2 Std. lang unter N_2-Atmosphäre und Rückfluss gekocht, wobei die Reaktionslösung erst bei einer Badtemperatur von 90° heftig anschaumte. Nach Vollendung der Reaktion wurde die Reaktionsflüssigkeit der Wasserdampfdestillation unterworfen. Das Destillat wurde mit 30 ml 1%iger $KMnO_4$-Lösung und 5 ml verd. H_2SO_4 versetzt und über Nacht bei Raumtemperatur umgerührt. Der $KMnO_4$-Überschuss wurde dann mit MeOH zersetzt und das entstandene MnO_2 durch Absaugen abgetrennt. Das Filtrat wurde im Vak. eingedampft und der Rückstand dabei mehrere Male mit ÄtOAc in der Wärme ausgezogen. Die ÄtOAc-Schicht wurde über Na_2SO_4 getrocknet, eingedampft und der dabei zurückbleibende farblose Sirup wurde in wenig H_2O gelöst, mit einem Überschuss gesättigter $Cu(OAc)_2$-Lösung versetzt und auf dem Wasserbad erhitzt. Nach dem Abkühlen wurde der entstandene blaue Niederschlag abgesaugt, in MeOH suspendiert und durch Durchleiten von H_2S zersetzt. Der durch Eindampfen des von CuS abgetrennten Filtrats erhaltene Rückstand ergab bei der zweimaligen Umlösung aus $CHCl_3$-Petroläther 6.5 mg farblose Prismen vom Schmp. 79~81° und $[\alpha]_D^{26}$ +18.6° (c=1.02, ÄtOH). Diese Substanz wurde durch die Mischprobe und IR (KBr) mit einer authentischen Probe von (+)-2-Methylglutarsäure identifiziert. $C_6H_{10}O_4$—Ber.: C, 49.31; H, 6.90. Gef.: C, 49.10; H, 6.64.

Zum Schluss sind wir Herrn Dr. K. Konobu und seinen Mitarbeiterinnen im Mikroanalysenlaboratorium unseres Instituts für die Durchführung der Mikroanalysen und Herrn Dr. J. Koizumi von der Nipponshinyaku & Co. für die Messung der optischen Drehungen von einigen Substanzen zum Dank verpflichtet.

Zusammenfassung

Die Konfiguration der Methylgruppe im Bisdesoxydihydromonotropein, einem Hydrierungsprodukt des Monotropeins bzw. Asperulosids wurde durch mehrere Abbaureaktionen untersucht, wobei die Richtigkeit der von uns vorgeschlagenen Struktur (II) für dessen Acetat bewiesen wurde.

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The synthesis of Cholestane-1,7-dione.

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In connection with some other work, the need arose for synthesizing cholestane-1,7-dione (VIII) from cholesterol which has not so far been reported in the literature. The oxygenation at C-7 of cholesterol was achieved through a well known route. Cholesterol acetate[1] was oxidized by the *tert*-butyl chromate method[2] to 3β-acetoxycholest-5-en-7-one,[3] which upon hydrogenation with 10% palladium charcoal in ether-ethyl acetate followed by sodium borohydride reduction in methanol-ether yielded cholestane-3β,7β-diol 3-acetate (Ia).[4] The protection of the 7β-hydroxyl group was effected in anhydrous ether with 2,3-dihydropyran[5] in the presence of concentrated hydrochloric acid, whereby a

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1) Org. Syntheses, Coll. Vol. II, 675.
2) K. Heusler, A. Wettstein: Helv. Chim. Acta, **35**, 284 (1952); C.W. Marshall, R.E. Roy, I. Laos, B. Priegel: J. Am. Chem. Soc., **79**, 6308 (1957).
3) L.F. Fieser, M. Fieser, R.N. Chakravarti: J. Am. Chem. Soc., **71**, 2229 (1948).
4) O. Wintersteiner, M. Moore: *Ibid.*, **65**, 1503 (1943).
5) A.C. Ott, M.F. Murray, R.L. Pederson: *Ibid.*, **74**, 1239 (1952).

