Elution with 3% ether–benzene to 100% ether gave 73 mg. which, upon trituration with ethyl acetate–petroleum ether (b.p. 60–68°), yielded 60 mg. of a diol, m.p. 175–181°. Repeated recrystallization from ethyl acetate afforded *dl*-**3α,17α-dihydroxy-13-iso-18-nor-5β-androstane** (XVI. $R^1 = R^2 = H$) as colorless prisms, m.p. 181–182°, $\lambda_{max}^{CHCl_3}$ 2.78 μ (OH), 2.92 μ (OH).

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.1; H, 11.0.

In another experiment starting with 150 mg. of the hydroxy ketone, m.p. 135–140°, 48 mg. of the diol XV ($R^1 = R^2 = H$), m.p. 146–150°, and 56 mg. of the diol XVI ($R^1 = R^2 = H$), m.p. 170–178°, were obtained after chromatography.

A 48-mg. sample of the diol XV ($R^1 = R^2 = H$), m.p. 146–150°, was treated with 0.30 ml. of acetic anhydride in 1.4 ml. of pyridine for 3 hr. at room temperature, followed by the addition of water and extraction of the aqueous phase with ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure left 58 mg. of an oil which would not crystallize, $\lambda_{max}^{CH_2Cl_2}$ 2.80 μ (OH), 5.8 μ (C=O), 8.1 μ ($OCOCH_3$).

The oil was dissolved in 8 ml. of acetone, and 0.07 ml. of Jones reagent (prepared as described above) was added at 10–15°. The mixture was stirred for 10 min. during which time the temperature rose to room temperature. Water was then added, the aqueous mixture extracted with ether, the combined ether layers washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 55 mg. of an oil which was chromatographed on 2.5 g. of Florisil. Elution with 10% petroleum ether–benzene to 2% ether–benzene gave 44.5 mg. of crude oily crystals which, on recrystallization from petroleum ether (b.p. 60–68°), gave 15 mg. of the crude keto acetate XI (R = Ac), m.p. 120–140°. Further recrystallization from petroleum ether (b.p. 60–68°) afforded 8 mg., m.p. 135–143°, alone or upon admixture with an authentic sample of the keto acetate XI (R = Ac). The infrared spectra of the two samples were identical.

To 56 mg. of the diol, m.p. 170–176°, dissolved in 1.57 ml. of pyridine was added 0.34 ml. of acetic anhydride. The mixture was allowed to stand at room temperature for 3 hr. and then water was added, followed by extraction of the aqueous layer with ether; the combined ether layers were washed with water and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave 69 mg. of an oil which was chromatographed on 3.5 g. of Florisil. Elution with benzene gave 48 mg. of oily crystals, which on recrystallization from methanol yielded 25 mg., m.p. 120–126°. Four recrystallizations from methanol gave *dl*-**3α,17α-diacetoxy-13-iso-18-nor-5β-androstane** (XVI. $R^1 = R^2 = Ac$) as colorless plates, m.p. 128–128.5°, $\lambda_{max}^{CHCl_3}$ 5.78 μ (C=O), 8.0 μ ($OCOCH_3$).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.6; H, 9.55.

Equilibration Experiments.—The C/D *cis* and *trans* ketones VI and V in the A/B *trans* series and the C/D *cis* and *trans* ketones XI (R = H) and X (R=H) in the A/B *cis* series were equilibrated in the following manner.

A 4-mg. sample of the ketone was dissolved in 0.5 ml. of dioxane, 1 drop of concentrated hydrochloric acid and 2 drops of water were added. The mixture was allowed to stand at room temperature for 12 hr. Water was then added and the aqueous mixture was extracted with chloroform. The combined chloroform extracts were washed with water, 10% potassium bicarbonate solution, water, and dried over anhydrous sodium sulfate. Evaporation of the solvent left an oily residue which was dissolved in chloroform to give a 10% solution. The infrared spectrum of this solution was compared with the spectra of synthetic mixtures of the pure epimers. All the spectra were determined using 10% chloroform solutions and the intensities of characteristic bands in the 8.5–10.0-μ region were used for analysis. The equilibrium position of ketones VI and V thus was estimated to be between 50 and 75% in favor of the ketone VI. The position of the equilibrium of the ketones XI (R = H) and X (R = H) was estimated to be between 60 and 65% in favor of the ketone XI (R = H).

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α-Halo Ketones. II.[1] Rearrangement, Reduction, Elimination, and Displacement in the Reaction of Pyridines with 2α-Bromocholestan-3-one

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The reactions of a bromo ketone, 2α-bromocholestan-3-one (**1**), with pyridine, β-picoline, γ-picoline, 2,4-lutidine, 2,6-lutidine, and γ-collidine have been examined. The structures and amounts of the major products have been determined, and the paths by which they are formed have been circumscribed. Reported discrepancies in the reactions of **1** with 2,4-lutidine, 2,6-lutidine, and γ-collidine have been resolved.

Although the reaction of α-halo ketones with various pyridines has been widely used to introduce unsaturation into conjugation with carbonyl groups,[3] the reaction often yields a mixture of products over which there is disagreement in some cases. The ordinary course of the reaction, dehydrohalogenation and displacement, is often apparently accompanied by varying amounts of reduction and double bond rearrangement. In many cases the reduction and double bond migration are questionable since no evidence has been provided that the halo ketone was free from unhalogenated ketone or isomeric halo ketone. For a closer study

(1) Part I, *J. Org. Chem.*, **27**, 1186 (1962).

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(3) In addition to other references cited herein see *inter alia:* (a) M. Gates and G. M. K. Hughes, *Chem. Ind.* (London), 1506 (1956); (b) R. T. Arnold, J. S. Buckley, and R. M. Dodson, *J. Am. Chem. Soc.*, **72**, 3153 (1950); (c) A. Aebi, D. H. R. Barton, and A. S. Lindsay, *J. Chem. Soc.*, 3124 (1953); (d) E. W. Warnhoff, D. G. Martin, and W. S. Johnson, *Org. Syn.*, **37**, 8 (1957); (e) C. Meystre and A. Wettstein, *Experientia*, **2**, 408 (1946); (f) H. E. Zimmerman and A. Mais, *J. Am. Chem. Soc.*, **81**, 3644 (1959).

of the general reaction the steroid skeleton is particularly suitable both because of the considerable previous work on introduction of unsaturation into the A-ring of 3-keto steroids by this method and because of the many derivatives of known structure and stereochemistry in this series of compounds. On the other hand, the steroid dehydrohalogenation literature contains inconsistencies and contradictions.

For the A/B *trans* 3-keto steroids the results with 2α-bromocholestan-3-one (**1**) are typical. The action of boiling pyridine led to a high yield of a pyridinium salt **2** as the only reported product,[4] while 2,4,6-trimethylpyridine (γ-collidine) in which the nitrogen is sterically shielded gave no collidinium bromide but instead dehydrohalogenation. One group[5] found only Δ^1-cholesten-3-one (**3**) as the product of the latter reaction, whereas another worker[6] found Δ^1-cholesten-3-one together with cholestan-3-one (**4**), and still another group[7] found a mixture of Δ^1-cholestenone (**3**) and Δ^4-cholestenone (**5**), but no cholestanone (**4**). The bicyclic analog **6** of 2α-bromocholestan-3-one has been reported[8] to give exclusively the Δ^4-conjugated ketone (part structure **5**) with γ-collidine. However, in a reinvestigation[9] of this reaction Djerassi has isolated both the Δ^4- and the Δ^1-ketones. The results with 2,4-dimethylpyridine (2,4-lutidine) and 2,6-dimethylpyridine (2,6-lutidine) are equally confusing. Inhoffen reported[10] that 2α-bromocholestanone (**1**) formed a pyridinium salt, m.p. 299–300°, in unspecified yield with 2,6-dimethylpyridine, but with 2,4-dimethylpyridine only dehydrohalogenation to Δ^1-cholestenone (**3**) occurred and no quaternary salt formation. These findings are inconsistent with those from the γ-collidine reaction and are at variance with expectations based on hindrance by the 2- and 6-methyl groups to approach of the nitrogen. Inhoffen rationalized the results by suggesting that the compound from 2,6-lutidine (and from other pyridines) arose by attack at the 4-position of the pyridine ring and was actually a tertiary amine hydrobromide (**7**). This supposition was also invoked to explain why no addition compound formed with 2,4-lutidine, its 4-position already being substituted. On the other hand, there is no doubt that the salt from 2α-bromocholestanone and pyridine is a true pyridinium bromide. Ruzicka[4b] found the salt exhibited the properties of the α-pyridinium ketones studied extensively by Kröhnke.[11] In particular the salt was transformed[4d] by reaction with *p*-nitrosodimethylaniline into cholestane-2,3-dione which was converted into cholestan-2-one thus establishing the C-2 attachment of the pyridine to the steroid nucleus.[12] However, there remains some question about the purity of the quaternary salt in view of the products obtained from it in subsequent reactions.

