Acid-Catalyzed Cyclization of 21-Benzylidene-16-dehydropregnenolone Acetate

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21-Benzylidene-16-dehydropregnenolone acetate was cyclized with $HClO_4$ both in the presence and absence of trimethyl orthoformate to give methoxy (hydroxy) compounds with a new ring fused between the side chain and the steroid nucleus. The degradation of the new ring in order to demonstrate the structure of the compounds is also reported.

Some examples of the formation, in steroids, of a new ring fused to ring D in positions 16 and 17 have appeared recently in the literature.[1] In the present study, the reaction of 21-benzylidene-16-dehydropregnenolone acetate (I) in dioxane with catalytic amounts of $HClO_4$, both in the presence and absence of trimethyl orthoformate and small quantities of methanol, has been investigated. From this reaction, a steroid with a new pentacyclic ring has been isolated. This paper reports its structure and proposes a mechanism of formation for this ring. As far as we know the reaction reported represents a new type of cyclization in the steroid field.

21-Benzylidene-16-dehydropregnenolone acetate[2] (I) reacted in dioxane with $HClO_4$ to give the compound II; the structure assigned to compound II is supported by uv spectral data, (compound I absorbs at 308 mμ, while the product II shows no absorption above 220 mμ) and by the ir spectrum of II which has an OH band at 3500 cm^{-1}, a carbonyl band at 1750 cm^{-1} assigned to a carbonyl group in a pentacyclic ring, and a band at 1740 cm^{-1} due to the carbonyl group of the 3 acetate.

If the cyclization of I was carried out with $HClO_4$ in the presence of trimethyl orthoformate, compound III was obtained; its ir spectrum, compared with the spectrum of II, exhibited a band at 1100 cm^{-1} (saturated ether) and no hydroxylic band.

Furthermore, the monoacetyl derivative II, treated with diazomethane in the presence of BF_3, gave III, thus demonstrating the relationship between the methoxylated and hydroxylated series.

If small quantities of methanol were added to the reaction mixture of I with trimethyl orthoformate and $HClO_4$ in dioxane, compound VIa was obtained.[3] This product by refluxing in acetone in the presence of aqueous HCl gave compounds IV and V. These two compounds were interconvertible into the 3 acetates III and II, respectively, by the hydrolysis–acetylation sequence; the fact that only one hydroxyl group of compound V was acetylated by the acetic anhydride–pyridine reagent supports the hypothesis of the presence of a tertiary hydroxy group. See Scheme I.

The infrared spectrum of VIa showed C=O and C—O stretching frequencies of the acetyl group at 1730 and 1250 cm^{-1}, a C=C stretching band at 1660 cm^{-1}, and a saturated ether band at 1100 cm^{-1}. The corresponding 3 alcohol, VIb, besides the bands at 1660 and 1100 cm^{-1}, showed a band at 1240 cm^{-1} assigned to a vinylic ether. The presence of these functional groups was also supported by the nmr spectrum of VIa, which presented three singlets at δ 1.95 (3 H, CH_3COO), 3.06 (3 H,CH_3—O—C—C), 3.70 (3 H,CH_3—O—C=C), and a doublet at 4.95 (1 H,C=CH—CH, J = 2.5 Hz).

From the spectral data given above, the presence of a cyclopentane ring with a hydroxy (ethereal) substituent is indicated; compounds II–V have a carbonyl group in this ring. Since compound VI, the enol form of III, showed, in the nmr, a doublet at δ 4.95 (J = 2.5 Hz) (an olefinic H coupled with a tertiary H in the α position), a CH_2 group must be adjacent to the carbonyl function. (The stereochemistry will be discussed later.)

In order to confirm this formula and to establish the position of the hydroxyl (ethereal) group, product II was converted into a known compound. Condensation of II with ethyl formate in the presence of NaH gave the hydroxymethylene derivative VII; its formation confirmed the presence of an activated CH_2 group.

By H_2O_2–NaOH[4] oxidation of VII, the acid VIII was isolated (but not purified and fully characterized); the presence in crude VIII of two COOH groups was confirmed by alkalimetric titration. This acid, when oxidized with $NaBiO_3$ in aqueous acetic acid,[5] gave the keto acid IXa, which was characterized as the acetoxymethyl ester IXb. Unfortunately, the C=O stretching frequency of the ester group overlapped that of the C=O pentacyclic absorption in ring D, but the latter was evident in the infrared spectrum of the sodium salt of IXa which showed, besides the band at 1580 (R—COO^-), a band at 1735 cm^{-1}.

