Careful control of reaction conditions were found to be necessary in preparing β-azidopropionitrile (VI). A solution of 5.3 g. (0.1 mole) of glacial acetic acid was treated with exactly 6.5 g. (0.1 mole) of sodium azide in 30 ml. of water and the reaction mixture stood for two to three days. In all experiments in which the concentration of hydrazoic and acetic acids was greater than that of acrylonitrile, the only product found in yields 15–20% was the monohydrate of hydracrylic acid (VIII) isolated as a colorless oil and purified by distillation, b.p. 30° (5 mm.), $n^{20}D$ 1.3749, d^{20}_4 1.0474. Strong infrared absorption at 2.7 and 5.9 μ indicated the presence of the hydroxyl and carbonyl functions, respectively.

Anal. Calcd. for $C_3H_6O_3 \cdot H_2O$: C, 33.56; H, 7.46; *MR*D, 22.8. Found: C, 33.95; H, 7.66; *MR*D, 23.5.

Triazoacetone was prepared according to the method of Forster and Fierz,[18] from chloroacetone and sodium azide. After three fractional distillations of the product a pure sample was obtained, b.p. 42–43° (2 mm.), $n^{20}D$ 1.4520.

The 2,4-dinitrophenylhydrazone derivative of β-azidopropionaldehyde (IVa) was prepared by adding five drops of the aldehyde to 8 ml. of a 1% hydrochloric acid solution of the hydrazine reagent and heating the mixture on the steam-cone for five minutes. Dilution with water brought about the separation of an orange-red solid, m.p. 115–120°. After four recrystallizations from aqueous ethanol it separated as a very fine powder, constant m.p. 129–130°.

Anal. Calcd. for $C_9H_9N_7O_4$: C, 38.71; H, 3.25; N, 35.12. Found: C, 39.50; H, 3.17; N, 35.07.

The hydrazide of β-azidopropionic acid was prepared from methyl β-azidopropionate (IVb) and hydrazine hydrate according to the directions of Curtius.[18] **The benzal derivative** was prepared by adding an equimolar quantity of benzaldehyde to the hydrazide (a thick sirup) and heating five minutes on a steam-cone. The clear solution which resulted was allowed to stand several hours in the refrigerator or until crystallization had occurred. After six recrystallizations from aqueous ethanol, the derivative separated as very fine, faintly yellow needles, m.p. 115–116° (lit.[18] m.p. 116–117°).

A picrate derivative of 1-α-pyridyl-2-azidoethane (VII) was prepared in ether. There was an immediate precipitate which was separated by filtration and recrystallized from ethanol from which it separated as yellow needles, m.p. 112–113°.

Anal. Calcd. for $C_{13}H_{11}N_7O_7$: C, 41.38; H, 2.94; N, 25.99. Found: C, 41.38; H, 2.81; N, 25.90.

Infrared Spectra.—The absorption curves given in Figs. 1 and 2 were determined with a Baird Associates double-beam infrared spectrophotometer with a sodium chloride prism, from 2% solutions in chloroform by Mr. David Brown of the Chemical Engineering Department of this University.

(18) M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, **93**, 81 (1908).

ANN ARBOR, MICHIGAN RECEIVED MAY 24, 1951

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

A New Route to 11-Ketosteroids by Fission of a $\Delta^{9(11)}$-Ethylene Oxide[1,2]

BY HANS HEYMANN AND LOUIS F. FIESER

A previously reported product of chromic acid oxidation of methyl 3-keto-9α,11α-oxidocholanate (I) is shown to be the 3β-hydroxy-11-keto-3α,9α-oxidohemiketal (Va). This is formed *via* the 11β-hydroxy compound IVa, which can be produced by acid-catalyzed hydration of I. Similar fissions of the keto oxide I have been accomplished with hydrogen chloride and with acetic acid–boron fluoride; the hemiketals II–V have been interrelated and shown to possess highly reactive 3β-hydroxyl groups. Fission involves concerted attack of the carbonyl and oxide groups; the mechanistic formulation (a) is supported by evidence that excludes the alternate mechanism (b). The 11β-substituents in the hemiketals, shown to be β-oriented, possess unusual reactivity that is attributed to neighboring-group action of the bridging 3α,9α-oxygen atom. The 11β-hydroxy and 11-keto hemiketals IVa and Va are reducible, best by the action of sodium borohydride on the free acids, to the 3α- and 3β-acetoxy-9α,11β-dihydroxy compounds, XI and XII. These substances are convertible into the 3-epimeric 9α,11α-oxides, X and XIII; and by a series of smooth transformations, into the epimeric 3-hydroxy-11-ketocholanic acid derivatives XXII and XXIV and into the Δ^8-11-ketones XIX and XX. The triol derivative XII was proved to contain an 11β-hydroxyl group and was correlated with an 11-hydroxysteroid (XV) of the configuration attributed to cortical hormones. One surprising reaction encountered is the *cis* dehydration of triol XI to the 11-keto compound; another is Wolff–Kishner reduction of a 9α-hydroxy-11-ketone (XIV) to the $\Delta^{9(11)}$-ethylene. Of four routes found for conversion of a 3α-hydroxy-$\Delta^{9(11)}$-steroid to the 3α-hydroxy-11-ketone, three offer promise of preparative value. One involves the sequence (Chart 2): Va → XI → XIV → XVIII → XXII; others are outlined in Chart 3.

A previous paper from this Laboratory[3] reported attempts to find a way of utilizing a 9,11-unsaturated steroid as starting material for production of an 11-ketosteroid that could be used as an intermediate in the partial synthesis of cortisone. Dr. S. Rajagopalan found that the oxide resulting from the action of perbenzoic acid on methyl $\Delta^{9(11)}$-lithocholenate, now regarded as the α-oxide on the basis of evidence to be presented below, is converted by mild oxidizing agents into the 3-ketone (I), of formula $C_{25}H_{38}O_4$, and that on more drastic oxidation (CrO_3) it affords a substance $C_{25}H_{38}O_5$.

The present investigation of the new oxidation product has established that the substance is the 11-keto-3α,9α-oxidohemiketal whose structure is represented by Va. The infrared spectrum revealed the presence of hydroxyl, keto and ester functions; the free hydroxyl group, although resistant to oxidation, proved to be not only readily acylable in the presence of acids, but capable of being etherified under very mild conditions of acid catalysis reminiscent of the formation of acetals and glycosides. The substance also reacts with mercaptans, and the crystalline thioethyl derivative (Ve) on desulfuration with Raney nickel and saponification afforded the known 3α,9α-oxido-11-ketocholanic acid.[4] Confirmatory evidence of the presence of an 11-keto group was found in Clemmensen reduction of the hemiketal to 11-ketocholanic acid.[5]

On subsequent experimentation, we found that the 3-keto-9,11-oxide I can be converted into a series of related 11-substituted-3,9-oxidohemiketal derivatives. Hydrogen chloride converts I into the 11-chloro compound IIa, which readily forms a methyl ether and an acetate, and from which the keto oxide I can be regenerated. Acetolysis of I

(1) This work was supported by a grant from the Rockefeller Foundation.

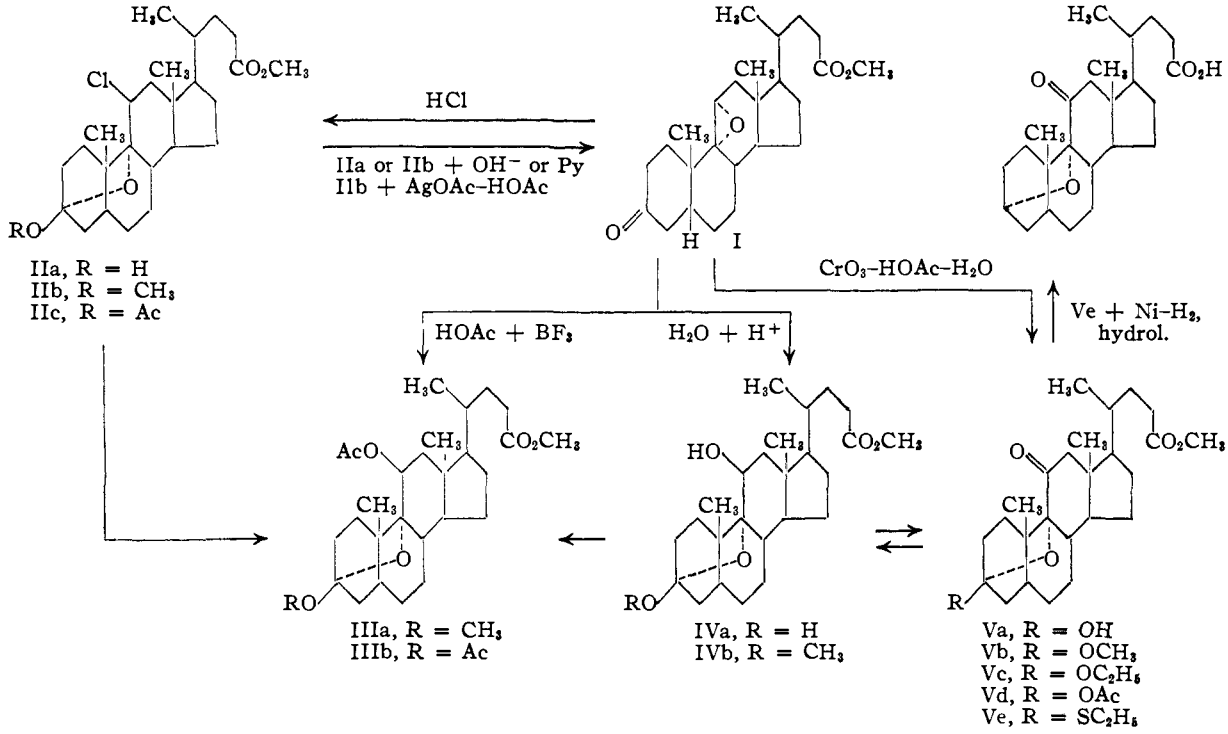
(2) See Communication to the Editor, L. F. Fieser, H. Heymann and S. Rajagopalan, THIS JOURNAL, **72**, 2307 (1950).

(3) L. F. Fieser and S. Rajagopalan, *ibid.*, **73**, 118 (1951).

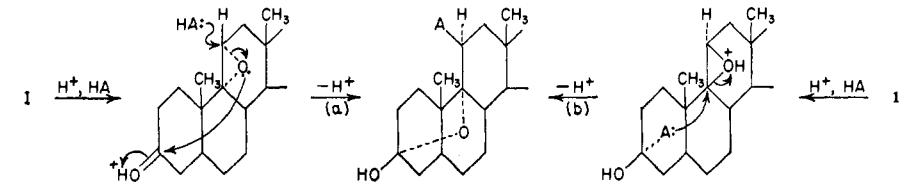
(4) R. B. Turner, V. R. Mattox, L. L. Engel, B. F. McKenzie and E. C. Kendall, *J. Biol. Chem.*, **166**, 345 (1946).

(5) H. Reich and T. Reichstein, *Helv. Chim. Acta*, **26**, 562 (1943).

CHART I



afforded a non-crystalline 11-acetoxy hemiketal that yielded a crystalline methyl ether (IIIa) and acetate (IIIb). Particularly interesting is the observation that the 3-keto-9,11-oxide I adds a mole of water in the presence of a suitable acid catalyst and yields the 11-hydroxy hemiketal (IVa), which is the precursor of the 11-ketone (Va), the initially discovered product of oxidation of the 3-keto-9,11-oxide with chromic acid in aqueous acetic acid. Reconversion of the 11-ketone to the 11-hydroxy precursor was accomplished by reduction of the 3-methyl ether derivative Vb as the sodium salt with sodium borohydride. As the arrows in the diagram indicate, the 11-chloro and 11-acetoxy hemiketals, II and III, have been correlated with the 11-hydroxy compound IV. Thus treatment of IVb, the 3-methyl ether of the 11-hydroxy hemiketal, with acetic anhydride and boron fluoride etherate effects acetylation of the 11-hydroxyl group and affords IIIb (the unusual feature of acylation of the 11β-hydroxyl group is discussed below). Reaction of the 3-acetate of the 11-chloro derivative (IIc) with silver acetate in acetic acid gives the 3-acetate of the 11-acetoxy derivative, IIIb. Thus correlation of all four 11-substituted hemiketals (II–V) is complete. In each of these series, the 3-hydroxyl group is very readily etherified or acetylated in the presence of an acid catalyst; acetylation in pyridine solution proceeds only slowly. Rapid exchanges of methyl for acetyl and *vice versa* are illustrated by the conversion of the 3-acetate-11-ketone (Vd) into the 3-methyl ether (Vb) with boiling methanol containing perchloric acid and the reverse change, Vb → Vd, with acetic anhydride–boron fluoride. The free hemiketal Va is regenerated from its 3-acetate (Vd) with sodium methoxide; the 3-methyl ether IVb is hydrolyzed to the 3-hydroxy compound IVa by aqueous acid.



