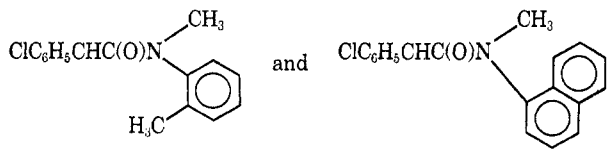
rotation as the exchange mechanism. The data in Table II for I show that the exchange rate is essentially independent of solvent and dielectric constant. This solvent independence argues against an ionic activated state. On the other hand, this independence is consistent with rotation. These compounds may vary in their degree of association with solvent from solvent to solvent. However, it is difficult to imagine that the energy of this association varies more than a few hundred small calories. It is even less likely that a rotational activated state should associate with solvents very differently from the ground state.

The increased exchange barrier for III, IV, and V as compared to I and II also is consistent with rotation. The free energy of exchange (ΔF^*) for III is about 80% of the sum of ΔF^*'s for I and II. It might have been supposed that $\Delta F^*_{III} = \Delta F^*_{II} + \Delta F^*_{I}$; however, there probably is sufficient distortion of the molecule to allow these groups to come into maximum steric conflict with the *ortho* hydrogen atoms of the fluorene nucleus one at a time rather than absolutely simultaneously. Bond distortion is accepted as the principal means of steric relief for rotation in biphenyls.[9]

The difference, $\Delta F^*_{II} - \Delta F^*_{I} \simeq 1.7$ kcal/mol, is very close to the similar difference (1.4 kcal/mol) noted for rotation around the aryl–nitrogen bond in the following compounds.[7] The larger "size" of the fused ring



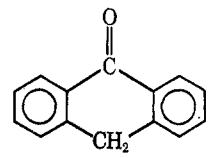
may be due in part to its increased rigidity over the methyl group.

Substitution in the *meta* position may be too remote from the rotational axis to slow rotation down to the pmr time scale. Compound VI gave no evidence of slow rotation even at −85° (dissolved in CH_2Cl_2). The absence of detectable slow rotation in VI is consistent with the similar observation for rotation around the aryl–nitrogen bond in *meta*-substituted anilides.[10] There is a possibility that rotation is slow in VI but cannot be detected by pmr. If one isomer predominated over the other by a large factor, the minor isomer would not be observable, especially at low temperature where viscosity effects broaden signals.

The entropy of activation for site exchange is a small negative quantity for these compounds. The average of ΔS^* (calculated for transmission coefficient = 1) for I for all solvents is −6 eu. (We do not regard the apparent differences from solvent to solvent as real. ΔF^* from signal shape analysis is a much more accurate quantity than E_a.[11]) ΔS^* for III is +2 eu. Because the data for III depend on reequilibration experiments, this value is probably more significant than those obtained for I. Small negative entropies of activation were found for rotation around the aryl–nitrogen bond in *ortho*-substituted anilides.[10,12] It seems reasonable that small entropies of activation must be the rule for intramolecular processes. It is difficult to visualize any large restraint or lack of it in the activated state for rotation, for example, as compared to the ground state. Except where the activated state may be a triplet state, small entropies of activation are the rule for first-order gas reactions[13] and for isomerization of olefins in the liquid state.[14]

The Role of the Fluorene Nucleus in Slow Rotation.—We believe that, as Adams[3] supposed, the fluorene nucleus plays a vital role in making rotation slow in these molecules. As Adams pointed out, molecular models show that unjoined and unfixed aromatic rings are free to rotate in a synchronous manner. However, it seems likely that the work of Akkerman and Coops[15] with α-diarylcarboxylic acids can be extended to various triarylmethanes and derivatives and that sufficiently large *ortho* substituents alone will slow the rotation even for unfixed systems. However, the synthesis of such compounds may present some formidable problems.

Carbinols and triarylmethanes derived from anthrone



would represent an interesting intermediate state between the rigid, fixed fluorene nucleus, and a completely unfixed triaryl array. The extra flexibility permitted by the interposed CH_2 group should decrease the barrier to rotation as compared to the barrier in fluorene derivatives. We have, however, been unable to prepare the carbinols from anthrone by conventional Grignard syntheses.