Ruzicka[4b] reported that thermal decomposition of the dry pyridinium bromide at 250–300° gave Δ^4-cholestenone (**5**). In the pregnane series Butenandt[5] found that pyrolysis of the pyridinium salt from 2α-bromo-5α-pregnane-3,20-dione (part structure **2**) gave the Δ^1-ketone (part structure **3**) whereas Marker[13] isolated both the Δ^1- and the Δ^4-ketones (part structures **3** and **5**) from the same decomposition. Ruzicka[4b] also found the pyridinium salt from 2α-bromoandrostane-3,17-dione (part structure **2**) yielded the Δ^4-ketone (part structure **5**) on pyrolysis. The Δ^4-compounds could have arisen by elimination with rearrangement from C-2 pyridinium bromides or by normal elimination from C-4 pyridinium bromides present as impurities. It is not unreasonable to suspect the presence of C–4 pyridinium salts in view of the formation of a mixture of 2α- and 4α-acetoxycholestanones (**14**) from which a sharp melting 1:1 complex can be crystallized[14] when 2α-bromocholestanone (**1**) is refluxed with potassium acetate in acetic acid. Furthermore the high melting points (*ca.* 300°) of the different pyridinium compounds which depend on the rate of heating and are accompanied by decomposition fall within a narrow temperature range and give little or no depression on mixture thus making the melting point an unreliable criterion of purity.

In the present work some of these conflicting points have been re-examined. The major reaction products have been determined, and the possible ways in which they are formed have been limited. In addition the effect of pyridine structure on product composition has been studied.

Re-examination of Previous Work.—Attention was first turned to the lutidine reactions with **1**. The reported facts could be reconciled if the compound obtained by Inhoffen[10] with 2,6-dimethylpyridine was in fact a quaternary salt but not derived from 2,6-lutidine. Since this base (b.p. 144°) is almost always contaminated with β- and

(4) (a) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935); (b) L. Ruzicka, Pl. A. Plattner, and R. Aeschbacher, *Helv. Chim. Acta*, **21**, 866 (1938); (c) E. Schwenk and B. Whitman, *J. Am. Chem. Soc.*, **69**, 949 (1937); (d) L. Ruzicka, Pl. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 524 (1944).

(5) A. Butenandt, L. Mamoli, H. Dannenberg, L.-W. Masch, and J. Paland, *Ber.*, **72**, 1617 (1939).

(6) R. P. Jacobsen, *J. Am. Chem. Soc.*, **62**, 1620 (1940).

(7) C. Djerassi and C. R. Scholz, *ibid.*, **69**, 2404 (1947).

(8) M. Yanagita and A. Tahara, *J. Org. Chem.*, **18**, 792 (1953).

(9) C. Djerassi and D. Marshall, *J. Am. Chem. Soc.*, **80**, 3986 (1958).

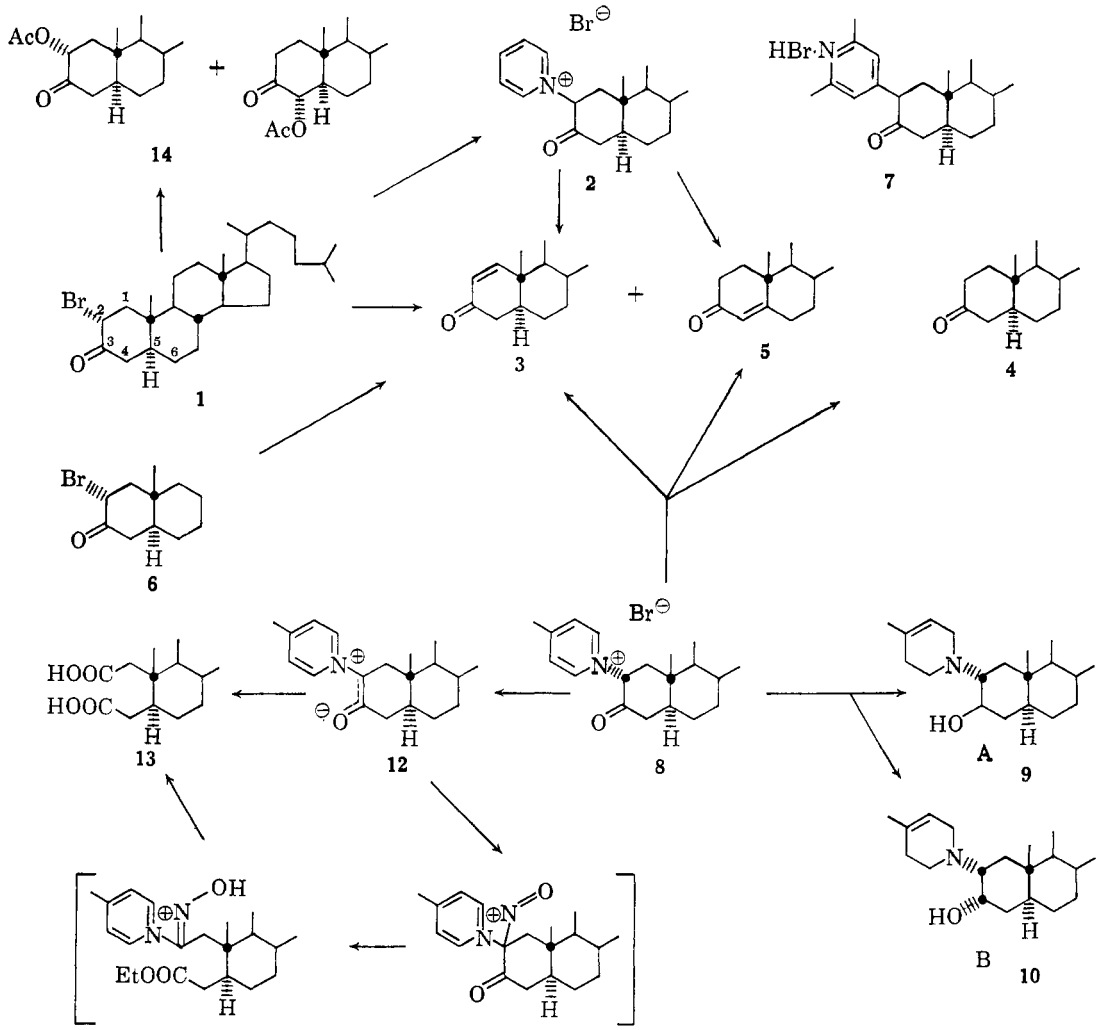
(10) H. H. Inhoffen, G. Zühlsdorff, and Huang-Minlon, *Ber.*, **73**, 451 (1940).

(11) (a) F. Kröhnke, *Ber.*, **68**, 1177 (1935); (b) F. Kröhnke, and E. Börner, *ibid.*, **69**, 2006 (1936).

(12) The possibility that the pyridinium compounds are 2-keto-3-pyridiniumcholestanes arising by a reaction formally analogous to the rearrangement observed with the acetoxycholestanones[14b] is not excluded by Ruzicka's work.[4d] It is, however, excluded in the present work by the zinc reduction of the pyridinium, β- and γ-picolinium salts to cholestan-3-one.

(13) R. E. Marker, E. L. Wittle, and L. Plambeck, *J. Am. Chem. Soc.*, **61**, 1333 (1939).

(14) (a) L. F. Fieser and M. A. Romero, *ibid.*, **75**, 4716 (1953); (b) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).



γ-picoline (b.p. 144 and 145°, respectively),[15] which are only separated by azeotropic distillation or conversion to a pure salt of 2,6-lutidine and regeneration, either of these might have been responsible for the compound isolated by Inhoffen. The analytical figures given[10] do not distinguish between $C_{34}H_{54}NOBr$ (from lutidine) and $C_{33}H_{52}NOBr$ (from picoline). The point was settled by refluxing 2α-bromocholestanone with 2,6-dimethylpyridine which had been purified *via* the crystalline picrate. A crystalline salt separated and after fourteen hours there was obtained a 94% yield of pure 2,6-dimethylpyridine hydrobromide. The unpurified salt was completely water soluble and gave no yellow color with sodium hydroxide solution, a color reaction characteristic of α-pyridinium, α-hydrogen ketones.[11a] However, reflux of 2α-bromocholestanone with γ-picoline did give an 88% yield of a water-insoluble γ-picolinium bromide, m.p. 305–306° dec. Similarly β-picoline gave 82% of a water-insoluble β-picolinium salt, m.p. 295–296° dec. Both salts gave intense yellow-orange colors in basic solution and exhibited the expected changes in ultraviolet and visible spectra in going from neutral to basic to acidic solution (see Experimental). Further evidence that the salts are α-pyridinium ketones was provided in the demonstration that the salts incorporated the above amines and that no rearrangement had occurred. Zinc–acetic acid reduction of the salt from γ-picoline gave cholestanone (**4**) and γ-picoline isolated as its methiodide. The salt from β-picoline was similarly reduced to cholestanone and β-picoline isolated as the picrate.[12] Inhoffen's compound may have been either of these quaternary bromides or a mixture of both, but it was not derived from 2,6-dimethylpyridine.