mixture of two isomeric pyranyl ethers was obtained. Chromatography of this mixture on alumina furnished one of the two isomers as a crystalline product (Ib), m.p. 185~190°, $[\alpha]_D$ −73°. Hydrolysis of Ib with methanolic potash and subsequent oxidation of Ic with chromium trioxide in pyridine[6] led to the ketone (IIa). IIa was hydrolyzed with hydrochloric acid in ethanol to IIb, which upon bromination in glacial acetic acid in the presence of hydrobromic acid[7] afforded the bromo ketone (III). Dehydrobromination of III in dimethylacetamide with calcium carbonate[8] led to IV, which was then epoxidized with alkaline hydrogen peroxide[9] to furnish the epoxy ketone (V).

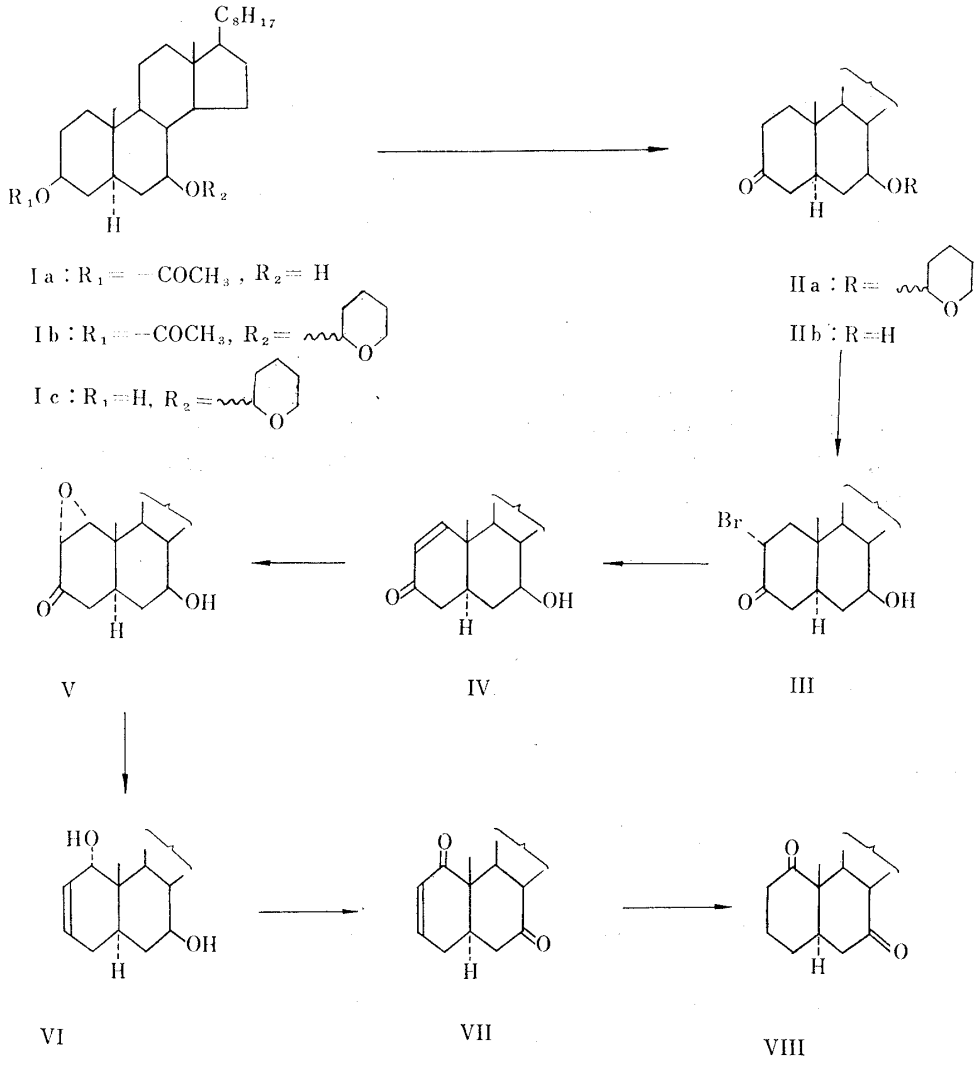

Chart 1.