Registry No.—I, 18181-25-4; II, 18153-38-3; III, 18153-39-4; IV, 18153-40-7; V, 18153-41-8; *meta* VI, 18153-42-9; *para* VI, 18153-43-0; VII, 18153-44-1.

(9) F. H. Westheimer, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, Chapter 12.
(10) T. H. Siddall, III and W. E. Stewart, *J. Phys. Chem.*, **73**, 40 (1969).
(11) A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *J. Amer. Chem. Soc.*, **88**, 3185 (1966).
(12) B. J. Price, J. A. Eggleston, and I. O. Sutherland, *J. Chem. Soc., B*, 922 (1967).
(13) V. N. Kondratev, "Kinetics of Gas Reactions," Academy of Sciences USSR, Moscow, 1958.
(14) R. B. Cundall, "Progress in Kinetics," Vol. 2, G. Porter, Ed., The MacMillan Co., New York, N. Y., 1964, Chapter 4.
(15) O. S. Akkerman and J. Coops, *Rec. Trav. Chim. Pays-Bas*, **86**, 755 (1967).

The Preparation of 3β-Acetoxy-17β-hydroxy-5α-androstane-16α-propionic Acid δ-Lactone

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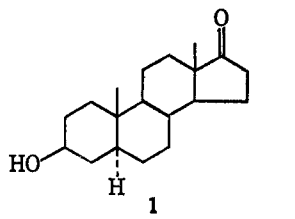
Received July 11, 1968

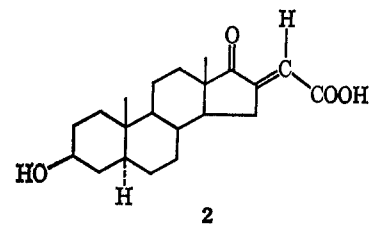
In previous studies it was found that steroidal 17β-hydroxy-16β-acetic acids[1,2] and 17β-hydroxy-16β-propionic acids[3] were readily converted into the corresponding *cis*-fused γ- and δ-lactones, respectively. In contrast, the formation of the *trans*-fused γ-lac-

(1) P. Kurath and W. Cole, *J. Org. Chem.*, **26**, 1939 (1961).
(2) P. Kurath and W. Cole, *ibid.*, **26**, 4592 (1961).
(3) P. Kurath and W. Cole, *ibid.*, **28**, 102 (1963).

CHART I



1



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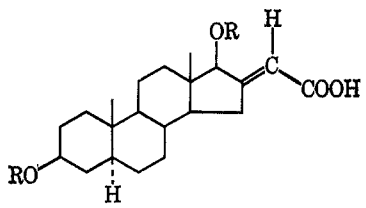
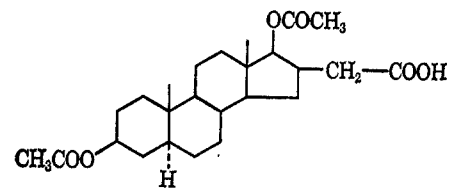


3a, R = H
b, R = CH_3CO



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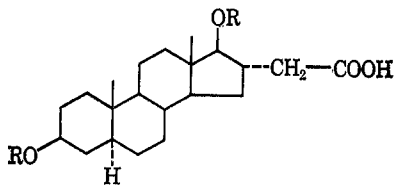
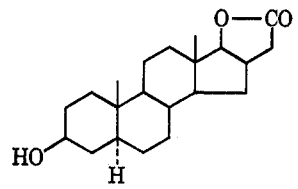
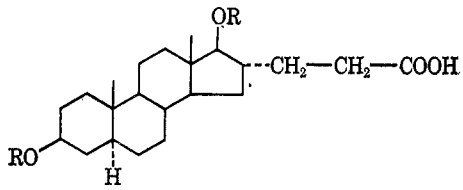


