesium silicate. The material eluted with the late 2% acetone–methylene chloride (3 × 25 ml.) and the early 5% acetone–methylene chloride (2 × 25 ml.) fractions was crystallized from acetone–petroleum ether to give IX (85 mg.), m.p. 220–201°, $[\alpha]^{25}D$ −135° (chloroform); λ_{max} 250 mμ (ε 14,800); $\lambda_{max}^{Basic\ MeOH}$ 253 mμ (ε 18,000), 393 mμ (ε 9650); ν_{max} 1748, 1723, 1712, 1667, 1630, 1252, and 1227 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{28}O_5$ (384.45): C, 71.85; H, 7.34. Found: C, 71.91; H, 7.48.

3,17α-Diacetoxy-6-methylpregna-3,5-dien-20-one (X).—17α-Hydroxy-6α-methylpregn-4-ene-3,20-dione (XXI, 10.0 g.) was added to acetic anhydride (60 ml.), and *p*-toluenesulfonic acid monohydrate (1.0 g.). The reaction mixture was heated on a steam bath for 1 hr., cooled, and poured into water. The solid was collected and crystallized from methanol to give X (9.0 g.); m.p. 162–165°, $[\alpha]^{25}D$ −132° (chloroform); λ_{max} 243 mμ (ε 16,400); ν_{max} 1770, 1740, 1720, 1670, 1640, 1250, and 1216 cm.$^{-1}$; lit.,[10] m.p. 160–162°; $[\alpha]D$ −146°; λ_{max}^{EtOH} 244 mμ (ε 19,950).

17α-Acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione and 17α-Acetoxy-6α-hydroxy-6β-methylpregn-4-ene-3,20-dione (XI and XII).—3,17α-Diacetoxy-6-methylpregna-3,5-dien-20-one (X, 2.0 g.) was dissolved in ether (100 ml.) and refluxed for 3.5 hr. with ethereal 0.62 *N* monoperphthalic acid (16 ml.). The solution was cooled and washed with a dilute sodium bicarbonate solution and then with a saturated saline solution. The dried solution was evaporated to give an oil which was chromatographed on a synthetic magnesium silicate (65 g.).

The crystalline material eluted with the 15% acetone–petroleum ether fractions (5 × 100 ml.) was combined and crystallized from acetone–petroleum ether to give XI (0.435 g.), m.p. 218–224°. After two more crystallizations from the same solvent pair, there was isolated the 6β-hydroxy epimer XI (0.281 g.), m.p. 226–228°; $[\alpha]^{25}D$ ±0° (chloroform); λ_{max} 238 mμ (ε 13,300); ν_{max} 3430, 1742, 1725, 1662, 1267, and 1257 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_5 \cdot C_3H_6O$: C, 70.40; H, 8.63. Found: C, 70.40; H, 8.78.

A second fraction eluted by the late 20% acetone–petroleum ether (4 × 100 ml.) and the early 30% acetone–petroleum ether (2 × 100 ml.) fractions was collected. Crystallization from acetone–petroleum ether afforded the 6α-hydroxy epimer XII (0.343 g.), m.p. 240–243°. Crystallization from the same solvent pair raised the m.p. to 245–247°; ν_{max} 3490, 1740, 1723, 1667, 1613, 1269, 1258, 1235, and 1222 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_5 \cdot C_3H_6O$: C, 70.40; H, 8.63. Found: C, 70.75, 70.65; H, 9.29, 9.00.

6β,17α-Dihydroxy-6α-methylpregn-4-ene-3,20-dione (XIII).—17α-Acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XI, 50 mg.) was dissolved in methanol (20 ml.) and then 2.5% methanolic potassium hydroxide (0.25 ml.) was added. The solution was refluxed for 1 hr. under nitrogen. The reaction mixture was neutralized with acetic acid and poured into water. Extraction of the aqueous solution with methylene chloride and evaporation gave a solid, m.p. 238–258°. Crystallization from acetone–petroleum ether gave the diol XIII (23 mg.), m.p. 266–270°; $[\alpha]^{26}D$ ±0° (chloroform); λ_{max} 237 mμ (ε 13,100); ν_{max} 3450, 1712 (sh.), 1698, and 1610 cm.$^{-1}$. This material was identical to the diol prepared by the procedure described below.

