Stereochemistry of the Catalytic Hydrogenation of 3β-Acetoxy-19-hydroxycholest-5-ene

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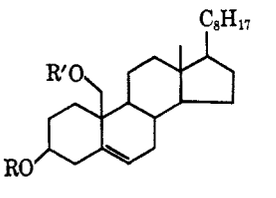
Received May 25, 1966

Catalytic hydrogenation of 3β-acetoxy-19-hydroxycholest-5-ene in acidic and neutral media was studied. Hydrogenation of the above compound led to significant increase of the 5β-dihydro compound compared with that of the 19-unsubstituted one. In acidic medium, the proportion of 5α isomer is increased when compared with that obtained under neutral conditions.

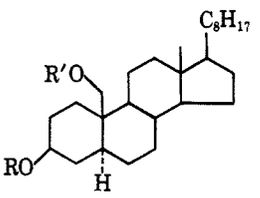
The catalytic hydrogenation of cholest-5-ene and its derivatives, which gives almost exclusively 5α-cholestane derivatives if the molecule is devoid of 3α substituent, has been extensively examined, albeit mainly from the qualitative point of view. These results have been interpreted by the principle of steric hindrance involved during the catalytic hydrogenation.[2] As a part of the study on the synthesis and the reactions of 19-substituted steroids, the catalytic hydrogenation of 3β-acetoxy-19-hydroxycholest-5-ene was studied. Recently, Crabbé, *et al.*, reported the results of the investigation dealing with the catalytic hydrogenation of 19-substituted 4-ene and 5-ene steroids and showed that the catalytic hydrogenation of 19-hydroxy-3-oxo-4-ene steroids over palladized charcoal afforded predominantly A/B-*cis* dihydro derivatives.[3]

The course of the catalytic hydrogenation of 19-substituted steroids appears to be controlled by both the steric hindrance and electronic properties of 19 substituents. For example, the reduction of 3β-acetoxy-19-hydroxycholest-5-ene[4,5] would be expected to give more 5β-dihydro derivative than 3β-acetoxycholest-5-ene. Because of the interaction between the lone electron pair of the oxygen atom and the catalyst, such unsaturated steroids can be adsorbed on the catalyst not only by the less hindered rear side but by the same side as the hydroxyl group, and hence both α- and β-face hydrogenation should occur. This effect has been recognized with the allylic hydroxyl group.[6-8] We wish to report the result of the investigation concerned with the effect of 19-hydroxyl group on the hydrogenation of 5-ene steroids.

The hydrogenation of 3β-acetoxy-19-hydroxycholest-5-ene (Ia) in acetic acid over platinum dioxide was first examined and the reaction afforded a mixture from which two isomeric dihydro compounds, mp 117–118 and 93–94°, were isolated in the yields of 60 and 33%, respectively, by column chromatography. The mixture was analyzed quantitatively by gas–liquid partition chromatography (glpc) to be composed of 59% of the former and 36.5% of the latter. The stereochemistry of these two isomers was established by nmr spectroscopy and chemial evidences. The isomer of higher melting point is 5α-dihydro compound and another is 5β-dihydro compound as shown below. Under the same condition, the catalytic hydrogenation of 3β-acetoxycholest-5-ene gave 88.4% of 3β-acetoxy-5α-cholestane and 10.6% of the 5β isomer.



Ia, R = Ac; R′ = H
b, R = H; R′ = H



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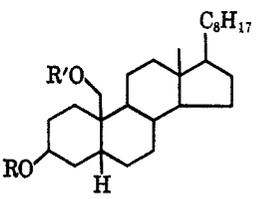
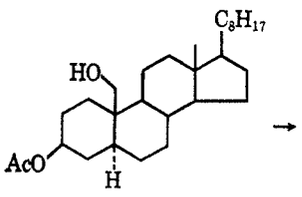
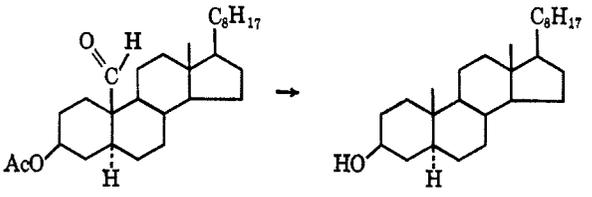


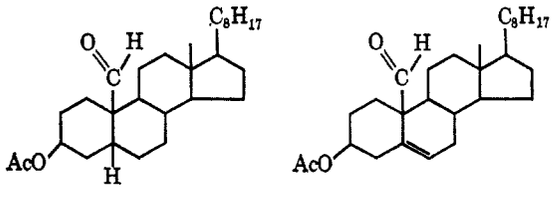
IIIa, R = Ac; R′ = H
b, R = H; R′ = H



II



IV



V VI

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(2) For example, see L. F. Fieser and M. Fieser "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 273.