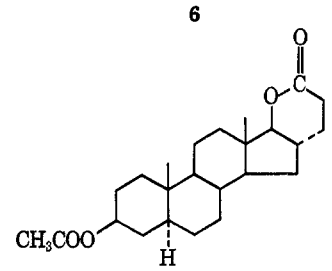
5a, R = H
b, R = CH_3CO



6



7a, R = H
b, R = CH_3CO



8

tones from 17β-hydroxy-16α-acetic acids did not occur.[4,5]

The question of ease of formation of the *trans*-fused δ-lactones from steroidal 17β-hydroxy-16α-propionic acids was raised, since Valcavi and Sianesi[6] assigned the *cis* stereochemistry to a series of δ-lactones on the basis of their ease of formation.[7] Our examination of molecular models suggested that *trans*-fused δ-lactones might be readily formed from steroidal 17β-hydroxy-16α-propionic acids. In order to test our working hypothesis we decided to prepare the title compound.

The key intermediate in the proposed synthesis, 3β,17β-dihydroxy-5α-androstan-16α-acetic acid (**5a**)[4,8] was prepared from 3β-hydroxy-5α-androstan-17-one (**1**)[9] according to our previously described procedure.[1,2] The condensation of **1** with glyoxylic acid[10] led to the isolation of the α,β-unsaturated keto acid **2** (Chart I). Sodium borohydride reduction of **2** afforded the dihydroxy acid **3a**, and the latter was converted into the diacetate **3b**. Catalytic hydrogenation of **3b** led to the isolation of 3β,17β-diacetoxy-5α-androstan-16β-acetic acid (**4**)[1] by direct crystallization in 78% yield. The residue contained in the mother liquors resulting from the purification of **4** was subjected to alkaline hydrolysis, and subsequent acidification of the reaction mixture was followed by the separation of the desired 3β,17β-dihydroxy-5α-androstan-16α-acetic acid (**5a**) (15% yield) from a small amount of the γ-lactone **6**.[1]

The 3β,17β-diacetoxy-5α-androstan-16α-acetic acid (**5b**),[4] prepared by acetylation of **5a**, was converted into its acid chloride which in turn was allowed to react with diazomethane to yield the corresponding diazoketone. Treatment of the latter in benzyl alcohol solution with 2,4,6-trimethylpyridine at elevated temperature[11] and hydrolysis of the resulting intermediate led to the isolation of 3β,17β-dihydroxy-5α-androstane-16α-propionic acid (**7a**). Warming of **7a** in a solution of acetic anhydride and acetic acid[6] led to the formation of 3β-acetoxy-17β-hydroxy-5α-androstane-16α-

(4) P. Kurath, W. Cole, J. Tadanier, M. Freifelder, G. R. Stone, and E. V. Schuber, *J. Org. Chem.*, **28**, 2189 (1963).

(5) W. Hückel and W. Gelmroth, *Ann.*, **514**, 233 (1934); see footnotes 2 and 3 in ref 4.

(6) U. Valcavi and I. L. Sianesi, *Gazz. Chim. Ital.*, **93**, 803 (1963); *cf.* U. Valcavi, *ibid.*, **93**, 794, 929 (1963).

(7) Subsequently, direct comparison of 3β,17β-dihydroxyandrost-5-ene-16β-propionic acid δ-lactone and two of its derivatives prepared by the Italian workers[6] with the corresponding compounds made in this laboratory[3] established the identity of the two series of compounds obtained by different synthetic routes. Dr. Valcavi has informed us in his letter of April 14, 1964, that the optical rotation reported[6] for his hydroxy lactone is in error. We express our gratitude to Dr. Valcavi for the opportunity to exchange samples for comparison.

(8) Ö. K. J. Kovács, A. F. Aboulezz, and B. Matkovics, *Acta Chim. Acad. Sci. Hung.*, **48**, 241 (1966).

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(10) M. S. Newman, W. C. Sagar, and C. C. Cochrane, *J. Org. Chem.*, **23**, 1832 (1958); ref 1 and 2.

(11) A. L. Wilds and A. L. Meader, Jr., *ibid.*, **13**, 763 (1948); ref 3.

propionic acid δ-lactone (**8**) which was separated from a small amount of the diacetate **7b**.

