(m.p. 130~132°, white prism from benzene) and 0.06 g. of isonicotinamide (5 %) were obtained. From 2) and 3) 0.15 g. and 0.17 g. of the aldoxime were respectively obtained. Total yield of the aldoxime was 0.8 g. (65.6 %).

N-Oxidation of Isonicotinaldehyde Oxime with Monoperphthalic Acid——To a solution of 0.22 g. of isonicotinaldehyde oxime in 10 ml. of Me_2CO, 6 ml. of Et_2O solution of monoperphthalic acid (0.0075 g. of active O_2 in 1 ml.) was added. The mixture was allowed to stand for a week in a refrigerator. After precipitated phthalic acid was removed by filtration, the filtrate was condensed. The residual solid was recrystallized from EtOH to white needles, m.p. 215~217° (decomp.). Yield, 0.18 g. (72 %). *Anal.* Calcd. for $C_6H_6O_2N_2$: C, 52.17, H, 4.38, N, 20.28. Found : C, 52.16, H, 4.40, N, 19.99.

Reaction of Isonicotinonitrile 1-Oxide with $NaNH_2$——To a mixture of 0.05 g. of isonicotinonitrile 1-oxide and 0.02 g. of $NaNH_2$ in 10 ml. of liq. NH_3, was added 0.05 g. of amyl nitrite and 0.05 g. of iso-amyl alcohol in 10 ml. of liq. NH_3. The reaction mixture was concentrated to 3 ml. After allowing to stand for 10 min. at room temperature., 0.04 g. of NH_4Cl in 5 ml. of NH_3 was added. Liq. NH_3 was evaporated and the residue was purified by recrystallization from EtOH to give 0.04 g. of isonicotinamide 1-oxide, m.p. 293~296° (decomp.).

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Summary

The reactions of picolines and their N-oxides with amyl nitrite in the presence of metal amide or sodium hydroxide in liquid ammonia afforded the corresponding aldoximes and acid amides in comparatively good yields. It may be concluded that the methyl group of picoline is much less reactive than that of N-oxide and that the reactivity of methyl group in the pyridine ring increases in the order of 3-, 2-, and 4-position.

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83. Tatsuhiko Nakano,[*1] Masahisa Hasegawa,[*1] and Carl Djerassi[*2] : Bromination of 2-Oxo Steroids.[1]

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The most important and generally accepted views on the stereochemistry of the bromination of cyclohexanones in general and keto steroids in particular are attributed to Corey.[2] According to these generalizations, the kinetically controlled bromination product is always that in which the bromine atom assumes an axial orientation, since orbital overlap in the transition state is most favorable in such a geometric arrangement. If there exist no serious steric interactions between the axial bromine atom and other substituents, then the kinetic product is also the thermodynamically favored one.

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1) Most of this work was done by one of us (T. N.) during the tenure of his postdoctorate fellowship at Stanford University while on leave from Kyoto University. For preliminary communication see C. Djerassi, T. Nakano, Chem. & Ind. (London), **1960**, 1385.

2) E. J. Corey : J. Am. Chem. Soc., **75**, 2301 (1953); *Ibid.*, **76**, 175 (1954); Experientia, **9**, 329 (1953).

In the presence of such steric interference, the axial bromo ketone is converted into the equatorial one under conditions of thermodynamic control. However, recent studies[3] on the bromination of certain 3-oxo-steroids have disclosed that this commonly accepted stereochemical course of such brominations is not necessarily correct in all instances as far as the isolated products are concerned. Consequently, it seemed interesting to undertake a similar investigation of steroids with carbonyl groups in other positions of the molecule, such as 2-oxo-steroids. The present paper describes the hitherto unreported bromination[4] of cholestan-2-one (IV) together with some quantitative aspects of various optical rotatory dispersion measurements of its bromination products.

Cholestan-2-one used for this investigation was synthesized through a known route. Cholest-2-ene (I) prepared by the method of Douglas *et al.*[5] was treated with N-bromosuccinimide[6] in the presence of perchloric acid to afford 3α-bromocholestan-2β-ol (II) which was then oxidized with chromium trioxide to 3α-bromocholestan-2-one (III).[7] The latter III, when debrominated with zinc dust[7] in acetic acid, gave cholestan-2-one (IV) in a comparatively poor yield since in this case some cholest-2-ene was also produced. Debromination with chromous chloride,[8] however, furnished cholestan-2-one in an almost quantitative yield.

Direct bromination of cholestan-2-one (IV) was carried out by treating it with one equivalent of bromine in acetic acid in the presence of hydrogen bromide. In contrast to the extremely slow halogenation[9] of cholestan-1-one, bromination proceeded very rapidly, and there was obtained 3α-bromocholestan-2-one (III), which had already been prepared earlier[7] by oxidation of 3α-bromocholestan-2β-ol. Quantitative calculation