The formation of IXa by $NaBiO_3$ oxidation of VIII demonstrated that compound VIII is an α-hydroxy acid, and hence that the hydroxy group was in the C-17 position. This fact was also supported by the failure to eliminate the hydroxy or methoxy group in II or III, respectively, with acid or base.

Treatment of the acid IXa with copper chromite in quinoline[6] in order to decarboxylate it, furnished the known[7] 16-benzylidenedehydroisoandrosterone (X), identical with an authentic sample prepared by condensing benzaldehyde with dehydroisoandrosterone; evidently the action of copper chromite induced a dehydrogenation in addition to the decarboxylation. See Scheme II.

We turned, then, to determine the stereochemistry of the new asymmetric centers. The newly formed ring junction must be *cis* because *trans*-fused pentacyclic

(1) F. v. Werder, K. H. Bork, K. Irmscher, B. Hampel, and K. Brueckner, *Ann. Chem.*, **685**, 218 (1965); J. M. Allison, D. Burn, F. K. Butcher, M. T. Davies, and V. Petrow, *Tetrahedron*, **23**, 1515 (1967).

(2) Condensation of 20-keto-21-methyl derivatives of steroids with benzaldehyde has been reported: W. M. Hoehn and H. L. Mason, *J. Amer. Chem. Soc.*, **60**, 1493 (1938); R. E. Marker and E. L. Wittle, *ibid.*, **61**, 1329 (1939).

(3) These are the conditions generally used for the preparation of enol ethers from α,β-unsaturated carbonyl groups.

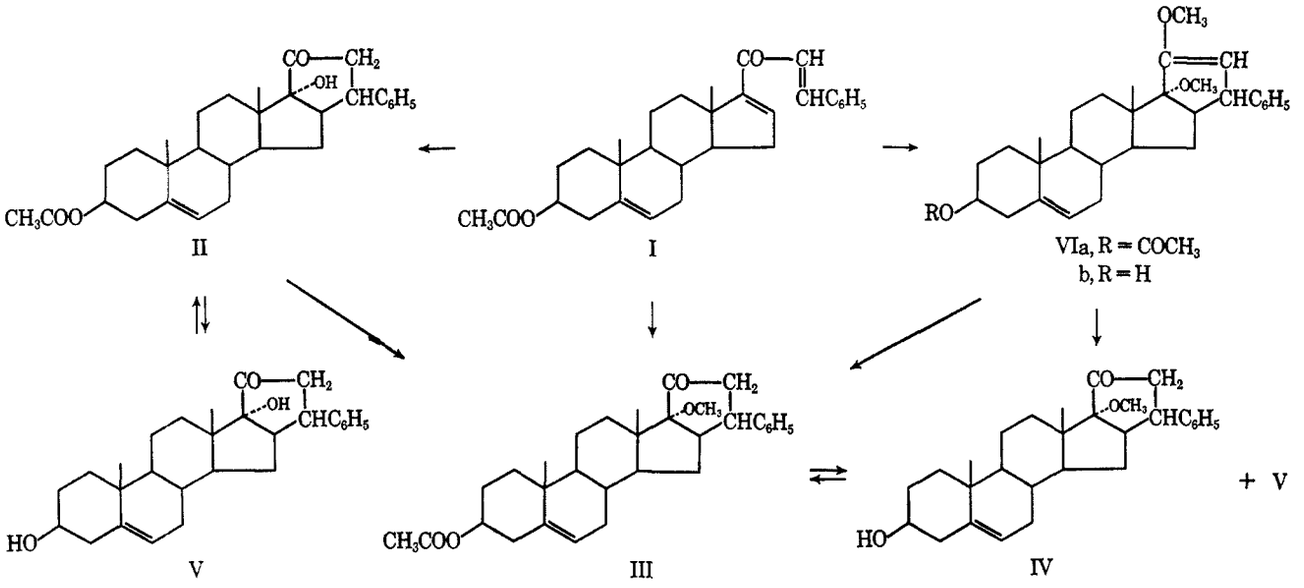
(4) H. Hanna, T. Rüll, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1209 (1961).