Subsequent application of the recently recorded hydrazine reduction[10] of V to the allylic alcohol (VI) constituted the simplest access to 1-oxygenated steroid. VI was then oxidized with chromium trioxide-sulfuric acid[11] in acetone to VII. Catalytic hydrogenation of VII with 10% palladium charcoal in methanol provided cholestane-1,7-dione (VIII).

6) R.E. Beyler, L.H. Sarett : J. Am. Chem. Soc., **75**, 422 (1953).
7) L.F. Fieser, X.A. Dominguez : *Ibid.*, **75**, 1704 (1953).
8) G.F.H. Green, A.G. Long : J. Chem. Soc., **1961**, 2532.
9) P.L. Julian, E.W. Meyer, W.J. Karpel, I.R. Waller : J. Am. Chem. Soc., **72**, 5145 (1950); P. Striebel, C. Tamm : Helv. Chim. Acta, **37**, 1094 (1954).
10) P.S. Wharton, D.H. Bohlen : J. Org. Chem., **26**, 3615 (1961); P.S. Wharton : *Ibid.*, **26**, 4781 (1961); C. Djerassi, D.H. Williams, B. Berkoz : *Ibid.*, **27**, 2205 (1962).
11) P. Bladon, J.M. Fabian, H.B. Henbest, H.P. Koch, G.W. Wood : J. Chem. Soc., **1951**, 2407.

Experimental*2

Cholestane-3β,7β-diol 3-Acetate (Ia)[4]——$NaBH_4$ (1.3 g.) was added to a solution of 10 g. of 3β-acetoxycholestan-7-one[1~3] in 200 ml. of MeOH and 150 ml. of Et_2O. The solution was stirred for 2 hr., diluted with H_2O, neutralized with dil. HCl, and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried, and evaporated, yielding 10 g. of a sticky residue. Crystallization from MeOH–Et_2O gave 5.2 g. of Ia, m.p. 112~115°, $[\alpha]_D$ −2° (c=2.43). IR λ_{max} μ: 2.77, 5.80, 7.98.

7β-(Tetrahydro-2-pyranyloxy)cholestan-3β-ol Acetate (Ib)——To a solution of 19 g. of Ia in 380 ml. of anhyd. Et_2O was added 21 g. of 2,3-dihydropyran (freshly distilled from NaOH pellets) followed by 6 drops of conc. HCl. The solution was set aside for 10 days. Washing with H_2O, drying, and evaporation left 30 g. of an oil. This was chromatographed in hexane on 300 g. of Merck's Al_2O_3. The hexane eluate fraction gave 21 g. of an oily material which resisted crystallization after various attempts. This product seemed to be one of the two isomeric pyranyl ethers since it, after hydrolysis with MeOH–KOH followed by oxidation with CrO_3–pyridine and acid hydrolysis, led to IIb. Elution with hexane–benzene (1:1) afforded 4 g. of Ib as a crystalline product, m.p. 185~190°, from Me_2CO. IR λ_{max} μ: 5.80, 7.98. $[\alpha]_D$ −73° (c=2.16). *Anal.* Calcd. for $C_{34}H_{58}O_4$: C, 76.93; H, 11.01. Found: C, 76.78; H, 11.02.

