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Synthesis of 6β-Bromomethyl- and 6β-Chloromethyl-19-norcholest-5(10)-en-3β-ol

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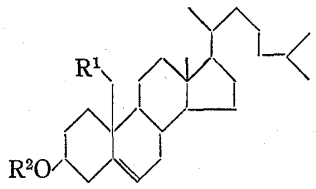
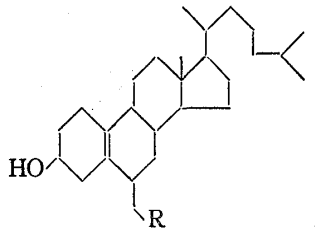
The title compounds were synthesized by homoallylic rearrangement of 19-bromo- and 19-chlorocholest-5-en-3β-ol, respectively.

In the course of our work on the synthesis and development of new iodinated steroids as an adrenal-scanning agent, we found that homoallylic rearrangement of 19-iodocholest-5-en-3β-ol (I) leads to the selective formation of 6β-iodomethyl-19-norcholest-5(10)-en-3β-ol (II) in good yield.[2] Furthermore, we have also found[3] that the radioiodinated (II) is by far a more effective adrenal concentrating agent and should be a better scanning agent than the radioiodinated (I) previously reported. In connection with our interest in the reactivity of 19-halogenated 5-en-steroid system, a facile synthesis of the 6β-bromomethyl (III) and 6β-chloromethyl analog (IV) was required, which would be readily applicable to the formation of a radioactive tracer.



I : R^1=I, R^2=H
V : R^1=OTs, R^2=H
VI : R^1=OTs, R^2=Ac
VII : R^1=Br, R^2=Ac
VIII : R^1=Br, R^2=H
IX : R^1=Cl, R^2=H



II : R=I
III : R=Br
IV : R=Cl

Ts=tosyl

Chart 1

With the knowledge of our earlier work[2] concerning the formation of II, the initial step includes the preparation of 19-bromo- (VIII) and 19-chlorocholest-5-en-3β-ol (IX), respectively. 19-Bromocholest-5-en-3β-ol 3-acetate (VII) was conveniently prepared by the nucleophilic displacement of cholest-5-ene-3β,19-diol 19-toluene-*p*-sulfonate 3-acetate (VI) with LiBr in isopropanol. Selective hydrolysis of VII in dioxane with NaOH resulted in the isolation of pure (VIII) in 64.4% yield. However, an approach to obtain VIII from the reaction of cholest-5-ene-3β,19-diol 19-toluene-*p*-sulfonate (V) with LiBr in isopropanol, as was expected,[4] resulted in the formation of a mixture of III and VIII as shown by nuclear magnetic resonance

1) Location: *a) Maidashi, 3-1-1, Higashi-ku, Fukuoka, 812, Japan; b) Tokuriki Build. Nihonbashi 3-10-5, Chuo-ku, Tokyo, 103, Japan.*
2) M. Kojima, M. Maeda, H. Ogawa, K. Nitta, and T. Ito, *J. Chem. Soc. Chem. Commun.*, **1975**, 47; M. Maeda, M. Kojima, H. Ogawa, K. Nitta, and T. Ito, *Steroids*, **26**, 241 (1975).
3) M. Kojima, M. Maeda, H. Ogawa, K. Nitta, and T. Ito, *J. Nucl. Med.*, **16**, 666 (1975); K. Nitta, H. Ogawa, T. Ito, M. Kojima, and M. Maeda, *Chem. Pharm. Bull.* (Tokyo), "in press."
4) Similar phenomenon was noticed in the reaction of V with NaI and has been described in ref. 2.

(NMR) analysis. When the above reaction was subjected to prolonged heating, thin-layer chromatography (TLC) indicated a graduate increase in the yield of III with concomitant decrease of VIII initially formed. The former procedure, therefore, is preferable by virture of simplicity of work-up and the purity of the formed (VIII). On the other hand, 19-chlorocholest-5-en-3β-ol (IX) was obtained directly from V with LiCl in 37.9% yield. In this case, even in the complete disappearance of the starting material (V), the presence of the 6β-chloromethyl (IV) as a by-product was not observed.

The structures (VIII) and (IX) rest on the method of preparation and the great similarity of the C_{19}-methylene protons NMR pattern to that of I.

Smooth conversion to III was achieved by heating of VIII in glacial AcOH at 80—90° for 5 hr or refluxing acetonitrile in good yield. However, for the conversion of IX to IV under the similar conditions, longer reaction time was required. Thus, heating of IX in glacial AcOH at 80—90° for 13.5 hr gave IV in 21.3% yield.