(5) B. Camerino and U. Valcavi, *Gazz. Chim. Ital.*, **93**, 723 (1963).

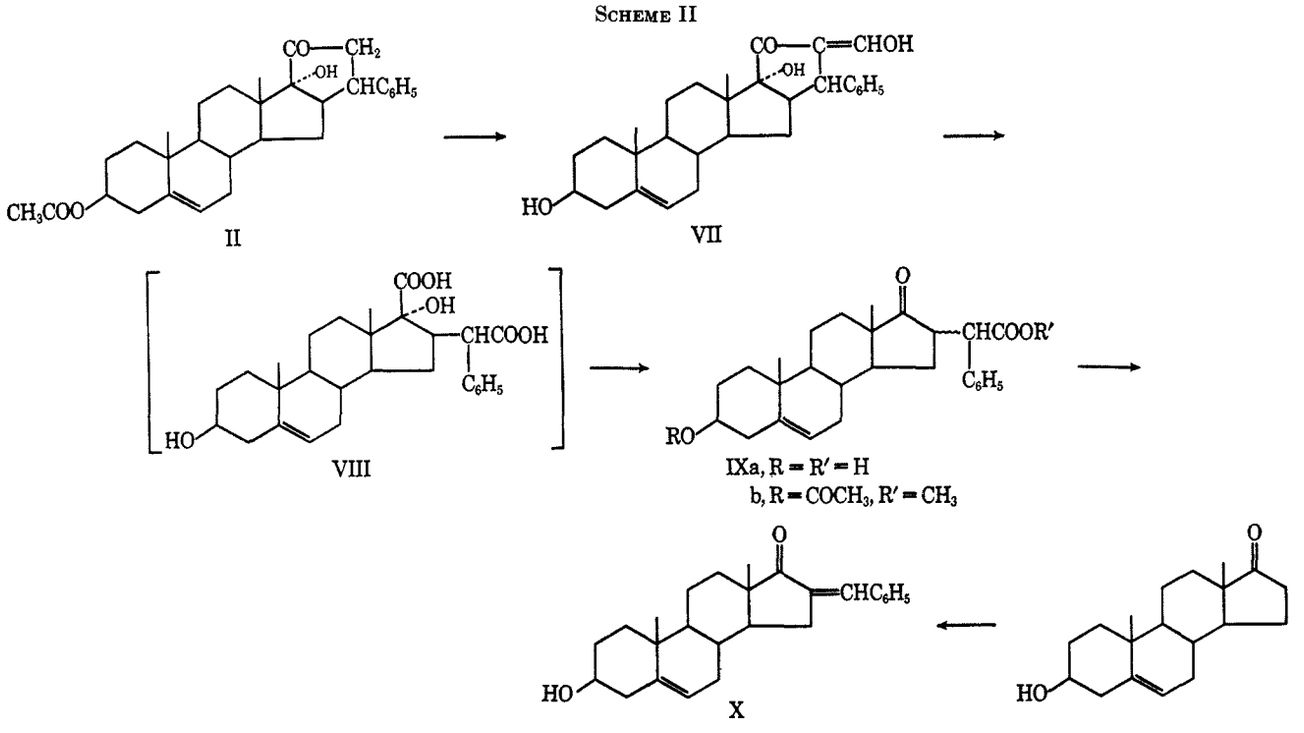
(6) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., New York, N. Y., 1967.

(7) L. Velluz and A. Petit, *Bull. Soc. Chim. Fr.*, **12**, 949 (1945).

SCHEME I



SCHEME II



rings are highly strained[8] and it is very improbable that a *trans* junction could be formed by direct cyclization. This *cis* junction may be either 16α,17α or 16β,17β.

The ORD curve of the compound II exhibited a negative Cotton effect and application of the octant rule to the molecular models indicated that in a β,β fusion the major portion of the ring system fell into a negative octant. Compound III showed a weak, positive Cotton effect superimposed on a negative plain dispersion curve which may be attributed to the asymmetry introduced in the environment of the keto group by the CH_3 of the ether group, which lies in a positive octant.[9]

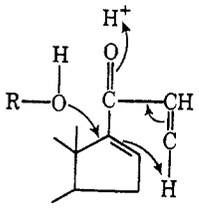
As for the configuration of the phenyl group, we suggest that, since this cyclization gave rise to a double-bond shift, the reaction will be thermodynamically controlled. Thus, the phenyl nucleus will lie in the less sterically hindered position, *e.g.*, for a β,β junction, the α position; in this configuration, also, the phenyl group lies in a negative octant.