6α,17α-Dihydroxy-6β-methylpregn-4-ene-3,20-dione (XIV).—A solution of 17α-acetoxy-6α-hydroxy-6β-methylpregn-4-ene-3,20-dione (XII, 0.1 g.) in methanol (10 ml.) and 2.5% methanolic potassium hydroxide (0.5 ml.) was refluxed 1 hr. under nitrogen. After being neutralized with acetic acid, the reaction mixture was concentrated at reduced pressure and then poured into water. The solid was collected and crystallized several times from acetone–petroleum ether to give the pure diol (32 mg.), 238–243°, raised to 245–247° when dried *in vacuo* at 80° for 12 hr., $[\alpha]^{25}D$ +51° (chloroform); λ_{max} 242 mμ (ε 14,600); ν_{max} 3420, 1703, 1665, 1612, and 1230 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_4 \cdot {}^1/_2C_3H_6O$: C, 72.46; H, 9.06. Found: C, 72.40; H, 9.17.

17α-Acetoxy-6-methylpregna-4,6-diene-3,20-dione (XV).—A. 17α-Acetoxy-6α-hydroxy-6β-methylpregn-4-ene-3,20-dione (XII, 0.25 g.) was dissolved in a solution of acetic acid (10 ml.), acetic anhydride (2.5 ml.) and *p*-toluenesulfonic acid monohydrate (0.25 g.). After standing overnight at room temperature, the reaction mixture was poured into water and filtered. Crystallization of this material from acetone–petroleum ether gave the dienone XV (0.182 g.); m.p. 215–216°; $[\alpha]^{25}D$ +8° (chloroform); λ_{max} 289 mμ (ε 24,200); ν_{max} 1742, 1722, 1675, 1640, 1592, 1268, and 1250 cm.$^{-1}$, lit.,[10] m.p. 218–220°; $[\alpha]D$ +11°; λ_{max}^{EtOH} 289 mμ (ε 24,000).

B. 17α-Acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XII, 50 mg.) was dissolved in acetic acid (5 ml.) and refluxed for 1 hr. The reaction mixture was cooled, poured into water, and the solid collected (25 mg.), m.p. 199–205°. Crystallization from acetone–petroleum ether gave the dienone, m.p. 205–211°. This was identical to material isolated by method A.

C. A solution of 17α-acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XI, 0.25 g.) in acetic anhydride (2.5 ml.), acetic acid (10 ml.), and *p*-toluenesulfonic acid monohydrate (0.25 g.) was allowed to stand at room temperature for 17 hr. The reaction mixture was poured into water and filtered. Crystallization of this material gave 0.181 g., m.p. 209–213°, identical to the compound isolated by method A.

17α-Acetoxy-6α-hydroxy-6β-methylpregna-1,4-diene-3,20-dione (XVI).—17α-Acetoxy-6α-hydroxy-6β-methylpregn-4-ene-3,20-dione (XII, 0.3 g.) was dissolved in dry dioxane (25 ml.) and to this solution was added 2,3-dichloro-5,6-dicyanobenzoquinone (0.3 g.). The reaction mixture was refluxed for 20 hr., cooled and the hydroquinone separated by filtration. The filtrate was evaporated and the residue was dissolved in ethyl acetate. This solution was washed with water, cold 1% sodium hydroxide solution, and saturated saline solution, dried, and evaporated. The residue was crystallized from acetone–petroleum ether to give 0.165 g., m.p. 271–273°. After two more crystallizations it had m.p. 282–284°; $[\alpha]^{25}D$ −7° (chloroform); λ_{max} 245 mμ (ε 15,400); ν_{max} 3460, 1732 (broad), 1667, 1227, 1255, and 1230 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{32}O_5$ (400.50): C, 71.97; H, 8.05. Found: C, 71.63; H, 7.75.