The structures (III) and (IV) were confirmed by their spectral properties which were very similar to those of II.[5]

The resistance to the conversion of VIII and IX into III and IV respectively, as in the case of I, was also observed in solvents of poor ionizing powder such as benzene, CCl_4, $CHCl_3$, or ether, suggesting that the ionization of the C_{19}-halogen bond is a very important factor influencing the rate of reaction. It is probable more reasonable to consider the rearrangement observed with 19-halogenated cholest-5-en-3β-ol as a preceding ionizing to a homoallylic cation involving an ion-pair intermediate that is transformed to a thermodynamically favored covalent halide, as was formally suggested.

Experimental

Melting points are uncorrected. The NMR spectra were obtained with a JNM PS-100 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as internal reference. The infrared (IR) spectra were measured with a JASCO DS-701G infra-red spectrometer. Optical rotations were determined with a JASCO DIP-SL automatic polarimeter. Thin-layer chromatography (TLC) was performed with a Wakogel B—O Silica gel and Silica gel 60 F254 (E. Merck). Column chromatography was carried out with silica gel (Kanto Chemical Co., Inc., 200 mesh, Japan).

19-Bromocholest-5-en-3β-ol 3-acetate (VII)——A solution of cholest-5-ene-3β,19-diol 19-toluene-*p*-sulfonate 3-acetate (VI)[6] (830 mg) and anhydrous LiBr (365 mg) in isopropanol (60 ml) was gently refluxed for 3 hr. The solution was concentrated to about 5 ml *in vacuo* and poured into ice–H_2O. The resulting mixture was extracted with ether. The ether was washed with H_2O and dried over Na_2SO_4. Removal of the solvent left a colorless semisolid, which was solidified on trituration with methanol. Recrystallization from ether–methanol gave VII (539 mg, 76.6%) as needles, mp 93.5—94°. *Anal.* Calcd. for $C_{29}H_{47}O_2Br$: C, 68.62; H, 9.33. Found: C, 68.57; H, 9.39. $[\alpha]_D^{20}$ −54.5° (c=1.00, $CHCl_3$); IR ν_{max}^{KBr} (cm^{-1}): 1730 and 1250 (CH_3COO); NMR δ: 0.72 (s, 3H, 18-Me), 2.01 (s, 3H, CH_3COO), 3.50 and 3.74 (dd, 2H, J=10 Hz, 19-CH_2Br), 4.64 (m, 1H, 3-H), and 5.68 ppm (m, 1H, vinylic).

19-Bromocholest-5-en-3β-ol (VIII)——A solution of NaOH (264 mg) in 20% aqueous methanol (25 ml) was added dropwise to a solution of VII (520 mg) in dioxane (20 ml) in ice–H_2O. The solution was stirred for 30 min at room temperature and then poured into ice–H_2O. The resulting mixture was extracted with ether and the ether was washed with H_2O and dried over Na_2SO_4. Removal of the ether gave a colorless solid, which was recrystallized from ether–methanol to give pure (VIII) (307 mg, 64.4%) as needles, mp 114—115°. *Anal.* Calcd. for $C_{27}H_{45}OBr$: C, 69.66; H, 9.74. Found: C, 69.52; H, 10.05. $[\alpha]_D^{20}$ −49.2° (c=1.00, $CHCl_3$); IR ν_{max}^{KBr} (cm^{-1}): 3360 (OH); NMR δ: 0.74 (s, 3H, 18-Me), 1.63 (s, 1H, OH), 3.56 (m, 1H, 3-H), 3.51 and 3.77 (dd, 2H, J=10 Hz, 19-CH_2Br), and 5.64 ppm (m, 1H, vinylic).

19-Chlorocholest-5-en-3β-ol (IX)——A solution of cholest-5-ene-3β,19-diol 19-toluene-*p*-sulfonate (V)[7] (1 g) and anhydrous LiCl (200 mg) in isopropanol (70 ml) was gently refluxed for 80 min. The solution was concentrated to about 5 ml *in vacuo* and poured into ice–H_2O. The resulting mixture was extracted with ether. The ether was washed with H_2O and dried over Na_2SO_4. Removal of the ether left a colorless semi-

5) The β-configuration to the C_6-substituents is assigned from the assumed mode of formation of the rearrangement product *via* the homoallylic cation, though the stereochemistry is unproven.
6) M. Akhtar and D.H.R. Barton, *J. Am. Chem. Soc.*, **86**, 1524 (1964).
7) R.E. Counsell, V.V. Ranade, R.J. Blair, W.H. Beierwaltes, and P.A. Weinhold, *Steroids*, **16**, 317 (1970).

solid, which was solidified on trituration with petroleum ether and recrystallization from petroleum ether gave pure (IX) (287 mg, 37.9%) as needles, mp 123—124.5°. *Anal.* Calcd. for $C_{27}H_{45}OCl$: C, 77.01; H, 10.77. Found: C, 77.13; H, 10.85. $[\alpha]_D^{18}$ −43.9° (c=1.00, $CHCl_3$); IR ν_{max}^{KBr} (cm^{-1}): 3300 (OH); NMR δ: 0.71 (s, 3H, 18–Me), 1.60 (s, 1H, OH), 3.60 (m, 1H, 3–H), 3.58 and 3.83 (dd, 2H, J=10 Hz, 19–CH_2Cl), and 5.64 ppm (m, 1H, vinylic).