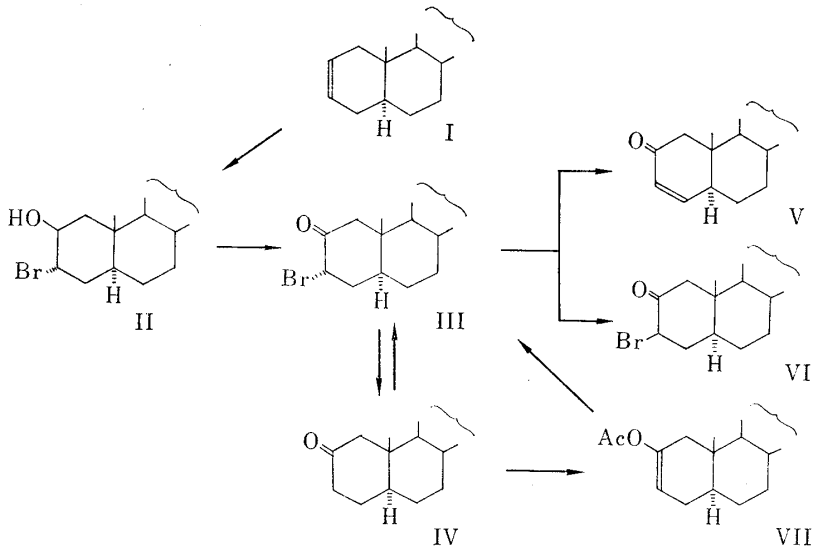


Chart 1.

3) C. Djerassi, N. Finch, R. Mauli : J. Am. Chem. Soc., **81**, 4997 (1959); C. Djerassi, N. Finch, R.C. Cookson, C.W. Bird : *Ibid.*, **82**, 5488 (1960); R. Mauli, H.J. Ringold, C. Djerassi : *Ibid.*, **82**, 5494 (1960); R. Villotti, H.J. Ringold, C. Djerassi : *Ibid.*, **82**, 5693 (1960).
4) L.F. Fieser, M. Fieser : "Steroids," 1959, Chapter 8 (New York : Reinhold Publ. Corp.).
5) G.H. Douglas, P.S. Ellington, G.D. Meakins, R. Swindells : J. Chem. Soc., **1959**, 1720.
6) In one experiment, 2β-bromocholestan-3α-ol was obtained by the 'abnormal addition' of hypobromous acid to cholest-2-ene. A similar phenomenon was also observed in the eremophilone series. See L.H. Zalkow, F.X, Markley, C. Djerassi, J. Am. Chem. Soc., **82**, 6354 (1960).
7) G.H. Alt, D.H.R. Barton : J. Chem. Soc., **1954**, 4284.
8) G. Rosenkranz, O. Mancera, J. Gatica, C. Djerassi : J. Am. Chem. Soc., **72**, 4077 (1950).
9) H.P. Sigg, C. Tamm : Helv. Chim. Acta, **43**, 1402 (1960). See also C.W. Shoppee, S.K. Roy, B.S. Goodrich, J. Chem. Soc., **1961**, 1583.

using the optical rotatory dispersion curve[10] of the total crude bromination product with reference to those of the pure 3α-(III) and 3β-(VI) bromo isomers described below showed that no more than ca. 56% of 3α-bromo compound could have been produced in this bromination. For the sake of comparison, physical constants of cholestan-2-one (IV) and its bromo derivatives are listed in Table I.

Table I. Constants of Cholestan-2-one and its Bromo Derivatives

Compound	m.p. (C°)	$[\alpha]_{589}$	UV λ_{max}^{EtOH} mμ (log ε)	IR $\lambda_{max}^{CHCl_3}$ μ	Rotatory dispersion curve peak or trough
Cholestan-2-one	130~131	+ 25°	293 (1.39)	5.89	310 (+1249°)
3α-Bromocholestan-2-one	153~154	+150°	310 (2.10)	5.87	332.5 (+2760°)
3β-Bromocholestan-2-one	119~121	+ 60°	301 (1.88)	5.82	318 (+1112°)
1α-Bromocholestan-2-one	95~ 96	− 22°	306 (1.92)	5.86	327.5 (− 977°)

Table II. Hydrogen Bromide Catalyzed Equilibration of 3α-Bromocholestan-2-one and 3β-Bromocholestan-2-one

Initial $[\alpha]_D$ value in acetic acid at room temperature	3α-Bromocholestan-2-one +152° (c=0.48)	3β-Bromocholestan-2-one + 42° (c=0.45)
$[\alpha]_D$ after 24 hr. at room temperature with addition of two drops of saturated hydrogen bromide in acetic acid	+104° (c=0.48)	+100° (c=0.45)

Dehydrobromination of III with anhydrous lithium carbonate and lithium bromide[11] in dimethylformamide solution furnished cholest-3-en-2-one (V), m.p. 112~113°, $[\alpha]_D^{26}$ +109° (c=1.35, $CHCl_3$), UV : $\lambda_{max}^{95\%EtOH}$ 230 mμ (log ε 3.97), as well as 3β-bromocholestan-2-one (VI). The equatorial nature of the bromine atom in compound (VI) was established by ultraviolet, infrared, and optical rotatory dispersion measurements. Equilibration experiments of pure 3α-(III) and 3β-(VI) bromocholestan-2-ones with hydrogen bromide in acetic acid for 24 hours (see Table II) showed, as calculated from the changes of their $[\alpha]_D$ values (and subsequently confirmed by direct isolation experiments), an equilibrium composition of approximately 57% III and 43% VI.[12]

It is interesting to note that treatment of 3α-bromocholestan-2-one (III) with lithium carbonate and lithium bromide in dimethylformamide yielded the epimeric 3β-bromo compound (VI) and that this isomerization also occurred when the 3α-bromide was heated for a short time in dimethylformamide with lithium carbonate alone. However, when the 3α-bromide was heated with collidine[13] alone, no appreciable amount of 3β-bromo compound was produced. Heating of the 3α-bromo compound either with lithium bromide or lithium chloride in acetone or alone with dimethylformamide and chromatography of the respective total crude products on alumina did not furnish any detectable amount of epimeric 3β-bromo or 3β-chloro compound.[14] In contrast to the smooth dehydrohalogenation of 2α-bromochlolestan-3-one, reaction of 3α-bromocholestan-2-one with 2,4-dinitrophenylhydrazine[15] did not proceed in a satisfactory manner and provided in poor yield an unidentified 2,4-dinitrophenylhydrazone.[16]

Enol acetylation of choloestan-2-one (IV) was conducted by using isopropenyl acetate-*p*-toluenesulfonic acid[17] or acetic anhydride-perchloric acid.[18] In either case, there

10) C. Djerassi : "Optical Rotatory Dispersion," 1960, Chapter 9 (New York : McGraw-Hlli Book Co...)