Under conditions of oxidation suitable for conversion of the 3-keto-9,11-oxide I into the 11-ketohemiketal Va, both methyl 3α-acetoxy-9,11-oxidocholanate[6] and methyl 9,11-oxidocholanate,[7,8] remained unattacked; moreover, methyl 3α-hydroxy-9,11-oxidocholanate on mild treatment with hydrogen chloride gives a mixture of dienes, whereas the corresponding 3-keto compound I gives rise to the 11-chlorohemiketal II. These observations show that the 3-keto group facilitates fission of the oxide ring and that formation of the ketals II–V must occur by a concerted series of changes involving both the carbonyl and oxide functions. Dr. R. B. Turner of this Laboratory suggested that the changes involved in the oxidation reaction are initiated by attacks by a proton at the carbonyl group and by a molecule of water (HA) at C_{11}, as represented in formulation (a), and indeed this suggestion led us to try the reactions of acid catalyzed hydration and acetolysis, and the cleavage with hydrogen chloride described

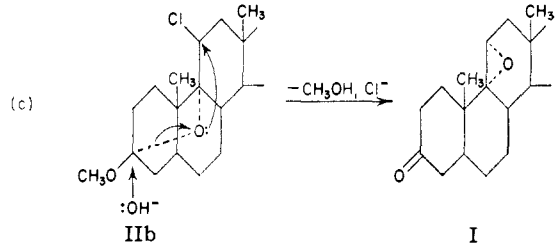
(6) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943).
(7) H. B. Althor and T. Reichstein, *ibid.*, **26**, 492 (1943).

above. The alternate formulation (b) appeared to us unlikely because the 9,11-oxide ring in the starting material would have to be represented as β-oriented, in violation of the rule of rear attack,[8] but it would account for the hydration reaction just as well as (a). However, if the hydration proceeded as in (b), the comparable fissions with hydrogen chloride or acetic acid would involve initial hydration, followed by replacement of a preformed 11-hydroxyl group by chlorine or by an acetoxyl group. The 11-hydroxyl group of the 11-hydroxy hemiketal methyl ether IVb is indeed changed to acetoxyl upon gentle treatment with acetic acid–boron fluoride, and hence the acetolysis of the keto oxide I to the 11-acetoxy compound IIIb does not distinguish between the two mechanisms. However, a decision in favor of formulation (a) can be made with reference to the fission of I with hydrogen chloride in chloroform to the 11-chloro hemiketal IIa, since similar treatment does not at all affect the 11-hydroxyl group of the 11-hydroxy hemiketal ether IVb.[9]

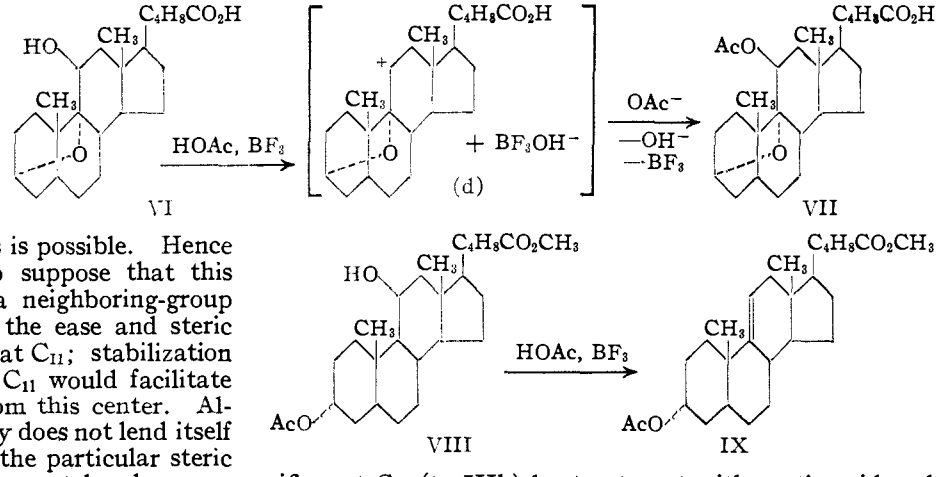
Mechanism (a) seems sufficiently well grounded by the experimental evidence to warrant the conclusion that in the conversion of the 3-keto-9,11-oxide to a hemiketal the C_3–O–C_9 bridge is formed without rupture of the C_9–oxygen bond. Since the C_3–O–C_9 bridge can exist only in the α-configuration,[10] the oxide must be the 9α,11α-oxide. In view of the generally accepted concept of trans-fission of ethylene oxides, the C_{11}-substituents in the fission products II, III and IV must be β-oriented.

The 11β-substituents of the 3α,9α-oxido hemiketals are more reactive than would be expected on purely structural grounds. The space drawing (Fig. 1) roughly conveys the idea, seen more clearly on inspection of actual models, that the oxido-oxygen atom is practically within bonding distance of C_{11}. Moreover, the bridging oxygen atom occupies a fixed position, since no rotation about any of the bonds is possible. Hence it seems reasonable to suppose that this bridging atom exerts a neighboring-group action[11] in determining the ease and steric course of displacements at C_{11}; stabilization of a positive charge at C_{11} would facilitate separation of anions from this center. Although oxygen ordinarily does not lend itself to such stabilization,[11] the particular steric arrangement of the system at hand seems specifically favorable for neighboring group participation of the oxygen atom in the ionization reactions.

Such participation of the oxidic oxygen accounts for a marked lability of the 11β-chlorine atom in the hemiketal IIa and its derivatives. Thus the 3-acetate IIc reacts with silver acetate in hot acetic acid with displacement of the 11β-chlorine atom by an acetoxyl group without inversion and yields IIIb. That the free hemiketal IIa is transformed on attempted crystallization from methanol into its 3-methyl ether IIb is probably due to catalysis by a trace of hydrogen chloride resulting from ionization at C_{11}. Both the free 11β-chloro hemiketal IIa and its 3-methyl ether IIb are converted under basic catalysis into the 3-keto-9,11-oxide I; the concerted changes involved seem attributable to an attack by hydroxide ion at C_3 induced by the electron deficiency of the dioxygenated 3-carbon atom, as shown in formulation (c).



The 11β-acetoxy group of the 3,9-oxido ketals is not altered by either 0.06 *N* alcoholic alkali or 0.4 *N* methanolic hydrochloric acid in 3–4 hr. periods of refluxing. Methyl 11β-acetoxy-3α,9α-oxido cholanate is hydrolyzed nearly completely by 3.6 *N* methanolic alkali in one hour at the boiling point; the 16-hour period reported[12] is not required. More striking is the observation that the 11β-hydroxy hemiketal methyl ether IVb is acetylated at C_{11} (to IIIb) by treatment with acetic acid and boron fluoride (followed by remethylation), and that 11β-hydroxy-3α,9α-oxidocholanic acid (VI)[12] under similar conditions is smoothly acetylated to VII.[12] In sharp contrast, the non-oxidic methyl 3α-acetoxy-11β-hydroxycholanate (VIII)[13] prepared by reduction of the corresponding 11-ketone (free acid) with sodium borohydride followed by re-esterification and reacetylation, underwent



(8) L. F. Fieser, *Experientia*, **6**, 312 (1950); *cf.* T. F. Gallagher and T. H. Kritchevsky, THIS JOURNAL, **72**, 882 (1950).

(9) Fission of I with acetic acid containing 36% hydrochloric acid to a concentration of 0.4 *N* in hydrogen chloride also affords IIa (73% yield); similar treatment of IVb gave a mixture from which 35% of the hydrolysis product IVa was isolated, but the mother liquor contained halogenated material.

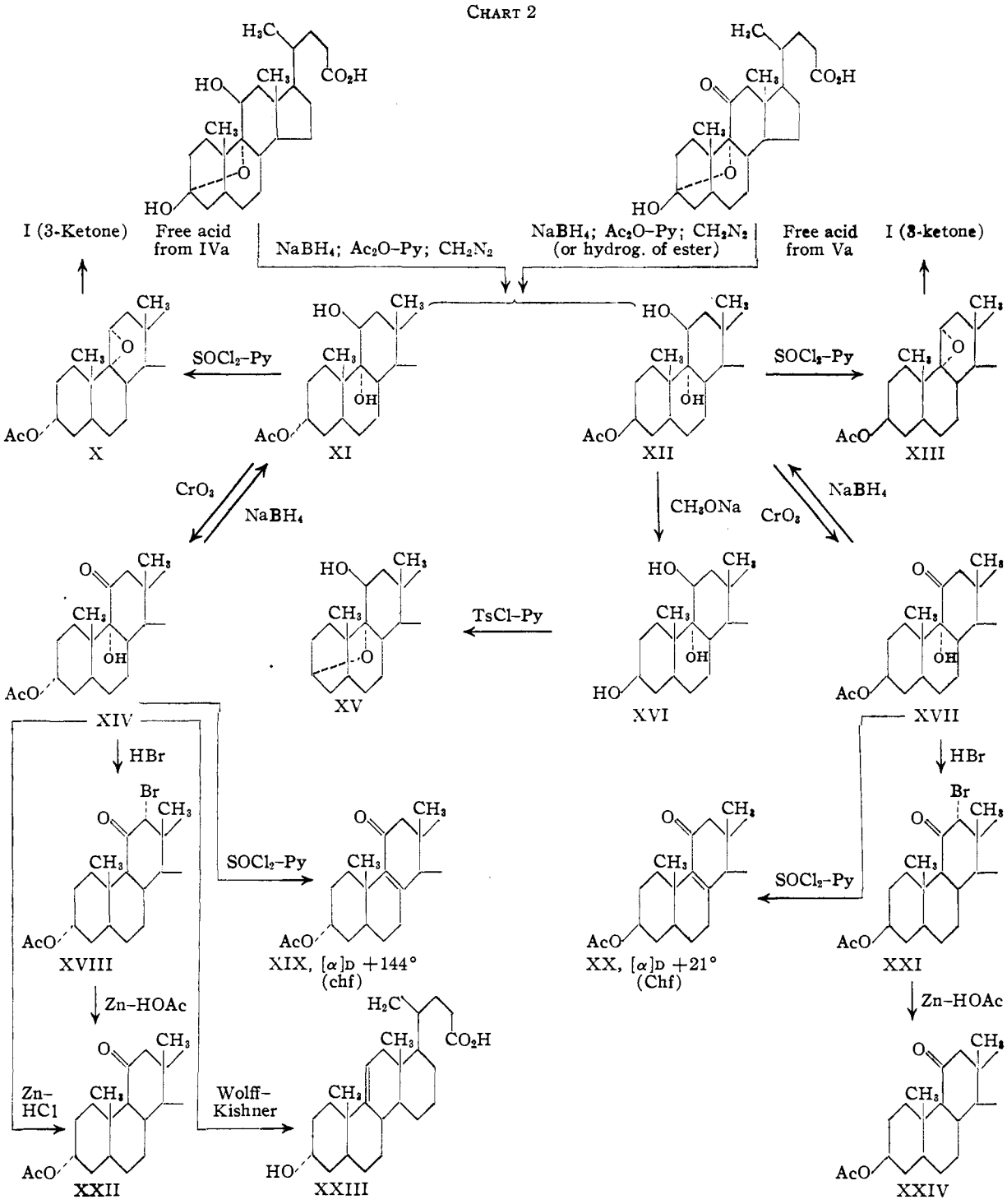
(10) V. R. Mattox, R. B. Turner, L. L. Engel, B. F. McKenzie, W. F. McGuckin and E. C. Kendall, *J. Biol. Chem.*, **164**, 569 (1946).

(11) See, for example, S. Winstein and E. Grunwald, THIS JOURNAL, **70**, 828 (1948).

(12) V. R. Mattox, R. B. Turner, B. F. McKenzie, L. L. Engel and E. C. Kendall, *J. Biol. Chem.*, **173**, 283 (1948).

(13) A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **26**, 586 (1943).

CHART 2



smooth dehydration to IX on treatment with acetic acid–boron fluoride, as expected on the basis of observations of Reichstein and Seebeck[6] and of earlier findings.[14] The oxidic oxygen in VI thus exerts a neighboring-group action to promote ionization at C_{11} to produce an ion that is stabilized by resonance, for example, by distribution of the positive charge to oxygen.

On hydrogenation in acetic acid over platinum, the 11-keto hemiketal Va consumed two moles of hydrogen in 24 hours, and chromatography of the acetylated product afforded two acetate esters that were shown by evidence to be cited presently to be methyl 3α- and 3β-acetoxy-9α,11β-dihydroxycholanate (Chart 2, XI and XII); they are formed in the ratio $\alpha:\beta = 1:2$. A more convenient process, in which the ratio of α- to β-epimer is eight to one, consists in reduction of the free acid of Va with sodium borohydride in boiling aqueous alcohol, followed by acetylation and re-esterification. Under milder conditions Va itself was reduced

(14) C. W. Shoppee, *Helv. Chim. Acta*, **23**, 740 (1940); C. W. Shoppee and T. Reichstein, *ibid.*, **24**, 351 (1941); C. W. Shoppee, *ibid.*, **26**, 543 (1943), footnote no. 4.

without reduction of the ester group, but variable results and incomplete reduction prompted saponification of the ester group to avoid attack at this point and adoption of the more drastic conditions of reduction.

The 3α-acetoxy compound XI (but not the β-epimer) was also isolated from the borohydride reduction of the free acid from the 11-hydroxy hemiketal IVa, for which the β-orientation of the 11-hydroxyl group has been demonstrated. Since in XI the 9-hydroxyl group is established to be α-oriented by its genetic relationship to the 3α,9α-oxide bridge, epimer XI contains a *trans*-9,11-glycol grouping; in accordance with this relationship, the substance is smoothly dehydrated by thionyl chloride and pyridine to the known methyl 3α-acetoxy-9α,11α-oxidocholanate (X). Epimer XII, which likewise must contain a 9α-hydroxyl group, was proved also to be a *trans* glycol by conversion with thionyl chloride–pyridine to an oxide (XIII) that was shown to be a 9α,11α-oxide by deacetylation and oxidation to the known 3-keto-9α,11α-oxide I. The triol monoacetate XII is thus proved to have a β-oriented 11-hydroxyl group by evidence that is perhaps more secure than existing evidence regarding the 11-hydroxy steroids of the cortical hormone series, since the latter is based upon considerations of degree of steric hindrance and ease of dehydration to an ethylene.[15] A correlation between the two series was achieved by deacetylation of XII and treatment of the resulting triol XVI with tosyl chloride in pyridine; the intermediate tosylate evidently underwent an intramolecular displacement reaction with ring closure under the conditions of the experiment, for the product was methyl 11β-hydroxy-3α,9α-oxidocholanate (XV), identical with a sample of ester prepared from authentic 11β-hydroxy-3α,9α-oxidocholanic acid.[12]

The configuration at C_3 of the triol monoacetate XI resulting from reduction of the hemiketals IVa and Va is established as α by the conversion to the known methyl 3α-acetoxy-3α,9α-oxidocholanate (X), which is convertible to the 3-ketone I.[3] The second reduction product, the triol monoacetate formulated as XII, was converted through the 9,11-oxide XIII into the same 3-ketone I, and hence differs from XI only in the configuration at C_3. The inference that XII is the 3β-acetoxy epimer was proved by oxidation of XII to the 11-ketone XVII, reaction of this with hydrogen bromide, which proceeded as in established instances[4] with rearrangement to give the 12-bromo-11-ketone XXI, and removal of the bromine atom by reduction with zinc and acetic acid to the known[16] methyl 3β-acetoxy-11-ketocholanate (XXIV). The 3α-configuration assigned to the other triol monoacetate (XI) was confirmed by similar transformation to the known methyl 3α-acetoxy-11-ketocholanate (XXII).[12] Dehydration of the 3-epimeric 9α-hydroxy-11-ketones XIV and XVII with thionyl chloride–pyridine afforded the unsaturated 11-ketones formulated as XIX and XX. Both substances absorb at the expected wave length (λ_{max}^{alc} 254 mμ), but the extinction coefficient is surprisingly low (log ε 3.9). A further unanticipated relationship is the very large difference in rotation ($M_\alpha - M_\beta = +549$); the proximity, in one conformation of the molecule, of the α-acetoxy group to the unsaturated ketonic system may be the cause of the anomaly.[17] Reduction of the unsaturated ketones remains to be investigated thoroughly. Preliminary experiments with XIX indicate that the substance is converted on hydrogenation in part to the corresponding $\Delta^{8,9}$-lithocholenic acid derivative.