The reaction of 2α-bromocholestanone (**1**) with a sample of 2,4-dimethylpyridine purified *via* its crystalline hydrobromide gave a 95% yield of pure completely water-soluble 2,4-dimethylpyridine hydrobromide as the only solid separating from the reaction mixture. However, when commercial 2,4-lutidine known by gas–liquid chromatography to contain about 10–15% of a mixture of β- and γ-picoline was used for the reaction, the precipitated solid was a mixture of 2,4-dimethylpyridine hydrobromide and a pyridinium salt. Zinc–acetic acid

(15) E. A. Coulson and J. I. Jones, *J. Soc. Chem. Ind. (Trans.)* (London), **65**, 169 (1946).

reduction of the quaternary bromide gave cholestanone and a basic fraction from whose impure methiodide was crystallized some γ-picoline methiodide.

γ-Collidine purified *via* its hydrobromide gave a 103% yield of completely water-soluble γ-collidine hydrobromide after a twelve-hour reflux with **1**.

Structure and Decomposition of the Pyridinium Salts.—Since the quaternary salts from pyridine, β- and γ-picoline can all reasonably be presumed to have the same basic structure and purity, only one of these, the γ-picolinium compound (chosen for solubility and because all major reaction products were found in the γ-picoline reaction), was examined in detail. Recrystallization did not change the melting point of the crude salt which gave a single spot on a thin-layer chromatogram. The quaternary bromide **8** was reduced in methanol with sodium borohydride to a mixture of two stereoisomeric amino alcohols, A, m.p. 164–165.5°, $[\alpha]_D$ −8.2° and B, m.p. 157–159°, $[\alpha]_D$ −13.5°, in which the picoline ring has been reduced to the tetrahydro stage. Had **8** been contaminated with any C-4 picolinium isomer four amino alcohols would have been expected. These alcohols are **9** and **10** since the ultraviolet spectra have only the rising end absorption of a trisubstituted double bond, and the 165.5° isomer is not oxidized by manganese dioxide. The nuclear magnetic resonance spectrum of each has a single vinyl hydrogen at $\delta = 5.25$ p.p.m. In isomer B the single proton at C-3 absorbs at $\delta = 3.85$ p.p.m. (equatorial H, axial OH) while in isomer A this proton appears about $\delta = 3.25$ p.p.m. (axial H, equatorial OH).[16]

The picolinium group was shown to be at C-2 by permanganate oxidation of the yellow anion **12** to the known secocholestane-2,3-dioic acid (**13**), which was obtained in 32% yield from direct crystallization of the reaction mixture. This acid was also obtained in 18% yield from **8**, isoamyl nitrite and sodium ethoxide followed by hydrolysis in a reaction analogous to Ruzicka's condensation of **2** with *p*-nitrosodimethylaniline.[4d] The more stable equatorial 2α-configuration for the bulky picoline ring of **8** was established by equilibration of the 2-position with one third the equivalent amount of sodium carbonate in methanol. The yellow color of the solution clearly indicated the presence of the anion **12**. The picolinium bromide recovered (97%) from this equilibration was identical (m.p., m.m.p., infrared, $[\alpha]_D$) with the starting material.

The nuclear magnetic resonance spectrum of the γ-picolinium salt **8** in deuteriochloroform confirmed the chemical evidence.[17] In the aromatic hydrogen region there was an A_2B_2 grouping of four protons with peaks at 554 and 561 c.p.s. (tetramethylsilane = 0) attributable to the two α-protons and peaks at 466 and 473 c.p.s. from the two β-protons. The γ-methyl group appeared at 2.68 p.p.m. Most importantly there was a symmetrical one proton quartet centered at 7.00 p.p.m. which can only be the proton on C-2 (bearing the carbonyl group and the nitrogen) which is split by the two non-equivalent protons on C-1. Had the picoline ring been attached to C-4 this peak would only have been a doublet. The coupling constants for the quartet, $J = 14$ and 5 c.p.s. are those expected of an axial 2β-proton coupled with adjacent axial and equatorial hydrogens.[16b] The C-19 methyl group is a strong narrow peak at 1.47 p.p.m. Had **8** been contaminated with any C-4 picolinium isomer the C-19 methyl absorption should have been two sharp peaks in this region. Hence, all of the chemical and physical evidence is in accord with the γ-picolinium bromide, and probably the other pyridinium salts, being a pure compound with the structure and stereochemistry of **8**. With this in mind the pyrolysis of these salts was reinvestigated.

The thermal decomposition of the crystalline γ-picolinium bromide **8** *in vacuo* began slowly around 235° and was appreciable at 250–275° leaving very little (3.5%) residue. The sublimate was a mixture of γ-picoline hydrobromide, Δ^1-cholestenone (**3**) (13%), Δ^4-cholestenone (**5**) (39%), cholestanone (**4**) (26%), and undecomposed starting material **8** (13%). Both rearrangement and, surprisingly, reduction had occurred in addition to normal elimination. Pyrolysis of the pyridinium salt **2** in the same temperature range gave an ether-soluble product fraction whose infrared and ultraviolet spectra indicated the same components in about the same proportions as from **8**. Previous reports[4b,5,13] of isolation of only one or both of the conjugated ketones must be ascribed to loss of other components during purification. The fact that the products from pyrolysis of the quaternary salts are the same, albeit in different proportions, as those formed in the reaction of the bromo ketone **1** with refluxing pyridines suggested that the products of the latter reaction might result wholly or in part by way of the pyridinium compounds as intermediates, provided that their decomposition in solution at lower temperatures was appreciably more rapid than in the crystalline state. When the pure γ-picolinium bromide **8** was refluxed in γ-picoline with γ-picoline hydrobromide under the same conditions used for the original reaction with **1**, the starting material **8** was recovered in 99% yield. The other 1% was an ether soluble fraction whose ultraviolet spectrum was not that of a cholestenone. Therefore, in the reaction of 2α-bromocholestanone (**1**) with γ-picoline (and probably with β-picoline and pyridine),

(16) (a) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958). (b) Similar quartet coupling constants have been found for several 2α-halo-3-cholestanones; unpublished work.

(17) This nuclear magnetic resonance spectrum was determined by the Varian Co., Palo Alto, Calif. We would like to thank Dr. LeRoy F. Johnson for his comments on the spectrum and the suggestion that the unexpectedly low resonance position of the C-2 proton may result from close proximity to the bromide ion associated with the positively charged nitrogen.

TABLE I

PRODUCTS FROM REACTION OF 2α-BROMOCHOLESTAN-3-ONE WITH PYRIDINES

Amine	Normal b.p., °C.	Reflux time, hr.	Pyridinium salt,[a] %	Amine HBr,[a] %	Yield ether-sol. frac.,[a] %	Δ⁴-Ketone 5,[a] %	Δ¹-Ketone 3,[a] %	Cholestan-3-one 4,[a,d] %
Pyridine	115	2	82	Not detm.	15	0 (<0.4)	4.7	10.4[b]
β-Picoline	144	3	82	13	14.5	2.1	10.3	2.1
γ-Picoline	145	3	88	9.3	12.6	1.5	9.1	2.1
2,4-Lutidine	157	4	0	95	100	25	55	20
2,6-Lutidine	144	14	0	94	100	30	24	46
2,4,6-Collidine	171	12	0	103	99	25	38	37
Pyrolysis of 8					89[c]	44	15	29

[a] All yields are based on actual bromo ketone content of the sample used. [b] Questionable since the ultraviolet spectrum of the crude ether-soluble product shows other components besides 3, 4, and 5. [c] Corrected for recovered 8. [d] Not including 4 already present in 1.

none of the cholestanone or cholestenones arises by decomposition of the quaternary salt **8**. This fact makes it unlikely that the reactions with γ-collidine, 2,6-lutidine, and 2,4-lutidine, from which no quaternary salts were isolated, proceed by a slow formation of pyridinium salts which decompose rapidly to products; the rate of decomposition of a 2,4 - dimethylpyridinium and the 4 - methylpyridinium derivative would not be expected to differ that much. Consequently, in the reaction of a pyridine with **1**, it follows that dehydrohalogenation with and without rearrangement and any reduction occur in reactions competitive with quaternary salt formation and involving 2α-bromocholestanone directly.