The nmr spectrum of compound II is in accord with the assignment of a β,β junction between rings D and E. The resonance of the C-18 methyl group occurs at 44 cps (in CCl_4) while this peak is to be expected, in the 17α isomer, at 60 cps;[10,11] in fact in the latter conformation the 18-methyl group lies in the area, where the keto

(8) N. L. Wendler in "Molecular Rearrangement," part II, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter 16.
(9) M. Tomoeda and J. Yoshizawa, *Tetrahedron Lett.*, 975 (1967).
(10) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).
(11) J. E. Pike, G. Slomp, and F. A. MacKellar, *J. Org. Chem.*, **28**, 2502 (1963).

group causes a downfield shift, whereas in that of the β isomer it lies in the shielding cone of the ketone.

A possible mechanism for the cyclization is the following.



In acidic medium, the protonation of the carbonyl group is followed by a shift of the double bond and introduction of a hydroxy or a methoxy group from the α side.

Some examples of the cyclization of cross-conjugated ketones which probably occur by the mechanism proposed above, are described in the literature.[12,13] In the cases reported, the presence of a double bond instead of a methoxy (or hydroxy) group is probably due to the expulsion of a proton from the intermediate carbonium ion.

Experimental Section[14]

21-Benzylidene-pregna-5,16-dien-3β-ol-20-one Acetate[2] (I).—A solution of KOH (10 g) in 80% aqueous *t*-butyl alcohol (100 cc) was added to a warm solution of 16-dehydropregnenolone acetate (30 g) in 90% *t*-butyl alcohol (300 cc) and benzaldehyde (20 cc), and the reaction mixture was refluxed with stirring, under nitrogen, for 2 hr and then kept at room temperature overnight. The solid reaction product, 21-benzylidene-pregna-5,16-dien-3β-ol-20-one (29.5 g, mp 172–177°) was obtained by filtration, followed by washing with 50% *t*-butyl alcohol and water. Acetylation with acetic anhydride (30 cc) and pyridine (150 cc) at room temperature for 20 hr afforded, after the usual work-up, I (23.5 g): mp 164–166 and 173–174°; $[\alpha]_D$ −64.5°; uv max 308 mμ (ϵ 19,240).

Anal. Calcd for $C_{30}H_{36}O_3$: C, 81.28; H, 8.22. Found: C, 81.04; H, 8.16.

3β-Acetoxy-17α-hydroxy-1′-phenyl-16α,17α-(16,17-propanoandrost-5-en)-3′-one (II).—A solution of 21-benzylidenepregna-5,16-dien-3β-ol-20-one acetate (11 g) in anhydrous dioxane (100 cc), was treated overnight at room temperature with 70% $HClO_4$ (2.5 cc). Pyridine (5 cc) was then added, the reaction mixture was diluted with NaCl solution, and the steroid was extracted with ethyl acetate; the organic layers were washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was dissolved in benzene and chromatographed on Florisil (150 g). Elution with benzene afforded crude II which, when crystallized from acetone–ethyl ether–petroleum ether, afforded 7.5 g of II with mp 182–185°. Recrystallization from methanol furnished the analytical sample: mp 187–190°; $[\alpha]_D$ −110°; ir (KBr), 3500, 1750, 1740, 1250 cm^{-1}; nmr ($CDCl_3$), δ 1.08 (3 H) and 0.80 (3 H); ORD (*c* 1%, $CHCl_3$), $[\Phi]_{700}$ −377°, $[\Phi]_{400}$ −1510°, $[\Phi]_{310}$ −9620°, $[\Phi]_{292}$ −990°.

Anal. Calcd for $C_{30}H_{38}O_4$: C, 77.89; H, 8.28; mol wt, 462.61. Found: C, 77.83; H, 8.10; mol wt (benzene), 466.

