itated from the solution was filtered, washed with water, and recrystallized from methanol. About 0.06 g. of red needles were obtained which melted at 141–142°. The infrared spectra and the ultimate composition of this product are the same as those of VIII.

Anal. Calcd. for $C_{20}H_{16}N_4O$: C, 73.2; H, 4.87; N, 17.06. Found: C, 73.0; H, 4.92; N, 17.02.

B. With Acid.—Three drops of concentrated H_2SO_4 was added to 50 ml. of methanol–water (4:1) solution containing 0.2 g. of IX. The solution was boiled for about 15 min. and cooled. The solid precipitate was filtered, washed with water, and recrystallized from methanol to yield about 0.09 g. of red needles, m.p. 141–142°. The infrared spectra and the ultimate composition of this product are the same as those of VIII.

Anal. Calcd. for $C_{20}H_{16}N_4O$: C, 73.2; H, 4.87; N, 17.06. Found: C, 72.92; H, 4.83; N, 17.00.

The Spectral Results.—Ultraviolet spectra were measured in methanol solution with a Cary 14 spectrophotometer, infrared spectra were obtained in a Fluorolube mull with a Perkin-Elmer 237 spectrophotometer, and n.m.r. spectra were obtained in carbon disulfide solution with a Varian A-60 analytical n.m.r. spectrometer.

Acknowledgment.—The author is indebted to Dr. C. H. Ruof for his help in preparing this paper and wishes to thank Mr. J. L. Parsons for the discussion of the infrared absorption spectra.

The Reduction of 12-Keto Steroids[1]

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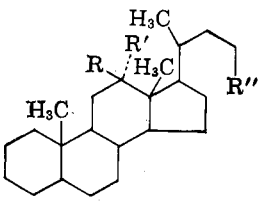
In contrast to the accepted generalization, it has been found that reduction of certain 12-keto steroids with lithium–liquid ammonia or sodium in alcohol affords predominantly the axial alcohol. It has been found that this anomaly is apparently a function of the structure of the side chain attached at C-17, and may be associated with a shielding of the oxygen in the 12-position by the C-21 methyl group. Other reactions in support of this hypothesis are discussed.

It has been generally accepted that the reduction of cyclic ketones by either sodium in alcohol, or lithium–liquid ammonia–alcohol gives rise exclusively or almost exclusively to the alcohol containing the thermodynamically more stable equatorial hydroxyl group.[2-6] These methods have found rather extensive use in steroid chemistry, and, in fact, provide the only practicable method for the preparation of steroid 11α-ols.[7-13] Although in the case of some bridged bicyclic ketones it has been found that sodium in alcohol reduction leads to a preponderance of the thermodynamically less stable alcohol[14] and although the reduction of camphor with potassium, rubidium, or cesium in liquid ammonia with ethanol as a proton source gives principally the less stable *exo* alcohol,[14] it seems to be generally accepted that reduction of cyclic ketones in general, and steroidal ketones in particular with either of the above reagents gives principally the more stable of a pair of epimeric alcohols, almost invariably the equatorial isomer.

In direct contrast to the above generalizations we found in attempting to prepare 12β-hydroxycholanic acid (Ia) by either lithium–liquid ammonia or sodium–



Ia, R = OH; R′ = H; R″ = CO_2H
b, R, R′ = O; R″ = CO_2H
c, R = H; R′ = OH; R″ = CO_2CH_3
d, R, R′ = O; R″ = CH_3
e, R′ = H; R′ = OH; R″ = CH_3
f, R = OH; R′ = H; R″ = CH_3

n-propyl alcohol reduction of 12-ketocholanic acid[15] (Ib) the only isolable product was the 12α- (axial) ol, isolated as the methyl ester (Ic). Initially it was felt that these anomalous reductions were caused by an electrostatic effect associated with the carboxylate anion, and in order to check this hypothesis 12-cholanone (Id), prepared by oxidation of 12α-cholanol[16] (Ie), was subjected to reduction under similar conditions. Once again the axial alcohol was the principal product. From the lithium–liquid ammonia reduction, the 12α-ol was obtained in 71% yield, while sodium–*n*-propyl alcohol reduction gave the α–β-ol in a ratio of 1.7:1. The structure of 12β-cholanol (If) was confirmed by its oxidation to 12-cholanone, and analytical data.

At this stage there appeared to be several possible alternative explanations for these somewhat puzzling reductions. First, the possibility that the stereochemis-

(1) A preliminary communication discussing a portion of this work appeared: J. W. Huffman, D. M. Alabran, and T. W. Bethea, *J. Org. Chem.*, **27**, 3381 (1962).

(2) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(3) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(4) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

(5) W. Klyne, "Progress in Stereochemistry," Vol. 1, Butterworth and Co. (Publishers), Ltd., London, 1954 pp. 57, 74.

(6) W. G. Dauben and K. S. Pitzer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 47.

(7) W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Am. Chem. Soc.*, **77**, 478 (1955).

(8) F. Sondheimer, O. Mancera, G. Rosenkranz, and C. Djerassi, *ibid.*, **75**, 1282 (1953).

(9) K. Heusler, H. Heusser, and R. Anliker, *Helv. Chim. Acta*, **36**, 652 (1953).

(10) F. Sondheimer, R. Yashin, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 2696 (1952).

(11) H. L. Herzog, M. A. Jevnik, and E. B. Hershberg, *ibid.*, **75**, 269 (1953).