The carbonyl absorption in the infrared spectrum of the 16α-propionic acid lactone **8** was observed at 1723 cm^{-1} while the corresponding absorption of the 16-epimeric 3β-acetoxy-17β-hydroxy-5α-androstane-16β-propionic acid δ-lactone[3] was reported at 1721 cm^{-1}. The low values of these bands led us to assign the half-chair conformation to the δ lactones (reported values 1730–1750 cm^{-1}) rather than the half-boat conformation which is characterized by higher values for the carbonyl absorptions (1758–1765 cm^{-1}).[12]

Comparison of the chemical shifts of the C_{18}-methyl protons of the lactone **8** and 3β-acetoxy-17β-hydroxy-5α-androstane-16β-propionic acid lactone at 51.5 and 50.5 Hz, respectively, suggested that the C_{18}-angular methyl groups in these compounds occupied similar environments. This observation is consistent with the proposal of the half-chair conformations of the δ-lactone rings which result in similar special arrangements of the lactone carbonyls and the C_{18}-methyl groups for both compounds. The 17α-proton signal of the lactone **8** is found as a doublet centered at 222 Hz (J = 8.5 Hz) while the corresponding doublet for the 16β epimer is centered at 256 Hz (J = 9.5 Hz).

The infrared absorption of the lactone carbonyls and the nmr results support the planar conformation of the five atoms C–C(=O)—O—C in the lactone ring which was recently demonstrated by single-crystal X-ray studies[12,13] as well as by optical rotatory dispersion and circular dichroism investigations.[14]

This work demonstrates that both *cis*-fused[3] and *trans*-fused δ-lactones are readily formed from the corresponding steroidal 17β-hydroxy-16-propionic acids.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus. Optical rotations were measured with a Hilger and Watts polarimeter, and the infrared spectra were obtained with a Perkin-Elmer 521 grating spectrophotometer in chloroform solutions unless stated otherwise. The ultraviolet spectra were measured in methanol solutions. The nmr spectra were recorded with a Varian A-60 nmr spectrometer at 60 MHz; 5–10% solutions in deuteriochloroform (unless otherwise stated) were employed using tetramethylsilane as an internal reference. Chemical shifts are reported in hertz from tetramethylsilane (0 Hz) in the direction of decreasing field.

3β-Hydroxy-17-oxo-5α-androstan-Δ$^{16,\alpha}$-acetic Acid (2).—A solution of 12.00 g of *d*-tartaric acid in 15 ml of water was added to an agitated suspension of 18.20 g of potassium *m*-periodate in 2.15 ml of concentrated sulfuric acid and 96 ml of water at 5°. The reaction mixture was vigorously stirred for 1 hr at 30–35° and then at 5° for 0.5 hr. Precipitated inorganic material was removed by filtration. A solution of 12.00 g of sodium hydroxide in 80 ml of water was added to the above prepared glyoxylic acid solution with vigorous stirring, and this was followed by the addition of a solution of 23.00 g of 3β-hydroxy-5α-androstan-17-one (**1**) in 450 ml of methanol. The mixture was stirred at room temperature for 1.5 hr, and then refluxed for 3 hr. The solution was poured into 1 l. of ice–water; a small amount of unreacted **1** was removed by extraction with ether. The alkaline phase was acidified to pH 2 by the dropwise addition of concentrated hydrochloric acid.[15] The yellow precipitate was separated by filtration, washed with water, and dried under reduced pressure to yield 22.60 g of the crude condensation product **2**. Recrystallization of the compound from methanol–water gave 20.70 g (75%) of fluffy, pale yellow needles, mp 220–222° with previous softening at 150–165°.

An analytical sample was obtained from methanol–water: mp 222.5–224°; $[\alpha]^{25}D$ −24° (c 0.73); λ_{max} 241 nm (ε 11,700); $\tilde{\nu}_{max}$ 3680, 3604, 3505, 2700–2400, 1720, 1690, 1649, 1632, 1592 cm^{-1}.

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.59; H, 8.99.