Curiously enough, methyl 3α-acetoxy-9α-hydroxy-11-ketocholanate (XIV) is converted by Wolff–Kishner reduction[18] into $\Delta^{9(11)}$-lithocholenic acid[3,6,10] (XXIII). The hemiketal Va is similarly reduced to $\Delta^{9(11)}$-cholenic acid[7]; here the potential carbonyl group at C_3 is reduced simultaneously with reduction of the potential ketol group at C_9–C_{11}. Analogous behavior of α-hydroxycarbonyl compounds has been reported and accounted for[19]; we have observed an additional case: Wolff–Kishner reduction of 3β-acetoxy-5α-hydroxycholestane-6-one[20a] yields cholesterol and a small amount of the expected cholestane-3β,5α-diol.[20b] The unusual feature of the present observations is the evident attack of the 11-carbonyl group of 9-oxygenated 11-ketones under conditions demonstrated by Huang-Minlon[18] to leave 11-ketones without oxygen function on C_9 unaltered.

Four routes have been found for conversion of a 3α-hydroxy-$\Delta^{9(11)}$-steroid through the oxide into the corresponding 3α-hydroxy-11-ketosteroid. Two are outlined on Chart 2. One, which appears promising on the basis of the yields obtained thus far, involves reduction of a hemiketal, IVa or Va, to the triol monoacetate XI, oxidation at C_{11} (XIV), reaction with hydrogen bromide (XVIII), and debromination (XXII). A second route is by Clemmensen reduction of the 3α,9α-dihydroxy ketone XIV, for this eliminates the 9α-hydroxyl group, probably *via* the 12-chloro derivative, and gives XXII; the hemiketal Va is similarly reducible to methyl 11-ketocholanate.[5] The yield was good in the latter case but not in the former.

Chart 3 outlines the other two routes and shows the steps by which the required intermediates are obtained from the primary starting material, methyl 3α-hydroxy-9α,11α-oxidocholanate (XXV). The intermediate 3-ketone is not isolated; XXV is oxidized with aqueous chromic acid in acetic

(15) See R. B. Turner in L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publishing Corp., New York, N. Y., p. 654; *cf.* also p. 408.

(16) J. Press, P. Grandjean and T. Reichstein, *Helv. Chim. Acta*, **26**, 589 (1943).

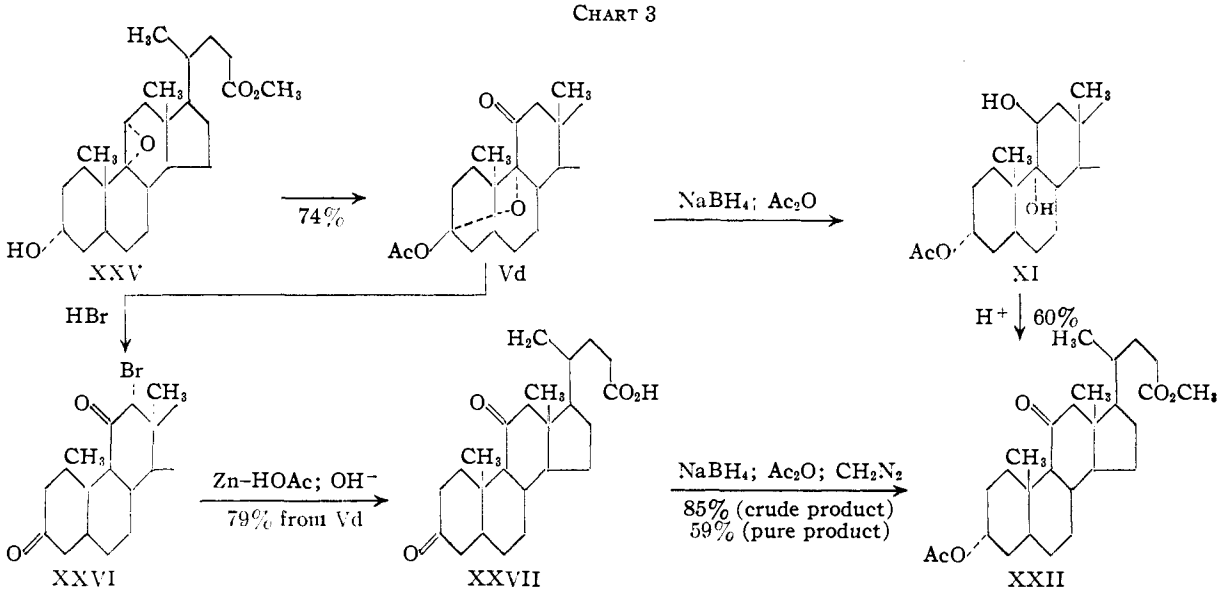
(17) H. E. Stavely, *Federation Proc.*, **9**, 233 (1950), U. S. Patent 2,545,978 (1951), reports the preparation from methyl 3α-acetoxy-$\Delta^{9(11)}$-cholenate of a substance regarded as having the structure XIX, but the melting point 145–148° is quite different from that of our compound. The evidence does not exclude the possibility that the product was methyl 3α-acetoxy-12-keto-$\Delta^{9(11)}$-cholenate (m.p. 145–147°[6]) and that the 11-keto ester obtained from the same intermediate was derived from residual methyl Δ^{11}-lithocholenate present in the starting material by the Reichstein synthesis (*cf.* ref. 13).

(18) Modified procedure of Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946); **71**, 3301 (1949).

(19) D. H. R. Barton, N. J. Holness and W. Klyne, *J. Chem. Soc.*, 2456 (1949).

(20) (a) R. H. Pickard and J. Yates, *ibid.*, **93**, 1678 (1908); L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **71**, 3938 (1949); (b) Pl. A. Plattner, Th. Petrzilka and W. Lang, *Helv. Chim. Acta*, **27**, 513 (1944).

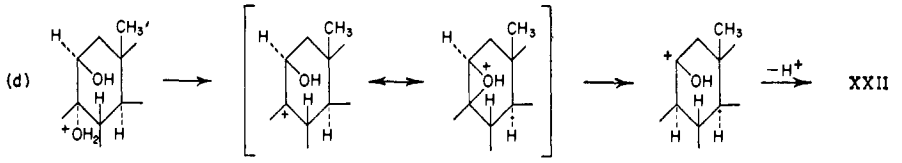
CHART 3



acid solution directly to the 3-hydroxy-11-keto-hemiketal, which is isolated and purified very easily as the 3-acetate Vd, which has excellent properties of crystallization. Compound Vd is then cleaved with hydrogen bromide to methyl 3,11-diketo-12α-bromocholanate[4] (XXVI), which on debromination and hydrolysis affords 3,11-diketocholanic acid[4,13,21] (XXVII) in 79% over-all yield from Vd. On gentle reduction with sodium borohydride, the diketo acid is transformed into an eight-to-one mixture of the epimeric 3α- and 3β-hydroxy derivatives, separable by chromatography of the methyl ester acetates. More drastic reduction produces 3α,11β-dihydroxycholanic acid, isolated as the methyl ester acetate.

The fourth method involves sodium borohydride reduction of Vd and isolation of the predominant 3α-epimer as the acetate XI, as described above. This *trans*-glycol, under strongly acidic conditions, undergoes dehydration to the 11-ketone XXII. The yield is about 60% and no identifiable by-products could be isolated.

The reaction, which provides a convenient and short route to the 11-ketone XXII, may be interpreted as an example of a pinacol rearrangement as formulated in scheme (d): the C_9-hydroxyl group accepts a proton and is eliminated as water with formation of a carbonium ion that is stabilized by formation of a three-membered ring intermediate[22] subsequently the 11α-hydrogen atom shifts with its bonding pair of electrons to the 9α-position to give the conjugate acid of the final product XXII. Stabilization of the intermediate ion is suggested because a coplanar carbonium ion appears unfavorable from inspection of models, which show that *trans*-4,5-dihydrohydrindene possesses more steric strain than the saturated hydrocarbon. The same steric effect is suggested as an explanation for the failure of concerted *trans*-dehydration to take place, involving the β-oriented hydrogen atom at C_8; the transition state for the reaction leading to the Δ^8-compound is unfavorable energetically when compared to the changes formulated in scheme (d). Such steric factors should be absent in the case of *trans*-cholestane triol; however we failed to gain support for our suggestion from attempted dehydration of cholestane-3β,5α,6β-triol 3-acetate.[19]



Hydrogen bromide in dry chloroform led to an unpromising mixture of bromine-containing material, and potassium bisulfate in hot acetic acid did not affect the glycol, although the 3,6-diacetate of the triol rearranges to Westphalen's diol diacetate with potassium bisulfate in acetic anhydride.[23]

Acknowledgment.—We are greatly indebted to the Rockefeller Foundation for a grant, to Dr. Max Tishler of the Merck Laboratories for supplies of chemicals and general coöperation, and to Wei-Yuan Huang and Koji Nakanishi for careful determination of optical constants.

Experimental[24]

Methyl 3α-Hydroxy-$\Delta^{9(11)}$-cholenate.[6,10]—Wolff-Kishner reduction of 3α-hydroxy-12-keto-$^{9(11)}$-cholenic acid was carried out essentially as described previously.[3] A readily filterable product resulted on pouring the hot reaction mixture into warm acetic acid. The moist cake was taken up

(21) For the methyl ester, *cf.* also W. P. Long and T. F. Gallagher, *J. Biol. Chem.*, **182**, 511 (1946).

(22) *Cf.* reference 11, in particular p. 835.

(23) V. A. Petrow, *J. Chem. Soc.*, 998 (1939).

(24) All melting points are corrected. Solvents for optical measurements are indicated as follows: alc = ethanol; chf = chloroform; an = acetone; di = dioxane; me = methanol; nu = nujol. Many of the optical measurements were carried out by Messrs. Wei-Yuan Huang and Koji Nakanishi. Microanalyses were carried out by Mrs. Shirley Golden; by the laboratory for Microchemistry of Dr. Carl Tiedcke, and by the Microchemical Laboratory directed by Mr. S. M. Nagy of the Massachusetts Institute of Technology.

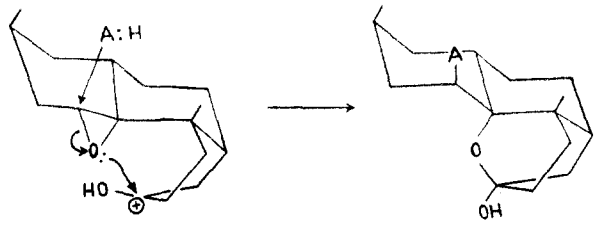


Fig. 1.

in benzene, separated from the water and the solvent was evaporated. Esterification was accomplished by exposure for one hour to 0.1 *N* methanolic hydrogen chloride. The crude product was dissolved in about 1.5 volumes of ligroin[25] (70–90°), and the solution was seeded. Crystallization was allowed to proceed overnight. Thus, in a typical run, 61 g. of the acid yielded 28.6 g. (46%) of product, m.p. 103.4–104.6°. In another run, 10 g. of methyl 3α-hydroxy-12-keto-$\Delta^{9(11)}$-cholenate gave 3.6 g. (37.2%) of reduced ester, m.p. 103.1–106° and 107–108°. The material was converted to the 3-acetoxy-9,11-oxide by the usual means, and chromatographed on alumina. Neither methyl acetyllithocholate nor methyl 3α-acetoxy-11,12-oxidocholanate were detected; these compounds generally arise as by-products in the Wolff-Kishner reduction.[6]

Attempts to alter the reduction method so as to produce a higher proportion of the desired $\Delta^{9(11)}$-isomer failed. The Wolff-Kishner reaction proceeds as described, or not at all. Hydrogen iodide–phosphorus or sodium–liquid ammonia did not lead to tractable products. Sodium borohydride, when applied to the ester, apparently attacked the carbomethoxyl group, although the reagent is useful in converting the 12-keto group to the corresponding alcohol[26] when applied to the free acid.

Methyl 3α-Hydroxy-9α,11α-oxidocholanate.[2,3]—The compound may be prepared from the pure olefinic ester by the action of freshly prepared perbenzoic acid; the presence of chlorine, phosgene or hydrogen chloride in aged solutions of the oxidizing agent leads to poor results.

When impure olefinic ester is used, such as the crude product from the Wolff-Kishner reduction, chromatographic purification of the acetylated mixture on acid-washed alumina is necessary.[6] The most easily eluted fractions contain acetyllithocholate; the desired product is of intermediate adhering power, and the most strongly adsorbed fractions, requiring ether–benzene mixtures for elution, represent methyl 3α-acetoxy-11,12-oxidocholanate.

Liberation of the 3-hydroxyl group proceeds smoothly by methoxide-catalyzed methanolysis. The acetoxy compound (16.2 g.) was boiled for one hour with 150 cc. of 0.3 *N* methanolic sodium methoxide. The solution was cooled, neutralized with acetic acid, and diluted to 1 l. The precipitated solid was collected and dried at 80° under reduced pressure. The yield was 14.45 g. (98%), m.p. 129.5–132.5°. Crystallization from ligroin and from acetone eventually yielded stout needles, m.p. 135.4–136.4°; $[\alpha]^{21}D$ +22° ± 2° (0.9% chf).