(12) J. B. Bream, D. C. Eaton, and H. B. Henbest, *J. Chem. Soc.*, 1974 (1957).

(13) H. L. Heuser, R. Anliker, and O. Jeger, *Helv. Chim. Acta*, **35**, 1537 (1952).

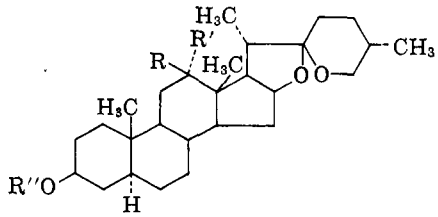
(14) reg. (a) G. Ourisson and A. Rassat, *Tetrahedron Letters*, **21**, 16 (1960), and references cited therein; (b) K. D. Hardy and R. J. Wicker [*J. Am. Chem. Soc.*, **80**, 640 (1958)] have also discussed the problems in using the results of sodium in alcohol reductions as a criterion of stability of the alcohols.

(15) J. Barnett and T. Reichstein, *Helv. Chim. Acta*, **21**, 926 (1938).

(16) R. T. Blickenstaff and F. C. Chang, *J. Am. Chem. Soc.*, **81**, 2835 (1959).

try at C-12 in the bile acids is incorrectly assigned may be excluded in view of the preponderance of evidence to the contrary.[17] Since the 5β-steroids we have discussed, and shall discuss below, have all been prepared from desoxycholic acid, the stereochemical assignments at C-12 appear firm. A second explanation, namely, that in some ketones the stereochemical course of metal–ammonia or metal–alcohol reductions is profoundly altered, appeared, more attractive. Examination of Dreiding models of 12-cholanone indicates that in the most favored conformation of the side chain, the C-12 carbonyl is shielded by the methyl at C-21, which may account for the anomalous course of these reductions.

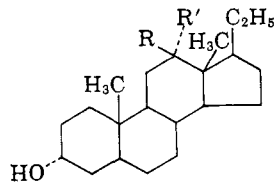
In order to check this hypothesis, hecogenin-3-tetrahydropyranyl ether[18] (IIa) was reduced with both lithium–liquid ammonia and sodium in alcohol, and in both cases the only isolable product was the rockogenin derivative (IIb), having an equatorial 12-hydroxyl.



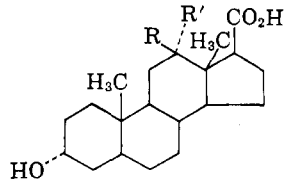
IIa, R, R′ = O; R″ = C_5H_9O
b, R = OH; R′ = H; R″ = C_5H_9O
c, R = OH; R′ = H; R″ = $C_5H_7O_3$

In hecogenin the C-12 methyl group is rigidly held such that it cannot shield the 12-position, and the reductions proceed normally. However, hecogenin possesses a *trans* A–B ring fusion as contrasted to the *cis* fusion in the compounds derived from the bile acids.

In order to ensure that the nature of the ring fusion was not influencing the course of the reduction, 3α-hydroxy-5β-pregnan-12-one (IIIa) was prepared from the commercially available 3α,12α-diacetoxypregnan-20-one by the following sequence. Wolff–Kishner re-



IIIa, R, R′ = O
b, R = H, R′ = OH
c, R = OH, R′ = H



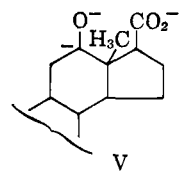
IVa, R, R″ = O
b, R = H, R′ = OH

duction afforded the 3α,12α-diol (IIIb), which upon treatment with succinic anhydride afforded the 3-succinoxy compound. Oxidation and hydrolysis gave the desired hydroxy ketone (IIIa). When IIIa was reduced with lithium–liquid ammonia a diol which was not IIIb was obtained. Since it is most improbable that the 3α-hydroxyl is epimerized under these conditions, it follows that the reduction product must be the 12β-ol (IIIc), and that the mode of the A–B ring fusion probably does not affect the course of the reduction of the 12-keto group. It should be pointed out that, although the 21-methyl group in the pregnane is not held rigidly so that it cannot interfere with the carbonyl group, the favored conformation of the ethyl group is such that it should not shield the carbonyl.

Initial experiments, reported in the preliminary communication,[1] using 3α-hydroxy-12-ketoetianic acid (IV) indicated that the ring fusion probably did affect the course of reduction. This compound afforded 40 ± 5% of the 12α-hydroxy acid when reduced with lithium–liquid ammonia and 36 ± 5% with sodium in alcohol (balance of the product in both cases 12β-ol). It appears likely, if one accepts the mechanism suggested by Barton[19] for the reduction of ketones by metals in liquid ammonia, that in the intermediate in the reduction of the etianic acid (V), there would exist an electrostatic repulsion between the 17β-carboxylate anion and a 12β-oxyanion. This would then lead to the formation of somewhat more of the 12α-hydroxy compound, as was observed.

In our initial communication[1] we had considered and rejected as a possible explanation for these anomalous reductions the explanation that the axial alcohol was the more stable isomer in the case of the compounds bearing a free methyl group attached to C-20. The reason for this rejection was based on the overwhelming body of evidence that equatorial isomers are more stable[20] than their axial epimers. Although a few cases have been noted where the axial alcohol may be more stable than the equatorial, these results are based on reduction studies,[21] and additional study of these compounds appears desirable. In addition, these compounds, 19-hydroxytriterpenes, are structurally sufficiently different from the 12-substituted steroids that using these compounds as models for the study of 12-substituted steroids may be inadvisable.