3β-Acetoxy-17α-methoxy-1′-phenyl-16α,17α-(16,17-propanoandrost-5-en)-3′-one (III). A. From 21-Benzylidenepregna-5,16-dien-3β-ol-20-one Acetate (I).—Perchloric acid (70%) (1 cc) was added to a solution of the steroid I (5 g) in anhydrous dioxane (50 cc) and trimethyl orthoformate (5 cc) and the solution was allowed to stand at room temperature for 2 hr. Pyridine (2 cc) and water were then added to the reaction mixture and the product was extracted with ethyl ether; the extract was washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude product which, crystallized from methanol–ether, afforded III (650 mg, mp 203–206°). Recrystallization from methanol furnished the analytical sample: mp 220–223°; $[\alpha]_D$ −78°; nmr, δ 7.22 (5 H), 3.30 (3 H), 1.97 (3 H), 1.03 (3 H) and 0.99 (3 H); ORD (*c* 0.2%, $CHCl_3$), $[\Phi]_{700}$ −285°; $[\Phi]_{389}$ −860°; $[\Phi]_{353}$ +310°; $[\Phi]_{341}$ −2410°; $[\Phi]_{313}$ −571°.

Anal. Calcd for $C_{31}H_{40}O_4$: C, 78.09; H, 8.53. Found: C, 78.11; H, 8.42.

The mother liquors were evaporated to dryness; the crude residue (4.5 g) was dissolved in acetone (450 cc); water (45 cc) and concentrated hydrochloric acid (4.5 cc) were added; and the reaction mixture was heated under reflux for 10 hr. The solution was then concentrated under vacuum to one-third of its volume; water was added; and the product was isolated by extraction with ethyl acetate. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness, and the residue was dissolved in benzene and chromatographed on Florisil. Elution with benzene–ether (9:1) furnished a crude compound which crystallized from methanol to give the product (1.3 g) of mp 160–162°, identical with compound IV (see below) by comparison of their infrared spectra and by the fact that the mixture melting point showed no depression.

B. From 17α-Methoxy-1′-phenyl-16α,17α-(16,17-propanoandrost-5-en-3β-ol)-3′-one (IV).—A solution of IV (50 mg) in pyridine (0.5 cc) and acetic anhydride (0.2 cc) was allowed to stand at room temperature for 20 hr and water was added. III, which was precipitated (50 mg), was identical with the compound obtained by procedure A.

C. From 3β-Acetoxy-17α-hydroxy-1′-phenyl-16α,17α-(16,17-propanoandrost-5-en)-3′-one (II).—To a solution of II (500 mg) in CH_2Cl_2 (30 cc) and BF_3–etherate (0.05 cc), a solution of CH_2N_2 in CH_2Cl_2 (30 cc) prepared from 5 g of nitrosomethylurea was added at 0° and the reaction mixture was stirred at room temperature for 30 min. After treatment with acetic acid, the organic layer was washed with water and dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was crystallized from acetone–petroleum ether and melted at 216–218°; it was identical with the compound prepared by procedures A and B.

D. From 3β-Acetoxy-3′,17α-dimethoxy-1′-phenyl-16α,17α-(16,17-propanoandrost-2′,5-diene) (VIa).—A 2.3-g sample of VIa was heated at reflux with acetone (230 cc) and 5% hydrochloric acid (25 cc) for 4 hr; the solution was concentrated and diluted with water; and the compound was extracted with ethyl acetate. The combined extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness. The solid residue (2.1 g) was allowed to react with acetic anhydride (2 cc) and pyridine (10 cc) at room temperature for 20 hr. The solution was then diluted with water and the steroid extracted with ethyl acetate and worked up in the usual way. Crystallization from acetone–petroleum ether gave III (1.5 g) having mp 213–218°, identical with the compound obtained by procedures A, B, and C.

17α-Methoxy-1′-phenyl-16α,17α-(16,17-propanoandrost-5-en-3β-ol)-3′-one (IV) and 1′-Phenyl-16α,17α-(16,17-propanoandrost-5-ene-3β,17α-diol)-3′-one (V).—A solution of VIa (500 mg) in acetone (50 cc), water (9 cc), and concentrated HCl (1 cc) was heated under reflux for 20 hr. It was then concentrated to one-third of its volume, and the product was extracted with ethyl ether. The organic layer was washed with 5% sodium bicarbonate solution and water and dried over anhydrous Na_2SO_4. The residue (450 mg), obtained by evaporation of the solvent, was a mixture of two compounds which were separated by preparative thin layer chromatography on silica gel, followed by extraction with acetone. The less polar compound that crystallized from methanol afforded IV (130 mg): mp 161–163°; $[\alpha]_D$ −59° (CH_3OH).