17α-Acetoxy-6β-hydroxy-6α-methylpregna-1,4-diene-3,20-dione (XVII).—A solution of 17α-acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XI, 1.5 g.) in dioxane (15 ml.) was refluxed with 2,3-dichloro-5,6-dicyanobenzoquinone (1.06 g.) for 72 hr. and cooled. The precipitated hydroquinone was collected and the filtrate evaporated. The residue was dissolved in ether and washed with water, cold 1% aqueous sodium hydroxide solution, and saturated saline solution. After being dried, the ether extract was evaporated to give a crystalline residue which was recrystallized from acetone–petroleum ether affording 0.945 g., m.p. 239–241°; $[\alpha]^{25}D$ −30° (chloroform); λ_{max} 244 mμ (ε 18,200); ν_{max} 3500, 1740, 1718, 1669, 1638, 1262, and 1252 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{32}O_5$ (400.50): C, 71.97; H, 8.05. Found: C, 71.65; H, 8.34.

3,17α-Diacetoxy-1,6-dimethyl-19-norpregna-1,3,5(10),6-tetraen-20-one and 17α-Acetoxy-6-methylpregna-1,4,6-triene-3,20-dione (XVIII and XX).—A mixture of 17α-acetoxy-6β-hydroxy-6α-methylpregna-1,4-diene-3,20-dione (XVII, 0.3 g.), acetic anhydride (10 ml.), and *p*-toluenesulfonic acid monohydrate (0.25 g.) was allowed to stand at room temperature for 20 hr. It was then poured into water and filtered to give a solid (0.29 g.)

which was dissolved in a minimum amount of benzene and chromatographed on a synthetic magnesium silicate. The material eluted with the last 2% acetone–petroleum ether fraction (25 ml.) and with the 3% acetone–petroleum ether (6 × 25 ml.) fractions was combined and crystallized from aqueous methanol to give 0.105 g., m.p. 148–150°. Another crystallization raised the m.p. to 149–151°; $[\alpha]^{25}D$ −111° (chloroform); λ_{max} 222, 228, and 265 mμ (ε 31,000, 28,300, and 8900); $\lambda_{max}^{Basic\ MeOH}$ 238 and 322 mμ (ε 34,300 and 2460); ν_{max} 1780, 1750, 1605, 1267, 1256 (sh), and 1215 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{32}O_5$ (424.52): C, 73.56; H, 7.60. Found: C, 73.16; H, 7.76.

On further development of the column there was obtained a second crystalline fraction eluted in later 7% acetone–petroleum ether (3 × 25 ml.) and the 10% acetone–petroleum ether (6 × 25 ml.) fractions. Crystallization of this combined material from acetone–petroleum ether gave 70 mg., m.p. 206–208°. Another crystallization raised the m.p. 213–215°; $[\alpha]^{25}D$ −29° (chloroform); λ_{max} 227, 252, and 304 mμ (ε 14,700, 11,200, and 9600); ν_{max} 1742, 1722 (sh), 1667, 1620, 1590, 1267, and 1251 cm.$^{-1}$; lit.,[10] m.p. 225–227°; $[\alpha]D$ −38°; λ_{max}^{EtOH} 228, 253, and 304 mμ (ε 13,000, 11,700, and 9120).

Anal. Calcd. for $C_{24}H_{30}O_4 \cdot {}^1/_2C_3H_6O$: C, 74.42; H, 8.08. Found: C, 74.25, 74.41; H, 8.22, 8.31.

17α-Acetoxy-3-hydroxy-1,6-dimethyl-19-norpregna-1,3,5(10),6-tetraen-20-one (XIX).—3,17α-Diacetoxy-1,6-dimethyl-19-norpregna-1,3,5(10),6-tetraen-20-one (XVIII, 60 mg.) in methanol (10 ml.). Nitrogen was bubbled through the mixture and then 10% aqueous potassium carbonate (0.5 ml.) was added. The nitrogen stream was continued for 45 min. and then the solution was neutralized with acetic acid. The solvents were partially removed *in vacuo* and the mixture was filtered to give 40 mg., m.p. 240–245°. After two crystallizations from acetone–petroleum ether there was obtained 32 mg., m.p. 251–252°; $[\alpha]^{30}D$ −92° (chloroform); λ_{max} 225, 265, 275, and 305 mμ (ε 27,700, 7400, 6100, and 2140); $\lambda_{max}^{Basic\ MeOH}$ 237 and 322 mμ (ε 29,900 and 2200); ν_{max} 3450, 1728, 1718 (sh), 1612, 1590, 1280, and 1265 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 74.98, 74.82; H, 8.38, 8.13.