However, following the appearance of our original communication, a paper appeared suggesting that, in the 12-cholanols which have a "free" side chain, the axial isomer was the more stable, while in those compounds having the side chain held rigidly (*e.g.*, hecogenin) the normal relationship prevails.[22] The evidence presented



V

by these authors, namely the formation of 12α-aminocholane from the reduction of the oxime with sodium in ethanol, and equilibration studies on the 12-cholanols, seemed in our opinion, to be worthy of further investigation. In particular one experiment mentioned by these authors, namely that when 12α-cholanol was treated with nitrous acid it was oxidized to the ketone, while 12β-cholanol gave the nitrite ester, appears inconsistent with the argument that the axial alcohol is the more stable isomer. Although there are no published studies of the relative stabilities of nitrite esters, it

(17) These data have been discussed thoroughly by R. B. Turner, "Natural Products Derived Related to Phenanthrene," L. A. Fieser and M. Fieser, Ed., Reinhold Publishing Corp., New York, N. Y., 1949, pp. 654–662.

(18) R. Hirschman, C. S. Snoddy, C. F. Hiskey, and N. L. Wendler, *J. Am. Chem. Soc.*, **76**, 4013 (1954).

(19) D. H. R. Barton and C. H. Robinson, *ibid.*, 3045 (1954).

(20) E. L. Eliel ("Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 234–239) summarizes these arguments.

(21) T. R. Ames, J. L. Beton, A. Bowers, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 1905 (1954).

(22) M. Alauddin and M. Martin-Smith, *J. Org. Chem.*, **28**, 886 (1963).

TABLE I

Compd.	Relative rate of oxidation	% formed on reduction of corresponding ketone[a] Sodium–alcohol	Lithium–ammonia	Sodium borohydride
Rockogenin-3-methyl succinate or tetrahydropyranyl ether	1.00	80	*ca.* 100	70
12α-Cholanol	2.38	61, 55[b]	*ca.* 74, 71[b]	75
12β-Cholanol	1.07	39, 45[b]	*ca.* 0, 20[b]	25
12α-Hydroxycholanic acid	...	67 ± 8	89	57
12β-Hydroxycholanic acid	...	23 ± 8	*ca.* 0	40
3α,12α-Dihydroxyetianic acid	...	36 ± 5	40 ± 5	57[c]
3α,12β-Dihydroxyetianic acid	...	64 ± 5	60 ± 5	43[c]
3α,12α-Dihydroxypregnane	...	...	*ca.* 0	...
3α,12β-Dihydroxypregnane	...	...	100	...

[a] All values are relative per cents, *i.e.*, product ratios. [b] See ref. 22. These values were determined by gas chromatography and are perhaps somewhat more accurate than our figures obtained by isolation techniques. [c] S. Pataki, K. Meyer, and T. Reichstein, *Helv. Chim. Acta*, **36**, 1295 (1953).

would seem reasonable that a greater amount of steric strain is relieved when the less stable ester is converted to a ketone and that consequently the less stable alcohol should be the more readily oxidized under these conditions. In addition, in our hands (see Experimental) the 12α-ol was eluted from an alumina column with less polar solvents than the equatorial isomer[23] suggesting a normal stability relationship.

Although the English workers report that the equilibration of the 12-cholanols with sodium amyloxide gave a 2:1 ratio of α- to β-ol, there was an unspecified loss of material, which may make these experiments unreliable for arriving at conclusions regarding the relative stabilities of the alcohols. Attempted equilibration of the 12α-ol under Meerwein–Pondroff–Verley conditions[24] gave recovered 12α-ol, even after 240 hr. at 110°. Meerwein–Pondorff–Verley reduction of 12-cholanone failed when isopropyl alcohol was used as a solvent, and, when toluene was employed, an approximately 1:1 ratio of α to β-ol was obtained, whether the reaction was carried out for less than 2, or more than 80 hr. Once again, significant loss of material occurred, which would tend to cast considerable doubt on any otherwise unsupported conclusions drawn from these results.

Of other methods available for determining the relative thermodynamic stability of epimeric alcohols, the most sensitive and least equivocal procedure appeared to be the relative rates of chromic acid oxidation of the alcohols. It has been repeatedly shown that there is an inverse relationship between the rate of chromic acid oxidation of alcohols and their relative thermodynamic stabilities.[25-30] The only exception to this generalization is found in the case of the extremely hindered (three axial–axial, hydroxyl–methyl interactions) triterpenoid alcohol, 3β,28-diacetoxy-6β-hydroxy-18β-12-oleanene[31]; however, the very hindered steroidal 11β-ols follow the established generalization.[27,31] We have found that the relative second-order rate constants at 24° in 90% acetic acid for the oxidation of 12α-cholanol (Ie), 12β-cholanol (If), rockogenin-3β-methyl succinate (IIc) are, respectively, 2.38, 1.07, and 1.00. These rate constants were determined by measuring the decrease in intensity of the chromate absorbance at 380 mμ as a function of time. All reactions followed good second-order kinetics, with a variation of no more than 15% in the values determined for the rate constants at several points during each reaction. The runs were carried out in duplicate, and the values obtained in separate runs were within the limits of the 15% deviation mentioned. Since 12α-cholanol is oxidized more than twice as fast as the 12β-ol it appears that the 12α-ol is less stable than the corresponding equatorial isomer.[25,27,31] Alauddin and Martin–Smith[22] concluded that 12β-cholanol should be somewhat less stable than the 12-spirostanols, since the C-21 methyl group seemed to interact seriously with the 12β-hydroxyl in the cholanol. In order to ensure that these interactions did not hinder the esterification of the 12-cholanols sufficiently to give anomalous oxidation rates, both 12α- and 12β-cholanol were treated with acetic anhydride and pyridine. Since both alcohols gave acetates under these conditions it seems most unlikely that the rate of chromate ester formation could be sufficiently retarded to give misleading kinetic results.[31]