11) R. Joly, J. Warnant : Bull. Soc. chim. France, **1958**, 367. See also B. Pelc, S. Hermanek, J. Holubek, Coll. Czech. Chem. Comm., **26**, 1852 (1961).

12) It is pertinent to note that K.L. Williamson and W.S. Johnson (J. Org. Chem., **26**, 4563 (1961)) observed only partial conversion of 3α-acetoxycholestan-2-one to the 3β-epimer upon treatment with acid, in contrast to the virtually quantitative transformation of the axial 2β-acetoxycholestan-3-one into its 2α-isomer.

13) M. Uksoković, M. Gut, R.I. Dorfman : J. Am. Chem. Soc., **82**, 958 (1960).

was obtained a single, homogeneous enol acetate (VII), m.p. 76~77°, which upon kinetically controlled bromination[3] using epichlorohydrin[19] in carbon tetrachloride led to 3α-bromocholestan-2-one (III). Examination of the optical rotatory dispersion curve[10] of the crude enol acetate bromination product with reference to those of the pure 3α-(III) and 3β-(VI) bromo isomers showed that no more than 9% of the equatorial 3β-bromo ketone (VI) could have been present. Corey's generalization[2] is, therefore, applicable to the kinetically controlled bromination of steroidal 2-keto enol acetates.

Of interest was the observation that enolisation of 2-oxo steroids apparently proceeds unilaterally towards C-(3). No trace of 1-bromocholestan-2-one was encountered either in the bromination of the ketone (IV) or of its enol acetate (VII). Formation of 3α-(III) or 3β-(VI) bromocholestan-2-one through migration of an initially formed 1-bromo-2-ketone was excluded by preparing 1α-bromocholestan-2-one (X) by an alternative procedure involving oxidation of 1α-bromochlestan-2β-ol (IX)[20] and subjecting the ketone (X) to hydrogen bromide catalyzed equilibration. Cholest-1-ene (VIII)[20] required as the starting material was prepared in one step from cholest-1-en-3-one by reduction with lithium aluminum hydride in the presence of anhydrous aluminum chloride[21] or by the procedure of Henbest and Wilson.[20] The 1α-bromo ketone (X) thus obtained, when equilibrated in acetic acid solution in the presence of hydrogen bromide, was found to be unchanged, the axial character of the bromine atom having been established by ultraviolet, infrared, and optical rotatory dispersion (negative Cotton effect in agreement with axial haloketone rule[10]) criteria.

In connection with the above investigation, we have also had occasion to treat successively 1α,2α-epoxycholestane (XI) with hydrogen bromide and chromium trioxide to

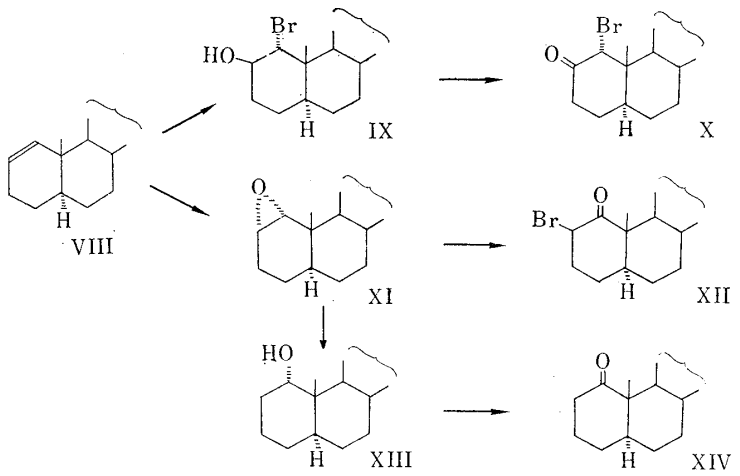


Chart 2.

14) Compare similar experiments on certain 2-oxo-steroids by N.L. Wendler and H.L. Slates (J. Org. Chem., **26**, 4738 (1961)).

15) V.R. Mattox, E.C. Kendall : J. Am. Chem. Soc., **70**, 882 (1948); C. Djerassi : *Ibid.*, **71**, 1003 (1949).

16) R.E. Engle (Ph. D. thesis, Wayne State University 1958, p. 55) was able to effect in poor yield dehydrobromination of 3α-bromo-17β-hydroxyandrostan-2-one 17-propionate with 2,4-dinitrophenylhydrazine to the corresponding Δ^3-2-ketone 2,4-dinitrophenylhydrazone.

17) R.B. Moffett, D.I. Weisblat : J. Am. Chem. Soc., **74**, 2183 (1952).

18) D.H.R. Barton, R.M. Evans, J.C. Hamlet, P.G. Jones, T. Walker : J. Chem. Soc., **1954**, 747.