Methyl 3-Keto-9α,11α-oxidocholanate (I).[3]—This compound is prepared more advantageously with the use of sodium dichromate than with the previously described reagents.[3] To a solution of 9.3 g. of methyl 3α-acetoxy-9,11-oxidocholanate in 85 cc. of glacial acetic acid was added the solution of 2.6 g. of sodium dichromate (dihydrate) in 25 cc. of the same solvent. After 12 hours at room temperature the mixture was diluted and 8.2 g. (89%) of I was collected, m.p. 125–127°. After recrystallization from 80% acetone 7 g. of long, flat, shiny needles was obtained, m.p. 128.3–129.3°. The formation of crystals as described is a good indication of purity of the material; impure preparations tend to form nondescript leaflets.

Methyl 3β-Hydroxy-3α,9α-oxido-11β-chlorocholanate (IIa) (a) **In Chloroform Solution.**—Dry hydrogen chloride was passed for fifteen minutes into a solution of 225 mg. of I in 1 cc. of alcohol-free chloroform. The solution stood for an additional 20 minutes; it was evaporated in a current of dry air, under reduced pressure, leaving a crystalline residue of IIa, weighing 235 mg. (96%), m.p. 146–150.6°, with gas evolution. Purified by crystallization from acetone and aqueous acetone, the material forms prisms, m.p. 148–150°, with gas evolution. The gas was identified as hydrogen chloride by passage, in a current of nitrogen, into silver nitrate solution acidified with nitric acid; 74 mg. of IIa yielded 18.2 mg. (84%) of silver chloride; the organic residue was intractable; $[\alpha]^{22}D$ +65.7 ± 0.8° (1.15% chf); λ_{max}^{chf} 2.85, 5.80 μ.

Anal. Calcd. for $C_{25}H_{39}O_4Cl$ (439.02): C, 68.39; H, 8.95; Cl, 8.07. Found: C, 68.38; H, 9.03; Cl, 8.18.

(b) **In Acetic Acid Solution.**—A solution of 160 mg. of in 2 cc. of glacial acetic acid was made 0.4 *N* in hydrogen chloride by addition of 0.07 cc. of 36% hydrochloric acid. The solution stood at room temperature for 17 hours; it was diluted and the precipitated solid was treated, in ethereal solution, with diazomethane to re-esterify any hydrolyzed material. Evaporation and recrystallization from aqueous acetone yielded 127 mg. (73%) of IIa, m.p. 148.5–149.5°, with gas evolution.

When methyl 3α-hydroxy-9α,11α-oxidocholanate (225 mg.) was allowed to stand overnight with 3 cc. of acetic acid containing 0.1 cc. of concentrated hydrochloric acid, no identifiable product could be obtained on dilution with water. The sirupy product was treated with diazomethane and acetylated with acetic anhydride and pyridine, and 232 mg. of a glassy substance resulted, λ_{max}^{alc} 246 mμ, log ε 3.7. (The molecular extinction coefficient is calculated on the assumption that the molecular weight is that of methyl acetoxycholadienate.) Fieser and Rajagopalan[3] obtained, on more drastic treatment with acid, a crystalline diene of constants similar to those found for the above amorphous product.

Reconversion of Methyl 3β-Hydroxy-3α,9α-oxido-11β-chlorocholanate (IIa) **into I (a) With Base.**—To a solution of 127 mg. of IIa in 5 cc. of methanol was added 2.90 cc. of 0.100 *N* sodium hydroxide solution, and a drop of phenolphthalein solution. The mixture was boiled under reflux, and after five minutes the color suddenly disappeared, and a small amount of a crystalline solid was deposited. Addition of more methanol to the hot mixture produced a clear solution, which on cooling deposited 92 mg. (79%) of I, m.p. 124–126°. After recrystallization from 80% acetone long flat needles were obtained, m.p. 126.8–128.8°, and 127.8–129.5° on admixture with authentic I.

In another experiment IIa was treated with hot methanolic pyridine; a quantitative yield of silver chloride (102%) was obtained on suitable working up of the reaction mixture; chromatography of the organic portion afforded 57% of I, m.p. 128.6–130.0° after recrystallization. There also was obtained a small quantity of less strongly adsorbed by-product which was not identified.

(b) **With Silver Acetate in Acetic Acid.**—This experiment is described under the heading: I from IIb.

Methyl 3β-Methoxy-3α,9α-oxido-11β-chlorocholanate (IIb).—A hot solution of 810 mg. of IIa in 5 cc. of 0.1 *N* methanolic hydrogen chloride was boiled for five minutes. The solid deposited after cooling was redissolved by reheating and addition of sufficient methanol. The solution deposited slender, shiny needles, of IIb (664 mg., 77.5%), m.p. 106.4–107.5°. Recrystallization from methanol furnished a pure sample, m.p. 106.8–107.8°; $[\alpha]^{20}D$ +57.7 ± 0.8° (1.461%, chf); no band at 2.8 μ in the infrared spectrum.

Addition of hydrogen chloride is not necessary, as IIa, in hot methanol, generates sufficient acid to catalyze conversion to IIb. Thus, when the product of the action of 0.4 *M* hydrogen chloride in acetic acid on 183 mg. of I in acetic acid was inadvertently recrystallized from methanol, 101 mg. (49%) of IIb resulted, m.p. 105.2–107.2°.

Anal. Calcd. for $C_{26}H_{41}O_4Cl$ (453.05): C, 68.93; H, 9.12; Cl, 7.82; CH_3O, 13.70. Found: C, 68.78; H, 9.08; Cl, 7.75; CH_3O, 13.44.

Reconversion of Methyl 3β-Methoxy-3α,9α-oxido-11β-chlorocholanate (IIb) **into I (a) With Alkali.**—A solution of 271 mg. of IIb in 10 cc. of 0.5 *N* sodium hydroxide in 50% ethanol was boiled for about three hours. The alcohol

(25) Dr. Huang-Minlon privately advised us of his observation that crystallization of the hydroxy ester from ligroin is a convenient and efficient method of obtaining the $\Delta^{9(11)}$-ester essentially free from the $\Delta^{11,12}$-isomer.

(26) B. F. McKenzie, V. R. Mattox, L. L. Engel and E. C. Kendall, *J. Biol. Chem.*, **173**, 271 (1948).

was distilled under reduced pressure, and the remaining aqueous solution was poured into dilute acetic acid. The precipitated acid was collected, dried, and esterified with diazomethane and the product was chromatographed on alumina. Only one solid product was obtained in ten fractions totalling 145 mg. (60%), m.p. about 127–130°. After recrystallization from methanol, and aqueous acetone, the characteristic flat needles of I were isolated; m.p. 128.8–129.9° alone or on admixture with authentic I: $[\alpha]^{20}D$ ±0.0° (1.20%, chf); λ^{chf}_{max} 5.80, 5.85 μ; no band at 2.80 μ.

The aqueous mother liquor from the precipitation of the carboxylic acid was acidified with nitric acid and treated with silver nitrate; 85 mg. (99%) of silver chloride was found.

(b) **With Silver Acetate in Acetic Acid Solution.**—A solution of 437 mg. of IIb in 5 cc. of glacial acetic acid was added to 300 mg. of silver acetate, and the mixture was warmed on the steam-bath for 40 minutes with occasional agitation. The silver salts were filtered; addition of water to the solution precipitated 353 mg. (91%) of I, m.p. 128.8–129.8°, not depressed on admixture of I.

Methyl 3β-Acetoxy-3α,9α-oxido-11β-chlorocholanate (IIc).—To a solution of 252 mg. of IIa in 2 cc. of acetic acid and 2 cc. of acetic anhydride was added the cooled mixture of 2 cc. of acetic anhydride and 0.2 cc. of 70% perchloric acid. The solution stood for two hours at room temperature and assumed a light brownish tinge. On dilution with water 220 mg. (80%) of yellowish IIc was deposited, m.p. 114–119°. Recrystallization from methanol afforded an analytical sample, m.p. 118.2–119.3°; $[\alpha]^{22}D$ +67.3 ± 1° (1.09%, chf).

Anal. Calcd. for $C_{27}H_{41}O_5Cl$ (481.06): C, 67.41; H, 8.59; Cl, 7.37. Found: C, 67.72, 67.64; H, 8.75, 8.54; Cl, 6.99.

Methyl 3β,11β-Diacetoxy-3α,9α-oxidocholanate (IIIb) (a) **By Acetolysis of I.**—To a mixture of 5 cc. of acetic acid and 5 cc. of acetic anhydride was added 0.25 cc. of 70% perchloric acid, giving a solution about 0.3 *N* in mineral acid. To it was added 1.48 g. of I and the mixture stood at room temperature for 45 minutes, turning slightly brown. Water was added, and the precipitated solid was crystallized from methanol; 1.38 g. (74%) of IIIb was obtained in two crops of large prisms, m.p. 116.6–118.8°. The material crystallizes slowly from methanolic solutions; the analytical sample melts 118.4–119.6° and after gradual resolidification at 134–134.8°; $[\alpha]^{22}D$ +65 ± 2° (0.88% chf); λ^{chf}_{max} no band at 2.8 μ.

Anal. Calcd. for $C_{29}H_{44}O_7$ (504.64): C, 69.02; H, 8.78. Found: C, 69.08; H, 8.77.

(b) **By Silver-Catalyzed Acetolysis of IIc.**—A mixture of 154 mg. of IIc, 5 cc. of acetic acid, and 100 mg. of silver acetate was warmed on the steam-bath for 40 minutes. The solution was filtered and evaporated to dryness in vacuum. After a precautionary treatment with ethereal diazomethane there was obtained 158 mg. (98%) of IIIb, m.p. 115–118.2°. Recrystallizations from methanol yielded prisms, m.p. 118.1–119.0°; on admixture with IIIb as prepared in (a) the melting point was 118.1–119.5° and 133–134.4°; $[\alpha]^{20}D$ +66.4 ± 0.9° (1.34%, chf).

(c) **By Acetylation of Methyl 3β-Methoxy-3α,9α-oxido-11β-hydroxycholanate** (IVb).—To a slightly warm solution of 147 mg. of IVb in 1 cc. of acetic anhydride was added 0.1 cc. of boron fluoride etherate, and the mixture stood at room temperature for two hours. Decomposition yielded a yellow solid that was chromatographed on alumina. Elution with benzene gave 130 mg. (76%) of IIIb in three fractions, m.p. about 119°. After recrystallization the product melted 118.4–119.6° and 134–134.8°, identical with the preparations described.

Methyl 3β-Methoxy-11β-acetoxy-3α,9α-oxidocholanate (IIIa) (a) **From IIIb by Acid Methanolysis.**—A solution of 164 mg. of IIIb in 5 cc. of approximately 0.4 *N* methanolic hydrogen chloride was boiled under reflux for three hours. The solution was cooled, diluted with water, and the precipitated solid, on recrystallization from methanol or aqueous methanol, yielded 106 mg. (68%) of IIIa, m.p. 115.4–117.8°. The analytical sample forms needles, m.p. 118.3–118.9°; $[\alpha]^{22}D$ +46.8 ± 1° (0.72% chf).

Anal. Calcd. for $C_{28}H_{44}O_6$ (476.63): C, 70.55; H, 9.31. Found: C, 70.49; H, 9.29.

(b) **By Acetolysis of I and Methylation.**—The oxidoketone I (218 mg.) was acetolyzed overnight with 1 cc. of acetic acid and 0.1 cc. of boron fluoride etherate. The product was allowed to stand for about one and three-quarters hour with 3 cc. of 0.1 *N* methanolic hydrogen chloride. On working up the mixture yielded 115 mg. (48%) of IIIa, m.p. 117–118.6°.

(c) **By Acetylation of Methyl 3β-Methoxy-3α,9α-oxido-11β-hydroxycholanate** (IVb) **and Remethylation.**—A sample of IVb (164 mg.) was dissolved in 2 cc. of warm acetic acid. The solution was allowed to cool and 0.2 cc. of boron fluoride etherate was added. The mixture stood at room temperature for 15 hours. Dilution with water, extraction with ether followed by treatment with bicarbonate and with diazomethane yielded a non-crystalline material. The glassy substance was treated briefly with approximately 0.1 *N* methanolic hydrogen chloride. The product was isolated by precipitation with water, and was recrystallized from methanol. The yield of IIIa was 98 mg. (55%), m.p. 117.6–118.6°.

(d) **By Partial Alkaline Hydrolysis of IIIb Followed by Methylation.**—The diacetate IIIb (400.7 mg.) was boiled under reflux with a mixture of 20.0 cc. of ethanol and 40.0 cc. of 0.100 *N* sodium hydroxide. The material had only partly dissolved after 100 minutes; at that time 3.0 cc. of 1.2 *N* sodium hydroxide solution was added, and after two additional hours of boiling only a trace of oily matter was left undissolved. By comparison with a blank experiment it was found that the diacetate had consumed 1.69 millimoles of alkali; the consumption calculated for the presence of two saponifiable groups is 1.62 millimoles. The alkaline solution was acidified, the product was recovered with ether and esterified with diazomethane. The product, presumably the hydroxyacetate, could not be crystallized. The glassy material was treated for ten minutes at room temperature with a solution in 2 cc. of methanol of 0.1 cc. of 32% hydrogen bromide in acetic acid. The material was precipitated by addition of water, and on recrystallization from dilute methanol yielded 212 mg. of IIIa in the form of needles, m.p. 115–117.2°. With allowance for the removal from the hydrolysis mixture of two 10-cc portions for titration, the yield of IIIa is 70%. The melting point of purified material was not depressed on admixture of a sample prepared as in (a).

Methyl 3β,11β-Dihydroxy-3α,9α-oxidocholanate (IVa) (a) **By Hydrolysis of the 3-Methyl Ether IVb.**—To a solution of 533 mg. of IVb in 5 cc. of acetic acid and 5 cc. of water was added 0.2 cc. of 70% perchloric acid. The mixture stood at room temperature for 15.5 hours. It was diluted and a solidifying gum was deposited. The product was boiled for one hour with 0.2 *N* sodium hydroxide in 50% aqueous ethanolic solution. The alcohol was removed in vacuum and on pouring the solution into dilute acetic acid there was deposited 465 mg. (93%) of the **free acid**, dec. at 260°. Purified from aqueous acetone, the acid decomposes at 269–270.5° (immersed into the bath at 268°); $[\alpha]^{22}D$ +65.3 ± 1.2° (0.575%, di).