In addition to the above evidence concerning the relative stability of the 12-cholanols, possible additional evidence may be obtained from the reduction of some 12-keto steroids with sodium borohydride. It has been established that in sodium borohydride reductions of moderately hindered ketones (*e.g.*, 2- and 7-cholestanone), steric approach control usually leads to formation of principally the thermodynamically less stable isomer.[32-34] Reduction of 12-cholanone with sodium borohydride in methanol gave a 3 to 1 ratio of α- to β-alcohol, and 12-ketocholanic acid afforded the axial alcohol in 60% yield. The result of the above oxidations and reductions are summarized in Table I.

On the basis of normal conformational considerations it would be expected that the 12-keto steroids should show considerable similarity to 1-keto steroids. While reduction of 1-oximino cholestane with sodium in alco-

(23) D. H. R. Barton, "Fortschritte der Chemis Organischer Naturstoffe," Vol. 19, L. Zechmeister, Ed., Springer-Verlag, Wien, Austria, 1961 p. 188.

(24) E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5992 (1957).

(25) C. F. Wilcox, M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963).

(26) H. Kwart and P. S. Francis, *J. Am. Chem. Soc.*, **81**, 2116 (1959).

(27) J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955).

(28) J. C. Richer, L. A. Pilato, and E. L. Eliel, *Chem. Ind.* (London), 2007 (1961).

(29) J. C. Richer and C. Gilardeau, Abstracts of Papers, XIXth International Congress of Pure and Applied Chemistry, London, July, 1963, p. 57.

(30) H. Favre and J. C. Richer, *Can. J. Chem.*, **37**, 411 (1959).

(31) J. Rocek, F. Westheimer, A. Eschenmoser, L. Moldovanyi, and J. Schreiber, *Helv. Chim. Acta*, **45**, 2554 (1962).

(32) W. G. Dauben, E. G. Blanz, J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956).

(33) D. M. S. Wheeler and J. W. Huffman, *Experientia*, **16**, 516 (1960).

(34) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962).

hol affords the axial amine as the only isolable product,[35] as does 12-oximinocholane,[22] the order of thermodynamic stability of the 12-cholanols, based on the chromic acid kinetics, appears to be more like that of the 7-substituted steroids. This may be found by comparing the relative rates of oxidation of the 12-cholanols with that of cyclohexanol, and thereby obtaining rates comparable with those determined by Eschenmoser for a series of steroidal alcohols.[27] On this scale (3β-cholestanol equal to 1.00), 12α-cholanol's rate of oxidation is 7.2; 12β-cholanol, 3.2; 1α-cholestanol, 13.0; and 1β-cholestanol 9.7. Since the relative rates of oxidation of 7α- and 7β-cholestanol are 12.3 and 3.3, respectively, the over-all stability of the 12 substituted steroids would seem to be more nearly comparable with the stability of these compounds than with that of the 1-substituted steroids.

The classical generalizations about reductions of ketones with metals in liquid ammonia and sodium in alcohol[2-6] all are based on the mechanism proposed by Barton.[19] This mechanism includes the assumption that these reactions proceed *via* a rather fast conversion of the ketone to a relatively long-lived carbon–oxygen dianion, which equilibrates to give largely the thermodynamically more stable isomer. If, however, the carbonyl group is shielded so that the formation of the dianion becomes slow relative to the rate of protonation, then it would be expected that the reaction would proceed to give the most rapidly formed product, namely that arising from the equatorial approach of a proton donor. In order to obtain some evidence that this may be the explanation for the apparently anomalous reductions of the 12-cholanones; 12-cholanone was stirred for 2 hr. in the absence of alcohol, with lithium in liquid ammonia. Alcohol was then added, and analysis of the product showed that the ratio of 12β- to 12α-ol was 19:1. A 40% yield of the pinacol was also obtained. The rationalization for this observation is that the dianion was formed, had time to equlibrate, and was then protonated to give the stable product. The results of Ourisson,[13] obtained by increasing the size of the metal from lithium through cesium in carrying out metal–ammonia reductions seem to be consistent with this hypothesis, however our explanation is tentative at best, and additional experiments are certainly in order.