Analysis of Products.—The other products of the pyridine reactions (see Table I) are consistent with this view. In no case was the yield of quaternary salt quantitative. For pyridine, β- and γ-picoline the yield varied between 82–88%. An ether-soluble fraction accounted for the rest of the material and in each case was a mixture of cholestanone (**4**), Δ¹- and Δ⁴-cholestenone (**3** and **5**) except that there was no detectable amount of Δ⁴-cholestenone in the pyridine product. Again previous reports[4-7,10] of isolation of only one or two of these compounds must be ascribed to loss during purification. There was no bromo ketone remaining in any of the products in Table I as suggested by the yields of bromide ion containing salts and as tested by the copper wire method, quantitative bromine analysis and thin-layer chromatography. In the products from pyridine, 2,6-lutidine and γ-collidine there were traces of other unidentified compounds.

Qualitative identification of components was done by infrared spectroscopy and thin-layer chromatography on silica gel with the cyclohexane–ethyl acetate (85:15) system.[18] For quantitative analysis of the three components a combination of thin-layer chromatography and ultraviolet spectroscopy was used since cholestanone and Δ¹-cholestenone were not well separated in 50–200-γ quantities by the chromatography system used. The amount of Δ⁴-ketone was found by comparing the intensity of the Δ⁴-cholestenone spot with spots of varying known amounts of authentic ketone. The Δ¹-cholestenone content was calculated from the ultraviolet spectrum taking into account the Δ⁴-cholestenone content and the ultraviolet spectra of pure Δ¹- and Δ⁴-cholestenone. The remainder of the product was taken as the cholestanone content. With such an analytical method the figures in Table I may be in error by a few per cent.

The reaction products from the γ-picoline and γ-collidine reactions and those from the pyrolysis of **8** were separated by chromatography. To facilitate the separation of cholestanone and Δ¹-cholestenone the cholestanone was first converted to 3α- and 3β-cholestanol by sodium borohydride reduction of the ketone mixture followed by re-oxidation of the allylic alcohols in the mixture to the conjugated ketones with manganese dioxide. Chromatography then gave pure Δ¹- and Δ⁴-cholestenone, 3α- and 3β-cholestanol. Sodium borohydride reduction of Δ¹-cholestenone at room temperature was found to give about 30–40% of cholestanol from reduction of the conjugated double bond. Under these conditions Δ⁴-cholestenone gave no detectable reduction of the conjugated double bond. However, most of the cholestanol found in the product separation studies arose from reduction of cholestanone since the amount of cholestanol in each case was larger than the amount of Δ¹-cholestenone.

Reduction and Rearrangement.—The cholestanone (**4**) in the ether-soluble part of the reaction product came from two sources. It was found by thin-layer chromatography that thrice recrystallized 2α-bromocholestanone (**1**) with the melting point and optical rotation reported for pure material still contained about 12 mole % of cholestanone,[19]

(18) M. Barbier, H. Jager, H. Tobias, and E. Wyss, *Helv. Chim. Acta*, **42**, 2440 (1959).

(19) This value was checked by both n.m.r. and v.p.c. analysis. In our hands 2α-bromocholestanone purified by recrystallization is invariably contaminated with 5–15% of cholestanone whose presence is revealed by thin-layer chromatography or nuclear magnetic resonance spectroscopy.[20] Since the specific optical rotations (sodium D line) of **1** and **4** in chloroform are almost identical, contamination could not be detected in this way. The capillary melting point of the contaminated bromo ketone is the same as that of pure **1** although on the hot stage the contaminated material begins to sinter at a somewhat lower temperature than pure **1**. The analysis of **1** in reference 4a is 0.88% low in bromine content and 0.60% high in carbon content as would be expected if it contained 5–10% of cholestanone.

which would be carried over into the ether-soluble fraction from the pyridine reactions. Most or all of the cholestanone present in the product from β- and γ-picoline and probably pyridine was present in the bromo ketone **1**, and little or no reduction took place. However, 20–46% of the product from 2,4- and 2,6-lutidine and 2,4,6-collidine is cholestanone from some reduction process which, incidentally, does not finally affect the oxidation state of the bromide. The reduction is not merely transfer of bromine from one molecule of **1** to another by means of a brompyridinium ion since no products were found that would result from loss of two molecules of hydrogen bromide from a dibromo ketone. Apparently the pyridine or possibly a trace of water is the hydrogen source.

In regard to the formation of Δ^4-cholestenone, there could not have been enough 4α-bromocholestanone present as an impurity in **1** to account by simple dehydrobromination for the high yield of Δ^4-ketone in three cases. Although the R_f values were such that thin-layer chromatography would not reveal small amounts of 4α-bromo ketone in **1**, the nuclear magnetic resonance spectrum of **1** in carbon disulfide gave no indication of any impurity except cholestanone. In addition to the two C-19 methyl peaks[18] there was the expected symmetrical quartet centered at 4.60 p.p.m. (J = 6 and 14 c.p.s.) from the axial C-2 hydrogen. There was no indication in this region of a doublet from the 4β-hydrogen of a 4α-bromo ketone such as that observed for 2α,4α-dibromocholestanone.

Both Δ^1-cholestenone and Δ^4-cholestenone are stable under the reaction conditions as expected. When each ketone was refluxed in γ-picoline with γ-picoline hydrobromide and the γ-picolinium bromide **8**, each was recovered in 97% yield without contamination by the other as shown by thin-layer and gas–liquid chromatography.[21] Therefore it would seem that the Δ^4-cholestenone (**5**) arises directly from 2α-bromocholestanone by a rearrangement. There are other reported examples[22] of this type of rearrangement in lithium salt–dimethylformamide dehydrohalogenations. Possible mechanisms for these latter reactions have been suggested.[3a,22b] Another possibility, debromination, in this case by a pyridine going to a bromopyridinium ion, followed by rebromination at C-2 and C-4 and dehydrohalogenation of the C-4 bromo isomer is not excluded.

Thus in the reaction of a pyridine with **1** the predominant course is quaternary salt formation in the absence of an α-substituent. The presence of only one α-methyl group on the pyridine suppresses quaternary salt formation completely in favor of reduction and both normal and abnormal dehydrohalogenation. The presence of two α-methyl groups increases the amount of reduction at the expense of normal dehydrohalogenation. This latter change may be merely a reflection of increased hindrance of approach of the nitrogen to the C-1 hydrogens.

Experimental

General procedure and instruments are the same as in part I.[1] Thin-layer chromatograms were run on Merck Silica Gel G with the solvent systems specified. In each chromatogram authentic samples were run for comparison. Sulfuric acid charring was used for detection. Gas–liquid chromatography of all the pyridines was carried out on a Perkin-Elmer Model 154 Vapor Fractometer with a 6-ft. tricyanoethoxypropane (TCEP) on Chromosorb P column at 73° and a helium flow rate of 45 ml./min. The gas–liquid chromatograms of the steroid derivatives were run on a 6-ft. column of Gas-Chrom P coated with 2% QF-1 at 235° and a helium pressure of 40 p.s.i. on a modified Barber Colman apparatus with a Glowall column. *All molar quantities and yields in experiments involving 2α-bromocholestanone are corrected for the cholestan-3-one content of the sample used.*[20]

Pure 2,6-Dimethylpyridine.—Commercial 2,6-lutidine (Matheson) (40 g.) containing a few per cent of an impurity of retention time 32 min. was dissolved in absolute ethanol and treated with an excess of warm ethanolic picric acid. The yellow precipitate (87 g., 69%) was collected on a filter. Two recrystallizations from acetone gave 74.5 g. of picrate of constant m.p. 163–164.5° (capillary) (reported,[15] 163–164°). The pure picrate was partitioned between dilute ammonium hydroxide and a chloroform–ether mixture. The organic solution was washed with dilute potassium hydroxide solution and dried over magnesium sulfate. The filtered solution was distilled through a 30-cm. vacuum-jacketed Vigreux column. There was collected 18.3 g. of colorless 2,6-dimethylpyridine, b.p. 140–141° (760 mm.) (uncorrected), n^{29}D 1.4937 (reported,[15] b.p. 144.0° (760); n^{20}D 1.4971). Gas–liquid chromatography gave a single peak of 25-min. retention time.

An 84-mg. sample was dissolved in methyl iodide. The colorless salt that precipitated weighed 160 mg. (82%), m.p. 240–241° dec. (reported,[23] m.p. 235–240° dec.). The melting point was unchanged on recrystallization of the salt from ethanol.

Hydrogen bromide gas was introduced into a solution of the pure 2,6-lutidine in anhydrous ether. The precipitated salt was recrystallized twice from chloroform–ethyl acetate to give colorless prisms, m.p. 211–212.5° with sublimation when the sample was placed on the hot stage at 200° (reported,[24] m.p. 210°).