Esterification with diazomethane furnished IVa, m.p. 164.2–164.8°; $[\alpha]^{20}D$ +58.5 ± 0.8° (1.279%, chf). The compound crystallizes from methanol in the form of stout needles.

Anal. Calcd. for $C_{24}H_{38}O_5$ (406.54): C, 70.90; H, 9.42. Found: C, 70.59, 70.45; H, 9.34, 9.28. Calcd. for $C_{25}H_{40}O_5$ (420.57): C, 71.39; H, 9.58. Found: C, 71.16; H, 9.45.

(b) **By Hydrolysis of I.**—The oxidoketone (282 mg.) was dissolved in 2 cc. of acetic acid and 2 cc. of water by warming on the steam-bath. To the hot solution was added 0.2 cc. of 70% perchloric acid, and heating was continued for ten minutes. The faintly yellow solution was cooled and diluted. The deposited semi-solid was collected, taken up in ether, washed with water and treated with diazomethane. Evaporation left a glass from which by crystallization with methanol 82 mg. (27%) of IVa was obtained in two crops, m.p. 159–163°. Purification raised the melting point to 163–164.8°, not depressed by admixture of material prepared as in (a).

Attempts to accomplish this hydrolysis in better yield were without success. An experiment similar to the one described but proceeding at room temperature for 16 hours rather than in the heat led to no crystalline products. Oxalic acid in aqueous acetic acid did not alter the starting material when allowed to act for 14 hours at room tempera-

ture, whereas in the heat conversion to non-crystalline products took place. Use of aqueous dioxane with perchloric acid as catalyst led to similarly unsatisfactory results. From an experiment in aqueous tetrahydrofuran with *p*-toluenesulfonic acid as catalyst, 31% of the starting material was recovered as the sole crystalline product after chromatography.

Methyl 3β-Methoxy-3α,9α-oxido-11β-hydroxycholanate (IVb).—Methyl 3β-methoxy-3α,9α-oxido-11-ketocholanate (Vb) (0.6 g.) was boiled for 50 minutes with 20 cc. of 0.2 *N* sodium hydroxide in 50% aqueous ethanol. Approximately 1 g. of sodium borohydride was added and boiling was continued for one additional hour. The solution was cooled and poured into dilute acetic acid, when 0.55 g. (94%) of crude acid precipitated, m.p. 225–229°. Esterification with diazomethane followed by crystallization from ethanol gave 0.42 g. of IVb, m.p. 146–149.4°. The analytical sample forms prisms, m.p. 150.2–151.0°; $[\alpha]^{21}D$ +49 ± 2° (2.32%, chf); λ_{max}^{chf} 2.81 μ.

Reduction of the 11-keto group of Vb could not be accomplished with either platinum, or palladium on charcoal, and hydrogen in acetic acid solution.

Anal. Calcd. for $C_{26}H_{42}O_5$ (434.60): C, 71.85; H, 9.74; CH_3O, 14.28. Found: C, 71.94, 71.48; H, 9.80, 9.63; CH_3O, 13.94.

Failure of IVb to React with Hydrogen Chloride.—A solution of 162 mg. of IVb in 1 cc. of alcohol-free chloroform was saturated with dry hydrogen chloride at room temperature by passage of the gas for 15 minutes. The solution was allowed to stand for 30 minutes and then evaporated to dryness. The residue melted at 143–146.4°; on recrystallization from aqueous acetone 132 mg. (81.5%) of unchanged IVb was obtained, m.p. 147.8–149.2°. A sample mixed with authentic IVb melted at 148–150.2°, but mixed with methyl 3β-hydroxy-3α,9α-oxido-11β-chlorocholanate (IIa) it melted at 129–146°.

In another experiment 160 mg. of IVb was dissolved in 2 cc. of acetic acid containing 0.07 cc. of 36% hydrochloric acid (final concentration 0.4 *N* in hydrogen chloride), and the mixture was allowed to stand at room temperature for 16 hours. After addition of water, the organic material was taken up in ether, the ether was washed with bicarbonate solution and treated with diazomethane. The crude solid obtained on evaporation of the solvent melted at about 125–130° with gas evolution. By recrystallization from aqueous acetone 56 mg. (35%) of IVa was obtained, m.p. 159.4–162.4°, identified by remethylation to IVb. The mother liquor did not yield crystalline material, but the presence of halogen was recognized by a strongly positive Beilstein test.

Methyl 3β-Hydroxy-3α,9α-oxido-11-ketocholanate (Va) (a) By Hydrolysis and Oxidation *via* I.—Methyl 3α-hydroxy-9α,11α-oxidocholanate (1 g.) was dissolved in 25 cc. of acetic acid. The solution was cooled to about 9° and 1 g. of chromic anhydride dissolved in 2 cc. of water was added at once. The solution was kept at 4° for 16 hours. On dilution with water 0.86 g. of Va settled out in the form of fine needles. By recrystallization from dilute methanol, Va is obtained either as a magma of fine hairlike needles, or in the form of larger, flat, elongated needles. The material crystallizes fairly well from aqueous methanol, acetone, or acetic acid; hydrocarbon solvents fail. Samples of the substance obtained in this way have been found to melt as low as 108–111° and as high as 122–127°; most samples melt at 118–120°; $[\alpha]^{23}D$ +102 ± 2° (1.01% chf); +96 ± 2° (di)[3]; λ_{max}^{chf} 2.85, 5.78, 5.85 μ.

A quantitative oxidation experiment was conducted by subjecting 1003 mg. of the oxido alcohol dissolved in 23.0 cc. of acetic acid to the action of 2.0 cc. of 4.90 *M* aqueous chromic acid solution, standardized iodometrically. After 18 hours at 7°, the solution was diluted to 100.0 cc., the deposited solid was filtered, and two 2-cc. aliquots of the filtrate were titrated; by comparison with a blank experiment the consumption of chromic acid in the oxidation was found to be 2.5 atoms of oxygen per molecule of oxido alcohol. The product isolated weighed 805 mg., m.p. 115–118°.

In one experiment, that did not go to completion, the oxido ketone I was detected among the products. The conditions were as described, except that about three times as much water was present. The crude product resulting from 2 g. of oxido alcohol was recrystallized to give two crops totalling 1.64 g., m.p. 95–100°, and was fractionated chromatographically. An easily eluted portion of 225 mg. was recognized as I, m.p. 128–130.4°, not depressed by an authentic specimen; the remainder (1.13 g.) consisted of the hemiketal Va.

The oxido ketone I (180 mg.), when subjected to oxidation as described, gave 88 mg. of crude Va; the product was recrystallized and identified as the methyl ether Vb, m.p. 123.4–124.9°, prepared as described below.

When impure starting material is employed for the oxidation reaction, isolation of Va meets with considerable difficulties and the yield is poor; however, the acetate Vd exhibits superior crystallizing properties and may be isolated with ease from complex mixtures. Examples of pertinent procedures are given in the section describing Vd.

The addition of small amounts of mineral acid did not influence the course of the reaction.

When methyl 3α-acetoxy-9α,11α-oxidocholanate (113 mg.) was subjected to oxidation conditions as described above for 24 hours, 0.100 millimole for chromic anhydride was consumed, whereas consumption of 0.340 millimole would be required for conversion to Va. The recovered organic product (86 mg., 76%), m.p. 116–119°, was unaltered starting material. More drastic conditions, *i.e.*, oxidation for one hour at 50–60° likewise failed to yield any identifiable product besides unchanged starting material.

Oxidation of 120 mg. of methyl 9α,11α-oxidocholanate under the conditions described yielded 96 mg. of a yellow resin from which by chromatography 33 mg. (20%) of unchanged starting oxide was isolated, m.p. (after recrystallization) 78.3–78.8°; $[\alpha]^{27}D$ +20 ± 1° (1.03% an).

Anal. Calcd. for $C_{25}H_{38}O_5$ (418.55); C, 71.66; H, 9.16. Found: C, 71.89; H, 9.20.

(b) By Oxidation from Methyl 3β-Methoxy-3α,9α-oxido-11β-hydroxycholanate (IVb).—A solution of 205 mg. of IVb in 2 cc. of acetic acid was treated with the solution of 150 mg. of chromic anhydride in a little water. The mixture stood at room temperature for ten hours; it was diluted and 183 mg. of Va (92%) was collected, m.p. 100–109°. After purification, the material melted at 116–119°; it was identified by conversion to the acetate Vd, m.p. 148.5–149.5°, not depressed by admixture of authentic Vd.

(c) By Alkaline Methanolysis from Methyl 3β-Acetoxy-3α,9α-oxido-11-ketocholanate (Vd).—A solution of 475 mg. of Vd in 50 cc. of 0.2 *N* methanolic sodium methoxide solution was boiled for one and three-quarters hour. After neutralization and dilution 347 mg. (81%) of crude Va was isolated, m.p. about 120°. The material yielded the characteristic fine-hairlike needles of Va on recrystallization and was further identified by reconversion to Vd, m.p. 145–147.2°, and by etherification to Vb, m.p. 120–122°.

Methyl 3β-Acetoxy-3α,9α-oxido-11-ketocholanate (Vd) (a) By Acetylation of the Hemiketal Va.—The acetylation proceeds slowly in hot pyridine–acetic anhydride,[3] but smoothly and quickly at room temperature in acetic anhydride containing about 2% of boron fluoride–etherate. The acetate crystallizes from not too dilute acetylation mixtures even though considerable amounts of impurities may be present. Thus it is possible to isolate pure Vd with ease from the oxidation of a crude 9,11- and 11,12-oxido ester mixture such as results by the action of perbenzoic acid on the crude mixture of esters obtainable from the Wolff–Kishner reduction of $\Delta^{9(11)}$-12-ketolithocholenic acid. Several examples will be given.

A solution of 9.75 g. of pure 3α-acetoxy-9α,11α-oxidocholanate, m.p. 119–121.4°, was methanolyzed by boiling for one hour with 150 cc. of 0.1 *M* methanolic sodium methoxide. The product was dissolved in 250 cc. of acetic acid and oxidized for 12 hours at about 10° with the solution of 10 g. of chromic anhydride in 20 cc. of water. The crude product, precipitated with water, was taken up in ether, washed with water and bicarbonate solution, and recovered after drying. The gelatinous mass was treated with 40 cc. of acetic anhydride and 0.5 cc. of boron fluoride etherate. After three-quarters of an hour crystals of Vd (4.75 g.) had been deposited, which were collected, washed with acetic acid and methanol, and dried, m.p. 147–149.1°. The mother liquor and the washings yielded, after decomposition and decoloration over a small column of alumina, 2.72 g. of additional product in several crops, m.p. 144–149°. The total yield, based on acetoxy-9,11-oxidocholanate was 74%. Compound Vd crystallizes from methanol or ethanol

in stout, prismatic needles, or in the form of plates; the analytical sample melts at 148.6–149.8°; $[\alpha]^{24}D$ +100.3 ± 2° (2.33%, chf), +96 ± 3° (di).[3]

In another experiment, the crude acid mixture resulting from Wolff–Kishner reduction of $\Delta^{9(11)}$-12-ketolithocholenic acid was esterified by the action of methanolic hydrogen chloride overnight at room temperature. Variation of the mineral acid concentration from 0.1 to 0.3 *N* caused no noticeable difference in the product composition. By addition of bicarbonate solution and water followed by ether extraction and evaporation, 67 g. of crude mixed esters was isolated as a semisolid. The material was treated with 400 cc. of 0.5 *M* perbenzoic acid solution in chloroform with initial ice-cooling, followed by standing overnight at room temperature. The reaction mixture was worked up by the normal treatment with potassium iodide, thiosulfate, and bicarbonate solutions, the solvent was removed, and the solid residue was boiled briefly with 100 cc. of ligroin (70–90°). The cooled suspension was filtered, and 63.5 g. of solid was obtained. The solid oxido ester mixture was dissolved in 800 cc. of acetic acid, the solution was cooled to 18° and, with continued ice-cooling, 60 g. of chromic anhydride dissolved in 150 cc. of water was added. The temperature rose to 25° within a few minutes then fell again. The solution was kept at 5° for 18 hours, and then poured into 3 l. of water. The supernatant liquid was decanted from the deposited gummy product, which was dissolved in ether. The ethereal solution was extracted with 0.1 *N* sodium hydroxide solution, dried, and evaporated. To the residue was added 75 cc. of acetic anhydride and 1 cc. of boron fluoride etherate. The solution gradually turned a dark brown, and soon crystals began to appear. They were collected and washed with 40 cc. of methanol that had been cooled in Dry Ice–acetone. The acetic anhydride mother liquor on cooling deposited a small second crop; the total yield of Vd was 24 g.; m.p. 143–147°; this corresponds to 30% of the theoretical yield based on crude Wolff–Kishner ester. Complete purification of the crude prepared as described is best achieved by chromatography.

Anal. Calcd. for $C_{27}H_{40}O_6$ (460.59): C, 70.38; H, 8.77. Found: C, 70.27; H, 8.76.

(b) **From the 3-Methyl Ether Vb.**—To a solution of 180 mg. of Vb in 2 cc. of acetic anhydride was added 0.1 cc. of boron fluoride etherate. The solution turned yellow while standing at room temperature for 5.5 hours. Water was added, the solid was collected, dissolved in ether, and decolorized by passage over a small column of alumina. After evaporation and recrystallization from methanol 106 mg. (50%) of Vd was obtained, m.p. 149–150°.

Methyl 3β-Methoxy-3α,9α-oxido-11-ketocholanate (Vb) (a) From the Hemiketal Va by Methylation.—To a solution of 172 mg. of Va in 5 cc. of methanol was added one drop (about 0.03 cc.) of 48% hydrobromic acid; a crystalline solid began to form almost immediately. The mixture was allowed to stand overnight, and 154 mg. (86%) of Vb was collected in two crops, m.p. 124.4–125.4°, and 122–124° for the second crop. (Actually, as was learned later, the reaction is complete within minutes.) The material forms slender needles, or sometimes square plates, on crystallization from methanol; the analytical sample melts 124.8–125.5°; $[\alpha]^{18}D$ +92.3 ± 2° (3.49 chf); λ_{max}^{chf} 5.77; 5.85 μ, no band at 2.8 μ.