Experimental[36]

Reductions of 12-Ketocholanic Acid. A. Lithium–Liquid Ammonia.—A solution of 0.20 g. of 12-ketocholanic acid[15] in 12 ml. of dry ether and 6 ml. of methanol was added to 50 ml. of liquid ammonia, and 1 g. of lithium was added over the period of 0.5 hr. The reaction was stirred at reflux for 15 min., and sufficient methanol was added to discharge the residual blue color. The ammonia was then allowed to evaporate, and the mixture was warmed to drive off the last traces of ammonia. The residual solid was slurried with water, acidified with 10% hydrochloric acid, and extracted twice with methylene chloride. The extracts were washed with water and dried; the solvent was removed *in vacuo* leaving a viscous, pale yellow oil. This oil was taken up in 15 ml. of methanol, 0.75 ml. of acetyl chloride was added, and the solution was allowed to stand for 15 hr. at room temperature. The mixture was warmed to about 40°, water was added to turbidity, and upon standing 0.14 g. (70%) of methyl-12α-hydroxy cholanate,[15] m.p. 116–119°, was obtained. The melting point was not depressed on mixing with an authentic sample. Concentration of the mother liquors afforded an additional 0.03 g. (15%) of inferior material, m.p. 114–117°.

B. Sodium–*n*-Propyl Alcohol.—To a refluxing solution of 0.15 g. of 12-ketocholanic acid in 20 ml. of *n*-propyl alcohol was added, over a 0.5-hr. period, 1.5 g. of sodium. The reaction mixture was heated at reflux for 1 hr., acidified with dilute hydrochloric acid, and concentrated to a small volume. After cooling, the residue was diluted with water and extracted with two portions of methylene chloride. The oil left after removing the solvent was converted to the methyl ester as in part A, and 0.055 g. (37%) of solid material, m.p. 115–117°, was obtained. The mother liquors were evaporated to dryness *in vacuo* and the oily residue (0.07 g.) was analyzed by infrared spectroscopy. From the infrared spectrum the mixture consisted of 50 ± 8% of methyl-12α-hydroxy-cholanate.

C. Sodium Borohydride.—To a solution of 0.3 g. of 12-ketocholanic acid in 25 ml. of methanol was added 1 g. of sodium borohydride, and the mixture was heated at reflux for 1 hr. After cooling, the reaction mixture was diluted with water, acidified with 10% hydrochloric acid, and extracted with two portions of methylene chloride. The organic extracts were combined and washed with water; the solvent was removed at reduced pressure leaving a yellow glass. Upon conversion to the methyl ester as in part A there was obtained 0.17 g. (57%) of methyl 12α-hydroxycholanate, m.p. 113–116°.

12-Cholanone. A.—Kiliani's reagent[37] was added dropwise to a solution of 0.43 g. of 12α-cholanol in 25 ml. of reagent grade acetone until a permanent yellow color remained for 10 min. A few drops of water were added, the chromic salts were collected, and 1 ml. of 10% sodium hydroxide was added to the filtrate. The pale yellow reaction mixture was poured into water and the precipitated solid was collected. Recrystallization from aqueous methanol gave 0.32 g. (75%) of 12-cholanone, m.p. 115–117°. Further recrystallization from methanol gave the analytical sample, m.p. 116–117°, $[\alpha]^{25}D$ +89 (*c* 0.873, chloroform).

Anal. Calcd. for $C_{22}H_{40}O$: C, 83.66; H, 11.70. Found: C, 83.47; H 11.88.

The 2,4-dinitrophenylhydrazone was prepared in the usual manner and formed small yellow-orange needles from ethanol–ethyl acetate, m.p. 213–215°.

Anal. Calcd. for $C_{30}H_{44}N_4O_4$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.86; H, 8.63; N, 10.49.

B.—A solution of 0.03 g. of **12β-cholanol** (*vide infra*) in 5 ml. of acetone was oxidized as described above to give 0.01 g. (33%) of 12-cholanone, m.p. 115–116°, undepressed on mixing with an authentic sample.

Reductions of 12-Cholanone. A. Lithium–Liquid Ammonia.—A solution of 0.20 g. of 12-cholanone in 10 ml. of dry ether was added to a solution of 0.35 g. of lithium in 25 ml. of liquid ammonia. The reaction mixture was stirred at reflux for 2 hr., 7 ml. of *n*-propyl alcohol was added, and the solution was stirred for another 40 min. The ammonia was evaporated; the residue was slurried with water, acidified, and extracted with two portions of ether. The ethereal extracts were combined and washed with water and 10% potassium hydroxide, and the solvent was removed at reduced pressure leaving 0.19 g. of pale yellow oil. This oil was dissolved in benzene and chromatographed an Activity I Bio-Rad neutral alumina. Elution with benzene gave 0.065 g. (32%) of a compound which gave crystals, m.p. 250–260° dec., from aqueous methanol.

Anal. Calcd. for $C_{48}H_{80}O_2$: C, 83.65; H, 11.70. Found: C, 83.92; H, 11.98.

Although there was insufficient material for further characterization, this material is undoubtedly a glycol obtained by bimolecular reduction of 12-cholanone.

Elution with additional quantities of benzene gave 0.005 g. (2.5%) of 12 α-cholanol, while the fractions eluted with benzene–10% ether afforded 0.092 g. (46%) of 12 β-cholanol. Recrystallization from aqueous acetone gave the pure alcohol as small cubes, m.p. 92–93°, $[\alpha]^{25}D$ +45 (*c* 0.332, chloroform).

Anal. Calcd. for $C_{24}H_{42}O$: C, 83.17; H, 12.22. Found: C, 83.48; H, 12.14.

(35) C. W. Shoppee, S. K. Roy, and B. S. Goodrich, *J. Chem. Soc.*, 1583 (1961).