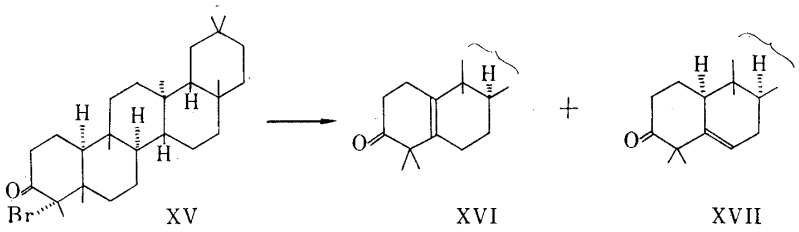
19) See M.P. Hartshorn, E.R.H. Jones : J. Chem. Soc., **1962**, 1312.

20) H.B. Henbest, R.A.L. Wilson : J. Chem. Soc., **1959**, 4136.

21) *a*) J. Broome, B.R. Brown, A. Roberts, A.M.S. White : J. Chem. Soc., **1960**, 1406. *b*) See however R. Albrecht, C. Tamm : Helv. Chim. Acta, **40**, 2216 (1957).

give 2β-bromocholestan-1-one (XIII) (strong negative Cotton effect), which could be obtained in very poor yield by direct bromination of cholestan-1-one[9] (XIV). In connection with the reported sluggishness[9] of the bromine uptake of cholestan-1-one, it is pertinent to note that we have been unable to prepare an enol acetate of this ketone.

Since J. M. Beaton, *et al.* reported that 4-bromofriedelin (XV),[22] on treatment with silver acetate, yielded XVI and XVII, a similar reaction was now performed on 1α-bromocholestan-2-one (X). However, no migration of the angular methyl group was observed and only 1-acetoxycholestan-2-one was obtained.



XV XVI XVII

Chart 3.

Experimental*3

Cholest-2-ene (I)[5]——The *p*-toluenesulfonate (20 g.) of cholestan-3β-ol was dissolved in 250 cc. of anhyd. benzene, poured unto 200 g. of basic Woelm alumina (activity I), and the mixture was kept at room temperature for 2 days with occasional shaking. The mixture was then poured on a column consisting of 300 g. of Alcoa activated alumina in benzene. Elution with benzene (ca. 1 L.) and crystallization from AcOEt-MeOH gave 10.17 g. of cholest-2-ene, m.p. 72~73°.

3α-Bromocholestan-2β-ol (II)——N-Bromosuccinimide (4.46 g.) in 50 cc. of dioxane and 4.5 cc. of *N* $HClO_4$ were added in succession to a solution of 8.92 g. of cholest-2-ene in 200 cc. of 5% aq. *tert*-BuOH and 100 cc. of dioxane at room temperature. After keeping at room temperature overnight, the solution was concentrated *in vacuo* below 45° to remove most of the solvent, diluted with H_2O, and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried, and evaporated, yielding 11.55 g. of a sticky residue. This was chromatographed in benzene on 300 g. of Merck's acid-washed alumina, and elution with 9:1 benzene-Et_2O gave 5.27 g. of product, which after crystallization from Et_2O-MeOH showed m.p. 135~136°.[7]

3α-Bromocholestan-2-one (III)[7]——3α-Bromochlestan-2β-ol (2.43 g.) in 150 cc. of AcOH was treated with 0.53 g. of CrO_3 in a minimum of H_2O at room temperature overnight. Crystallization of the product (which had precipitated during the oxidation) from $CHCl_3$-MeOH gave 1.41 g. of 3α-bromocholestan-2-one, m.p. 153~154°. UV : λ_{max}^{EtOH} 310 mμ (log ε 2.10). IR : $\lambda_{max}^{CHCl_3}$ 5.87 μ. R.D. in MeOH (c=0.05, 700~260 mμ) : $[\alpha]_{700}$ +68°, $[\alpha]_{589}$ +160°, $[\alpha]_{335}$ +2824°(peak), $[\alpha]_{285}$ −2820°(trough), $[\alpha]_{260}$ −1912°.

Cholestan-2-one (IV)——a) 3α-Bromocholestan-2-one (3.42 g.) was dissolved in 600 cc. of Me_2CO and treated under stirring in a current of N_2 in portions with ca. 140 cc. of freshly prepared $CrCl_2$ solution[8] over a period of 30 min. After stirring for a further 30 min., the solution was concentrated *in vacuo*, the residue was taken up in Et_2O, washed with H_2O, dried, and evaporated. Crystallization of the residue from Me_2CO-MeOH gave 2.72 g. of cholestan-2-one, m.p. 126~127°. Chromatography on Merck's acid-washed alumina in benzene raised the m.p. to 130~131°. IR : $\lambda_{max}^{CHCl_3}$ 5.89 μ. UV : λ_{max}^{EtOH} 293 mμ (log ε 1.39). R.D. in MeOH (c=0.05, 700~260 mμ) : $[\alpha]_{700}$ +21°, $[\alpha]_{589}$ +25°, $[\alpha]_{310}$ +1249°(peak), $[\alpha]_{267.5}$ −1176°(trough), $[\alpha]_{260}$ −1071°.

b) The bromo ketone (1.00 g.) was refluxed in 70 cc. of AcOH with 12.52 g. of Zn dust[7] for 4 hr. The crystalline product obtained represented a mixture which after chromatography in benzene on 30 g. of Merck's acid-washed alumina was separated into 0.14 g. of cholest-2-ene and 0.38 g. of cholestan-2-ene.