Anal. Calcd. for $C_{26}H_{40}O_5$ (432.58): C, 72.19; H, 9.32; CH_3O, 14.34. Found: C, 72.21; H, 9.05; CH_3O, 13.99.

Alkaline hydrolysis yields the **free acid**, which crystallizes from aqueous methanol, and has m.p. 169.5–170.5°; $[\alpha]^{20}D$ +86.9 ± 3° (0.23% chf).

Anal. Calcd. for $C_{25}H_{38}O_5$ (418.55): C, 71.66; H, 9.16; CH_3O, 7.41. Found: C, 71.70; H, 9.07; CH_3O, 6.57.

(b) **From the 3-Acetate Vd by Acid Methanolysis.**—To a hot solution of 1 g. of Vd in 15 cc. of methanol was added 0.2 cc. of 70% perchloric acid, and the mixture was boiled under reflux for five minutes. On cooling 0.7 g. (74.5%) of Vb crystallized, m.p. 118–123°, and dilution with water yielded a second crop of 0.2 g. (21%), m.p. 115–118°. Recrystallized, both crops gave 0.6 g. (64%) of Vb, m.p. 121.4–123.1°.

Methyl 3β-Ethoxy-3α,9α-oxido-11-ketocholanate (Vc).—A solution of 60 mg. of the hemiketal Va and 1 drop of 48% hydrobromic acid in 1 cc. of absolute ethanol stood at room temperature for 15 minutes. Addition of water caused 58 mg. (90%) of Vc to crystallize, m.p. 96–98°. Crystallization from aqueous acetone gave prisms, m.p. 96.5–98.2°; $[\alpha]^{20}D$ +91 ± 2° (2.19%, chf).

Anal. Calcd. for $C_{27}H_{42}O_5$ (446.61): C, 72.69; H, 9.49. Found: C, 72.92; H, 9.10.

Methyl 3β-Ethylthio-3α,9α-oxido-11-ketocholanate (Ve).—To a solution of 1.3 g. of the 3-methyl ether Vb in 2 cc. of ethyl mercaptan was added 6 drops (about 0.2 cc.) of 30% hydrogen bromide in acetic acid, and a pinch of sodium sulfate, and the mixture was allowed to react at room temperature for 12 hours. The mercaptan was removed in a current of air, water and ether were added, and the organic layer was washed with water, bicarbonate and lead acetate solution, dried, and evaporated. The resulting clear oil was chromatographed in benzene–petroleum ether solution on alumina; elution with the same solvent and finally with benzene gave 950 mg. of Ve, and ether eluted 88 mg. of starting material. The yield of Ve is 73%, based on the amount of Vb consumed. The thio compound crystallizes in stout needles from methanol; warmed with aqueous acid it is rapidly hydrolyzed as shown by the appearance of the odor of ethyl mercaptan. The analytical sample melts 67.2–68.5°; $[\alpha]^{22}D$ +100 ± 2° (2.29% chf).

Anal. Calcd. for $C_{27}H_{42}O_4S$ (462.67): C, 70.08; H, 9.15; S, 6.93. Found: C, 70.24; H, 9.32; S, 6.76.

3α,9α-Oxido-11-ketocholanic Acid from Ve.—A solution of 400 mg. of Ve in 30 cc. of methanol was treated with 5 cc. (about 7.5 g.) of settled Raney nickel for 15 hours with occasional stirring. The solution was filtered and the catalyst washed with methanol. On evaporation the filtrate gave 328 mg. of an oil that gave a strong sulfur test. The oil was redissolved in methanol and the solution was boiled for two hours with the same batch of catalyst to which 3 cc. of fresh Raney nickel was added. The catalyst was filtered and dissolved in mineral acid; no appreciable amount of organic material had remained adsorbed on the metal. The methanolic filtrate was evaporated and the residue was saponified with methanolic sodium hydroxide. The crude acid obtained on acidification of the hydrolysate was recrystallized twice from aqueous acetone, when 77 mg. (23%) of 3α,9α-oxido-11-ketocholanic acid was obtained, m.p. 167–173°. After further purification the acid melted at 174.9–175.6°; some samples also had a second, lower melting point at 168.4–169.6.[4] Mixed with an authentic sample of 3α,9α-oxido-11-ketocholanic acid[27] the m.p. was 174.6–175.7°; $[\alpha]^{21}D$ +88.1 ± 2° (2.51% chf).

Anal. Calcd. for $C_{24}H_{36}O_4$ (388.53): C, 74.19; H, 9.34. Found: C, 73.98; H, 9.32.

Wolff–Kishner Reduction of Methyl 3β-Acetoxy-3α,9α-oxido-11-ketocholanate (Vd).—A mixture of 1 g. of Vd in 10 cc. of triethylene glycol, 0.7 g. potassium hydroxide and 0.6 cc. of 85% hydrazine hydrate was boiled for one hour; the temperature of the liquid was 140°. Vapors were allowed to escape until the liquid reached the temperature of 190° and boiling under reflux was continued at that temperature for three hours. The cooled mixture was diluted and acidified; recrystallization of the crude acid from dilute methanol afforded 0.51 g. (65%) of $\Delta^{9(11)}$-**cholenic acid**,[5] m.p. 133–135°, and after resolidification 138.5–140.2°. The analytical sample, prepared by recrystallization from methanol and from dilute acetone melts at *ca.* 136°, resolidifies, and remelts 139–140.8°; $[\alpha]^{21}D$ +40.2 ± 2° (2.59% chf).

Methyl $\Delta^{9(11)}$-cholenate was prepared by means of diazomethane and purified from methanol; m.p. 67.4–68.2°; $[\alpha]^{19}D$ +40.4 ± 2° (2.03% chf); $\lambda_{max}^{CS_2}$ 3.22, 3.45–3.55, 5.75, 8.55 μ.[28]

Anal. Calcd. for $C_{24}H_{38}O_2$ (358.55): C, 80.30; H, 10.68. Found: C, 80.44, 80.22; H, 10.13, 10.01. Calcd. for $C_{25}H_{40}O_2$ (372.57): C, 80.59; H, 10.82. Found: C, 80.52; H, 10.90.

A sample of the acid was converted to **9,11-oxidocholanic acid** by perbenzoic acid in chloroform solution; the oxido acid had m.p. 157–159.2°, not depressed on admixture of an authentic sample prepared by Dr. Rajagopalan.[3]

Wolff–Kishner Reduction of 3β-Acetoxy-5α-hydroxycholestane-6-one.—A mixture of 1 g. of the acetoxy ketol,

(27) Prepared by hydrolysis of a sample of the methyl ester kindly supplied by Dr. Max Tishler.

(28) We are indebted to Dr. K. Dobriner for the spectrum determination and interpretation.

1.75 g. of potassium hydroxide, 2 cc. of 85% hydrazine hydrate, 30 cc. of triethylene glycol and 10 cc. of *n*-butanol was boiled under reflux, first for two hours at 130° (thermometer in liquid) and then for three hours at 215–220°. After cooling the mixture was poured into water, and the products were taken up in ether. The solvent was evaporated and the residue recrystallized from methanol, which deposited 0.43 g. (51%) of *cholesterol* in the form of long needles, m.p. 143–147°. One recrystallization raised the melting point to 148.4–149.4°, not depressed by authentic cholesterol.

The methanolic mother liquor was diluted with water, the precipitated solid was dried and extracted with 20–30 cc. of petroleum ether. The residue, on recrystallization from ethanol, gave fine needles of **3β,5α-dihydroxycholestane**,[19] m.p. 229–231°, $[\alpha]^{19}D$ +10.4 ± 3° (3.37%, chf); **monoacetate**, m.p. 184.6–185.6, $[\alpha]^{20}D$ +7.2 ± 3° (1.67%, chf).

Methyl 3α- and 3β-Acetoxy-9α,11β-dihydroxycholanate (XI and XII) (a) By Catalytic Hydrogenation.—A solution of 1.92 g. of the 11-keto hemiketal Va in 20 cc. of glacial acetic acid was hydrogenated for 20 hours over 250 mg. of Adams catalyst at atmospheric pressure. Consumption of hydrogen ceased when two moles had been absorbed; interruption of the reaction after consumption of only one mole leads to an unpleasant mixture of starting material with products in various stages of reduction. The solvent was removed in vacuum, and the residue acetylated for 20 hours at room temperature with 10 cc. of pyridine and 3 cc. of acetic anhydride; the acetylation is more conveniently accomplished by heating for one hour on the steam-bath. The mixture was decomposed by water and the oily product taken up in ether; the solution was washed with dilute hydrochloric acid and with bicarbonate solution, dried and evaporated. The residue was dissolved in benzene and chromatographed on alumina. Ether–benzene (1:19) eluted 448 mg. (21%) of XI, in fractions melting within the range 157–166°, and solvents ranging from ether–benzene (1:9) to pure ether eluted 997 mg. (40%) consisting essentially of XII. By recrystallization from methanol XI is obtained pure in the form of needles, m.p. 166.0–167.0°. $[\alpha]^{20}D$ +55.1 ± 2° (2.92% chf); λ_{max}^{chf} 2.86, 5.88 μ.

Anal. Calcd. for $C_{27}H_{44}O_5$ (464.62): C, 69.79; H, 9.54; Found (α-epimer): C, 70.22; H, 9.81.

Free 3α,9α,11β-Trihydroxycholanic Acid, obtained by saponification, crystallizes from aqueous acetone in the form of rectangular needles, m.p. 203.6–204.0°; $[\alpha]^{21}D$ +58.3 ± 2° (1.68% me).

Anal. Calcd. for $C_{24}H_{40}O_5$ (408.56): C, 70.50; H, 9.87. Found: C, 70.43; 9.76.

By acetylation for one hour with acetic anhydride, acetic acid and sodium acetate on the steam-bath, **3α-acetoxy-9α,-11β-dihydroxycholanic** acid was prepared; it crystallizes from dilute methanol in the form of needles, m.p. 208.8–210.4; $[\alpha]^{21}D$ +60.2 ± 2° (1.13% me).

Anal. Calcd. for $C_{26}H_{42}O_6$ (450.59): C, 69.30; H, 9.39. Found: C, 69.39; H, 9.30.

The 3β-acetoxy ester crystallizes from methanol in the form of prisms, m.p. 171.2–172.4°; $[\alpha]^{21}D$ +33.6 ± 2° (3.39% chf); λ_{max}^{chf} 2.86, 5.88 μ.

Anal. Calcd. for $C_{27}H_{44}O_5$ (464.62): C, 69.79; H, 9.54. Found (β-epimer): C, 70.17, 69.99; H, 9.76, 9.75.

By treatment with 0.3 *N* sodium methoxide in methanol for one hour at reflux temperature, methyl **3β,9α,11β-trihydroxycholanate** (XVI) is obtained; the compound crystallizes slowly from benzene–ligroin, and forms leaflets, m.p. 147.7–148.8°; $[\alpha]^{21}D$ +35.5 ± 0.7° (1.204% chf).

Anal. Calcd. for $C_{25}H_{42}O_5$ (422.59): C, 71.05; H, 10.02. Found: C, 71.22; H, 10.08.

(b) By Sodium Borohydride Reduction.—A solution of 5.6 g. of the 11-ketohemiketal acetate Vd and 2.5 g. of sodium hydroxide in 250 cc. of 50% aqueous ethanol was boiled for one hour. Then a solution of 1.3 g of sodium borohydride in 50 cc. of 0.1 *N* sodium hydroxide solution was added, and boiling was continued for 1.5 hours. The alcohol was removed under reduced pressure, and the solution poured into dilute acetic acid, when 4.85 g. of a solid was precipitated. A 1-g. aliquot was esterified for one hour at room temperature with 0.1 *N* methanolic hydrogen chloride, and, after the usual treatment, acetylated with pyridine and acetic anhydride for one hour on the steam-bath. The mixture was decomposed, the solid collected and chromatographed on alumina. Benzene and benzene–ether (19:1, 9:1 and 5:1) eluted nine fractions, melting within the range 130–160°; the less pure fractions were recrystallized and a total of 753 mg. (80%) of the α-epimer XI was obtained, melting within the range 150–162°. Benzene–ether (1:1) eluted 87 mg. (9%) of a material that crystallized when seeded with the β-isomer XII, but melted over a range of 148–160°. Recrystallization of this fraction finally gave 8 mg. of XII in characteristic prisms, m.p. 169–171°.

The remaining 3.85 g. of crude acid was esterified and the ester was acetylated with 3 cc. of pyridine and 3 cc. of acetic anhydride. A crystalline precipitate had appeared after standing overnight; it was collected, washed with methanol and found to consist of 1.8 g. (40% based on crude acid) of nearly pure XI, m.p. 163–166°. In spite of the loss incurred this method constitutes a rapid and convenient way of freeing XI from its β-epimer. The mother liquor from the acetylation was decomposed and the crude product was oxidized with chromic acid in acetic acid, yielding, after recrystallization, 1.35 g. of fairly pure XIV, m.p. 139–145°.

(c) By Reduction of 3β,11β-Dihydroxy-3α,9α-oxidocholanic Acid (*cf.* **ester IVa**) **with Sodium Borohydride.**—A solution of the acid (259 mg.), 0.25 g. of sodium borohydride in 3 cc. of ethanol, 3 cc. of water and 0.25 cc. of 6 *N* sodium hydroxide was boiled under reflux for one hour. The solution was poured into dilute acetic acid, and 229 mg. of solid was precipitated. The material was esterified with methanolic hydrogen chloride, and acetylated with acetic anhydride and pyridine. On decomposition the mixture afforded 223 mg. of a solid that was chromatographed on alumina. Nine fractions of XI were collected, totalling 210 mg. (71%) melting in the range 158–167°. Recrystallization yielded a sample of m.p. 163.4–165.0°, not depressed by XI prepared as described in (a) or (b). The β-epimer was not detected in this experiment.