(36) Melting points were determined on a Fisher-Johns melting point block and are uncorrected. Infrared spectra were carried out in chloroform solution as liquid films or in potassium bromide pellets on a Perkin-Elmer Model 137 spectrophotometer. Rotational data were obtained using a Rudolph Model 70 polarimeter.

(37) Y. Sato and N. Ikekawa, *J. Org. Chem.*, **24**, 1367 (1959).

When the reaction was carried out as described for the reduction of 12-ketocholanic acid, 0.19 g. of 12-cholanone afforded as the only isolable product 0.135 g. (71%) of 12α-cholanol.

B. Sodium–*n*-propyl alcohol.—To a solution of 0.1 g. of 12-cholanone in 15 ml. of *n*-propyl alcohol was added in portions, 1 g. of sodium, and the mixture was heated at reflux for 30 min. The pale amber solution was poured into water and extracted with two portions of ether. The ethereal extracts were combined, washed with water, and dried; the solvent was removed *in vacuo* leaving 0.09 g. of pale yellow oil. Chromatography as described in part A afforded 0.055 g. (55%) of 12 α-cholanol and 0.032 g. (32%) of the 12β-ol.

C. Sodium Borohydride.—To a solution of 0.3 g. of sodium borohydride in 10 ml. of methanol was added 0.1 g. of 12-cholanone, and the mixture was heated at reflux for 1 hr. After cooling, the colorless solution was poured into water, acidified with 10% hydrochloric acid, and extracted with two portions of ether. After drying and removing the solvent *in vacuo* there was obtained 0.07 g. of yellow oil, which partially crystallized on standing. Chromatography as described above afforded 0.04 g. (40%) of 12α-cholanol and 0.015 g. (15%) of 12β-cholanol.

D. Meerwein–Pondorff–Verley.—To a solution of 0.050 g. of 12-cholanone in 8 ml. of toluene was added 0.07 g. of purified aluminum isopropoxide and the solution was heated at reflux for 105 min. The colorless reaction mixture was poured into 10% hydrochloric acid and extracted with two portions of ether. The ethereal extracts were worked up as described above to give 0.0123 g. (25%) of recovered ketone, 0.0032 g. (6.9%) of 12α-cholanol, and 0.0021 g. (4%) of 12β-cholanol.

When 0.090 g. of 12-cholanone was treated under the same conditions for 88 hr., there was obtained 0.020 g. (22%) of recovered ketone, 0.015 g. (16%) of 12 α-cholanol, and 0.012 g. (13%) of 12-cholanol.

Attempted reductions of 12-cholanone with aluminum isopropoxide in isopropyl alcohol gave recovered ketone in essentially quantitative yield.

12α-Cholanyl Acetate.—A solution of 0.11 g. of 12α-cholanol in 5 ml. of pyridine and 2 ml. of acetic anhydride were heated on the steam bath for 16 hr. The dark brown reaction mixture was poured into water and extracted with three portions of methylene chloride. The extracts were combined, washed with water, dilute hydrochloric acid, and 5% sodium hydroxide. After drying the solvent was removed *in vacuo* leaving 0.11 g. of pale yellow oil. This material could not be induced to crystallize, but showed the expected infrared absorption at 5.78 μ.

12β-Cholanyl Acetate.—A solution of 0.05 g. of 12β-cholanol in 5 ml. of acetic anhydride and 2 ml. of pyridine was treated as described above for 12-cholanol. The acetate again could not be induced to crystallize, but showed the expected infrared absorption.

Attempted Equilibration of the 12-Cholanols.—To a solution of 0.25 g. of 12 α-cholanol in 20 ml. of dry toluene containing 0.025 g. of 12-cholanone was added 1.0 g. of purified aluminum isopropoxide. The reaction mixture was heated at reflux for 240 hr., cooled, poured into water, and worked up as described above to give 0.16 g. (64%) of 12α-cholanol and 0.09 g. of a mixture of 12-cholanone and unchanged 12α-ol (analysis by infrared spectroscopy).

3α,12α-Pregnanediol.—A solution of 10 g. of 3α,12α-diacetoxypregnan-20-one in 150 ml. of diethylene glycol containing 18 ml. of hydrazine hydrate was heated at reflux for 30 min. A solution of 6 g. of sodium dissolved in the minimum amount of diethylene glycol was then added and the mixture was heated at reflux for 6 hr. Water was then added and the amorphous, precipitated solid was collected. The diacetate gave needles from methanol, m.p. 158–159° (lit.[38] m.p. 158–158.5°).

3α-Succinoxypregnan-12α-ol.—A solution of 5.0 g. of the diol and 12.0 g. of succinic anhydride in 60 ml. of pyridine was allowed to stand at room temperature for 12 hr., warmed on the steam bath for 1 hr., then poured into iced dilute sulfuric acid to give the succinate as an amorphous powder. All attempts to recrystallize this material gave oils, and the crude material was oxidized directly to the ketone.

3α-Succinoxypregnan-12-one.—A solution of 2 g. of 3α-succinoxypregnan-12 α-ol was oxidized with Kiliani's reagent in the usual manner (*vide supra*). The product was crystallized from methanol to give white crystals, m.p. 167–168°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.50; H, 9.11.

3α-Hydroxypregnan-12-one.—A solution of 1.78 g. of the succinoxy compound in 80 ml. of 10% methanolic sodium hydroxide was heated at reflux for 3 hr. The product was precipitated by the addition of water, and recrystallization from methanol gave 1.0 g. of hydroxy ketone, m.p. 129–130°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.99; H, 10.65.