3,20-Bisethylenedioxy-6-methylpregn-5-en-17α-ol (XXII).—17α-Hydroxy-6α-methylpregn-4-ene-3,20-dione (XXI, 1.1 g.) was dissolved in a solution of benzene (50 ml.) and ethylene glycol (3.0 ml.). After the addition of *p*-toluenesulfonic acid (10 mg.), the reaction mixture was refluxed with constant water removal for 24 hr., cooled, and then washed with aqueous sodium bicarbonate and water. Evaporation of the dried extract gave the bisketal (1.2 g.) as a white crystalline solid, m.p. 213–218°. Repeated crystallizations from methanol raised the m.p. to 224–226°; ν_{max} 3560, 3500, 1465, 1375, 1265, 1185, 1100, 1073, and 1045 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_5 \cdot C_3H_6O$: C, 70.98; H, 9.45. Found: C, 71.23, 71.14; H, 9.26, 9.49.

5α,6α-Epoxy-3,20-bisethylenedioxy-6β-methylpregnan-17α-ol (XXIII).—A solution of 3,20-bisethylenedioxy-6-methylpregn-5-en-17α-ol (XXII, 1.0 g.) was dissolved in methylene chloride (100 ml.) and refluxed with an ethereal 0.62 *N* monoperphthalic acid solution (10 ml.) for 3 hr. and then allowed to remain at room temperature overnight. The reaction mixture was washed with an aqueous sodium bicarbonate solution, water, and then dried. Evaporation of the solvent left a white solid (0.44 g.), m.p. 259–262°. After crystallization from acetone–petroleum ether, the product melted at 265–267°; $[\alpha]^{25}D$ +6° (dioxane); ν_{max} 3600, 3450, 2960, 1465, 1368, 1362, 1178, 1105, 1085, 1070, and 1035 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_6$ (448.58): C, 69.61; H, 8.99. Found: C, 69.84; H, 9.36.

5α,6β,17α-Trihydroxy-6α-methylpregnane-3,20-dione (XXIV).—To a suspension of 5α,6α-epoxy-3,20-bisethylenedioxy-6β-methylpregnan-17α-ol (XXIII, 0.1 g.) in acetone (4 ml.) was added a 1.5 *N* aqueous perchloric acid solution (0.4 ml.). The reaction mixture was shaken to dissolve suspended material and then the solution was allowed to remain at room temperature for 2 hr. It was then neutralized with excess aqueous sodium bicarbonate. Evaporation of the organic extract afforded the triol XXIV (80 mg.), m.p. 220–235°. Repeated crystallization of this material from ethanol–petroleum ether (90–100°) gave XXIV (21 mg.), m.p. 243–246°; ν_{max} 3460, 2980, 1705, 1460, 1385, 1310, 1215, 1135, and 1085 cm.$^{-1}$; $[\alpha]^{25}D$ −21° (chloroform).

Anal. Calcd. for $C_{22}H_{34}O_5 \cdot {}^1/_2H_2O$: C, 68.18; H, 9.10. Found: C, 68.91, 68.78; H, 9.55, 9.04.

6β,17α-Dihydroxy-6α-methylpregn-4-ene-3,20-dione (XIII).—A. Methanolic potassium hydroxide (2.5%—1.0 ml.) was added to a solution of 5α,6β,17α-trihydroxy-6α-methylpregnane-3,20-dione (XXIV, 224 mg.) in methanol (10 ml.). After being refluxed for 1 hr. the solution was cooled, neutralized with acetic acid, and concentrated almost to dryness. The addition of water to the residue gave the diol XIII which was separated and dried, 165 mg., m.p. 266–270°. Repeated crystallization from acetone–petroleum ether raised the melting point to 270–271°; λ_{max} 237–238 mμ (ε 13,800); ν_{max} 3500, 2930, 1700, 1680, 1610, 1380, 1360, 1230, 1145, 1125, and 1075 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_4 \cdot {}^1/_2C_3H_6O$: C, 72.46; H, 9.06. Found: C, 72.32, 72.06; H, 9.17, 8.77.