(3) L. H. Knox, E. Blossey, H. Carpio, L. Cervantes, P. Crabbé, E. Velarde, and J. A. Edwards, *J. Org. Chem.*, **30**, 2198 (1965).

(4) J. Kalvoda, K. Heusler, H. Ueberwasser, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 1361 (1963).

(5) M. Akhtar and D. H. Barton, *J. Am. Chem. Soc.*, **86**, 1528 (1964).

(6) M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).

(7) S. Nishimura and K. Mori, *Bull. Chem. Soc. Japan*, **36**, 318 (1963).

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The nmr spectrum of the higher melting isomer showed a very broad signal (half-band width 17 cps) centered at 4.79 ppm corresponding to the axial 3α proton, while the other one exhibited a relatively sharp signal (half-band width 5.5 cps) at 5.08 ppm of the equatorial 3α proton. From these observations, it has been shown that the isomer of higher melting point is 3β-acetoxy-19-hydroxy-5α-cholestane (IIa) and another isomer is 3β-acetoxy-19-hydroxy-5β-cholestane (IIIa).

Chemical evidence supporting these conclusions was obtained from the sequence of reactions mentioned below. When the 5α-dihydro compound IIa was oxidized with an excess of chromium trioxide–*t*-butyl alcohol complex in benzene,[9] 3β-acetoxy-19-oxo-5α-cholestane (IV) was obtained in good yield. Similarly, 5β-dihydro compound IIIa afforded 3β-acetoxy-19-oxo-5β-cholestane (V). Reduction of the 19-oxo compound IV by Wolff–Kishner method afforded 3β-hydroxy-5α-cholestane, which was identical with an authentic sample. 3β-Hydroxy-5β-cholestane was obtained by the analogous reduction of the 5β isomer V. Optical rotatory dispersion of the above two 19-oxo compounds was examined. 3β-Acetoxy-19-oxo-5α-cholestane (IV) exhibited a positive Cotton effect curve, and its 5β isomer V a negative one. 3β-Acetoxy-19-oxocholest-5-ene (VI)[5] exhibited a negative Cotton effect curve, which has the same sign as that of the A/B-*cis* compound. These results are in agreement with the ones reported for similar 10β-formyl A/B-*trans*, A/B-*cis*, and 5-ene steroids.[10]

Secondly, the catalytic hydrogenation of 19-hydroxy compounds in neutral medium led to a significant increase of the 5β-dihydro compound. Thus, the reduction of Ia in ethanol over rhodium afforded a mixture consisting of 34.5% of 5α-dihydro compound and 57.5% of 5β-dihydro compound, while in acetic acid over rhodium, 58.3% of the former and 32.0% of the latter were obtained, This change of the proportion of 5α and 5β compounds with the medium was not found with 3β-acetoxycholest-5-ene, which was hydrogenated to give 91.4% of the 5α-dihydro compound and 3.0% of the 5β isomer in ethanol over rhodium. In acidic medium the interaction between 19-hydroxyl group and the catalyst is weakened by the protonation to the oxygen atom at C-19 and in this case the course of the reduction is very probably controlled by steric hindrance. Thus, α-face hydrogenation may be preferred.

Experimental Section[11]

Catalytic Hydrogenation of 3β-Acetoxy-19-hydroxycholest-5-ene (Ia). **A.**—A solution of 500 mg of Ia in 30 ml of acetic acid was hydrogenated in the presence of 50 mg of prereduced platinum dioxide under atmospheric pressure at room temperature for 2.5 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was taken up in ether, the organic layer was washed with saturated sodium bicarbonate solution and then with water to neutrality and dried over sodium sulfate, and the ether was removed. Chromatography of the residue on alumina, eluting with *n*-hexane–chloroform (9:1), gave 295 mg of 3β-acetoxy-19-hydroxy-5α-cholestane (IIa), mp 115–117°. Further elution with the same solvent gave 160 mg of 3β-acetoxy-19-hydroxy-5β-cholestane (IIIa), mp 90–93°.