Reduction of 3α-Hydroxypregnan-12-one with Lithium–Liquid Ammonia.—A solution of 0.19 g. of hydroxy ketone in 3 ml. of methanol and 6 ml. of anhydrous ether was reduced in the same manner as described for the reduction of 12-ketocholanic acid using 50 ml. of liquid ammonia and 0.5 g. of lithium. The semisolid crude product was treated with acetic anhydride and pyridine in the usual manner, and the crude diacetate was dissolved in benzene and filtered through a column of alumina to give the diacetate as intractable oil. Hydrolysis in 10% methanolic sodium hydroxide afforded 0.16 g. of pure 3α,12β-pregnanediol, m.p. 165–168°, $[\alpha]^{25}D$ + 115° (*c* 1.77, chloroform).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.70; H, 11.32. Found: C, 78.47; H, 11.21.

The infrared spectra of this compound and its diacetate were markedly different from those of the 3α,12α-diol and its diacetate.

3α,12α-Dihydroxy-5β-etianic Acid.—To a stirred solution of 5 g. of 3α,12α-diacetoxy pregnan-20-one in 100 ml. of dioxane was added slowly a chilled solution of sodium hypobromite prepared from 8 g. of bromine in 50 ml. of 12% sodium hydroxide. During the addition, the reaction mixture was held at 5°. The pale yellow solution was stirred at 5–10° for 5 hr.; aqueous formaldehyde was added; the reaction mixture acidified with dilute hydrochloric acid and extracted with two portions of ether. The ethereal extracts were combined and extracted with 10% potassium hydroxide. The potassium hydroxide extracts were reacidified, affording a white solid, m.p. 190–225°. This solid was taken up in 50 ml. of 10% potassium hydroxide, and heated at reflux for 12 hr. Upon cooling the reaction mixture was washed with ether and acidified with dilute hydrochloric acid affording white crystals. Recrystallization from aqueous methanol gave 1.40 g. (35%)[39] of white needles, m.p. 291–293°.[40] This material was converted to 3α-hydroxy-12-keto-5β-etianic acid, m.p. 217–219°, by the method of Schwenk.[41]

Reductions of 3α-Hydroxy-12-keto-5β-etianic Acid. A. Lithium–Liquid Ammonia.—A solution of 0.1 g. of keto acid in 6 ml. of dry ether, 3 ml. of methanol, and 50 ml. of liquid ammonia was reduced following the same procedure as that described for 12-ketocholanic acid. Upon removing the solvent from the crude reaction mixture a crystalline residue was obtained. Recrystallization from aqueous methanol gave 0.025 g. (25%) of 3α,12β-dihydroxy-5β-etianic acid, m.p. 276–277°.[42] Although the melting point of this material was undepressed on mixing with the 12α-hydroxy acid the infrared spectrum was quite different, notably in the 2.5–3.0- and 8.0–10.0-μ regions. Concentration of the mother liquors afforded 0.010 g. of a mixture of the 12α- and 12β-hydroxy compounds, and further concentration of the mother liquors gave 0.015 g. (15%) of the 12α-hydroxy acid.

In another run, 0.1 g. of keto acid was reduced as described above and the total crude product was dissolved in 25 ml. of a 1:1 mixture of ether and tetrahydrofuran, and treated with 20 ml. of ethereal diazomethane (from 0.4 g. of nitrosomethylurea). The reaction mixture was allowed to stand at room temperature for 3 hr., and evaporated to dryness; the oily residue was taken up in ether. After washing with successive portions of water and aqueous 5% sodium bicarbonate, the ethereal solution was dried and the solvent was removed *in vacuo* to give 0.0624 g. of oil, $[\alpha]^{25}D$ +39° (*c* 0.624, chloroform). Since the specific rotations of 3α,12α- and 3α,12β-dihydroxymethyletianates are +80 and +17°, respectively,[7] this corresponds to 35% of the axial alcohol and 65% of the equatorial isomer.

B. Sodium–*n*-Propyl Alcohol.—A solution of 0.1 g. of 3α-hydroxy-12-ketoetianic acid in 15 ml. of *n*-propl alcohol was reduced, using 1 g. of sodium, as described for the reduction of 12-ketocholanic acid. Recrystallization of the crude product from

(38) N. G. Brink, D. M. Clark, and E. S. Wallis, *J. Biol. Chem.*, **162**, 698 (1945).

(39) This reaction was only run once, and no effort was made to improve the over-all yield.

(40) H. L. Mason and W. M. Hoehn [*J. Am. Chem. Soc.*, **60**, 1493 (1938)] gave the melting point of this compound as 283–286°.

(41) E. Schwenk, B. Riegel, R. B. Moffett, and E. Stahl, *ibid.*, **65**, 549 (1943).

(42) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 828 (1938).

aqueous methanol gave 0.030 g. (30%) of 3α,12α-dihydroxy-5β-etianic acid, and 0.035 g. (35%) of the 12β-isomer. There was also obtained 0.005 g. of a mixture of the two compounds.

When the reduction was repeated using 0.1 g. of keto acid, the crude product was methylated to give 0.0543 g. of ester, $[\alpha]^{25}D$ +37° (*c* 0.543, chloroform). This corresponds to 32 and 68% of the 12α- and 12β-hydroxy compounds, respectively.