Reaction of 2α-Bromocholestanone (1) with 2,6-Dimethylpyridine.—A solution of 1.000 g. (1.95 mmoles of **1**) of bromo ketone, m.p. 169–169.5° (capillary), in 4 ml. of the purified 2,6-lutidine was refluxed (oil bath 160°) for 14 hr. The solution gradually turned a clear brown color and deposited

(20) t 60 Mc. in carbon disulfide the following reproducible chemical shifts of the C-19 methyl group from internal tetramethylsilane were found: 2α-bromocholestanone, 64 c.p.s.; 4α-bromocholestanone, 62 c.p.s.; and cholestanone, 58 c.p.s. If the cholestanone content had been as low as 5%, it could easily have been detected; hence it is estimated that about 5–10% of 4α-bromocholestanone could have been detected.

(21) The Δ^1-cholestenone (**3**) sample was contaminated with 8% of cholestanone, but this same mixture was obtained after the attempted isomerization. It is our experience that samples of **3** (prepared from **1**) beginning to melt below 100°, though the melting range be 1–2°, are contaminated with a few per cent of cholestanone which is not removed by recrystallization from ethanol. Chromatography on alumina gives pure Δ^1-cholestenone, m.p. 101–102°, in the later fractions.

(22) (a) J. J. Beereboom and C. Djerassi, *J. Org. Chem.*, **19**, 1196 (1954); (b) M. E. Kuehne, *J. Am. Chem. Soc.*, **83**, 1492 (1961); (c) W. G. Dauben, G. A. Boswell, and W. R. Templeton, *ibid.*, **83**, 5006 (1961).

(23) R. Lukeš and M. Juraček, *Collection Czech. Chem. Commun.* **13**, 79 (1948).

(24) A. Marcuse and R. Wolffenstein, *Ber.*, **32**, 2525 (1899).

some crystalline material after about 1 hr. The solid was removed by filtration and washed with ether to leave 344 mg. (94%) of 2,6-dimethylpyridine hydrobromide, m.p. 211–212° with sublimation. The melting point was unchanged by recrystallization from chloroform–ethyl acetate and was undepressed on admixture with the authentic sample described above. The salt was completely soluble in water and on addition of potassium hydroxide to the aqueous solution no orange or yellow color appeared.

The ethereal filtrate was washed with dilute sulfuric acid until a test portion of the acid extract gave no lutidine odor on basification. Evaporation of the dried ether solution left 840 mg. (100%) of amber waxy material, λ_{max} 240 mμ (ε 6800), $\nu_{max}^{CS_2}$ 1712 cm.$^{-1}$ (cyclohexanone) and 1675 cm.$^{-1}$ (conjugated ketone). Thin-layer chromatography (cyclohexane–ethyl acetate, 85:15) gave two strong spots R_f 0.58 (**3** and **4**) and 0.38 (**5**) and two faint spots R_f 0.30 and 0.10.

When the reaction was run for only 5 hr., there was obtained 41% of 2,6-dimethylpyridine hydrobromide. The ether-soluble portion still contained bromo ketone **1**. Thin-layer chromatography (cyclohexane–ethyl acetate, 85:15) gave three spots R_f 0.80 (**1**), 0.67 (**3** and **4**), and 0.48 (**5**).

Anal. Calcd. for $C_{27}H_{45}OBr$: Br, 17.16. Found: Br, 7.75.

Reaction of 2α-Bromocholestanone (1) with γ-Picoline.—A solution of 7.000 g. (13.6 mmoles of **1**) of bromo ketone, m.p. 166–167° (capillary), in 30 ml. of 4-methylpyridine (retention time 50 min.) (containing less than 4% of β-picoline as determined by gas–liquid chromatography) was refluxed for 3 hr. A precipitate formed immediately after heating was begun. At the end of the reflux period the reaction mixture was diluted with ether and filtered. The dried flakes amounted to 6.888 g. The crystals were triturated with distilled water and filtered to leave 6.666 g. (88%) of the γ-picolinium salt **8**, m.p. 305–306° dec. This compound exhibited a negative temperature coefficient of solubility in chloroform. A sample was recrystallized four times by dissolving it in chloroform–acetone at 5° and heating the solution to boiling to cause crystallization. The hot solution was filtered to collect the small pearly leaflets, m.p. 305–306° (dec., sample placed on hot stage at 280°), $[\alpha]^{20}D$ −2.5° (*c* 2.37). Thin-layer chromatography (methanol–chloroform, 10:90) gave a single spot R_f 0.40.

Anal. Calcd. for $C_{33}H_{52}NOBr$ (558.70): C, 70.95; H, 9.38; N, 2.50. Found: C, 71.32; H, 9.35; N, 2.58.

Infrared spectrum: $\nu_{max}^{CHCl_3}$ 1730 (s) (C=O) and 1642 (s) cm.$^{-1}$.

Ultraviolet and visible spectrum: λ_{max}^{EtOH} 223 mμ (ε 9100) and 256 mμ (ε 5150); $\lambda_{max}^{EtOH-KOH}$ 298 mμ (ε 878) and 426 mμ (ε 5490); $\lambda_{inf}^{EtOH-KOH}$ 242 mμ (ε 6360). Immediately after acidification of the basic solution a new peak,[25] λ_{max} 326 mμ (ε 2550) appeared and then gradually disappeared as the spectrum became identical with that in neutral solution.

Nuclear magnetic resonance spectrum: (Me_4Si = 0) δ = 2.68 p.p.m. (3H, γ-CH_3 of picolinium ring); 408, 414, 422 and 427 c.p.s. (1H, quartet, γ-pic-CH-CO), 466 and 473 c.p.s. (2H, β-H of picolinium ring); 554 and 561 c.p.s. (2H, α-H of picolinium ring).

The aqueous filtrate from trituration of the γ-picolinium salt was evaporated to dryness at reduced pressure leaving 222 mg. (9.3%) of γ-picoline hydrobromide. Recrystallization from acetone gave 157 mg., m.p. 157–159.5°. Admixture with an authentic sample, m.p. 159.5–160°, gave no melting point depression.

The ethereal filtrate from the original reaction mixture was extracted with dilute sulfuric acid until all basic material had been removed. The washed and dried ether solution was evaporated to leave 1.324 g. (12.6%) of almost colorless solid, λ_{max} 232 mμ (ε 4550), $\nu_{max}^{CS_2}$ 1720 (cyclohexanone) and 1685 cm.$^{-1}$ (conj. ketone).

Anal. Calcd. for $C_{27}H_{45}OBr$: Br, 17.16. Found: Br, 0.00.

Thin-layer chromatography (cyclohexane–ethyl acetate, 85:15) gave two spots R_f 0.44 (**5**) and R_f 0.70 (**3** and **4**).

A solution of 500 mg. of this ether-soluble portion in 15 ml. of ether and 25 ml. of methanol was reduced with 500 mg. of sodium borohydride. Dilution of the solution with water and extraction with ether gave a crude product (493 mg.) whose infrared spectrum had no carbonyl absorption. The reduction product (485 mg.) was dissolved in 10 ml. of chloroform and the allylic alcohols present oxidized by stirring with 3 g. of active manganese dioxide[26] for 4 hr. Filtration and evaporation left 476 mg. of almost colorless material which was chromatographed on 15 g. of activity II alumina. Fractions were analyzed by thin-layer chromatography with the cyclohexane–ethyl acetate (85:15) system. Benzene–petroleum ether (1:9) eluted 87 mg. of Δ^1-cholestenone (**3**), R_f 0.68, which after recrystallization had m.p. 100–101°, undepressed on admixture with an authentic sample. Benzene–petroleum ether (1:3 and 1:1) eluted 82 mg. of a mixture of Δ^4-cholestenone (**5**), R_f 0.48, and cholestan-3α-ol, R_f 0.40. Pure cholestan-3α-ol was separated by recrystallization from methanol and had m.p. 185–187° (reported[27] 182°) and R_f 0.38 identical with that of cholestan-3α-ol from borohydride reduction of cholestan-3-one. The Δ^4-ketone was separated from the mother liquors of the recrystallization by addition of 2,4-dinitrophenylhydrazine solution. The orange-red precipitate amounted to 43 mg. After recrystallization from chloroform–ethanol pure Δ^4-cholesten-3-one 2,4-dinitrophenylhydrazone (red), m.p. 238–240°, was isolated. The melting point was undepressed on admixture with an authentic specimen (red), m.p. 241–242.5°. However, on admixture with an authentic sample of Δ^1-cholesten-3-one 2,4-dinitrophenylhydrazone (orange), m.p. 235–237°, the melting point was depressed to 205–231°. In continuation of the chromatogram pure benzene eluted 306 mg. of cholesten-3β-ol, R_f 0.23, which after recrystallization from ethyl acetate had m.p. 143–144°, undepressed on admixture with an authentic sample, m.p. 126–127° and 142–143° (dimorphic).