3β-Acetoxy-19-hydroxy-5α-cholestane (IIa).—IIa was recrystallized from methanol: mp 117–118°; $[\alpha]^{23}D$ +14.3° (*c* 1.47, $CHCl_3$); ν_{max}^{KBr} 3450, 1720, 1275, 1235, 1034 cm^{-1}; nmr δ 0.71, 2.02, 3.82, and 3.96 (19-CH_2OH, AB pattern, J = 11.5 cps), 4.79.

Anal. Calcd for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 78.24; H, 11.45.

3β-Acetoxy-19-hydroxy-5β-cholestane (IIIa).—IIIa was recrystallized from methanol: mp 93–94°; $[\alpha]^{23}D$ +26.8° (*c* 1.05, $CHCl_3$); ν_{max}^{KBr} 3530, 1720, 1250, 1049, 1018 cm^{-1}; nmr δ 0.66, 2.05, 3.57, and 3.95 (19-CH_2OH, AB pattern, J = 11 cps), 5.08.

Anal. Calcd for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 77.75; H, 11.07.

B.—A solution of 15 mg of Ia in 1 ml of ethanol was hydrogenated with 3 mg of prereduced rhodium hydroxide for 4 hr. The catalyst was removed by filtration and the ethanol was evaporated *in vacuo*. The residue was dissolved in ether and the solution was filtered to remove the catalyst. Evaporation of the solvent gave a product, which was analyzed by glpc.

C.—A solution of 15 mg of Ia in 1 ml of acetic acid was hydrogenated with 3 mg of prereduced rhodium oxide for 3 hr and worked up in the usual way.

3β,19-Dihydroxy-5α-cholestane (IIb).—A solution of IIa in ethanol was treated with 5% potassium hydroxide in ethanol at room temperature overnight and the crude product was recrystallized from methanol: mp 178°, $[\alpha]^{23}D$ +32.6° (*c* 1.23, $CHCl_3$).

Anal. Calcd for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 80.46; H, 12.20.

3β,19-Dihydroxy-5β-cholestane (IIIb).—A solution of IIIa in ethanol was hydrolyzed with 5% potassium hydroxide at room temperature: mp 199.5–200°.

Anal. Calcd for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 80.14; H, 12.33.

3β-Acetoxy-19-oxo-5α-cholestane (IV).—Chromium trioxide–*t*-butyl alcohol complex in benzene (prepared from 50 mg of chromium trioxide and 100 mg of *t*-butyl alcohol) was added dropwise to a solution of 100 mg of IIa in 1 ml of absolute benzene under ice cooling and the solution was left at 30° for 14 hr. After addition of 0.1 g of hydrazine sulfate in 2 ml of 20% sulfuric acid and 30 ml of toluene, the mixture was refluxed for 1.5 hr under a nitrogen stream. After cooling the organic layer was diluted with ether, washed with water, dried over sodium sulfate, evaporated to dryness *in vacuo*, and recrystallized from methanol: 70 mg, mp 101–103°; $[\alpha]^{23}D$ +30.4° (*c* 1.48, $CHCl_3$); nmr δ 0.61, 2.00, 4.7 (3α-H), 10.07 (–CHO); ORD, α_{290} −96°, α_{300} +400°, α_{340} +384° (sh) (*c* 0.5, dioxane).

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.35; H, 11.12.

3β-Acetoxy-19-oxo-5β-cholestane (V).—Oxidation of IIIa with chromium trioxide–*t*-butyl alcohol complex afforded 3β-acetoxy-19-oxo-5β-cholestane (V) in 70% yield: mp 91–93.5°; $[\alpha]^{23}D$ +4.5° (*c* 1.12, $CHCl_3$); nmr δ 0.74, 2.07, 5.13 (3α-H), 9.8 (–CHO); ORD, α_{270} +228°, α_{315} −4° (sh), α_{328} −36°, α_{340} −28° (sh) (*c* 0.5, dioxane).

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.54; H, 10.51.