Anal. Calcd for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81. Found C, 80.25; H, 8.87.

The more polar compound, crystallized from acetone–petroleum ether (bp 40–70°), gave V (20 mg) with mp 214–222°; ir (KBr) 3400, 1750 cm^{-1}.

Anal. Calcd for $C_{28}H_{36}O_3$: C, 79.96; H, 8.63. Found C, 79.75; H, 8.58.

Compound V was also obtained by refluxing compo und II in alkaline methanolic solution. Reacetylation of V afforded starting material II.

(12) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 1430 (1952).

(13) E. A. Braude and W. F. Forbers, *ibid.*, 2208 (1953).

(14) All melting points were determined on a Fisher-Johns block and are uncorrected. The ultraviolet spectra were carried out in ethanolic solution. The infrared spectra were run as KBr pellets. Unless otherwise noted, all rotations were measured in chloroform solution (*c* 1%) at the sodium D line. The nmr spectra were obtained on a Varian A-60 spectrometer using TMS as an internal standard. The ORD curves were obtained on a Rudolph spectropolarimeter using $CHCl_3$ as the solvent.

3β-Acetoxy-3′-17α-dimethoxy-1′-phenyl-16α,17α-(16,17-propanoandrost-2′,5-diene) (VIa).—To a solution of 21-benzylidenepregna-5,16-dien-3β-ol-20-one acetate (I, 6 g) in anhydrous dioxane (60 cc) and anhydrous methanol (0.6 cc), trimethyl orthoformate (6 cc) and 70% $HClO_4$ (0.06 cc) were added. The solution was kept at room temperature until the ultraviolet absorption disappeared; after 2 hr pyridine was added; the reaction mixture was poured into water; and the product was isolated by extraction with ethyl ether. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness. Crystallization from methanol afforded VIa (3.2 g) with mp 137–139°. An analytical sample of VIa was obtained by further recrystallization from the same solvent: mp 138–140°; $[\alpha]D$ −127°; ir (KBr), 1730, 1600, 1100 cm^{-1}; nmr (CCl_4), δ 1.95 (3 H), 3.06 (3 H), 3.70 (3 H), 4.95 (1 H, J = 2.5 Hz).

Anal. Calcd for $C_{32}H_{42}O_4$: C, 78.33; H, 8.63; mol wt, 494.66. Found: C, 78.42; H, 8.62; mol wt (dioxane), 498.

Alkaline hydrolysis of VIa carried out in methanolic solution at room temperature gave the 3 alcohol VIb; its ir spectrum in KBr showed bands at 1660 (C=C), 1240 (vinylic ether), and 1100 cm^{-1} (saturated ether).

1′-Phenyl-2′-hydroxymethylen-16α,17α-(16,17-propanoandrost-5-ene-3β,17α-diol)-3′-one (VII).—To a solution of 3β-acetoxy-17α-hydroxy-1′-phenyl-16α,17α-(16,17-propanoandrost-5-en)-3′-one (II) in anhydrous dioxane (30 cc) and ethyl formate (2 cc), under nitrogen, 2 g of a 50% dispersion of NaH in mineral oil was added, and the reaction mixture was stirred at room temperature for 2 hr. An additional 1 g of NaH was added, and the solution was allowed to stir overnight at room temperature. The excess NaH was then destroyed with methanol; the reaction mixture was diluted with ethyl acetate; and the steroid was extracted with 3% NaOH solution. Acetic acid was added to the aqueous layer, and the steroid was extracted with ethyl acetate. Evaporation of the solvent gave a crude residue which, after two crystallizations from acetone, afforded VII: mp 255–256°; $[\alpha]D$ −48° (dioxane); uv max, 283 mμ (ε 10,000); red color with $FeCl_3$.

Anal. Calcd for $C_{29}H_{36}O_4$: C, 77.64; H, 8.09. Found: C, 77.75; H, 8.28.