3β,17β-Dihydroxy-5α-androstan-Δ$^{16,\alpha}$-acetic Acid (3a).—To a solution of 11.49 g of the keto acid **2** in 540 ml of methanol cooled to 5° there was added dropwise with stirring a solution of 4.60 g of sodium borohydride in 16 ml of water over a period of 10 min. The colorless solution was allowed to reach room temperature and was then refluxed for 0.5 hr. After cooling, 110 ml of a 25% sodium hydroxide solution was added. Most of the methanol was removed under vacuum, 300 ml of water being added during evaporation. The resulting slurry was made acidic by the addition of 2 *N* hydrochloric acid, and the precipitated shiny platelets were collected on a filter, washed with water and dried under reduced pressure to yield 11.20 g of **3a**: mp 326–327° (evacuated capillary); $\tilde{\nu}_{max}^{Nujol}$ 3350 (sh), 3250 (broad), 2700–2400, 1676, 1645 cm^{-1}. The insolubility of this compound in the usual laboratory solvents precluded its recrystallization. A sample was submitted for analysis.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.23; H, 9.34.

3β,17β-Diacetoxy-5α-androstan-Δ$^{16,\alpha}$-acetic Acid (3b).—A solution of 11.00 g of the dihydroxy acid **3a** in 35 ml of acetic anhydride and 70 ml of pyridine was allowed to stand at room temperature overnight. The solution was then slowly diluted with 35 ml of water and warmed on the steam bath for 2 hr. The pale yellow solution was slowly poured into 700 ml of ice–water with stirring; the colorless precipitate was separated by filtration and washed with water. The product was dissolved in ether and the ether solution was washed with 2 *N* hydrochloric acid and water, dried over sodium sulfate, filtered, and evaporated to give 12.70 g of the crude diacetate **3b**. This compound was recrystallized from methanol–water to afford 11.50 g of colorless needles, mp 216.5–218°.

An analytical sample had the following physical properties: mp 217.5–219.5°; $[\alpha]^{27}D$ −88° (c 1.08); λ_{max} 218 nm (ε 12,800); $\tilde{\nu}_{max}$ 2700–2400, 1720, 1684, 1648 cm^{-1}.

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.41; H, 8.39. Found: C, 69.72; H, 8.33.

3β,17β-Diacetoxy-5α-androstan-16β-acetic Acid (4) and 3β,-17β-Dihydroxy-5α-androstan-16α-acetic Acid (5a).—A total of 54.26 g of 3β,17β-diacetoxy-5α-androstan-Δ$^{16,\alpha}$-acetic acid (**3b**) was hydrogenated in several portions over a 10% ratio of platinum oxide in acetic acid and worked up in the manner described for the reduction of the corresponding 5-unsaturated Δ$^{16,\alpha}$-acetic acid[1] to yield a first crop of 42.18 g (78%) of the known saturated 16β-acetic acid **4**,[1] mp 244–246°. A second crop of 10.32 g, mp 192–194°, and 1.43 g of oily residue represented a mixture of the 16β- and the 16α-acetic acids[4] (**4** and **5b**).

The second crop material (10.32 g) and the oily residue (1.43 g) from the above experiment were combined, hydrolyzed in a potassium hydroxide solution, and worked up by acidification and extraction with ethyl acetate.[4] Concentration and cooling of the ethyl acetate extract led to the isolation of 7.32 g (yield 15% based on **3b**) of the acid **5a**, mp 273–275°, which was identical with a reference sample of **5a**.[4] From the mother liquor residue, 2.16 g, the known lactone **6**[1] (0.68 g), mp 232–235°, was obtained after chromatography and recrystallization from acetone. The later chromatographic fractions were shown to contain a small additional amount of **5a**.

3β,17β-Diacetoxy-5α-androstan-16α-acetic Acid (5b).—A 26.18-g sample of the dihydroxy acid **5a** was converted into 25.87 g (80%) of the diacetoxy acid **5b**,[4] mp 205–206.5°, in the usual manner.

3β,17β-Dihydroxy-5α-androstane-16α-propionic Acid (7a).—A mixture of 3.08 g of 3β,17β-diacetoxy-5α-androstan-16α-acetic

(12) K. K. Cheung, K. H. Overton, and G. A. Sim, *Chem. Commun.*, 634 (1965).