Reduction of 3β-Acetoxy-19-oxo-5α-cholestane by Wolff–Kishner Method.—The mixture of 20 mg of the 19-oxo compound, 0.2 ml of hydrazine hydrate, and 0.1 ml of ethanol was heated in a sealed tube at 100° for 16 hr. After addition of *ca.* 40 mg of potassium hydroxide, the mixture was heated again in a sealed tube at 220–230° for 4 hr. After cooling, the mixture was dissolved in ether and the resulting ethereal solution was washed with water, dried, and evaporated. Recrystallization of the crude product from methanol gave 7 mg of 3β-hydroxy-5α-cholestane, identical with an authentic sample by a mixture melting point test and infrared comparison. Chromatography of the mother liquors on alumina, eluting with *n*-hexane–chloroform (9:1), gave an additional 10 mg of 3β-hydroxy-5α-cholestane.

Reduction of 20 mg of V by the same procedure afforded 13 mg of 3β-hydroxy-5β-cholestane, identical with an authentic sample.

(9) Houben-Weyl, "Methoden der Organischen Chemie," Bd VII/I, 1954, p S. 173.

(10) C. Djerassi, O. Halpern, V. Halpern, O. Schindler, and C. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958); P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965, p 146.

(11) All melting points are uncorrected. Nmr spectra were measured at 60 Mc on a Varian Associate A-60 spectrometer in chloroform-*d* solution. Chemical shifts are given with reference to tetramethylsilane. Rotatory dispersion was measured on a Nihon Bunko Model ORD/UV-5 spectrometer.

Acknowledgment.—The authors wish to express their sincere appreciation to Dr. Shigeo Nishimura, Tokyo University of Agriculture and Technology, for supplying rhodium catalysts and for his helpful discussions during the investigation. Thanks are also due to the Institute of Microbial Chemistry for nmr measurements, Teikoku Hormone Manufacturing Company, Ltd., and Yanagimoto Company, Ltd., for the elemental analyses, and Japan Spectroscopic Company, Ltd., for ORD measurements. Part of the expenses have been covered by the Grant in Aid for Fundamental Scientific Research of the Ministry of Education.

Diels–Alder Synthesis of 4-Methyl-$\Delta^{4(10)}$-1-octalone[1]

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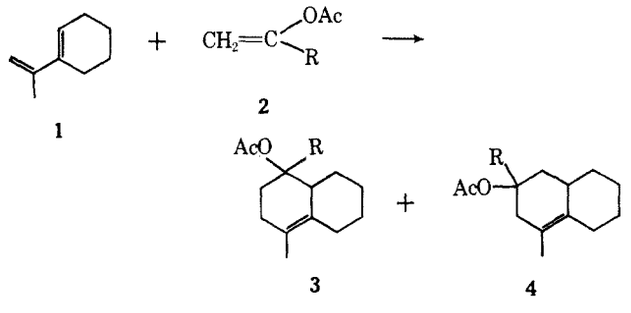
Received May 13, 1966

The Diels–Alder reactions of 1-isopropenylcyclohexene with methyl α-acetoxyacrylate, α-acetoxyvinyl methyl ketone, and α-acetoxyacrylonitrile afforded high yields of adducts, predominantly (~98%) of one orientation. The adducts of methyl α-acetoxyacrylate and α-acetoxyvinyl methyl ketone proved to be useful intermediates for the synthesis of 4-methyl-$\Delta^{4(10)}$-1-octalone.

This article is a summary of the results of a study of the Diels–Alder reaction of 1-isopropenylcyclohexene with various dienophiles (Scheme I) where the objective

SCHEME I



1 2 3 4

R = CN, CO_2CH_3, and $COCH_3$

was the selective synthesis of 4-methyl-$\Delta^{4(10)}$-1-octalone (**5**) in high yield so that the method could be applied to the preparation of some eudesmane sesquiterpenes. Although the net conversion **1** → **5** is formally described by the Diels–Alder addition of **1** and ketene, an indirect approach was necessary because ketenes do not react as dienophiles.[2] The dienophiles used and the results they gave are shown in Table I.[3] The high orientational selectivities observed parallel those of the closely related reactions of 1-vinylcyclohexene with dienophiles in the acrylic acid series; *e.g.*, with acrylonitrile 1-cyano adducts are favored over 2-cyano adducts by 95 to 5.[10]

We chose the simplest unambiguous route to **1**, subjecting 1-acetylcyclohexene to the Wittig reaction.[11] The product (66%) contained only small amounts of impurities as shown by its behavior on capillary gas–liquid partition chromatography (glpc) (96% one component),[12] nmr spectrum (1:1 ratio of vinyl to methyl hydrogens), ultraviolet spectrum [λ_{max} 233 mμ (ε 19,200)], and subsequent conversion to Diels–Alder adducts in greater than 90% yield.