Rockogenin-3-tetrahydropyranyl Ether. A.—To a solution of 3 g. of sodium borohydride in 30 ml. of methanol was added 1.0 g. of hecogenin-3-tetrahydropyranyl ether and the resulting mixture was heated at reflux for 1 hr. The reaction mixture was cooled, diluted with water, acidified with 5% hydrochloric acid, and extracted with methylene chloride. The organic extract was washed with water and dried; the solvent was removed *in vacuo*, leaving a crystalline residue. Recrystallization from acetone gave 0.71 g. (71%) of white crystals, m.p. 235–236°, $[\alpha]^{25}D$ −39.6° (chloroform).

Anal. Calcd. for $C_{32}H_{52}O_5$: C, 74.37; H, 10.24. Found: C, 74.18; H, 10.32.

B.—A solution of 6.0 g. of the hecogenin derivative in 70 ml. of a 1:1 methanol–ether mixture was added with stirring to 200 ml. of liquid ammonia. Over a period of 1 hr., 6.0 g. of lithium in small pieces was added, and finally 96 g. of ammonium chloride was added slowly. The reaction mixture was allowed to come to room temperature, and then warmed gently until the ammonia had evaporated. The solid residue was taken up in water and chloroform; the organic layer was drawn off, washed with dilute hydrochloric acid and 5% aqueous sodium bicarbonate, and dried; and the solvent was removed at reduced pressure. The solid residue was recrystallized from acetone to give 4.50 g. (75%) of white crystals, m.p. 235–236°, undepressed on mixing with material prepared by method A.

C.—To a solution of 2.1 g. of hecogenin-3-tetrahydropyranyl ether in 200 ml. of *n*-propyl alcohol was added, over a period of 1 hr., 20 g. of sodium, and the solution was heated at reflux for 1 hr. After cooling, the reaction mixture was poured into water and extracted twice with chloroform. The chloroform extracts were washed with water and dried; the solvent was removed *in vacuo* leaving a tan solid. Recrystallization from acetone gave 1.19 g. (57%) of rockogenin-3-tetrahydropyranyl ether, m.p. 235–236°.

Chromic Acid Oxidations.—To 5.00-ml. portions of 1.89×10^{-3} *M* chromic acid in 90.0% acetic acid in a spectrophotometer cell at 25 ± 1° were added 3.00 ml. of $1.5–2.0 \times 10^{-3}$ *M* solutions of the alcohol, and the decrease in intensity of the chromate absorption with respect to time was determined, employing a Beckman Model B spectrophotometer. In each run at least five points were taken, at approximately 2-min. intervals. The rate constants were calculated using the following equation.

$$\frac{-d[Cr(VI)]}{dt} = k[Cr(VI)][ROH]$$

This simplifies to the standard second-order rate expression.

$$k = \frac{2.3}{([Cr]_0 - [ROH]_0)_t} \log \frac{[ROH]_0[Cr]_t}{[Cr]_0[ROH]_t}$$

The results are summarized in Table II.

TABLE II

Compd.	Concn., *M* × 10³	*k* (moles/l./min. × 10⁻⁶)
Cyclohexanol	0.825	0.312 ± 0.045
12β-Cholanol (run 1)	0.609	1.42 ± 0.24
(run 2)	0.609	1.50 ± 0.17
12α-Cholanol (run 1)	0.659	3.06 ± 0.16
(run 2)	0.659	3.39 ± 0.03
Rockogenin-3β-methyl succinate		
(run 1)	0.680	1.31 ± 0.14
(run 2)	0.680	1.42 ± 0.13

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Huang-Minlon Reduction of Acetylenic Keto Acids

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Huang-Minlon reduction of 7-keto-16-heptadecynoic acid as well as 7-keto-15-heptadecynoic acid gave 16-ketoheptadecanoic acid along with heptadecanoic acid. Treatment of 10-undecynoic acid with strong alkali both in the presence and absence of hydrazine hydrate afforded 10-ketoundecanoic acid. These observations would possibly be explained by assuming alkaline hydration of the acetylenic triple bond. A preparation of *cis*-15-heptadecenoic acid was described.

In a previous Note[1] the migration of terminal double bond under the strongly alkaline condition was described. When 7-keto-16-heptadecenoic acid was subjected to the Huang-Minlon reduction, an isomeric mixture of 15-heptadecenoic acids was obtained. Similar result was also reported by Hünig and Eckart,[2] and according to them 16-heptadecenoic acid could be obtained by substituting triethanolamine[3] for diethylene glycol as the solvent.

The present investigation was aimed at elucidating the behavior of ω-acetylenic keto acid in the Huang-Minlon reduction and preparing *cis*-15-heptadecenoic acid.

The reaction of 10-undecynoyl chloride (I) with N-(1-cyclohexenyl)morpholine (II) was effected similarly as described before[1] and 7-keto-16-heptadecynoic acid (III) was obtained in 81% yield. On the analogy of the olefinic compound, the Huang-Minlon reduction of III would result in the formation of 15-heptadecynoic acid (IV), since the migration of the terminal acetylenic triple bond along the carbon chain caused by strong alkali has been recognized by several workers.[4] When III was treated with alkali and hydrazine hydrate in diethylene glycol, two kinds of reaction products (V and VI) were isolated in a ratio of about 1:10. Both were proved to be carboxylic acids, but they had no absorption maxima responsible for the presence of an acetylenic triple bond.

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