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*3 All melting points are uncorrected. The infrared and ultraviolet spectral measurements were performed by Miss B. Bach, while the rotatory dispersion data are due to Mrs. T. Nakano. All microanalyses were carried out by Dr. A. Bernhardt, Mulheim, Germany. Unless noted otherwise all rotations were measured in chloroform solution.

22) J. M. Beaton, F. S. Spring, R. Stevenson, J. L. Stewart : Tetrahedron, **2**, 246 (1958).

Bromination of Cholestan-2-one (IV)——Cholestan-2-one (0.20 g.) was dissolved in 20 cc. of glacial AcOH and 83 mg. of Br_2 in 10 cc. of glacial AcOH containing one drop of 48% aq.HBr was added dropwise under stirring at room temperature each time the solution was decolorized (ca. 10 min.). The solution was poured into H_2O, the resulting precipitate was filtered and dissolved in Et_2O. The Et_2O solution was washed once with H_2O, dried, and evaporated, yielding a crude crystalline residue, m.p. 137~140°. This was dried *in vacuo* at room temperature for 2 days. R.D. in MeOH (c=0.05, 700~265 mμ): $[\alpha]_{700}$ +47°, $[\alpha]_{589}$ +101°, $[\alpha]_{332.5}$ +1690° (peak), $[\alpha]_{277.5}$ −1780° (trough), $[\alpha]_{265}$ −154°. The above crude crystalline product, upon recrystallization once from Me_2CO, showed m.p. 148~149°, undepressed by admixture with 3α-bromocholestan-2-one. Yield, 0.18 g.

Reaction of 3α-Bromocholestan-2-one (III). a) With Lithium Carbonate and Lithium Bromide[11]——A mixture of 0.75 g. of 3α-bromo ketone, 0.70 g. of anhyd. Li_2CO_3, 0.80 g. of anhyd. LiBr in 15 cc. of dimethylformamide was heated under a dry N_2 current at 100° for 12.5 hr. The reaction mixture was acidified with 5% HCl, extracted with Et_2O, the Et_2O extract was washed with 10% HCl, then H_2O, dried, and evaporated. The crystalline residue (0.56 g.) was chromatographed in hexane on 15 g. of Merck's acid-washed alumina. Fractions 6~8 (6:1 to 3:1 hexane-benzene eluate) gave 0.10 g. of 3α-bromocholestan-2-one and fraction 9 (1:1 hexane-benzene eluate) gave 0.11 g. of 3β-bromocholestan-2-one, m.p. 119~121°, after crystallization from Me_2CO-MeOH. $[\alpha]_D^{26}$ +60° (c=0.83, $CHCl_3$). IR: $\lambda_{max}^{CHCl_3}$ 5.82 μ. UV: $\lambda_{max}^{Dioxane}$ 282 mμ (log ε 1.64). R.D. in MeOH (c=0.25, 700~261 mμ): $[\alpha]_{700}$ +60°, $[\alpha]_{589}$ +80°, $[\alpha]_{318}$ +1112° (peak), $[\alpha]_{266\sim267}$ −1464° (trough), $[\alpha]_{261}$ −1360°. *Anal.* Calcd. for $C_{27}H_{45}OBr$: C, 69.65; H, 9.75. Found: C, 70.05; H, 10.14.

Fractions 11~13 (benzene eluate) gave 0.19 g. of cholest-3-en-2-one, m.p. 112~113°, after crystallization from Me_2CO-MeOH. $[\alpha]_D^{26}$ +109° (c=1.35, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 83.92; H, 11.40. IR $\lambda_{max}^{CHCl_3}$ μ: 6.03, 11.40. UV: λ_{max}^{EtOH} 230 mμ (log ε 3.97). R.D. in dioxane (c=0.10, 700~280 mμ): $[\alpha]_{700}$ +49°, $[\alpha]_{390}$ +260', $[\alpha]_{382.5}$ +253°, $[\alpha]_{367.5}$ +359°, $[\alpha]_{355}$ +589°, $[\alpha]_{350}$ +557°, $[\alpha]_{340}$ +722°, $[\alpha]_{335}$ +665° $[\alpha]_{327}$ +752°, $[\alpha]_{322.5}$ +724°, $[\alpha]_{310}$ +811°, $[\alpha]_{280}$ +1500°.

b) With Calcium Carbonate——To a boiling solution of 1.00 g. of 3α-bromo ketone in 15 cc. of dimethylformamide was added under stirring 0.42 g. of $CaCO_3$ (Merck) at once. After 10 min., the solution was evaporated *in vacuo*, the residue was taken up in Et_2O, and the Et_2O solution was washed with H_2O, dried, and evaporated. The crystalline residue was recrystallized from Me_2CO to give 0.41 g. of 3α-bromocholestan-2-one, m.p. 142~143°. The mother liquor, after evaporation, was chromatographed in hexane on 18 g. of Merck's acid-washed alumina, whereupon, besides the starting material (3α-bromocholestan-2-one), there was obtained 57 mg. of 3β-bromocholestan-2-one, m.p. 114~116°.

c) With Collidine——3α-Bromo ketone (0.40 g.) was refluxed with 10 cc. of freshly distilled *s*-collidine for 2 hr. in an atmosphere of dry N_2. The solution was cooled, and filtered from the precipitate of collidine hydrobromide. The filtrate was acidified with 5% HCl to Congo red, extracted with Et_2O, and the Et_2O extract was washed with H_2O, dried, and evaporated, yielding 0.19 g. of a yellow crystalline residue. This was purified by recrystallization from Me_2CO-MeOH to show m.p. 105~110°. The infrared spectrum of this substance ($\lambda_{max}^{CHCl_3}$ μ: 5.86, 6.01) and its ultraviolet spectrum (λ_{max}^{EtOH} 228 mμ (log ε 3.50)) suggested that this substance was probably a mixture of 3α-bromocholestan-2-one and cholest-3-en-2-one (1:9). Because of the small amount, this mixture was not subjected to further separation by chromatography.