α-Acetoxyacrylonitrile was prepared by dehydrohalogenation of the cyanohydrin acetate of chloroacetaldehyde,[13] methyl α-acetoxyacrylate, and α-acetoxyvinyl methyl ketone by enol acetylation of methyl pyruvate and biacetyl, respectively, the latter in poor yield (12%) by a modification of the reported procedure.[14]

The orientation ratios (**3**:**4**) in the Diels–Alder reactions were determined by converting each adduct mixture to a mixture of the two possible α,β-unsaturated ketones (**6**, 4-methyl-Δ^9-1-octalone, and **7**, 4-methyl-Δ^3-2-octalone) using the reagents shown in Scheme II (which shows the transformations only for compounds derived from the predominant orientation of addition).[15] Analysis by glpc of the various α,β-unsaturated ketone mixtures showed that they contained 97.5–98.5% **6** and 1.5–2.5% **7**. Each conjugate pair of analyses was taken to represent the extent of formation of the two orientation adducts in the corresponding Diels–Alder reaction (see Table I). Although this method of analysis established that effectively only one orientation of addition occurred in the Diels–Alder reactions of **2** (R = CN, CO_2CH_3, and $COCH_3$), glpc

(1) This investigation was supported by Public Health Service Research Grant GM 09759 from the Division of General Medical Sciences, U. S. Public Health Service, and by National Science Foundation Research Grant GP 3567. Acknowledgment is also made of National Science Foundation Grant G 19108 which contributed to the purchase of the nmr spectrometer used in this research.

(2) See J. C. Martin, P. G. Gott, V. W. Goodlett, and R. H. Hasek, *J. Org. Chem.*, **30**, 4175 (1965).

(3) These dienophiles have rarely been used previously in Diels–Alder reactions and then only with symmetrical dienes. α-Acetoxyacrylonitrile has yielded adducts with cyclopentadiene,[4] 6,6-dimethylfulvene,[5] and butadiene.[6] Esters of α-acetoxyacrylic acid have been added to butadiene,[7] 2,3-dimethylbutadiene,[8] 1,4-diphenylbutadiene,[8] and 1,4-dichlorobutadiene.[9]

(4) P. D. Bartlett and B. E. Tate, *J. Am. Chem. Soc.*, **78**, 2473 (1956).

(5) C. H. DePuy and P. R. Story, *ibid.*, **82**, 627 (1960).

(6) J. C. Little, *ibid.*, **87**, 4020 (1965). 1-Isopropenylcyclohexene, unlike butadiene, afforded *no* 1,2-cycloaddition products.

(7) J. Wolinsky, R. Novak, and R. Vasilleff, *J. Org. Chem.*, **29**, 3596 (1964).

(8) J. Monnin, *Angew. Chem.*, **69**, 762 (1957); *Helv. Chim. Acta*, **41**, 2112 (1958).

(9) E. E. Smissman and M. A. Oxman, *J. Am. Chem. Soc.*, **85**, 2184 (1963).

(10) I. N. Nazarov, A. I. Kuznetsova, and N. V. Kuznetsov, *Zh. Obshch. Khim.*, **25**, 88 (1955).

(11) Previously reported preparations of **1** almost certainly yielded mixtures of isomers. See H. Booker, L. K. Evans, and A. E. Gillam, *J. Chem. Soc.*, 1453 (1940); D. Nightingale, E. C. Milberger, and A. Tomisch, *J. Org. Chem.*, **13**, 357 (1948); V. R. Skvarchenko, L. Weeng-lien, and R. Ya. Levina, *J. Gen. Chem. USSR*, **30**, 2117 (1960). *Cf.* H. E. Eschinazi and H. Pines, *J. Org. Chem.*, **20**, 1666 (1955).

(12) All ratios and percentages quoted for glpc data are direct area comparisons of the observed peaks.

(13) R. M. Nowak, *J. Org. Chem.*, **28**, 1182 (1963).

(14) H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

(15) Ketones **6** and **7** were prepared and characterized *via* the Diels–Alder reaction of **1** with vinyl acetate, where the two orientation adducts were found to have formed in roughly equal amounts.