(13) J. F. McConnell, A. McL. Mathieson, and B. P. Schoenborn, *Tetrahedron Lett.*, 445 (1962); A. McL. Mathieson, *ibid.*, 81 (1963); G. A. Jeffrey, R. D. Rosenstein, and M. Vlasse, *Acta Cryst.*, **22**, 725 (1967); J. S. McKechnie and I. C. Paul, *J. Amer. Chem. Soc.*, **90**, 2144 (1968).

(14) (a) J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 7211, 7229 (1965); C. G. De Grazia, W. Klyne, P. M. Scopes, D. R. Sparrow, and W. B. Whalley, *J. Chem. Soc., C*, 896 (1966); (b) H. Wolf, *Tetrahedron Lett.*, 5151 (1966); (c) M. Legrand and R. Bucourt, *Bull. Soc. Chim. Fr.*, 2241 (1967).

(15) We thank Mr. Gerhard Diemer, Development Department, Abbott Laboratories, for the modifications of the original procedure.[10]

acid (**5b**), 1.3 ml of thionyl chloride, 3 drops of pyridine, and 300 ml of anhydrous ether was stirred at room temperature for 3 hr.[16] The reaction mixture was freed from a small amount of insoluble residue by filtration. The solvent was evaporated at 30–40° under reduced pressure, and several small portions of ether were added and likewise removed. A colorless residue of 3.12 g of the crude acid chloride, mp 137–142°; $\tilde{\nu}_{max}$ 1794, 1725 cm^{-1}, was isolated.

The acid chloride prepared as described above was dissolved in 75 ml of cold methylene chloride and added over a period of 20 min to an ice-cold solution of diazomethane, made from 11.48 g of N-nitrosomethylurea and 45 ml of a 40% potassium hydroxide solution in 240 ml of methylene chloride,[17] according to the procedure of Wettstein.[18] The resulting solution was allowed to stand at room temperature overnight, flushed with a stream of nitrogen, and filtered. The solvent was removed under reduced pressure at 40–50°, several small portions of methylene chloride were added and evaporated to leave an oil, 3.73 g, of crude yellow diazo ketone, $\tilde{\nu}_{max}$ 2100, 1720, 1632 cm^{-1}.

A mixture of the above prepared diazo ketone, 20 ml of 2,4,6-trimethylpyridine, and 20 ml of benzyl alcohol in a nitrogen atmosphere was immersed into an oil bath heated to 190–200°[11] and allowed to react for 15 min. The solution was cooled, ether was added, and the ether extract was washed with 2 *N* hydrochloric acid and water, dried, and evaporated to leave a solution of the crude reaction product in benzyl alcohol. This solution was diluted with 80 ml of methyl alcohol and 20 ml of water, 4.00 g of potassium hydroxide was added, and the solution was refluxed for 2 hr. The alkaline reaction mixture was diluted with 500 ml of water and the resulting solution was extracted with ether, the ether solution was extracted with several portions of 0.2 *N* sodium hydroxide solution and water and then discarded. The alkaline phase was made acidic by the addition of 2 *N* hydrochloric acid and warmed on the steam bath for 30 min. The suspension was allowed to cool, the precipitate was collected on a filter, washed with water, and dried at 80° under reduced pressure to yield 1.82 g of cream-colored dihydroxy acid **7a**, mp 219–223° dec.

An analytical sample of **7a** was obtained as a powder from acetone–water: mp 223–225° dec; $\tilde{\nu}_{max}^{Nujol}$ 3600–3100, 2700–2400, 1696 cm^{-1}; nmr (DMSO) 39 (C_{13}-methyl), 45 (C_{10}-methyl), 265 Hz (broad peak, 2 H, exchangeable with D_2O).

Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.62; H, 10.09.