Reaction of V with LiBr——A solution of V (104 mg) and anhydrous LiBr (47 mg) in isopropanol (20 ml) was gently refluxed. After 5.5 hr, TLC showed the presence of two products with the absence of unchanged starting material. The solution was concentrated to about 5 ml *in vacuo* and poured into ice–H_2O. The resulting mixture was extracted with ether. The ether was washed with H_2O and dried over Na_2SO_4. The residue obtained after evaporation of the ether was proved to be a mixture of III and VIII by the NMR spectroscopy. The ratio of III and VIII was estimated to be 1: 2 on the basis of integration of their C_{18}–methyl signals in the NMR spectrum.

Rearrangement of VIII to 6β-Bromomethyl-19-norcholest-5(10)-en-3β-ol (III)——(i) A solution of VIII (274 mg) in glacial AcOH (28 ml) was heated at 80—90° for 5 hr. TLC then showed complete disappearance of the starting material. The resulting solution was cooled to room temperature and shaken with a mixture of ether and H_2O. The separated aqueous layer was extracted with ether. The combined ether was washed with H_2O, 5% $NaHCO_3$, and H_2O. The ether solution was dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residual oil was chromatographed on silica gel eluting with $CHCl_3$ to give III (211 mg, 77%) as glass. *Anal.* Calcd. for $C_{27}H_{45}OBr$: C, 69.66; H, 9.74. Found: C, 69.64; H, 9.68. $[\alpha]_D^{18}$ +38.5° (c=1.00, $CHCl_3$); IR ν_{max}^{KBr} (cm^{-1}): 3360 (OH); NMR δ: 0.68 (s, 3H, 18–Me), 1.58 (s, 1H, OH), 3.30 (t, 1H, J=10 Hz, 6–CH_2Br) and 3.61 (dd, 1H, J=10, 2 Hz, 6–CH_2Br), and 4.0 ppm (m, 1H, 3–H).

(ii) A solution of VIII (100 mg) in acetonitrile (15 ml) was refluxed for 22.5 hr. After removal of the solvent *in vacuo*, the residual oil was chromatographed on silica gel eluting with $CHCl_3$ to give III (72 mg, 72%) as glass.

Rearrangement of IX to 6β-Chloromethyl-19-norcholest-5(10)-en-3β-ol (IV)——A solution of IX (183 mg) in glacial AcOH (20 ml) was heated at 80—90° for 13.5 hr. After the reaction mixture was treated as in the case of rearrangement of VIII, the obtained residual oil was chromatographed on silica gel. The first effluent with $CHCl_3$ gave a mixture of the acetyl compounds of both IX and IV (81 mg), as shown by NMR analysis. The second effluent with $CHCl_3$ gave IV (39 mg, 21.3%) as glass. *Anal.* Calcd. for $C_{27}H_{45}OCl$: C, 77.01; H, 10.77. Found: C, 76.86; H, 10.76. $[\alpha]_D^{20}$ +22.2° (c=0.60, $CHCl_3$); IR ν_{max}^{KBr} (cm^{-1}): 3380 (OH); NMR δ: 0.67 (s, 3H, 18–Me), 1.54 (s, 1H, OH), 3.40 (t, 1H, J=10 Hz, 6–CH_2Cl) and 3.68 (dd, 1H, J=10, 2 Hz, 6–CH_2Cl), and 4.0 ppm (m, 1H, 3–H). The third effluent with $CHCl_3$ gave the starting material (69 mg).

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Photodimerization of Ethyl 2-Ethoxy-1,2-dihydroquinoline-1-carboxylate

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Irradiation of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (**1**) in ether and ethanol resulted in the formation of a *trans* head-to-head dimer **2** and an ethanol adduct **5** in 66 and 45% yields, respectively.

Various types of photochemical reactions of 1-acyl-1,2-dihydroquinolines have been reported. These include (i) rearomatization to quinolines,[2,3] (ii) (2+2)π dimerization,[2] (iii)

1) Location: *133-1, Yamada-kami, Suita, Osaka, 565, Japan.*
2) P.T. Izzo and A.S. Kende, *Tetrahedron Letters*, **1966**, 5731.
3) Irradiation of ethyl 2-phenyl-1,2-dihydroquinoline-1-carboxylate in ether gave a mixture of at least four products, from which 2-phenylquinoline was isolated in 20% yield (unpublished result).