protons), etc. The product decomposed on attempted vpc analysis.

Anal. Calcd for $C_{12}H_{16}N_3O_4Cl$: Cl, 10.88. Found: Cl, 11.25.

A mixture of this product (0.3 g) in 20 ml of carbon tetrachloride containing 0.18 g of NBS and 0.2 g of barium carbonate was refluxed for 2 hr. The suspension was filtered, and the filtrate was evaporated to a syrup which exhibited a major spot on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.2). The product (0.3 g) was separated by preparative tlc and the zone corresponding to the major product was isolated and processed to give **methyl 2-azido-4-*O*-benzoyl-3-bromo-6-chloro-2,3,6-trideoxy-α-D-mannopyranoside** (**35**) as a syrup. Catalytic hydrogenation of this product in the presence of palladium on carbon and barium carbonate in methanol afforded a syrup which was dissolved in methanol and treated with acetic anhydride. Evaporation of the solution and purification of the syrupy product by preparative tlc gave **methyl 2-acetamido-4-*O*-benzoyl-6-chloro-2,6-dideoxy-α-D-*arabino*-hexopyranoside** (**36**) (49 mg): ir data, 1718 (ester), 1660 (amide I), 1560 cm^{-1} (amide II); nmr data, τ 5.40 (singlet, C-1 proton), 7.85 (center of a two-proton multiplet, C-3 proton), 7.96 (singlet, N-acetyl protons), etc.

Anal. Calcd for $C_{16}H_{20}ClNO_5$: N, 4.42. Found: N, 4.21.

Methyl 2-Acetamido-3,4-*O*-benzylidene-6-chloro-2,6-dideoxy-α-D-altropyranoside (**34**).—To a solution of **33** (0.4 g) in 50 ml of methanol were added excess Raney nickel (previously washed with methanol by decantation) and 5 ml of acetic anhydride. After stirring overnight at room temperature, the catalyst was filtered, the filtrate was evaporated to dryness, the residue was taken up in ether, and some insoluble matter was removed by filtration. Evaporation of the filtrate gave the crystalline product **34**, contaminated with some inorganic salts which were removed by washing the solid with cold 0.1 *N* acetic acid, followed by water. The insoluble crystalline product was homogeneous by tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.4, medium); yield 0.11 g; mp 209–210°; ir data, 1660 (amide I), 1560 cm^{-1} (amide II). Recrystallization of a portion from a small volume of methanol gave an analytical sample; mp 211–212° dec, $[\alpha]_D$ +95° (*c* 0.26, chloroform). This compound was previously reported[11] to have mp 179°, $[\alpha]_D$ + 72° (chloroform).

Anal. Calcd for $C_{16}H_{20}NO_5Cl$: C, 56.22; H, 5.89; N, 4.09; Cl, 10.37. Found: C, 55.93; H, 5.83; N, 3.81; Cl, 10.28.

Attempted Reaction of 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose with (Chloroethylidene)dimethyliminium Chloride.—A solution of 1 (1.3 g) in 15 ml of 1,1,2,2-tetrachloroethane was added to a cooled suspension of **3** (1 g) in 5 ml of the same solvent. After stirring for 1 hr at room temperature 1 g of **3** was added and the yellow solution was stirred for an additional 24 hr. A 2-ml aliquot was treated with aqueous bicarbonate and the organic layer was processed to give a syrup which exhibited essentially one spot on tlc (hydroxylamine positive) corresponding to the 6-*O*-acetyl derivative **7**: ir data, 1742 cm^{-1} (ester). A small amount of the 6-chloro derivative **8** was also present. The remainder of the reaction mixture was heated under reflux during 3 hr and the dark solution was processed as described for **8**. A syrup was obtained which was identical in all respects with **8** obtained *via* reaction with **2**; yield 0.36 g (25%).

Attempted Reaction of 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose with (Methoxymethylene)dimethyliminium Methylsulfate.—A solution of 1 (1.3 g) in 15 ml of chloroform was added to a solution of **12** (5 g) in 5 ml of chloroform. After stirring at room temperature for 4 hr, a portion was treated with aqueous sodium bicarbonate and the organic layer was processed to a colorless syrup which consisted of a mixture of starting material (preponderant) and the 6-*O*-formate ester **6**, as evidenced by tlc. Refluxing the remaining solution for 4 hr, followed by processing in the usual manner, gave a syrup which also consisted mostly of starting material and a small amount of the ester **6** (tlc, ir data).