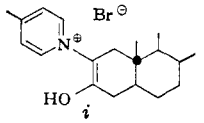
Equilibration of 8.—A solution of 200 mg. (0.358 mmole) of **8**, m.p. 305–306° dec., in 4 ml. of methanol and 2 ml. of water containing 11 mg. (0.103 mmole) of anhydrous sodium carbonate was allowed to stand at room temperature for 18 hr. The golden color of the slightly basic solution was discharged by the addition of a drop of hydrobromic acid. After most of the methanol had evaporated the residue was triturated with water, filtered, washed with water, and dried to leave 195 mg. (97%) of colorless crystals, m.p. 304–305.5° dec., $[\alpha]^{28}D$ −1.3° (*c*, 2.56). The mixture melting point with **8** was undepressed. The infrared spectrum in potassium bromide was identical with that of **8**.

Attempted Decomposition of γ-Picolinium Bromide.—A mixture of 1.000 g. of **8**, m.p. 302–303.5° dec., 40 mg. of γ-picoline hydrobromide and 6 ml. of redistilled γ-picoline was refluxed (oil bath 170°) for 3 hr. The cooled reaction mixture was diluted with ether and filtered to leave 1.033 g. of solid which was triturated with water and filtered. The water-insoluble portion amounted to 989 mg. (99% recovery) of **8**, m.p. 302.5–303.5° dec., undepressed on admixture with starting material. The infrared spectrum in potassium bromide was identical with that of the starting material.

The ether filtrate was washed with dilute hydrochloric acid to remove γ-picoline. Evaporation of the dried ether solution left 12 mg. of yellow oil whose ultraviolet spectrum was not that of a cholestenone.

Zinc Reduction of γ-Picolinium Salt 8.—A mixture of 162

(25) This peak is probably from the enol chromophore *i*.



i

(26) J. Attenburrow, *et al.*, *J. Chem. Soc.*, 1094 (1952).

(27) A. Windaus and C. Uibrig, *Ber.*, **47**, 2384 (1914).

mg. of **8**, 3 g. of activated zinc,[28] and 5 ml. of glacial acetic acid was refluxed with stirring (magnetic bar) for 5 hr. The cooled reaction mixture was decanted from unreacted zinc and diluted with water. The aqueous solution (A) was extracted with three portions of ether. The combined ether solutions were washed with 10% potassium hydroxide solution (yellow color), saturated sodium chloride solution, and dried over magnesium sulfate. Evaporation of the filtered solution left 63 mg. Two recrystallizations from 95% ethanol gave 30 mg. of cholestan-3-one (**4**), m.p. 129–130.5°, undepressed on admixture with an authentic sample.

The original acidic solution (A) was made basic with potassium hydroxide solution and extracted with three portions of ether. The ether solution was dried and treated with 1 ml. of methyl iodide. An oil slowly settled out. The ether solution was decanted and the residue (20 mg.) was recrystallized thrice from benzene–ethanol to give 8 mg. of γ-picoline methiodide, m.p. 153.5–154.5° dec. (reported,[29] 149–150°), undepressed on admixture with an authentic sample, m.p. 155–156° dec.

Oxidation of γ-Picolinium Salt 8.—To a colorless solution of 500 mg. of **8** (0.89 mmole), m.p. 302–303.5° dec., in 10 ml. of dioxane and 10 ml. of water was added a few drops of a concentrated potassium hydroxide solution. The deep orange solution was stirred (magnetic bar) and oxidized by dropwise addition of 2% aqueous potassium permanganate solution until the permanganate color persisted for a minute (*ca.* 20 ml. required). Addition of dilute sulfuric acid and a little sodium bisulfite gave a colorless aqueous layer which was extracted with three portions of ether. Concentration of the water-washed and dried solution left 375 mg. of a gum which was recrystallized twice from ethyl acetate–petroleum ether to give 124 mg. (32%) of colorless flat plates of secocholestane-2,3-dioic acid (**13**), m.p. 194.5–197°, $[\alpha]^{26}D$ +29° (*c* 2.00) (reported,[30] m.p. 193–196.5°, $[\alpha]D$ +25.9°, +27.3°).

Borohydride Reduction of γ-Picolinium Salt 8.—To a solution of 600 mg. (1.07 mmoles) of **8** in 30 ml. of methanol was added 500 mg. of sodium borohydride in small portions. The solution became momentarily yellow and then colorless. After 1 hr. the reaction mixture was poured into water and extracted with three portions of ether. Evaporation of the dried ether solution left 528 mg. (98%) of a colorless glass with no carbonyl infrared absorption. Thin-layer chromatography (methanol–chloroform, 3:97) gave two spots, R_f 0.51 and 0.26. Crystallization from chloroform–methanol gave a first crop (A) of 194 mg., m.p. 156–162°, and a second crop (B) of 164 mg., m.p. 154–158°.

Further recrystallization of (**A**) gave 177 mg. of small prisms of constant m.p. 164–165.5°, $[\alpha]^{25}D$ −8.2° (*c* 1.58), R_f 0.51.

Anal. Calcd. for $C_{33}H_{57}NO$ (483.79): C, 81.92; H, 11.88; N, 2.90. Found: C, 81.95; H, 11.86; N, 3.02.

Infrared spectrum: $\nu_{max}^{CS_2}$ 3500 cm.$^{-1}$ (OH), 1075 cm.$^{-1}$ (m) (not present in isomer B).

Ultraviolet spectrum: Rising end absorption only, ϵ_{204} 4120.

Further recrystallization of (**B**) gave 156 mg. of small micaceous sheets of constant m.p. 157–159°, $[\alpha]^{27}D$ −13.5° (*c* 2.08), R_f 0.26. The mixture melting point with (A) was depressed to 134–148°.

Anal. Calcd. for $C_{33}H_{57}NO$ (483.79): C, 81.92; H, 11.88. Found: C, 81.95; H, 11.91.

Infrared spectrum: $\nu_{max}^{CS_2}$ 3460 cm.$^{-1}$ (OH), 885 cm.$^{-1}$. (m) (not present in isomer A).

Ultraviolet spectrum: rising end absorption only, ϵ_{204} 3800.

Neither isomer was soluble in 10% aqueous hydrochloric acid, but both gave a precipitate when hydrogen bromide gas was passed into their ethereal solutions.

A solution of 30 mg. of the 165.5° isomer A in 2 ml. of chloroform with 150 mg. of active manganese dioxide[26] was stirred for 11 hr. Filtration, evaporation, and recrystallization from chloroform–methanol gave 18 mg. of recovered A, m.p. 163.5–165°, undepressed on admixture with starting material. The infrared spectrum in carbon disulfide was identical with that of the starting material and had no trace of carbonyl absorption.

Pyrolysis of γ-Picolinium Salt 8.—A 150-mg. sample of pure **8** was heated in a sublimation tube at 270–275° (<0.01 mm.) for 3 days until only a small amount (5.5 mg., 3.5%) of dark brown residue remained. The sublimate was partitioned between water and ether. The recovered **8** which had sublimed was insoluble in both solvents and amounted to 19 mg. (12.7%), m.p. 300–301° dec. Evaporation of the dried ether solution left 81 mg. (78%) of a mixture of cholestanone, Δ^1- and Δ^4-cholestenones, λ_{max} 237 mμ (ε 8800), $\nu_{max}^{CS_2}$ 1715 cm.$^{-1}$ (cyclohexanone) and 1678 cm.$^{-1}$ (conj. ketone). Thin-layer chromatography (cyclohexane–ethyl acetate, 85:15) gave three spots R_f 0.43 (**5**), 0.65 (**3** and **4**), and 0.00 (trace).

A 60-mg. sample of the ether-soluble fraction was dissolved in ether–methanol and reduced with sodium borohydride. The solution was diluted with dilute hydrochloric acid and extracted with ether. The 58 mg. of product was oxidized by stirring (magnetic bar) with 0.4 g. of active manganese dioxide[26] for 8 hr. Evaporation of the filtered solution left 57 mg. Thin-layer chromatography gave three spots R_f 0.16 (cholestan-3β-ol), 0.35 (**5**), and 0.57 (**3**). No allylic alcohols remained as evidenced by the R_f values and the absence of a purple color when the developed plate was first sprayed with sulfuric acid. The crude product was chromatographed on 1.5 g. of activity II alumina. Benzene–ether (9:1) eluted impure Δ^1-cholesten-3-one (**3**), m.p. 95–101° after recrystallization from 95% ethanol; benzene–ether (1:1) eluted Δ^4-cholesten-3-one (**5**), 9 mg. after recrystallization from 95% ethanol, m.p. 78–81.5°; pure benzene and pure ether eluted cholestan-3β-ol, 10 mg. after two recrystallizations from 95% ethanol, m.p. 142–143° (change of crystal form about 127°).