Methyl 3α,9α-Oxido-11β-hydroxycholanate (XV) from Methyl 3β,9α,11β-Trihydroxycholanate (XVI).—A solution of 25 mg. of the triol ester XVI and 62 mg. of freshly distilled *p*-toluenesulfonyl chloride in 0.25 cc. of pyridine (dried over barium oxide) was sealed in an ampoule and allowed to stand at room temperature for 18 hours. The liquid turned brown during this period. It was heated for about one minute on the steam-bath, and diluted with water. The precipitated solid was adsorbed on alumina; benzene eluted three fractions totalling 22 mg. (90%) of XV, m.p. 109–112.2°. Recrystallization from ligroin gave stout needles, m.p. 112.7–113.8°, not depressed on admixture with an authentic sample; $[\alpha]^{20}D$ +55.5 ± 0.3° (1.517% chf).

Authentic methyl 3α,9α-oxido-11β-hydroxycholanate was prepared by esterification, with diazomethane, of the acid (VI), obtained according to the literature[12] with the exception of a much shortened saponification period. Thus 755 mg. of methyl 3α,9α-oxido-11β-acetoxycholanate was boiled under reflux with 40 cc. of methanol and 60 cc. of 6 *N* sodium hydroxide solution. After one hour a crystalline solid appeared; boiling was continued for one additional hour, the solution was cooled and the solid, a sodium salt, collected. Redissolution in hot water and acidification gave 499 mg. (75%) of VI, m.p. 198–199°; the alkaline mother liquor gave 102 mg. (15%) of VI on acidification; this material melted 195–198°. The methyl ester melts 112.6–114.0°; $[\alpha]^{20}D$ +53.4 ± 0.6° (1.592% chf).

Anal. Calcd. for $C_{25}H_{40}O_4$ (404.57): C, 74.21; H, 9.97. Found: C, 73.95; H, 9.87.

Acetylation of 3α,9α-Oxido-11β-hydroxycholanic Acid (VI).—A hot solution of 154 mg. of VI in 2 cc. of glacial acetic acid was cooled to room temperature, 0.2 cc. of boron fluoride etherate was added, and the mixture allowed to stand for 17 hours. Dilution with water precipitated 172 mg. (100%) of 3α,9α-oxido-11β-acetoxycholanic acid (VII), m.p. 158–160.8°. After recrystallization from ligroin the acid had m.p. 161.0–162.8°; it was identified as the methyl ester, m.p. 96.0–97.1°, not depressed when mixed with an authentic sample prepared according to the literature.[12]

When **methyl 3α-acetoxy-11β-hydroxycholanate (VIII)** was subjected to the same acetylating conditions (233 mg. of the ester, 4 cc. of acetic acid and 0.4 cc. of boron fluoride etherate) 200 mg. (89%) of methyl **3α-acetoxy-Δ$^{9(11)}$-**

cholenate (IX) resulted, m. p. 136.2–138.0°. Recrystallization raised the melting point to 137.8–139.6°, in agreement with the literature[3,6,10]; no depression was noted on admixture of an authentic specimen; $[\alpha]^{22}D$ +59.0 ± 0.8° (1.392%, an).

Dehydration of the 9α,11β-Dihydroxy Esters XI and XII with Thionyl Chloride and Pyridine.—To a solution of 239 mg. of XI in 2 cc. of pyridine was added 0.2 cc. of thionyl chloride, and the mixture was allowed to stand in a closed vessel for three-quarters of an hour. The liquid which contained crystals of pyridine hydrochloride was poured on ice, the precipitated solid was collected and dissolved in ether. The solution was washed with dilute sulfuric acid and bicarbonate solution, dried and evaporated. The residue of 220 mg. (95.5%) had m.p. 119–122°; not depressed on admixture of authentic methyl 3α-acetoxy-9α,11α-oxidocholanate (X).

The β-epimer XII gave, under identical conditions, methyl **3β-acetoxy-9α,11α-oxidocholanate** (XIII) of m.p. 147.2–149.6 in 98% yield. Recrystallization from methanol and from ethanol gave pure XIII in the form of needles m.p. 149.0–150.7; $[\alpha]^{19}D$ +10.4 ± 0.8° (1.292% chf).

Anal. Calcd. for $C_{24}H_{42}O_5$ (446.61): C, 72.61; H, 9.48. Found: C, 72.66; H, 9.43.

A sample of XIII was converted to **methyl 3-keto-9α,11α-oxidocholanate** (I): a solution of 62 mg. of XIII in 5 cc. of 0.3 *N* methanolic sodium methoxide was boiled for one hour, diluted with water, neutralized with acetic acid, and extracted with ether. On evaporation the ether solution left a residue of 27 mg. of solid, which was oxidized overnight with the solution of 20 mg. of sodium dichromate ($Na_2Cr_2O_7 \cdot 2H_2O$). On dilution there was precipitated 24 mg. of solid, m.p. 105–115°, which was chromatographed on alumina. The fractionation afforded 13 mg. (48% for the oxidation) of solid, m.p. 126.5–129.4°; recrystallization from 80% acetone gave 11 mg. of I in characteristic flat needles, m.p. 128.7–129.9°, not depressed by an authentic sample; $[\alpha]^{22}D$ −1.3 ± 1.3° (0.710% chf).[3]

Methyl 3α- and 3β-Acetoxy-9α-hydroxy-11-ketocholanate (XIV and XVII).—A solution of 62 mg. of XI in 2 cc. of acetic acid was mixed with 200 mg. of chromic anhydride dissolved in 0.5 cc. of water and allowed to stand for two hours. Water was added, the mixture was extracted with ether, the solvent was removed and the residue recrystallized from dilute methanol, which deposited 33 mg. (50%) of XIV in the form of needles, m.p. 144–147°. The analytical sample melts at 149.0–150.4°; $[\alpha]^{22}D$ +83.4 ± 2° (1.32% chf); $\lambda_{max}^{CS_2}$ approx. 2.75 (hydroxyl), 5.75 (acetate), 5.77 (methyl ester), 5.85 (11-ketone), 8.08 (acetyl group) μ; λ_{max}^{chf} approx. 2.75, 5.77, 5.84, 5.87, 7.32 (3-acetoxy group).[28]

The 3β-epimer XII (248 mg.) was similarly oxidized with 0.25 g. of chromic anhydride, yielding 146 mg. (75%) of XVII, m.p. 143–144°. Recrystallization from methanol produced prisms of XVII, m.p. 134–135.5°, and, after resolidification, 143.8–144.6°; $[\alpha]^{21}D$ +58.2 ± 2° (1.22% chf); λ_{max}^{chf} 2.87, 5.89–5.94 μ.

Anal. Calcd. for $C_{27}H_{42}O_6$ (462.60): C, 70.10; H, 9.15. Found: α-epimer: C, 70.25; H, 9.16; β-epimer: C, 70.12; H, 9.10.

Methyl 3α- and 3β-Acetoxy-11-keto-$\Delta^{8,9}$-cholenate (XIX and XX).—To a solution of 84 mg. of the 9,11-ketol XIV in 0.5 cc. of pyridine was added 0.1 cc. of thionyl chloride, and the mixture was allowed to react for one hour at room temperature. The solution was poured on ice, the solid was collected and chromatographed on alumina. Ether–benzene mixtures eluted 73 mg. (90%) of XIX, m.p. 120–127°. Recrystallization from dilute methanol gave an analytical sample, in the form of flat needles, m.p. 128.7–129.9°; $[\alpha]^{24}D$ +144.4 ± 1° (1.62% chf); λ_{max}^{alc} 254 mμ (log ε 3.94); λ_{max}^{chf} 5.74, 5.98, 6.21 μ.

The 3β-epimer XVII (224 mg.) was dehydrated in similar fashion. Recrystallization of the crude product from methanol gave 150 mg. (69%) of XX in two crops, m.p. 145–148°. The analytical sample formed stout needles or prisms, m.p. 148.1–148.8°; $[\alpha]^{23}D$ +21.4° ± 2° (2.33% chf); λ_{max}^{alc} 255 mμ (log ε 3.95); λ_{max}^{nu} 5.70–5.75, 6.04, 6.23 μ.[29]

(29) This infrared absorption spectrum was kindly determined by Dr. R. W. Walker at the laboratories of Merck and Company, Inc.

Phosphorus oxychloride or oxalyl chloride fail to dehydrate XIV and XVII.

Anal. Calcd. for $C_{27}H_{40}O_5$ (444.59): C, 72.94; H, 9.07. Found α-epimer: C, 73.14; H, 9.24; β-epimer: C, 73.02; H, 8.99.

Hydrogenation of Methyl 3α-Acetoxy-11-keto-$\Delta^{8,9}$-cholenate XIX.—In acetic acid solution over Adams catalyst the compound consumes two molecules of hydrogen; if the reaction is interrupted after consumption of one mole, the resulting mixture of products appears to be more complex, but in either case only one apparently pure compound could be isolated. This substance crystallizes readily in needles when the crude reaction product is dissolved in a little hot acetone. From the hydrogenation (2 moles) of 134 mg. of XIX 67 mg. of nicely crystallized product was obtained, m.p. 125–135°. By chromatography and continued recrystallization the melting point rose to 143.6–145.4°, $[\alpha]^{26}D$ +81.5 + 5° (0.65% chf). The compound did not depress the melting point of a similarly melting sample of 3α-acetoxy-$\Delta^{8,9}$-cholenate prepared by Dr. William P. Schneider; although the infrared spectra are in fair agreement, the rotations differ: Dr. Schneider's preparation shows $[\alpha]^{26}D$ +69 ± 4° (0.87% chf).

An analysis was obtained on a sample, m.p. 138.8–141.8°, $[\alpha]^{26}D$ +74.5 ± 3° (1.96% chf); the data indicate the composition of a methyl acetoxycholenate.

Anal. Calcd. for $C_{27}H_{42}O_4$ (430.60): C, 75.30; H, 9.83. Found: C, 75.97; H, 9.90.

The hydrogenation product was conclusively identified by conversion to the corresponding oxide. The reaction of two moles of hydrogen with 750 mg. of XIX yielded, after one recrystallization of the product, 540 mg. of well-crystallized but impure methyl 3α-acetoxy-$\Delta^{8,9}$-cholenate, m.p. 129–138°. The olefinic ester (480 mg.) consumed 1.12 equivalents of perbenzoic acid during 16 hours at room temperature in benzene solution. Chromatographic fractionation afforded 210 mg. of the oxido ester, m.p. 100–109°, which was further purified by recrystallization from methanol and from ligroin. The compound forms matted, silky needles, m.p. 114.5–115.7°, not depressed on admixture of a sample of methyl 3α-acetoxy-8,9-oxidocholanate obtained by Dr. Schneider from his preparation of methyl 3α-acetoxy-$\Delta^{8,9}$-cholenate, m.p. 114.6–116.4°. The optical rotation of the two samples are, respectively, $[\alpha]^{25}D$ +22.8 ± 2° (3.51% chf); +22.7 ± 2° (3.17 chf). The infrared spectra of both samples agreed with one another, showing the following maxima: λ_{max}^{chf} 2.55, 5.82, 6.85, 7.32, 7.95, 8.75, 9.82, 10.22, 11.25 μ.

Anal. Calcd. for $C_{27}H_{42}O_5$ (446.61): C, 72.61; H, 9.48. Found: C, 72.75; H, 9.77.

Methyl 3α- and 3β-Acetoxy-11-keto-12α-bromocholanate (XVIII and XXI).—A solution of 43 mg. of the ketol XIV in 0.8 cc. of 32% hydrogen bromide in acetic acid was kept at room temperature for one hour. It was diluted with water and 46 mg. of solid, m.p. 160–170° was collected. On recrystallization there was obtained 30 mg. (61%) of the 3α-acetoxybromoketone XVIII, in the form of well-shaped needles, m.p. 176–181°. After recrystallization to constant melting point, the sample melted 184.4–185.2°, $[\alpha]^{23}D$ +9 ± 2° (0.99%, an), in agreement with the literature.[4,30] Debromination of this compound by zinc has been described in the literature.[4]

The 3β-acetoxy ketol XVII apparently reacts more rapidly and smoothly: to a solution of 72 mg. of XVII in a little acetic acid was added 1 cc. of 32% hydrogen bromide in acetic acid. After a few minutes at room temperature a crystalline solid appeared; the solution was diluted and filtered, affording 83 mg. (about 100%) of XXI, m.p. 212–216°. The compound crystallizes in the form of elongated plates from chloroform on dilution with methanol. The analytical sample melts 224.9–226.0°; $[\alpha]^{21}D$ −34.7 ± 2° (2.42% chf).

Anal. Calcd. for $C_{27}H_{41}O_5Br$ (525.51): C, 61.71; H, 7.86; Br, 15.21. Found: C, 61.49; H, 8.04; Br, 14.92.

Methyl 3β-Acetoxy-11-ketocholanate (XXIV).—A solution of 12 mg. of the bromoketone XXI in 0.3 cc. of acetic acid was heated on the steam-bath for 20 minutes with 35 mg. of zinc dust. Evaporation of the filtered solvent and recrystallization of the residue gave 9 mg. of XXIV, melting,

(30) G. H. Ott and T. Reichstein, *Helv. Chim. Acta*, **26**, 1799 (1943).

after another recrystallization from dilute methanol, at 174.8–176.2°; $[\alpha]^{23}D$ +39.6 ± 2° (2.22% an). The debromination reaction has been carried out previously by Press, Grandjean and Reichstein[16] who, however, employed a mixture containing XXI besides other bromo compounds. Whereas the melting point of our preparation agrees with that of the Swiss investigators, we find a significantly lower value for the optical rotation. Barton[31] called attention to the anomaly that the data reported[16] for methyl 3β-hydroxy-11-ketocholanate and its 3-acetate lead to a molecular rotation difference $M_{D(acetate)} - M_{D(hydroxy\ compound)} = +92°$ instead of the expected value of +17°. With the value determined for XXI in the present work, the molecular rotation difference is found to be +19°, in agreement with Barton's prediction.[31]

Anal. Calcd. for $C_{27}H_{42}O_5$ (446.61): C, 72.61; H, 9.48. Found: C, 73.07, 72.44; H, 9.48, 9.53.