Enol Acetate of Cholestan-2-one. a) With Isopropenyl Acetate and *p*-Toluenesulfonic Acid[17]——A solution of 2.06 g. of cholestan-2-one and 0.3 g. of *p*-toluenesulfonic acid monohydrate in about 20 cc. of isopropenyl acetate was slowly distilled with a fractionating column for 10 hr., during which time more isopropenyl acetate was added from time to time to keep the volume above 10 cc. The reaction mixture was evaporated below 50° *in vacuo* to dryness, the residue was taken up in Et_2O, washed with 5% aq· $NaHCO_3$, then H_2O, dried, and evaporated, yielding 2.35 g. of a brown oil. This was chromatographed in hexane on 50 g. of Merck's acid-washed alumina. Fractions 2~7 (9:1 to 6:1 hexane-benzene eluate) gave 1.73 g. of cholest-2-en-2-ol acetate, m.p. 76~77° from Me_2CO-MeOH. $[\alpha]_D^{26}$ +55° (c=1.23, $CHCl_3$). IR $\lambda_{max}^{CHCl_3}$ μ: 5.74, 5.91. *Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.05; H, 11.30.

b) With Acetic Anhydride and Perchloric Acid[18]——Cholestan-2-one (1.02 g.) in 10 cc. of CCl_4 was treated with 0.02 cc. of 50% aq. $HClO_4$ in 0.54 g. of Ac_2O at room temperature. After 2 hr., the solution was washed with 5% aq. Na_2CO_3, then H_2O, dried, and evaporated *in vacuo* to dryness. The residue was chromatographed in hexane on 30 g. of Merck's acid-washed alumina. Fractions 3~6 (9:1 hexane-benzene eluate) gave 0.43 g. of cholest-2-en-2-ol acetate, m.p. 75~76°, from Me_2CO-MeOH. No other crystalline product was isolated from the other fractions.

Bromination[19] **of Cholest-2-en-2-ol Acetate (VII)**——A solution of 0.25 g. of Br_2 in 2 cc. of dry CCl_4 was added to an ice-cold and stirred solution of 0.62 g. of the enol acetate in 20 cc. of dry CCl_4 containing 0.2 g. of freshly distilled epichlorohydrin during a period of 35 min. The solution was stirred for a further 25 min., diluted with $CHCl_3$, washed with aq. Na_2SO_3, H_2O, and finally dried over anhyd. $MgSO_4$. Evaporation of the solvent *in vacuo* yielded 0.78 g. of a crystalline mass, m.p. 141~144°.

This was dried *in vacuo* at room temperature for 2 days. R.D. in MeOH (c=0.05, 700~270 mμ): $[\alpha]_{700}$ +129°, $[\alpha]_{332.5}$ +2660° (peak), $[\alpha]_{280}$ −2280° (trough), $[\alpha]_{270}$ −2040°. Recrystallization once from $CHCl_3$-MeOH showed m.p. 152~153°. Yield, 0.44 g. A mixture m.p. with 3α-bromocholestan-2-one showed no depression.

Cholest-1-ene (VIII)——Cholestanol was oxidized by the method of Org. Synth., Coll. II, p. 139, to cholestan-3-one, which according to the method[23] was brominated to give 2α-bromocholestan-3-one.

2α-Bromocholestan-3-one (113.1 g.) was refluxed with 1 L. of dried (over KOH) freshly distilled *s*-collidine for 2.5 hr. The solution was concentrated *in vacuo* to one-third of its volume, acidified with HCl to Congo red under cooling, and extracted with Et_2O. The Et_2O extract was washed with 10% HCl, then H_2O, dried, and evaporated. The crystalline residue was recrystallized from Et_2O-MeOH to give 41.15 g. of cholest-1-en-3-one, m.p. 97~99°. Chromatography of its mother liquor on 400 g. of Alcoa activated alumina gave an additional amount (10.23 g.) of cholest-1-en-3-one (1:1 hexane-benzene to benzene eluate). Total yield, 51.39 g.[24] (60 %).

$LiAlH_4$ (0.52 g.) was added to a solution of 3.63 g. of $AlCl_3$[21] in 75 cc. of anhyd.Et_2O. Cholest-1-en-3-one (2.99 g.) in 50 cc. of anhyd. Et_2O was added during 10 min. and the reaction was completed by heating the mixture under reflux for 2.5 hr. AcOEt was added to decompose the excess reagent and the mixture was worked up in the usual way with 20% aq. H_2SO_4. Evaporation of the dried Et_2O solution gave 2.46 g. of an oil. This was chromatographed in hexane on 60 g. of Alcoa activated alumina. The hexane eluate fraction (ca. 150 cc.) gave 0.92 g. (35 %) of cholest-1-ene, m.p. 70~71°, form Me_2CO-Et_2O. Cholest-1-ene prepared from 3β-chlorocholest-1-ene by the method[25] had m.p. 66~69°, and the intensity value (ε 1080) of the UV absorption maximum at 263 mμ indicated that about 20% of the diene was present. The ultraviolet spectrum of cholest-1-ene obtained by the above method exhibited a maximum at 262 mμ (ε 160), which showed that no more than 2% of the diene was present, but the presence of some cholest-2-ene[21] was not excluded.