Pyrolysis of a sample of the pyridinium salt **2** under the same conditions gave an ether-soluble fraction λ_{max} 238 mμ (ε 8900), $\nu_{max}^{CCl_4}$ 1715 cm.$^{-1}$ (cyclohexanone) and 1678 cm.$^{-1}$ (conj. ketone).

Reaction of 2α-Bromocholestanone with β-Picoline.—A solution of 500 mg. (0.98 mmole of **1**) of bromo ketone, m.p. 166–167° (cap.), in 3 ml. of 3-methylpyridine (retention time 46 min.) was refluxed for 3 hr. (oil bath 160–165°). After about 10 min. a precipitate separated. The cooled reaction mixture was diluted with ether and filtered to leave 470 mg. of buff-colored powder which was triturated with water, filtered, and dried. The β-picolinium bromide, m.p. 293–294.5° dec., amounted to 448 mg. (82%). The compound had a negative coefficient of solubility. Two recrystallizations from chloroform–acetone by the technique described for **8** gave colorless rosettes, m.p. 295–296° dec. (sample placed on hot stage at 280°), $[\alpha]D$ −7.6° (*c* 1.96).

Anal. Calcd. for $C_{33}H_{52}NOBr$ (558.70): C, 70.95; H, 9.38; N, 2.50. Found: C, 71.24; H, 9.69; N, 2.60.

Infrared spectrum: 1730 cm.$^{-1}$ (s) (C=O), 1638 (w) cm.$^{-1}$.

Ultraviolet and visible spectra: λ_{max}^{EtOH} 264 mμ (ε 4830); $\lambda_{max}^{EtOH-KOH}$ 255 mμ (ε 5470), 302 mμ (ε 878), and 432 mμ (ε 5600). Immediately after acidification of the basic solution a new peak λ_{max} 330 mμ (ε 1810) appeared[25] and then gradually disappeared as the spectrum became identical with that in neutral solution.

The aqueous solution from trituration of the β-picolinium salt was evaporated to dryness to leave 22 mg. (13%) of oily β-picoline hydrobromide which was dissolved in 1 ml. of 95% ethanol. Addition of a solution of 90 mg. of picric acid in 10 ml. of ether gave a slow precipitation of 21 mg. of β-picoline

(28) J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 3504 (1953), footnote 22.

(29) G. R. Clemo and W. M. Gourlay, *J. Chem. Soc.*, 478 (1938).

(30) H. Heymann and L. F. Fieser, *Helv. Chim. Acta*, **35**, 631 (1952).

picrate, m.p. 144–147° dec. (cap.) (reported,[31] 144–147°) after two recrystallizations from acetone–ethanol.

The ethereal filtrate from the original reaction mixture was extracted with dilute hydrochloric acid until no more β-picoline remained. Evaporation of the dried ether solution left 103 mg. (14.5%) of almost colorless solid, λ_{max} 233 mμ (ε 5000), $\nu_{max}^{CS_2}$ 1715 cm.$^{-1}$ (cyclohexanone) and 1672 cm.$^{-1}$ (conj. ketone). Thin-layer chromatography (cyclohexane–ethyl acetate, 85:15) gave two spots, R_f 0.38 (**5**) and 0.60 (**3** and **4**).

Reduction of β-Picolinium Salt.—A mixture of 257 mg. (0.46 mmole) of the salt from **1** and β-picoline, 3 g. of activated zinc[28] and 3 ml. of glacial acetic acid was refluxed with stirring (magnetic bar) for 16 hr. The reaction was worked up as described for the zinc reduction of **8**. Evaporation of the ether solution containing the neutral material left 110 mg. (62%). Two recrystallizations of a 74-mg. sample from absolute ethanol gave 30 mg. of cholestan-3-one, m.p. 129–131°, undepressed on admixture with an authentic sample.

The dried ether extract of the basified reaction mixture was stirred (magnetic bar) with 84 mg. of picric acid. Filtration after 0.5 hr. gave 50 mg. (33%) of yellow needles of β-picoline picrate, m.p. 146.5–148° (cap.) (reported,[31] 144–147°). Recrystallization from ethanol–acetone did not change the melting point which was not depressed on admixture with an authentic specimen, m.p. 147.5–150° dec. (cap.).

Purification of 2,4-Dimethylpyridine.—Commercial 2,4-lutidine (Aldrich) (24 g.) containing about 10–15% of β- plus γ-picoline and about 2% of 2,6-lutidine was dissolved in 75 ml. of benzene and hydrogen bromide gas introduced. There was precipitated 37 g. (89%) of pink hydrobromide salt. Two recrystallizations from chloroform–methyl ethyl ketone gave 16 g. of pure 2,4-dimethylpyridine hydrobromide of m.p. 199.5–200° (subl., sample placed on hot stage at 180°) [reported,[32] 188–190° (unanalyzed)].

Anal. Calcd. for $C_7H_{10}NBr$ (189.08): C, 44.70; H, 5.36. Found: C, 44.41; H, 5.59.

The pure salt (16 g.) in aqueous solution was made basic with sodium hydroxide solution and extracted with two portions of ether. After distillation of the ether from the dried solution, the residue was distilled through a 15-cm. Vigreux column. There was collected 8.3 g. (91% recovery) of colorless 2,4-lutidine, b.p. 155–156° (757 mm.), $n^{22}D$ 1.4994 [reported,[33] b.p. 157° (760 mm.)]. Gas–liquid chromatography gave a single peak of 55-min. retention time.

The methiodide was prepared from 73 mg. of the pure 2,4-lutidine by reaction with methyl iodide at room temperature. The yellow solid (143 mg., 84%), m.p. 101–112°, was recrystallized twice from acetone to give 80 mg. of colorless flat prisms, m.p. 119–120° (reported,[34] m.p. 118°).

Reaction of 2α-Bromocholestanone with 2,4-Dimethylpyridine.—(a) A solution of 1.000 g. (1.95 mmoles of **1**) of bromo ketone, m.p. 166–167° (cap.), in 5 ml. of the purified 2,4-lutidine was refluxed (oil bath 180°) for 4 hr. The solution became greenish, then brown and some crystalline material separated during the reaction. The reaction mixture was cooled, diluted with ether, and filtered. There was collected 350 mg. (95%) of white prisms of 2,4-dimethylpyridine hydrobromide, m.p. 197–199° (subl., sample placed on hot stage at 170°), undepressed on admixture with the authentic sample prepared above. The salt was completely soluble in water and gave no yellow color on addition of sodium hydroxide solution. Removal of the ether from the filtrate and further reflux of the reaction for 8 hr. gave only 3 mg. more of hydrobromide salt.

The ether–lutidine solution was washed with dilute sulfuric acid until no more lutidine remained. The dried ether solution was evaporated to leave 843 mg. (100%) of brown glass, λ_{max} 234 mμ (ε 9400), $\nu_{max}^{CS_2}$ 1712 cm.$^{-1}$ (cyclohexanone) and 1678 cm.$^{-1}$ (conj. ketone). Thin-layer chromatography (cyclohexane–ethyl acetate, 85:15) gave two spots, R_f 0.48 (**5**) and 0.67 (**3** and **4**).

(b) When the reaction was carried out with 1.50 g. of **1** and 8 ml. of the unpurified 2,4-dimethylpyridine, there was obtained 601 mg. of precipitate of which 136 mg. was insoluble in water. Zinc–acetic acid reduction of the water-insoluble material gave cholestan-3-one and a basic fraction whose methiodide after recrystallization from acetone had m.p. 151–153.5° dec. which was undepressed on admixture with authentic γ-picoline methiodide, m.p. 155–156° dec.

Reaction of 2α-Bromocholestanone (1) with 2,4,6-Trimethylpyridine.—A solution of 1.000 g. (1.95 mmoles of **1**) of bromo ketone, m.p. 166–167°, in 4 ml. of γ-collidine that had been purified *via* its crystalline hydrobromide by the procedure described above for 2,4-lutidine was refluxed (oil bath 200°) for 12 hr. The clear brown solution was diluted with ether and filtered to remove 390 mg. (103%) of γ-collidine hydrobromide, m.p. 335–337° (sealed capillary, uncor.) undepressed on admixture with an authentic specimen. The salt was completely soluble in water to give a solution which remained colorless on addition of sodium hydroxide.