7β-(Tetrahydro-2-pyranyloxy)cholestan-3β-ol (Ic)——Ib (1 g.) was heated under reflux with 50 ml. of 5% MeOH–KOH for 2 hr. The solution was concentrated *in vacuo*, diluted with H_2O, and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried, and evaporated, leaving 1 g. of product. Recrystallization from benzene yielded 700 mg. of Ic, m.p. 190~195°, IR: λ_{max} 2.78 μ. *Anal.* Calcd. for $C_{32}H_{56}O_3$: C, 78.63; H, 11.55. Found: C, 78.85; H, 11.44.

7β-(Tetrahydro-2-pyranyloxy)cholestan-3-one (IIa)——A solution of 700 mg. of Ic in 10 ml. of pyridine was added with sitrring to a suspension of 1.0 g. of CrO_3 in 10 ml. of pyridine. After stirring at room temperature for 18 hr., 5 ml. of 95% EtOH was added and the solution was stirred for a further 30 min. Et_2O was added to the reaction mixture and the Et_2O layer was collected by decantation. This manipulation was repeated several times, and the combined Et_2O solutions were washed successively with dil. NaOH and H_2O, dried, and evaporated to afford 600 mg. of crude material. Recrystallization from Me_2CO gave 400 mg. of IIa, m.p. 189~191°, IR: λ_{max} 5.86μ. *Anal.* Calcd. for $C_{32}H_{54}O_3$: C, 78.96; H, 11.18. Found: C, 78.67; H, 11.15.

7β-Hydroxycholestan-3-one (IIb)——A solution of 15 g. of IIa in 5 ml. of conc. HCl, 20 ml. of H_2O, and 350 ml. of 95% EtOH was heated under reflux for 1.5 hr. The solution was concentrated, diluted with H_2O, and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried, and evaporated. Crystallization of the product from MeOH gave 6.7 g. of IIb, m.p. 163~164°, IR λ_{max} μ: 2.77, 5.85, $[\alpha]_D$ +28° (c=2.25). *Anal.* Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.77; H, 11.54.

2α-Bromo-7β-hydroxycholestan-3-one(III)——IIb (1.55 g.) was dissolved in 50 ml. of glacial AcOH and 0.7 g. of Br_2 in 10 ml. of glacial AcOH containing 1 drop of 48% HBr was added dropwise under stirring at room temperature each time the solution was decolorized. The solution was poured into H_2O, and the resulting precipitate was collected by filtration and dissolved in Et_2O. The Et_2O solution was washed with H_2O, dil. NH_4OH, and H_2O, and dried. Evaporation of the solvent yielded 2.0 g. of III, m.p. 137~139°, after recrystallization from Me_2CO. $[\alpha]_D$ +26° (c=1.96). IR λ_{max} μ: 2.80, 5.79. *Anal.* Calcd. for $C_{27}H_{45}O_2Br$: C, 67.34; H, 9.41. Found: C, 67.87; H, 9.62.

7β-Hydroxycholest-1-en-3-one (IV)——III (3.0 g.) was refluxed with 2.4 g. of $CaCO_3$ in 30 ml. of dimethylacetamide for 30 min., diluted with H_2O, and extracted with Et_2O. The Et_2O extract was washed with dil. HCl, then H_2O, dried, and evaporated, yielding 2.5 g. of product. This was chromatographed in benzene on 50 g. of Woelm neutral Al_2O_3. Elution with benzene and benzene–Et_2O (1:1) gave 1.3 g. of the compound, m.p. 80~81°, after recrystallization from hexane. IR λ_{max} μ: 6.05, 6.19, 6.31. UV: λ_{max} 286 mμ (ε 22200). *Anal.* Calcd. for $C_{27}H_{42}O$: C, 84.75; H, 11.07. Found: C, 84.87; H, 10.98. This compound was shown by direct comparison (mixture melting point and IR) to be identical with cholest-4,6-dien-3-one,[12] kindly supplied by Professor Arigoni.