1α-Bromocholestan-2-one (X)——1α-Bromocholestan-2β-ol[20] (0.44 g.) was dissolved in 15 cc. of AcOH and treated with 80 mg. of CrO_3 in the minimum of H_2O at room temperature overnight. The solution was poured into H_2O, extracted with Et_2O, and the Et_2O extract was washed with H_2O, 5% aq. $NaHCO_3$, then H_2O, dried, and evaporated. The residue was crystallized from Me_2CO-MeOH to give 0.31 g. of 1α-bromocholestan-2-one, m.p. 95~96°. IR: $\lambda_{max}^{CHCl_3}$ 5.86 μ. UV: λ_{max}^{EtOH} 306 mμ (log ε 1.92). $[\alpha]_D^{25}$ −22° (c=1.05, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{45}OBr$: C, 69.65; H, 9.75. Found: C, 70.05; H, 9.28. R.D. in MeOH (c=0.05, 700~255 mμ): $[\alpha]_{700}$ 0°, $[\alpha]_{589}$ −22°, $[\alpha]_{327.5}$ −977° (trough), $[\alpha]_{282.5}$ +1540° (peak), $[\alpha]_{255}$ +1145°.

Hydrogen Bromide Catalyzed Equilibration of 1α-Bromocholestan-2-one (X)——1α-Bromocholestan-2-one (0.26 g.) was dissolved in 5 cc. of glacial AcOH and three drops of a solution of dry HBr (ca. 17%) in glacial AcOH were added. The mixture was kept at room temperature for 25 hr. The solution was poured into H_2O, extracted with Et_2O, and the Et_2O extract was washed with 5% aq. Na_2CO_3, then H_2O, dried, and evaporated. The residue was crystallized from Me_2CO-MeOH to give 0.23 g. of 1α-bromocholestan-2-one, m.p. 95~96°.

1α,2α-Epoxycholestane (XI)[20]——A solution of 3.08 g. in 50 cc. of Et_2O was mixed with 150 cc. of an Et_2O solution containing 8.1 g. of monoperphthalic acid, and the solution was kept at room temperature for 5 days. The solution was filtered from the deposited crystals of phthalic acid, and the filtrate was washed with 5% aq. Na_2CO_3, then H_2O, dried, and evaporated. The residue was crystallized from Me_2CO to show m.p. 89~90°. Yield, 2.29 g.

2β-Bromocholestan-1-one (XII)——1α,2α-Epoxycholestane (0.96 g.) in 60 cc. of $CHCl_3$ was shaken with 20 cc. of 48% aq. HBr for 20 min. Washing with dil. Na_2SO_3 and then with H_2O and evaporating it *in vacuo* after drying gave 1.25 g. of a sticky residue. This did not crystallize after chromatography in benzene on 30 g. of silica gel. Therefore, the oily 2β-bromocholestan-1α-ol was oxidized directly to the corresponding ketone.

The sticky oil (0.95 g.) after chromatography was dissolved in 25 cc. of glacial AcOH and treated with 0.16 g. CrO_3 in a minimum of H_2O. The solution was kept at room temperature overnight, diluted with H_2O, and extracted with Et_2O. The Et_2O extract was washed with 3% aq. $NaHCO_3$, then with H_2O, dried, and evaporated. The residue was chromatographed in hexane on 30 g. of silica gel. Fractions 7~8 (6:1 hexane-benzene) crystallized from Et_2O-MeOH to show m.p. 114~116°. Yield, 0.21 g. IR: $\lambda_{max}^{CHCl_3}$ 5.89 μ. UV: λ_{max}^{EtOH} 316 mμ (log ε 1.95). R.D. in MeOH (c=0.05, 700~255 mμ): $[\alpha]_{700}$ −32°, $[\alpha]_{589}$ −48°, $[\alpha]_{345}$ −1048° (trough), $[\alpha]_{280}$ +1650° (peak), $[\alpha]_{255}$ +1545°. *Anal.* Calcd. for $C_{27}H_{45}OBr$: C, 69.65; H, 9.75; Br, 17.15. Found: C, 69.21; H, 9.29; Br, 16.69.

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24) For alternate methods of preparation see G.F.H. Green, A.G. Long: J. Chem. Soc., **1961**, 2532.
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Cholestan-1-one (XIV)[20]——A solution of 3.82 g. of the 1α,2α-epoxide and 2.4 g. of $LiAlH_4$ in 300 cc. of Et_2O was heated under reflux for 3 hr. Chromatography of the product gave 2.14 g. of cholestan-1α-ol (XIII), m.p. 101~103° from MeOH.

Oxidation of 1α-alcohol was carried out by the chromic acid-Me_2CO technique.[26] A solution of 2.14 g. of the 1α-alcohol in 150 cc. of Me_2CO was stirred vigorously, and 4.4 cc. of chromic acid solution was added dropwise at room temperature during 3 min. After a further 30 minutes' stirring at 30~35°, the excess of oxidant was destroyed by the addition of aq. Na_2SO_3. The solution was concentrated *in vacuo* below 40° to half its original volume, diluted with H_2O, and extracted with Et_2O. The Et_2O extract was washed with H_2O, 5% aq. Na_2CO_3, dried and evaporated. The residue was crystallized from MeOH to show m.p. 87~88.5°. Yield, 1.82 g. IR : $\lambda_{max}^{CHCl_3}$ 5.90 μ. UV : λ_{max}^{EtOH} 293 mμ (log ε 1.46). R.D. in MeOH (c=0.06, 700~262.5 mμ) : $[\alpha]_{700}$ +49°, $[\alpha]_{589}$ +55°, $[\alpha]_{335}$ +350°, $[\alpha]_{317.5}$ +328° (trough), $[\alpha]_{262.5}$ +1195°.