B. A solution of 17α-acetoxy-5α,6β-dihydroxy-6α-methylpregnane-3,20-dione (XXVIII, 128 mg.) in methanol (5 ml.) was refluxed for 1 hr. with methanolic potassium hydroxide (2.5%—0.5 ml.). The product was isolated as above and on crystallization there was obtained XIII (25 mg.), m.p. 271–274°. This was identical to the material prepared by procedure A.

17α-Acetoxy-5α,6α-epoxy-3β-hydroxy-6β-methylpregnan-20-one (XXVI).—To a solution of 17α-acetoxy-3β-hydroxy-6-methylpregn-5-en-20-one (XXV, 0.5 g.) in methylene chloride (50 ml.) was added 0.62 *N* monoperphthalic acid–ether solution (5.0 ml.) and the mixture was refluxed for 2 hr., cooled, and washed with a saturated sodium bicarbonate solution and water. The dried ether extract was evaporated leaving a gum which became crystalline on trituration with ether. Crystallization from acetone–petroleum ether gave the epoxide XXVI (409 mg.), m.p. 204–207°; $[\alpha]^{25}D$ −48° (chloroform); ν_{max} 3460, 2960, 1740, 1445, 1380, 1255, 1082, 1055, and 1015 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_5$ (404.53): C, 71.25; H, 8.97. Found: C, 70.96; H, 9.28.

17α-Acetoxy-3β,5α,6β-trihydroxy-6α-methylpregnan-20-one (XXVII).—Perchloric acid (1.5 N—5.0 ml.) was added to a solution of 17α-acetoxy-5α,6α-epoxy-3β-hydroxy-6β-methylpregnan-20-one (XXVI, 1.5 g.) in acetone (60 ml.). After 2 hr. at room temperature, the solution was neutralized with an aqueous sodium bicarbonate solution, and the organic solvent was removed by distillation *in vacuo*. Water was added to the resultant residue and the solid was collected by filtration. After being washed thoroughly with water, the material was dried to give the triol XXVII (1.7 g.), m.p. 220–230°. The melting point was raised to 241–243° after several crystallizations from acetone–petroleum ether; $[\alpha]^{25}D$ −51° (chloroform); ν_{max} 3400, 2925, 1710, 1450, 1375, 1260, 1145, and 1075 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{38}O_6 \cdot C_3H_6O$: C, 67.47; H, 9.23. Found: C, 66.93, 67.20; H, 9.26, 9.35.

17α-Acetoxy-5α,6β-dihydroxy-6α-methylpregnane-3,20-dione (XXVIII).—17α-Acetoxy-3β,5α-6β-trihydroxy-6α-methylpregnan-20-one (XXVII, 1.0 g.) was dissolved in reagent acetone (distilled from potassium permanganate) (100 ml.). Under a nitrogen atmosphere, 8 *N* chromic acid in 8 *N* sulfuric acid (1.3 ml.) was added to the above solution. The oxidation was allowed to proceed for 2 min., the mixture was poured into water, and the acetone removed at reduced pressure. The resulting white solid was collected, washed with water, and dried to give XXVIII (0.74 g.), m.p. 247–250°. Crystallization from acetone–petroleum ether raised the melting point to 250–252°; $[\alpha]^{25}D$ −9° (chloroform); ν_{max} 3450, 2930, 1712, 1375, 1263, 1140, and 1078 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_6 \cdot C_3H_6O$: C, 67.75; H, 8.85. Found: C, 68.27, 67.86, 67.56; H, 9.09, 9.03, 8.83.

17α-Acetoxy-6β-hydroxy-6α-methylpregn-4-ene-3,20-dione (XI).—A stream of dry hydrogen chloride was passed through a solution of 17α-acetoxy-5α,6β-dihydroxy-6α-methylpregnane-3,20-dione (XXVIII, 0.2 g.) in methylene chloride (50 ml.) maintained at 5°. After 75 min. the excess hydrogen chloride was removed by a stream of nitrogen bubbled through the reaction mixture. The methylene chloride solution was washed with an aqueous sodium bicarbonate solution and with water. After drying, evaporation of the solvent *in vacuo* gave a crystalline residue (112 mg.), m.p. 188–190°. Repeated crystallizaton from acetone–petroleum ether afforded XI (47 mg.), m.p. 216–217° dec.; $[\alpha]^{25}D$ +1° (chloroform); λ_{max} 235 mμ (ε 14,400); ν_{max} 3440, 2960, 1740, 1660, 1615, 1370, 1260, 1250, 1145, 1120, and 1078 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_5 \cdot C_3H_6O$: C, 70.40; H, 8.63. Found: C, 69.97, 70.76, 70.05; H, 8.81, 8.95, 8.40.