Elution with benzene–Et_2O (1:1) furnished 1.0 g. of V, m.p. 156~158°, after crystallization from MeOH–Me_2CO. IR λ_{max} μ: 2.78, 5.98, 6.23. UV: λ_{max} 230 mμ (ε 10400). $[\alpha]_D$ +52° (c=1.95). *Anal.* Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.67; H, 11.01.

7β-Hydroxy-1α,2α-epoxycholestan-3-one (V)——A solution of 400 mg. of IV in 40 ml. of MeOH was cooled with ice, and 0.6 ml. of 4*N* NaOH and 1.2 ml. of 30% H_2O_2 were added successively. The mixture was kept at 5° for 15 hr. After dilution with H_2O, the solution was extracted with $CHCl_3$, the $CHCl_3$

*2 Melting points are uncorrected. All rotations were determined at room temperature in $CHCl_3$ solution. UV spectra were measured in 95% EtOH on a Shimadzu Self-Recording UV-Spectrophotometer "SV-50." IR spectra were determined in $CHCl_3$ solution on a Hitachi Infrared-Spectrometer "EPI-S." Microanalyses were performed by Miss Y. Umano and Miss Y. Saito in the Microanalytical Laboratory of this Faculty.

12) H. P. Throndsen, G. Cainelli, D. Arigoni, O. Jeger: Helv. Chim. Acta, **45**, 2344 (1962).

extract was washed with H_2O, dried, and evaporated to yield 300 mg. of product. Crystallization from Me_2CO gave V, m.p. 144~147°, $[\alpha]_D$ +77°(c=1.78), IR λ_{max} μ : 2.78, 5.85. *Anal.* Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found : C, 77.73; H, 10.74.

Cholest-2-ene-1α,7β-diol (VI)——V (420 mg.) and 3.6 ml. of 80% $NH_2NH_2 \cdot H_2O$ were heated at 135~140° for 30 min. The solution was diluted with H_2O, extracted with $CHCl_3$, and the $CHCl_3$ extract was dried and evaporated. The residue was chromatographed in $CHCl_3$ on 10 g. of Mallinckrodt's silicic acid, and elution with $CHCl_3$ furnished 160 mg. of VI, m.p. 149~151°, after recrystallization from hexane-CH_2Cl_2. $[\alpha]_D$ +88° (c=1.80). IR λ_{max} μ : 2.79, 6.13. *Anal.* Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found : C, 80.81; H, 11.39.

Cholest-2-ene-1,7-dione (VII)——The standard chromic acid solution[11] (0.2 ml., equivalent to 53.4 mg. of CrO_3) was added dropwise at 0° during 10 min. to a solution of 100 mg. of VI in 10 ml. of Me_2CO. Stirring was continued for a further 30 min. at room temperature. Dilution with H_2O and extraction with $CHCl_3$ provided 100 mg. of crystalline product, which was passed in hexane solution through 5 g. of Merck's Al_2O_3. The material eluted with hexane-benzene (1:1) and benzene was crystallized from 95% EtOH to afford 83 mg. of VII, m.p. 130~132°, $[\alpha]_D$ −26° (c=1.15), IR λ_{max} μ : 5.84, 5.96, 6.13. UV : λ_{max} 225 mμ (ε 7770). *Anal.* Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found : C, 81.28; H, 10.43.

Cholestan-1,7-dione (VIII)——VII (82 mg.) was hydrogenated in MeOH with 10% Pd-C at room temperature and atmospheric pressure until the uptake of H_2 ceased. Filtration of the catalyst and evaporation of the filtrate to dryness left 82 mg. of a crystalline residue, which was chromatographed in hexane on 4 g. of Merck's Al_2O_3. Elution with hexane-benzene (1:1) and recrystallization from 95% EtOH afforded 70 mg. of VIII, m.p. 110~111°, $[\alpha]_D$ +40°(c=1.48), IR : λ_{max} 5.85 μ. *Anal.* Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found : C, 80.66; H, 11.36.

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