(3β-Acetoxyandrost-5-en-17-one-16ξ-yl)-phenylacetic Acid Methyl Ester (IXb).—To a solution of KOH (12.5 g) in water (350 cc), the steroid VII (2.5 g) and 35% H_2O_2 (35 cc) were added, the reaction mixture was stirred at room temperature for 2 hr; a further 5 cc of H_2O_2 was added; and the mixture was stirred overnight. Addition of acetic acid, extraction with ethyl acetate, washing with $FeSO_4$ and water, and drying over anhydrous Na_2SO_4 gave crude VIII (2.4 g). This was then dissolved in 60% aqueous acetic acid (150 cc), and the solution was stirred with $NaBiO_3$ (20 g) for 20 hr at room temperature, filtered to remove inorganic salts, ice cooled, and treated with 10% KOH solution (1 l.). The steroid was extracted with CH_2Cl_2, and the organic layers, after washing with water, drying over anhydrous Na_2SO_4, and evaporating to dryness, afforded the crude IXa (1.2 g); the ir spectrum of the Na salt showed bands at 1735 and 1580 cm^{-1}. This crude product was dissolved in CH_2Cl_2 (30 cc) and treated with diazomethane solution in CH_2Cl_2 (30 cc) prepared from nitrosomethylurea (2.5 g). This solution was kept at room temperature for 1 hr, acetic acid (2 cc) was then added, and the solution was washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness. The crude residue was allowed to react in pyridine (5 cc) acetic anhydride (1 cc) solution at room temperature overnight; the solution was diluted with water and extracted with ethyl acetate. The organic layers were washed with water, dried over anhydrous Na_2SO_4, and evaporated, giving crude IXb which, after crystallization from acetone–petroleum ether, gave 350 mg of pure product: mp 210–216°; $[\alpha]D$ −93°; ir (KBr), 1740, 735, 700 cm^{-1}; nmr, δ 7.30 (5 H), 3.55 (1 H, J = 8 Hz), 1.85 (3 H), 1.00 (3 H), 0.95 (3 H).

Anal. Calcd for $C_{30}H_{38}O_5$: C, 75.28; H, 8.00. Found: C, 74.85; H, 7.99.

16-Benzylideneandrost-5-en-3β-ol-17-one (X).[6]—A suspension of IXb (300 mg) in methyl alcohol (25 cc), was refluxed with a solution of $KHCO_3$ (300 mg) in water (5 cc). The steroid gradually went into solution and, after 1 hr, acetic acid was added. The solution was concentrated and then diluted with water; the steroid was extracted with ethyl acetate; and the organic layer, after washing with water, drying over anhydrous Na_2SO_4, and evaporation, afforded crude IXa (270 mg) which was dissolved in quinoline (5 cc) and treated with copper chromite (270 mg) reflux for 30 min. The reaction mixture was diluted with ethyl acetate, filtered with the aid of Celite, washed with hydrochloric acid, dilute $NaHCO_3$ solution, and water, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was dissolved in benzene–petroleum ether (8:2) and chromatographed on Florisil (10 g); elution with benzene–ethyl ether (9:1) gave a crude product which, crystallized from acetone–petroleum ether, afforded 16-benzylideneandrost-5-en-3β-ol-17-one (X): mp 193–197°; $[\alpha]D$ −33.5°; uv max, 295 mμ (ε 20,800); ir (KBr), 3200, 1720, 1640 cm^{-1}. 16-Benzylideneandrost-5-en-3β-ol-17-one was prepared by reaction of dehydroisoandrosterone with benzaldehyde: mp 201–203°; $[\alpha]D$ −29°; uv max, 295 mμ (lit.[6] mp 209–210°; $[\alpha]D$ −26.5°); this compound was shown to be identical with compound X, by comparison of their infrared spectra and by mixture melting point.

Registry No.—21-Benzylidenepregna-5,16-dien-3β-ol-20-one, 17243-77-5; I, 17243-78-6; II, 17243-79-7; III, 17243-80-0; IV, 17243-81-1; V, 17243-82-2; VIa, 17278-19-2; VIb, 17243-83-3; VII, 17243-84-4; IXa, 17243-86-6; IXb, 17243-85-5; X, 17243-87-7.

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