17α-Acetoxy-3β-hydroxy-5β-methyl-A-homo-B-norpregnane-4a,20-dione (XXIX).—A. A solution of 17α-acetoxy-5α,6α-epoxy-3β-hydroxy-6β-methylpregnan-20-one (XXVI, 0.3 g.) in methylene chloride (5 ml.) was cooled to −60° and to this was added a cooled solution (−60°) of tetrahydrofuran (1.1 ml.), methylene chloride (0.5 ml.), and anhydrous hydrogen fluoride (0.8 ml.). After being kept at −5° for 5 hr., the solution was poured carefully into a saturated sodium bicarbonate solution. The organic phase was separated, and the aqueous layer was extracted with methylene chloride. The combined organic solutions were washed with water and dried. Evaporation left an amorphous residue which was dissolved in a small amount of benzene and added to a column of synthetic magnesium silicate (12 g.). Elution with 3% acetone–petroleum ether gave a crude crystalline material. Crystallization from acetone–petroleum ether yielded XXIX (118 mg.), m.p. 189–190°. This melting point was raised to 194–196° by several crystallizations, λ_{max} none; $[\alpha]^{25}D$ −30° (chloroform); ν_{max} 3350, 2940, 1730, 1695, 1445, 1370, 1255, and 1045 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_5$ (406.54): C, 71.25; H, 8.97. Found: C, 70.66; H, 9.33.

B. Boron trifluoride in ether (20 ml.) was added to a solution of XXVI (1.9 g.) in ether (100 ml.) and benzene (100 ml.). After 18 hr. the solution was neutralized with saturated sodium bicarbonate solution. The organic phase was separated, washed with water, and dried. Evaporation of the solvent afforded a gum which was dissolved in anhydrous ether and seeded with material obtained from procedure A above. In this manner a crystalline product (1.2 g.) was obtained, m.p. 174–184°. Crystallization from acetone–petroleum ether gave XXIX (0.62 g.), m.p. 195–197°, identical to the product obtained by procedure A.

17α-Acetoxy-5β-methyl-A-homo-B-norpregnane-3,4a,20-trione (XXX).—To a solution of 17α-acetoxy-3β-hydroxy-5β-methyl-A-homo-B-norpregnane-4a,20-dione (XXIX, 0.1 g.) in reagent acetone (distilled from potassium permanganate) (2 ml.) was added 8 *N* chromic acid in 8 *N* sulfuric acid dropwise until the orange color of the oxidizing agent persisted. The solution was poured into water and filtered. Two crystallizations of the solid from acetone–petroleum ether provided XXX (55 mg.), m.p. 239–240°; $[\alpha]^{25}D$ −104° (chloroform); $\lambda_{max}^{Basic\ MeOH}$ 300 mμ (ε 18,100); ν_{max} 1740, 1720, 1700, 1262, and 1248 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{38}O_5$ (402.51): C, 71.61; H, 8.51. Found: C, 71.46; H, 8.64.

17α-Hydroxy-5β-methyl-A-homo B-norpregnane-3,4a,20-trione (XXXI).—5α,6α - Epoxy - 3,20 - bisethylenedioxy - 6β - methylpregnan - 17α - ol (XXIII, 0.2 g.) was suspended in acetone (8 ml.) and 72% perchloric acid (2 drops) was added. Solution was effected immediately. The mixture after 2 hr. at room temperature was treated with dilute sodium bicarbonate solution, and the solid which separated was collected by filtration and washed with water. This material was crystallized several times from acetone–water to give XXXI (30 mg.), m.p. 194–196°; $[\alpha]^{25}D$ −124° (chloroform); $\lambda_{max}^{Basic\ MeOH}$ 300 mμ (ε 18,600); ν_{max} 3460, 2970, 1720, 1695, 1390, 1355, 1200, and 1080 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_4$ (360.48): C, 73.30; H, 8.95. Found: C, 73.17; H, 9.33.