Treatment of 1α-Bromocholestan-2-one (X) with Silver Nitrate[22]——1α-Bromocholestan-2-one (0.39 g.) in 150 cc. of Et_2O was added to a solution of 0.39 g. of $AgNO_3$ in 4 cc. of H_2O and 190 cc. of AcOH, and the mixture was heated until the vapor temperature reached 110°, when refluxing was continued for 40 min. The reaction mixture was evaporated *in vacuo* to dryness, and the residue was dissolved in Et_2O. After filtration of the insoluble inorganic material, the Et_2O solution was washed with 5% aq. Na_2CO_3, then H_2O, dried, and evaporated, yielding 0.36 g. of a crystalline residue. This crude material exhibited no selective UV absorption. This was chromatographed in hexane-benzene on 10 g. of Merck's acid-washed alumina. Fraction 8 (benzene eluate) gave 0.16 g. of crystals, m.p. 112~120° after recrystallization from Et_2O-MeOH. IR $\lambda_{max}^{CHCl_3}$ μ : 5.75, 5.82. UV : λ_{max}^{EtOH} 292 mμ (log ε 1.59). *Anal.* Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found : C, 77.88; H, 10.65. R.D. in MeOH (c=0.05, 700~260 mμ) : $[\alpha]_{700}$ +24°, $[\alpha]_{589}$ +140°, $[\alpha]_{315}$ +856°, $[\alpha]_{272.5}$ −808°, $[\alpha]_{260}$ −688°. This compound corresponds to 1β-acetoxycholestan-2-one.

Fraction 9 (9:1 benzene-Et_2O) gave 92 mg. of crystals, m.p. 134~140° after recrystallization from Et_2O-MeOH. IR $\lambda_{max}^{CHCl_3}$ μ : 5.75, 5.82. UV : λ_{max}^{EtOH} 295 mμ (log ε 1.79). *Anal.* Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88; O, 10.79. Found : C, 78.51; H, 11.06; O, 10.73. R.D. in MeOH (c=0.05, 700~260 mμ) : $[\alpha]_{700}$ +72°, $[\alpha]_{589}$ +88°, $[\alpha]_{320}$ +964°, $[\alpha]_{277.5}$ −728°, $[\alpha]_{260}$ −556°. The infrared spectra of the above two compounds were similar, but not identical. The latter compound seems to represent a mixture of 1β- and 1α-acetoxycholestan-2-one.

Attempt to Prepare the Enol Acetate of Cholestan-1-one (XIV)——i) A mixture of 0.8 g. of cholestan-1-one, 10 cc. of isopropenyl acetate, and 0.1 g. of *p*-toluenesulfonic acid monohydrate was concentrated by slow distillation during 10 hr. After the addition of AcONa, the solution was evaporated *in vacuo* and the product was extracted with Et_2O. The Et_2O solution was washed with H_2O, 3% aq. Na_2CO_3, then H_2O, dried, and evaporated. The residue was crystallized from MeOH-Me_2CO to show m.p. 87~89°, undepressed by admixture with cholestan-1-one. Yield, 0.49 g. Chromatography of the mother liquor gave no enol acetate.

ii) Cholestan-1-one (0.56 g.) in 9.5 cc. of CCl_4 was treated at room temperature with 0.02 cc. of 50% aq. $HClO_4$ in 0.5 cc. of Ac_2O. After 1.5 hr. at room temperature, the solution was washed with H_2O, 5% aq. Na_2CO_3, then H_2O, dried, and evaporated. The residue was crystallized from MeOH-Et_2O to show m.p. 87~88°, undepressed by admixture with cholestan-1-one. Yield, 0.35 g.

iii) A solution of 0.49 g. of cholestan-1-one, 30 cc. of Ac_2O, and 0.5 g. of *p*-toluenesulfonic acid was slowly distilled through a short column for 10 hr. Most of the Ac_2O was removed *in vacuo*, the residue was taken up in Et_2O, washed with H_2O, 5% aqueous K_2CO_3, then H_2O, dried, and evaporated, yielding 0.93 g. of a brown oily residue. Chromatography of this on 30 g. of Merck's acid-washed alumina recovered 0.19 g. of cholestan-1-one, but no enol acetate was obtained.

Summary

Bromination or enol acetylation of cholestan-2-one proceeds only towards C-3. Kinetically controlled bromination yields the axial 3α-bromo ketone, which can be equilibrated with hydrogen bromide to a ca. 1:1 mixture of 3α- and 3β-bromide. The latter is produced, together with cholest-3-en-2-one, upon treatment of 3α-bromocholestan-2-one with lithium cabonate and lithium bromide in dimethylformamide. 1α-Bromocholestan-2-one, synthesized independently from 1α,2α-epoxycholestane, is not an intermediate in the formation of the 3α-bromo-2-ketone and is recovered unchanged after exposure to hydrogen bromide. The preparation of 2β-bromocholestan-1-one and its reaction with silver nitrate in acetic acid are also reported as are unsuccessful attempts to form the enol acetate of cholestan-1-one.

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