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Synthesis of 4,4-Dimethyl-2-nitro-5α-cholest-1-en-3-one[1)]

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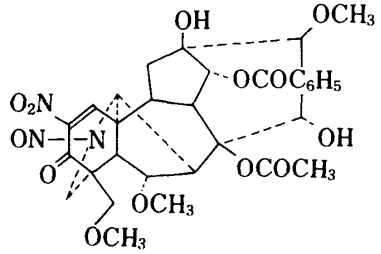
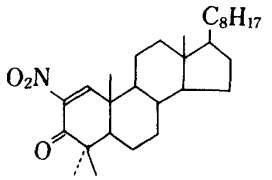
Treatment of 4,4-dimethyl-5α-cholest-1-en-3-one with nitric acid gave 4,4-dimethyl-2-nitro-5α-cholest-1-en-3-one. A possible mechanism for the nitration is proposed.

Keywords——benzeneselenic anhydride; 4,4-dimethyl-2-nitro-5α-cholest-1-en-3-one; nitration; nitronitrosoaconitinic acid; 2-nitro-2-cyclohexen-1-one system

The structure of nitronitrosoaconitinic acid (I), the oxidation product of aconitine (II) with nitric acid, has been proposed.[2a,b)] The pK_a value of I was determined to be 4.9, a value which is nearly equal to those of carboxylic acids, and the 2-nitro-2-cyclohexen-1-one system of I has been considered to be responsible for this acidity. In order to confirm this assumption, we planned to prepare 4,4-dimethyl-2-nitro-5α-cholest-1-en-3-one (III), which contains this system. The synthesis of this compound is reported here.

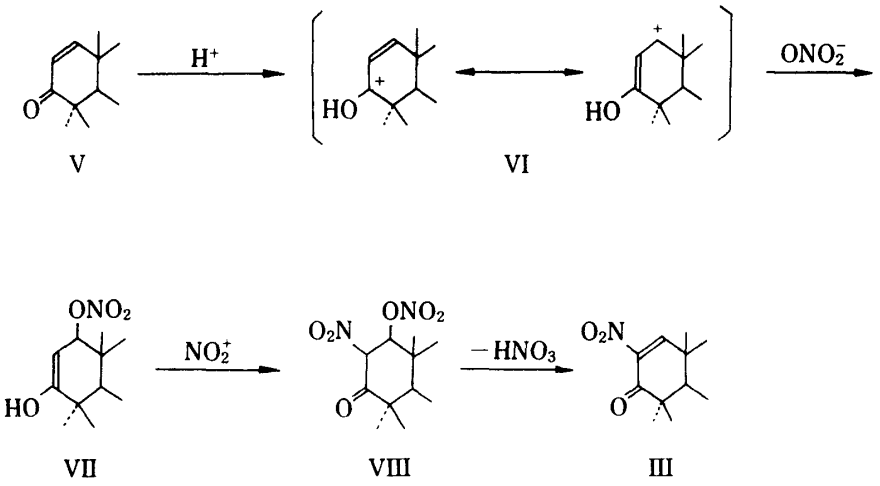


I



III

Oxidation of 4,4-dimethyl-5α-cholestan-3-one (IV)[3)] with benzeneselenic anhydride (Barton method)[4)] gave 4,4-dimethyl-5α-cholest-1-en-3-one (V).[5)] The mass, ^1H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra of V are consistent with the proposed structure. Fuming nitric acid oxidation of compound V gave compound III. The structure of



V VI VII VIII III

Chart 1

compound III was determined on the basis of spectral data.

Mass spectral analysis (M^+: *m/e* 457) of III gave a molecular formula of $C_{29}H_{47}NO_3$. The infrared (IR) spectrum (in KBr) displayed absorptions at 1680, 1533, and 1360 cm^{-1}, indicating the existence of an α,β-unsaturated carbonyl moiety and nitro group. The ^1H NMR spectrum (in $CDCl_3$) of this compound showed, in addition to the signal of an olefinic proton at C-1 at δ 7.69 (singlet), four three-proton signals at δ 0.66, 0.79, 0.81, and 1.16 (each singlet) due to four methyl groups. The signals at δ 152.4 (d) and 146.7 (s) in the ^{13}C NMR spectrum were assigned to the olefinic carbons, C-1 and C-2. The ^{13}C signal of the carbonyl group appeared as a singlet at δ 193.8. The formation of III from V on treatment with fuming nitric acid at 0°C may be expressed in the following way, V→VI→VII→VIII→III, as shown in Chart 1. No previous report has appeared on the mechanism of such a nitration.

A study on the acidity and pK_a value of III will be reported in a subsequent paper.[1)]

Experimental

The melting points are uncorrected. The IR spectra were determined in KBr discs. The MS were measured with Shimadzu-9000B spectrometers. ^1H NMR and ^{13}C NMR spectra were determined with a JEOL 100 spectrometer in the Fourier transform mode in chloroform-d_1 solution with Me_4Si as an internal standard, with multiplicity given for off-resonance proton decoupling, in 5-mm (o.d.) tubes. All values are reported in ppm downfield (δ) from the Me_4Si signal. Peak assignments are based on comparison with the known chemical shifts of several derivatives of cholest-4-en-3-one.

4,4-Dimethyl-5α-cholest-1-en-3-one (V)[5)]——A mixture of 4,4-dimethyl-5α-cholestan-3-one (IV) (1.02 g) and benzeneselenic anhydride[4)] (1.11 g) in 20 ml of chlorobenzene was heated at 100°C for 1 h with stirring. After the removal of precipitate, the filtrate was chromatographed on a silica gel column. The column was then eluted with cyclohexane–benzene (1: 99). Recrystallization of the product from ethanol gave crystals. mp 89—90°C (lit.,[5)] mp 90—91°C), 0.79 g, 70%. ^{13}C NMR ($CDCl_3$) δ: 156.8 (d, C-1), 125.7 (d, C-2), 204.6 (s, C-3), 21.6, 26.8 (q, 28 and 29 CH_3): MS *m/e*: 412 (M^+).

4,4-Dimethyl-2-nitro-5α-cholest-1-en-3-one (III)——To a solution of 4,4-dimethyl-5α-cholest-1-en-3-one (V) (0.5 g) in absolute ether, 10 ml of HNO_3 (d=1.50) was added. The mixture was stirred at 0°C for 2.5 h, then made alkaline with 50% sodium hydroxide solution and extracted with benzene. After removal of the solvent, the benzene extract gave a residue, which was chromatographed on a silica gel column. The column was eluted with benzene. The eluate yielded crystals. mp 97—98°C, 0.45 g, 81%. UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 246 (3.8) and 322 (2.6 sh). *Anal.* Calcd for $C_{29}H_{47}NO_3$: C, 76.08; H, 10.53; N, 3.05. Found: C, 75.77; H, 10.66; N, 2.98.

References and Notes

1) A part of this study was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1980 (Abstr., p. 126) and at the 101st Annual Meeting of the Pharmaceutical Society of Japan, Kumamoto, April 1981 (Abstr., p. 521).
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