Synthesis of α-Amino-γ-hydroxy Acids: γ,γ′-Dihydroxyvaline

EUGENE GALANTAY, ATTILA SZABO, AND JOSEF FRIED

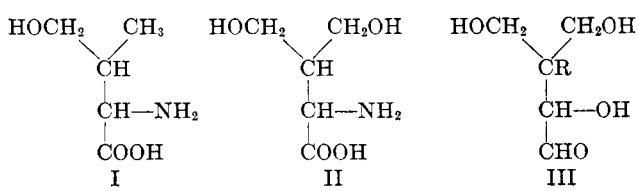
The Squibb Institute for Medical Research, New Brunswick, New Jersey

Received July 27, 1962

γ-Hydroxyvaline (I) and γ,γ′-dihydroxyvaline (II) have been prepared by a modified Erlenmeyer synthesis. The geometry of the intermediate azlactones IVb and IVc and of the corresponding benzoylamino acrylic esters VIIb and VIIc has been determined.

Until a few years ago, homoserine was the only α-amino-γ-hydroxy acid known with certainty to occur in Nature. Recently, however, a prodigious number of such compounds has been detected, both in free form and as peptide constituents and their chemistry has been the subject of considerable study.[1]

We wish to describe a simple synthetic method leading to α-amino acids with chain branching in the beta position and carrying hydroxyl groups in one or both of the gamma positions. The method offers an alternate synthesis for γ-hydroxyvaline (I), recently isolated from crowngall tumors of *Kalanchoe daigremontiana* and synthesized from α-chloro-β-methyl-γ-butyrolactone.[2] More importantly, however, it has permitted us to prepare a new, otherwise difficulty accessible amino acid, γ,γ′-dihydroxyvaline (II). Although this compound has not been found to occur naturally, closely related structures like the sugars cordicepose and apiose (III. R = H and OH respectively) have been isolated,[3] and the role of γ,γ′-dihydroxyvaline itself as a possible biogenetic precursor of the antibiotic Cephalosporin C has been discussed.[4] The method of synthesis is based on the observation that the Erlenmeyer azlactone synthesis, although seldom practicable with ketones,[5] can be successfully extended to the acetates of α-hydroxy and α,α′-dihydroxy ketones by applying the modified conditions of Baltazzi and Robinson.[5c] Thus, by using equimolecular amounts of ketone and hippuric acid, three moles of acetic anhydride, lead(II) acetate as a base, and tetrahydrofuran as the solvent, the azlactones IV are formed in practical yields, readily isolable by crystallization.[6]



The exocyclic double bond in compounds IV can be hydrogenated (palladium–charcoal, dioxane) to give the "dihydro," azlactones V with little or no hydrogenolysis of the allylic acetate groups and the azlactones hydrolyzed with hydrochloric acid to the aminohydroxy acid lactone hydrochlorides VI, which can then be converted to the free amino acids by treatment with ammonia.

(1) For reviews, see Th. Wieland, *Angew. Chem.*, **72**, 892 (1960); H. Musso, *ibid.*, **68**, 313 (1956); A. I. Virtanen, *ibid.*, **67**, 381 (1955).

(2) J. K. Pollard, E. Sondheimer, and F. C. Steward, *Nature*, **182**, 1356 (1958).

(3) W. G. Overend, M. Stacey in "Advances in Carbohydrate Chemistry," Vol. 8, Academic Press Inc., New York, N. Y., 1953, p. 52; C. S. Hudson, *ibid.*, Vol. 4, 1949, p. 57.

(4) E. P. Abraham and G. F. Newton, *Biochem. J.*, **79**, 377 (1961).

(5) (a) H. E. Carter, *Org. Reactions*, **III**, 206 (1946); (b) J. W. Cornforth in "Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 730 ff; (c) E. Baltazzi and R. Robinson, *Chem. Ind.* (London), 191 (1954).

(6) Substitution of 2-phenyl-2-oxazolin-5-one [J. M. Stewart and D. W. Woolley, *J. Am. Chem. Soc.*, **78**, 5336 (1956)] for hippuric acid did not improve the yields.