Methyl 3,11-Diketo-12α-bromocholanate (XXVI) from Methyl 3β-Acetoxy-3α,9α-oxido-11-ketocholanate (Vd).—A bomb tube containing 103 mg. of Vd was cooled in Dry Ice–acetone, while dry hydrogen bromide was passed in and condensed. When the organic material was covered by a layer of the liquid hydrogen halide, the tube was sealed and transferred to an ice-bath. Soon the organic solid and the hydrogen bromide formed an orange-colored liquid phase, that floated upon a second, colorless liquid phase consisting essentially of hydrogen bromide. After three hours the tube was cooled again in Dry Ice, opened, and the hydrogen bromide was allowed to evaporate. The residue was dissolved in chloroform, washed with water and treated with diazomethane. (This treatment was found to be unnecessary since no hydrolysis occurs.) The solid residue obtained on removal of the solvents weighed 103 mg. (95%), m.p. 153–162°. Recrystallization from dilute acetone gave 80 mg. (74%) of XXVI, m.p. 159–162.8°. The analytical sample forms stout needles, or prisms, m.p. 163.6–164.7°; $[\alpha]^{26}D$ −30 ± 2° (2.36% chf); λ_{max}^{chf} 5.75, 5.80 μ, in agreement with the data reported for this compound by the workers at the Mayo Clinic.[4]

Anal. Calcd. for $C_{25}H_{37}O_4Br$ (481.47): C, 62.36; H, 7.74; Br, 16.60. Found: C, 62.39; H, 7.70; Br, 16.31.

3,11-Diketocholanic Acid (XXVII) from Methyl 3,11-Diketo-12α-bromocholanate (XXVI) and from Vd.—To a hot solution of 86 mg. of XXVI in 1 cc. of acetic acid was added a pinch of zinc dust and the mixture was heated on the steam-bath for 15 minutes. The solution was filtered, and evaporated in vacuum. The residue was boiled for one hour with 5 cc. of ethanol, 0.5 cc. of 6 *N* sodium hydroxide solution, and 5 cc. of water, the alcohol was removed and the acid was precipitated with acetic acid. On recrystallization 48 mg. (69%) of XXVII was obtained, m.p. 173.2–177.8°. Another recrystallization from dilute acetone gave pure XXVII, m.p. 176.2–178.2°; $[\alpha]^{29}D$ +62 ± 2° (2.16% an), in agreement with the literature.[4,12,21]

In another experiment 3 g. of the 11-ketohemiketal acetate Vd was cleaved with 14 g. of dry hydrogen bromide as described above. The total crude but well crystallized bromodiketo ester (XXVI) was dissolved in 50 cc. of acetic acid and heated with 4 g. of zinc dust on the steam-bath for 20 minutes. The resulting orange solution was filtered and evaporated. The residue was saponified by boiling for two hours with 70 cc. of 50% aqueous ethanol and 10 cc. of 6 *N* sodium hydroxide. Filtration and acidification gave 2.3 g. (91%) of crude XXVII, m.p. 168–174°. Recrystallization from dilute acetone gave 2 g. (79%) of faintly tan needles in two crops, m.p. 174.5–177.4° and 170–175°.

By treatment of XXVII with ethylene glycol and *p*-toluenesulfonic acid in boiling benzene followed by alkaline saponification, the cyclic ketal **3,3-ethylenedioxy-11-ketocholanic acid** was prepared. The compound crystallized from dilute acetone, or from ethyl acetate–petroleum ether; m.p. 162.4–164.1°; $[\alpha]^{21}D$ +51.0 ± 1° (1.433% chf).

Anal. Calcd. for $C_{26}H_{40}O_5$ (432.58): C, 72.19; H, 9.32. Found: C, 72.13; H, 9.62.

Reduction of 3,11-Diketocholanic Acid (XXVII) to Methyl 3α- and 3β-Acetoxy-11-ketocholanate (XXII and XXIV).—A solution of 1 g. of XXVII in 3 cc. of ethanol and 12 cc. of 0.8 *N* sodium hydroxide solution was treated at ice temperature with 0.2 g. of sodium borohydride, and the solution was kept at 4° for 20 hours. The crude acid precipitated by dilute acetic acid (m.p. 203–212°) was esterified with diazomethane, and the ester was acetylated by heating it on the steam-bath for one hour with 2 cc. of pyridine and 2 cc. of acetic anhydride. The crude product (1.1 g.) melted 119–125°; it was chromatographed on alumina; there was obtained 976 mg. (85%) in 12 fractions consisting essentially of XXII and 123 mg. (11%) in two fractions that were mainly the 3β-epimer XXIV. Purification of the best fractions gave 679 mg. (59%) of XXII, m.p. 131–133.2° and 36 mg. (3%) of XXIV, m.p. 172.4–174.8°.

Methyl 3α-Acetoxy-11β-hydroxycholanate (VIII) from Methyl 3α-Acetoxy-11-ketocholanate (XXII).—To a solution of 529 mg. of XXII in 40 cc. of methanol at room temperature was added 104 mg. of sodium borohydride. The solution was kept at room temperature for 12 hours and diluted with water; excess reducing agent was destroyed by acetic acid. The semi-solid product was taken up in ether and petroleum ether was added, but the product appeared to be impure owing to incomplete reduction. The material was saponified by boiling for one hour with 15 cc. of 0.2 *N* aqueous methanolic sodium hydroxide, and after addition of 0.5 g. of sodium borohydride boiling was continued for one hour. The crude reduced acid was precipitated by dilute acetic acid; it was esterified with diazomethane and acetylated overnight with 2 cc. of pyridine and 1 cc. of acetic anhydride. By dilution with water 426 mg. (80%) of crude VIII was precipitated, m.p. 138–147°. Recrystallization from ether–petroleum ether gave 233 mg. (44%) m.p. 146–149° in agreement with the literature.[13]

Wolff-Kishner Reduction of the 9,11-Ketol XIV.—A solution of 200 mg. of XIV in 10 cc. of triethylene glycol containing 1 cc. of 85% hydrazine hydrate and 0.9 g. of potassium hydroxide was treated as recommended by Huang-Minlon.[18] The crude acid, precipitated by dilute mineral acid, was crystallized from dilute acetone to give 132 mg. (81.5%) of 3α-hydroxy-$\Delta^{9(11)}$-cholenic acid (XXIII), m.p. 190–191.2°; $[\alpha]^{29}D$ +47 ± 2° (2.14%, alc); these data agree with those reported in the literature.[6,10] Esterification and acetylation gave IX, m.p. 137.8–139.4°, and a sample of IX was converted to the oxide with perbenzoic acid. Only the 9,11-oxide (X) was detected, m.p. 120.0–121.2°, not depressed by an authentic sample; $[\alpha]^{25}D$ +49 ± 2° (3.08% an) in agreement with reported data.[6,13] Thus no migration of the double bond occurs under Wolff–Kishner conditions in the present reaction.

Reduction of Methyl 3α-Acetoxy-9α-hydroxy-11-ketocholanate (XIV) and of the 3β-Epimer (XVII) with Sodium Borohydride (a) α-Epimer.—A solution of 110 mg. of XIV in 10 cc. of 50% aqueous alcoholic sodium hydroxide (0.2 *N*) was boiled for three hours, and then treated at room temperature for 12 hours with 200 mg. of sodium borohydride. Finally the mixture was boiled for one hour, and the free acid liberated; 75 mg. (78%) of 3α,9α,11α-trihydroxycholanic acid resulted, m.p. 201–204°. Recrystallization gave 67 mg. m.p. 201.8–203.3°, not depressed by the acid prepared directly from XI.

(b) **β-Epimer.**—To a solution of 532 mg. of XVII in 15 cc. of methanol was added 102 mg. of sodium borohydride. Soon well-shaped prisms of XII were being deposited. The solution was allowed to stand overnight, and the solid was collected in two crops of 312 and 210 mg. (98%), m.p. 171.0–172.3° and 168–169.8°.

Clemmensen Reduction of Methyl 3α-Acetoxy-9α-hydroxy-11-ketocholanate (XIV).—A solution of 80 mg. of XIV in 10 cc. of acetic acid and 10 cc. of concentrated hydrochloric acid was boiled with 6 g. of freshly poured, amalgamated mossy zinc for 17 hours. The product was recovered from the solvent, treated with ethereal diazomethane and then acetylated by heating on the steam-bath for one-half hour with pyridine–acetic anhydride. Chromatography on alumina gave 18 mg. (23%) of solid material in two fractions consisting essentially of XXII. After two recrystallizations from dilute acetone and methanol the compound had m.p. 129.4–131.8°, not depressed by an authentic sample of XXII.[32]

Clemmensen Reduction of Methyl 3β-Methoxy-3α,9α-oxido-11-ketocholanate (Vb).—To 28 g. of freshly poured and amalgamated mossy zinc was added a solution of 543 mg. of Vb in 50 cc. of acetic acid and 60 cc. of 6 *N* hydro-

(31) D. H. R. Barton, *J. Chem. Soc.*, 1116 (1946).

(32) A sample of authentic XXII was kindly supplied by Dr. R. B. Turner.

chloric acid. The mixture was boiled for five hours; a small amount of an oily phase was observed at the end of the period. Dilution with water, extraction of the precipitated partly crystalline material with ether, treatment with diazomethane, and evaporation gave 465 mg. (95%) of crude methyl 11-ketocholanate, m.p. about 75–84°. Chromatography on alumina gave 325 mg. (67%) in 10 fractions, which were further purified by recrystallization from dilute methanol. The keto ester forms square prismatic needles, m.p. 89.4–90.5°; $[\alpha]^{20}D$ +48.1 ± 2° (2.10% an).[5]

Anal. Calcd. for $C_{25}H_{40}O_3$ (388.57): C, 77.27; H, 10.38. Found: C, 76.94; H, 10.41.

Other reducing agents such as zinc and ammonia, hydrogen iodide and phosphorus, zinc amalgam or magnesium amalgam in toluene, sodium amalgam in aqueous medium, either led to intractable products or recovery of starting material when applied to attempted reduction of Va, Vb or Vd.

Dehydration of Methyl 3α-Acetoxy-9α,11β-dihydroxycholanate (XI) to Methyl 3α-Acetoxy-11-ketocholanate (XXII).—Dry hydrogen bromide was passed into a solution of 297 mg. of XI in 5 cc. of alcohol-free chloroform for 20 minutes at room temperature. The solution became slightly cloudy owing to the water liberated. The solvent was removed in vacuum and the residue dissolved in benzene, which was distilled in like manner. The solid residue (m.p. 120–125°) was recrystallized from aqueous acetone, which deposited 183 mg. (64%) of XXII, m.p. 124–129°. Further purification raised the melting point to 131.2–132.6°, not depressed by an authentic sample of XXII[32]; $[\alpha]^{23}D$ +67.9 ± 2° (2.21% an).

In a similar experiment the yield of XXII melting at 129.6–131.4° was 55%. Other reagents that also accomplish the dehydration are boron fluoride etherate, hydrogen bromide (32%) in acetic acid, or sulfuric acid in warm acetic acid, but the yields are poor. Hydrogen chloride in chloroform does not bring about the reaction.

The mother liquor from the dehydration described in detail contained halogenated material (Beilstein test) that proved to be intractable. In one boron fluoride catalyzed dehydration the total crude product was chromatographed; the most easily eluted fractions gave, after recrystallization, 36% of pure XXII, m.p. 131.5–134.0°; the more strongly adsorbed material did not crystallize, and no conclusions as to its nature could be drawn from an infrared spectrum.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1a]]

Preparation of Esters by Reaction of Ammonium Salts with Alcohols[1b]

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A modified esterification procedure by which ammonium salts of organic acids react with alcohols to produce esters and ammonia was investigated. This reaction seems to be generally suitable for the preparation of esters of organic acids. Similarly, reaction of amine salts with alcohols gives ester and amine. This method of esterification may be useful for preparing esters from acid-sensitive alcohols and organic acids as well as for preparing esters of certain fermentation acids.

Ammonium salts of organic acids differ markedly from metallic salts in chemical properties. When heated, ammonium salts are converted into amides, accompanied by dissociation into ammonia and the acid.[3] Ammonium salts have been distilled under vacuum, partial dissociation into an acid salt ($RCOONH_4 \cdot RCOOH$) taking place; the acid salt distilled as a pure compound.[4,5]

Other investigators have reported the reaction of ammonium salts with an excess of formaldehyde to liberate the free acid in quantitative yield,[6] and more recently the reaction of ammonium and substituted ammonium salts with diazomethane to produce the methyl ester and ammonia or amine, respectively,[7] has been reported.

In this paper, we describe another novel reaction of ammonium and amine salts of organic acids, namely, the interaction between these salts and alcohols to produce an ester and ammonia or an amine.

$$RCOONH_4 + R'OH \rightleftharpoons RCOOR' + NH_3 + H_2O$$

The reaction bears some resemblance to direct esterification, and from an over-all viewpoint may be considered a direct esterification of ammonium salts with alcohols. This method of producing esters, therefore, may be of interest, particularly where the acidic conditions of conventional esterification are deleterious to the reactants as well as in preparing esters of certain fermentation acids.

As far as we can ascertain, there is no mention in the literature that ammonium salts as such are capable of undergoing an esterification type of reaction. There are many instances in which ammonium salts of organic acids have served as starting material for the preparation of esters, but in each case the organic acid was first liberated by addition of equivalent amounts of a strong mineral acid.

These reactions of ammonium salts are typical reactions of either carboxylic acid (the reactions with diazomethane or alcohols), or of ammonia (the reaction with formaldehyde). Perhaps they may be best explained on the basis of dissociation of the salt into acid and ammonia or amine.

The ammonium salts were esterified by refluxing the mixture of ammonium salt and alcohol under conditions permitting continuous removal of both ammonia and water from the reaction mixture. This was conveniently accomplished by using an entraining agent, which in most cases was the alcohol used in the reaction. When water-soluble alcohols were used toluene or some other suitable solvent was added to serve as an entraining agent. Esterification of amine salts was carried out in the

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(3) C. D. Hurd, "Pyrolysis of Carbon Compounds," A. C. S. Monograph 50, Reinhold Publishing Corp., New York, N. Y., 1929, page 507.

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