3β-Acetoxy-17β-hydroxy-5α-androstane-16α-propionic Acid δ-Lactone (8).—A solution of 0.50 g of the dihydroxypropionic acid **7a** in 9 ml of acetic anhydride and 13 ml of glacial acetic acid was heated on the steam bath for 2 hr.[6] The solution was cooled and slowly diluted with water. The precipitate was collected on a filter, washed with water, and dried under vacuum at 80° to yield 0.41 g of beige solid. The material was chromatographed on a column prepared from 50 g of silica gel in benzene. The residues from the benzene–ethyl acetate (19:1) eluates amounted to 0.32 g of the lactone **8** as a colorless solid. Recrystallization of this substance from acetone–*n*-hexane gave 0.27 g of colorless needles: mp 212.5–213.5°; $[\alpha]^{24}D$ +41° (*c* 1.00); $\tilde{\nu}_{max}$ 1723 cm^{-1}; nmr 50.5 (C_{10}-methyl), 51.5 (C_{13}-methyl), 122 (acetate methyl), 217.5 and 226 (d, J = 8.5 Hz, 17α-H), 285 Hz ($W_{1/2}$ ~20 Hz, 3α-H).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.47; H, 9.34.

Further elution of the column with benzene–ethyl acetate (9:1, 4:1, and 1:1) gave 0.07 g of a mixture which was shown by tlc to contain the lactone **8** and the diacetoxypropionic acid **7b** described below.

3β,17β-Diacetoxy-5α-androstane-16α-propionic Acid (7b).—A sample of the dihydroxypropionic acid **7a** was acetylated in acetic anhydride–pyridine and worked up in the usual manner. The product of the reaction was separated into a neutral and an acidic fraction. A small sample of the above described lactone **8** was obtained from the neutral fraction and purified by recrystallization and sublimation, mp 212.5–214°.

The acidic fraction was purified by chromatography on silica gel. The benzene–ethyl acetate (4:1) eluates contained the desired 3β,17β-diacetoxy-5α-androstane-16α-propionic acid (**7b**) which was recrystallized from methanol–water and acetone–hexane. An analytical sample had the following physical constants: mp 156.5–157.5; $[\alpha]^{24}D$ −56° (*c* 0.62); $\tilde{\nu}_{max}$ 2700–2400, 1715 cm^{-1}; nmr 47 (C_{13}-methyl), 49.5 (C_{10}-methyl), 122 and 124 (acetate methyls), 270 and 277 (*d*, J = 7 Hz, 17α-H), 285 Hz ($W_{1/2}$ ~20 Hz, 3α-H).

Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.54; H, 8.85.

(16) W. Cole and P. L. Julian, *J. Amer. Chem. Soc.*, **67**, 1369 (1945).
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Metabolites of *Clitocybe illudens*. IV.[1] Illudalic Acid, a Sesquiterpenoid, and Illudinine, a Sesquiterpenoid Alkaloid

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The structures of illudalic acid (I) and illudinine (II) reported here (Chart I) are both derivable from the same basic "protoilludane" skeleton (III) as those of illudin S and M,[1a,b] illudol[1c] and marasmic acid.[3] Illudalic acid was isolated as "a fourth crystalline compound"[4] accompanying illudin M in culture liquids of the basidiomycete, *Clitocybe illudens*. It was acidic and had a molecular weight (cryoscopic) of 365. However, mass spectrometric determination gave the molecular weight 276. This, together with the elemental analysis, led to the correct formula, $C_{15}H_{16}O_5$. The circumstances of isolation of illudinine suggest that it has a special biogenetic relationship to illudalic acid. The alkaloid was obtained from a strain of the fungus originally selected for enhanced production of illudalic acid. In time, this strain apparently mutated, and, instead of illudalic acid produced a new compound, illudinine.

Illudalic acid (I) had $\lambda_{max}^{H_2O}$ 247, 270 (sh) and 332 mμ (ε 29,000, 12,000 and 760) shifting to 260 and 347 mμ (ε 16,000 and 2000) in sodium hydroxide solution. The compound dissolved in sodium bicarbonate solution with evolution of carbon dioxide. Potentiometric titration in 80% methyl Cellosolve gave pK_a 7.85. The nmr spectrum showed two low-field proton signals, one at τ −2.4 (singlet, which disappeared on adding D_2O) and the other at −0.2 (singlet). The first could be assigned to a strongly chelated phenol, and the second to an aldehyde. Acetylation of illudalic acid

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