The ethereal filtrate was washed with dilute hydrochloric acid until all collidine had been removed. Evaporation of the dried ether solution left 831 mg. (99%) of tan gum, λ_{max} 235 mμ (ε 7500), $\nu_{max}^{CS_2}$ 1715 cm.$^{-1}$ (cyclohexanone) and 1678 cm.$^{-1}$ (conj. ketone). Thin-layer chromatography (cyclohexane–ethyl acetate, 85:15) gave four spots R_f 0.39 (**5**), 0.60 (**3** and **4**), 0.30 (trace), and 0.00 (trace).

A 500-mg. sample of this ether-soluble fraction was reduced with sodium borohydride and then oxidized by active manganese dioxide by the procedure described for the γ-picoline reaction above. Separation of the products by alumina chromatography and recrystallization of appropriate fractions gave Δ^1-cholestenone (**3**), cholestan-3β-ol, and Δ^4-cholestenone 2,4-dinitrophenylhydrazone whose melting points were undepressed by authentic specimens.

Reaction of 2α-Bromocholestanone (1) with Pyridine.—The reaction was repeated according to the directions of Ruzicka, Plattner, and Aeschbacher.[4b] From 1.000 g. (1.95 mmoles of **1**) of bromoketone, m.p. 169–169.5°, refluxed with 5 ml. of reagent pyridine for 2 hr. was isolated by filtration 868 mg. (82%) of colorless needles, m.p. 301–303° dec. (sample placed on hot stage at 280°). The pyridinium compound also exhibited a negative temperature coefficient of solubility in chloroform. It was recrystallized from this solvent by the technique described for **8**. The colorless pyridinium salt **2** had m.p. 301–302.5° dec., $[\alpha]^{26}D$ −5.7° (*c* 1.22) (reported,[4a] m.p. 310° dec.). A sample dissolved in aqueous ethanol acidified with dilute nitric acid gave an instantaneous precipitate with silver nitrate solution.

Infrared spectrum: $\nu_{max}^{CS_2}$ 1730 cm.$^{-1}$ (s) (C=O) and 1635 (m) cm.$^{-1}$.

Ultraviolet spectrum: λ_{max}^{EtOH} 260 mμ (ε 4760); $\lambda_{max}^{EtOH-KOH}$ 245 mμ (ε 6750), 318 mμ (ε 950), and 431 mμ (ε 7000).

The filtrate from removal of the pyridinium salt was diluted with ether, washed with dilute acid, dried, and evaporated to leave 208 mg. (15%) of colorless glass, λ_{max} 230 mμ (ε 1940), $\nu_{max}^{CS_2}$ 1710 cm.$^{-1}$ (cyclohexanone) with shoulders. Thin-layer chromatography (cyclohexane–ethyl acetate, 85:15) gave a strong spot R_f 0.58 (**3** and **4**) and two weak spots R_f 0.68 (?) and 0.75 (?). A 700 γ spot after chromatography and charring gave no trace of a spot corresponding to **5**. Therefore less than 10 γ (1.4%) of **5** could have been present.

Reduction of Pyridinium Salt 2.—A mixture of 160 mg. of **2**, 5 g. of activated zinc,[28] and 5 ml. of glacial acetic acid was

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refluxed with stirring (magnetic bar) for 10 hr. The reaction was worked up as described for the zinc reduction of **8**. Evaporation of the ether solution containing the neutral material left 94 mg. Two recrystallizations from 95% ethanol afforded 44 mg. of cholestan-3-one, m.p. 129.5–130.5° undepressed on admixture with an authentic sample.

Mixture Melting Points.—When the pyridinium bromide **2** (m.p. 301–302.5° dec.) and the γ-picolinium bromide **8** (m.p. 305–306° dec.) were thoroughly ground together and put on the hot stage at 275°, the melting point was 293–295° dec.

When the γ-picolinium bromide **8** (m.p. 305–306° dec.) and the β-picolinium bromide (m.p. 295–296° dec.) were thoroughly ground together and put on the hot stage at 270°, the melting point was 291–294° dec.

Stability of Cholestenones to the Reaction Conditions.—(a) A mixture of 300 mg. of Δ^4-cholesten-3-one (**5**), m.p. 80–81.5°, 400 mg. of the γ-picolinium bromide **8**, and 40 mg. of γ-picoline hydrobromide in 10 ml. of γ-picoline was refluxed (oil bath 170°) for 3 hr. The reaction mixture was diluted with ether, filtered and the filtrate washed with dilute hydrochloric acid. Evaporation of the dried ether solution left 290 mg. (97% recovery) of Δ^4-cholesten-3-one whose infrared spectrum was identical with that of starting material. Thin-layer chromatography gave a single spot R_f 0.52 corresponding to authentic **5**. Gas–liquid chromatography gave a single symmetrical peak of retention time 28 min., the same as an authentic sample of **5**.

(b) A mixture of Δ^1-cholesten-3-one (**3**), m.p. 98–100.5°, 400 mg. of **8** and 40 mg. of γ-picoline hydrobromide in 10 ml. of γ-picoline was treated exactly as was the sample of **5** in (a) above. Evaporation of the dried ether solution left 291 mg. (97% recovery) of Δ^1-cholesten-3-one (**3**) whose infrared spectrum was identical with that of starting material. Thin-layer chromatography gave a single spot R_f 0.75 corresponding to authentic **3** (and **4**). Gas–liquid chromatography gave two peaks of retention time 21.3 min. (91.7%) and 18.2 min. (8.3%). The starting material also gave the same two peaks with the same retention times and relative areas. The minor component was a small amount of cholestan-3-one which had not been separated by recrystallization[21]

Borohydride Reduction of Δ^1-Cholestenone (3).—A 60-mg. sample of **3** containing 8% of cholestan-3-one was dissolved in ether–methanol and reduced at room temperature with excess borohydride. The crude product, isolated by dilution with dilute hydrochloric acid and ether extraction, was oxidized with active manganese dioxide[26] for 12 hr. in chloroform solution. Thin-layer chromatography (cyclohexane–ethyl acetate, 85:15) gave three spots, R_f 0.15 (cholestan-3β-ol), 0.27 (cholestan-3α-ol), and 0.53 (**3**). Comparison of the intensity of the R_f 0.15 spot with spots of varying known amounts of authentic cholestan-3β-ol indicated that 30–40% of the material was cholestan-3β-ol. Upon chromatography on 1.5 g. of activity II alumina there was eluted 26 mg. with pure benzene and pure ether. Recrystallization from 95% ethanol gave 20 mg. (33%) of pure **cholestan-3β-ol**, m.p. 143–144°, of which at least 25% must result from reduction of the conjugated double bond of Δ^1-cholesten-3-one as well as the carbonyl group.

Isolation of Impurity in 1.—2α-Bromocholestan-3-one (**1**) m.p. 169–169.5° (cap.), $[\alpha]^{26}D$ +46° (*c* 2.20) (reported,[35] m.p. 168–169°, $[\alpha]D$ +42°) prepared according to Fieser and Dominguez[35] gave two spots on thin-layer chromatography, R_f 0.73 (intense) and 0.64 (weak). A solution of 30 mg. was spotted on four 8 × 8 in. thin-layer chromatographic plates which were developed in cyclohexane–ethyl acetate (85:15). One edge of the developed chromatogram was charred with sulfuric acid to reveal the position of the two lines. The two compounds were separated by scraping the appropriate portion of the silica gel with a razor blade. The two portions of silica gel were extracted with ether. Evaporation of solvent left 4 mg. (12%) of the impurity which gave a single spot R_f 0.65 alongside a sample of pure cholestan-3-one, R_f 0.66. Recrystallization from 95% ethanol gave cholestan-3-one, m.p. 120–128°. The 2α-bromocholestanone extracted from silica gel had m.p. 168–169.5° after three recrystallizations from 95% ethanol and gave a single spot, R_f 0.73 on a thin-layer chromatogram.

Reaction of 8 with Isoamyl Nitrite.—To a solution of 1.0 g. of sodium in 50 ml. of anhydrous ethanol was added 500 mg. (0.89 mmole) of **8** and 8 ml. of isoamyl nitrite. The deep red solution was refluxed for 17 hr. Then to saponify any esters 3 g. of sodium hydroxide and water were added to the refluxing solution. After most of the ethanol was removed by distillation, water was added and the distillation continued to remove isoamyl alcohol. The residue was acidified with hydrochloric acid and heated on the steam bath for 0.5 hr. The solution was made basic and washed with ether. Then the solution was acidified with hydrochloric acid and extracted with ether. Evaporation of the water washed and dried ether solution left 345 mg. of brown gum which was chromatographed on 10 g. of silicic acid. Chloroform and chloroform–methanol (99:1) eluted crystalline material which after recrystallization from ethyl acetate–petroleum ether gave 70 mg. (18%) of colorless leaflets of secocholestane-2,3-dioic acid, m.p. 193–197°, undepressed on admixture with the sample prepared by permanganate oxidation of **8**.

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