SHORT COMMUNICATIONS

The Structure of "α-Cholestanol"

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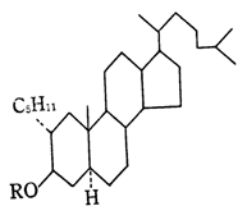
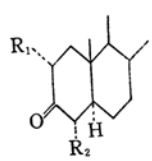
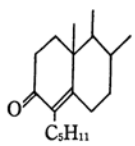
"α-Cholestanol" obtained[1,2] by the treatment of cholesterol with sodium and isoamyl alcohol, has been presumed to be isoamylated dihydrocholesterol,[3,4] but it has received no generally accepted structural assignment. We will now describe findings which show Diels and Abderhalden's "α-cholestanol" ($C_{32}H_{58}O$, m. p. 124~127°C, sintering at 120°C, $[\alpha]_D$ −15° ($CHCl_3$)) to be 2α-isoamylcholestan-3β-ol (I).



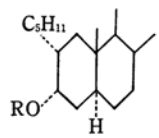
I: R=H
IV: R=Ac



II: R_1=Isoamyl, R_2=H
VII: R_1=H, R_2=Isoamyl



VI



III: R=H
V: R=Ac

The secondary alcoholic function of I has been well characterized[2,3,5] by the formation of a benzoate and by oxidation to a ketone (II) named "α-cholestanone" ($C_{32}H_{56}O$, m. p. 118~120°C, $[\alpha]_D$+23° ($CHCl_3$), $[\alpha]_D$+22°C (MeOH), ν_{max} 1702 cm^{-1} ($CHCl_3$)). The absence of a double bond has now been confirmed by the following results; (i) Neither I

1) C. Neuberg, *Salkowski Festschrift*, 279 (1904).
2) O. Diels and E. Abderhalden, *Ber.*, **39**, 884 (1906).
3) A. Windaus and C. Uibrig, ibid., **46**, 2487 (1913).
4) H. Sobota, "The Chemistry of the Steroids," The Williams and Wilkins Co., Baltimore (1938), p. 210; L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corporation, New York, (1959), p. 29.
5) O. Diels and K. Linn, *Ber.*, **41**, 544 (1908); O. Diels and E. Stamm, ibid., **45**, 2228 (1912).

nor II had any peak due to an olefinic proton in the NMR spectra (ii) the ketone II was stable to acid or base and showed no absorption due to α,β-unsaturated ketone in the infrared and ultraviolet spectra.

The reduction of II with lithium aluminum hydride in ether gave rise to I (80%), along with an isomeric alcohol III (16%) ($C_{32}H_{58}O$; m.p. 95~96°C), which had a larger R_f value than the former I on thin layer chromatography. The acetylation of I with acetic anhydride and pyridine at room temperature yielded an acetate (IV) ($C_{34}H_{60}O_2$, m.p. 67~68°C, $[\alpha]_D$ −32° ($CHCl_3$), ν_{max} 1245 cm^{-1} (CS_2) (type A),[6] τ_{CDCl_3} 5.60 (half-width 23 c.p.s.)). The same treatment of III afforded an isomeric acetate (V) ($C_{34}H_{60}O_2$, m.p. 97~98°C, ν_{max} 1241 and 1234 cm^{-1} (CS_2) (type B)[6], τ_{CDCl_3} 5.14 (half-width 6 c.p.s)). All these results indicate[6,7] that the alcohol I has an equatorial hydroxyl group and that its isomer III has an axial one.

The lower carbonyl-stretching frequency of II, compared with those of the usual 3-keto steroids, suggests[8,9] that II is a C-2 or C-4 alkylated steroid, and the rotatory dispersion curve showed a positive Cotton effect, implying that the ketone was a derivative of 5α-cholestane. By following Atwater's procedure,[10] Δ^4-cholesten-3-one was isoamylated, using isoamyl iodide and potassium in boiling *t*-butyl alcohol; we thus isolated 4-isoamyl-Δ^4-cholesten-3-one (VI) (m.p. 66~67°C, $[\alpha]_D$+92° ($CHCl_3$), λ_{max} 251 mμ (ε 15400, ethanol), ν_{max} 1670 and 1605 cm^{-1} (Nujol)). The NMR spectrum of VI showed no signal due to the olefinic proton. Thus, all the spectral behavior indicated that an extra alkyl group was introduced at the C-4 position, as had been expected. The Birch reduction of VI under the conditions employed for the reduction[6] of 4-methyl-Δ^4-cholesten-3-one afforded the corresponding dihydro compound, $C_{32}H_{56}O$ (m.p. 68~69°C, $[\alpha]_D$+26° ($CHCl_3$), ν_{max} 1702 cm^{-1}), which had a positive Cotton effect. In view of the analogous reduction products of 4-methyl-[8] or 4-ethyl-Δ^4-cholesten-3-one,[11] the dihydro compound may be assigned the 4α-isoamylcholestanone structure (VII). The physical constants and the infrared spectrum of VII were different from those of II.

The isoamylation at the 2-position of cholesten-3-one was then attempted by a procedure[8] similar to that used for monomethylation, treating it with isoamyl iodide and potassium in boiling *t*-butyl alcohol for 10 min. The resulting crude product was successfully separated in a few components by chromatography on alumina. The material (16%), which was eluted with petroleum ether - benzene (24 : 1 and 4 : 1), had an m.p. of 118~120°C and was found to be identical with "α-cholestanone" (II). Since the direct alkylation of cholestanone should afford 2α-alkyl derivative,[8] the ketone II can be identified as 2α-isoamylcholestan-3-one. In agreement with this structure, there is no appreciable solvent effect[8] in the specific rotation of II, as has been mentioned above. Therefore, "α-cholestanol" is 2α-isoamylcholestan-3β-ol.

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7) C. W. Shoppee and G. M. Summer, *J. Chem. Soc.*, **1950**, 687; V. Cerny, J. Joska and L. Labler, *Collection Czechoslov. Chem. Communs.*, **26**, 1658 (1961); O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3863 (1962).
8) Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, **80**, 5220 (1958).
9) C. Cherrer, *Compt. rend.*, **225**, 1063 (1947).
10) N. W. Atwater, *J. Am. Chem. Soc.*, **79**, 5315 (1957).
11) B. R. Brown, P. W. Trown and J. M. Woodhouse, *J. Chem. Soc.*, **1961**, 2478.