Attempted Reaction of Methyl 4,6-*O*-Benzylidene-2-deoxy-2-iodo-α-D-altropyranoside with (Chloromethylene)dimethyliminium Chloride.—To a solution of **2** (0.39 g) in 6 ml of 1,1,2-trichloroethane was added 0.15 g of **37** in portions at 0°. An aliquot was processed after stirring at room temperature for 3 hr. Examination by tlc revealed the presence of the unsaturated derivative **39**, and two slow-moving components, in addition to some starting material, (chloroform–2,2,4-trimethylpentane–methanol 100:30:1). Prolonged reaction periods led to extensive decomposition (tlc) and no definite products could be isolated. The unsaturated derivative **39**, mp 116–118° (lit.[44,45] 119–129°), could be isolated in about 10–15% yield by preparative tlc of the product after a reaction time of 3–4 hr. The ir spectrum and vpc characteristics of **39** were identical with those of an authentic sample.

Treatment of **39** with stoichiometric amounts of **2** even at temperatures as low as −10° led to the formation of several products and eventual decomposition as evidenced by tlc. At −70°, compound **39** remained mostly unchanged during a few hours in the presence of an equimolar amount of **2**.

Registry No.—**8**, 13454-63-2; **14**, 19685-14-4; **19**, 19685-15-5; **20**, 19685-16-6; **21**, 19685-17-7; **24**, 19685-18-8; **26**, 19684-26-5; **29**, 19684-27-6; **30**, 19684-28-7; **33**, 19684-23-2; **34**, 19684-24-3; **36**, 19684-25-4.

Bile Acids. XXVII. Mechanism of Allomerization of Steroids with Raney Nickel[1]

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The transformation of 3-hydroxy 5β-steroids to 5α compounds by heating with Raney nickel in boiling *p*-cymene proceeds by dehydrogenation to the 3-keto 5β derivative and desaturation to the 3-keto Δ^4-steroids. An equilibrium is established between the 3-keto 5β-, 3-keto Δ^4-, and 3-keto 5α-steroid with the latter predominating. The 4α hydrogen of the steroid is transferred to the *p*-cymene. *p*-Cymene can be replaced with similar aromatic or cycloalkyl hydrocarbons.

Previously[2] it was reported that 3-hydroxy steroids and steroidal sapogenins with *cis*-A/B configuration (5β) undergo epimerization at the 5 position to provide 3-keto-*trans*-A/B (5α) compounds on heating under reflux with freshly prepared Raney nickel in a solvent such as *p*-cymene. This procedure has been successfully applied to normal (5β) cholanoates with various substituents for the preparation of allo-(5α) cholanoates like allodeoxycholic acid,[3] allochenodeoxycholic acid,[4] 3β,7α,12α-trihydroxy-5α-cholanoic acid,[5,6] and allo-

(1) (a) This investigation was supported in part by N.I.H. Grant HE-07878 and AM-09992. (b) The following abbreviations have been used: tlc, thin layer chromatography; glpc, gas–liquid partition chromatography; plc, preparative layer chromatography; ORD, optical rotatory dispersion; unless otherwise mentioned, R_t, retention time relative to methyl deoxycholate (methyl 3α,12α-dihydroxy-5β-cholanoate; absolute time, 30 min on QF-1, 36 min on OV-17). R_f and R_t values of different compounds reported in this manuscript have been compared with those of authentic samples and found to be identical.

(2) D. Chakravarti, R. N. Chakravarti, and M. N. Mitra, *Nature*, **193**, 1071 (1962).

(3) H. Danielsson, A. Kallner, and J. Sjövall, *J. Biol. Chem.*, **238**, 3846 (1963).

(4) S. A. Ziller, Jr., M. N. Mitra, and W. H. Elliott, *Chem. Ind.* (London), **24**, 999 (1967).

(5) I. G. Anderson and G. A. D. Haslewood, *Biochem. J.*, **93**, 34 (1964).

(6) M. N. Mitra and W. H. Elliott, *J. Org. Chem.*, **33**, 175 (1968).

cholic acid.[6] Although this method of transformation of 5β-steroids to 5α-steroids had been substantiated by tlc, glpc, ord, mass spectrometry, and chemical degradation in many cases,[3,4,6,7] no work was carried out on the mechanism by which this transformation takes place. In this paper investigations with a mechanistic approach are reported.

When methyl lithocholate (**1**) or methyl 3-dehydrolithocholate (**2**) is heated in boiling *p*-cymene in the presence of freshly prepared W-2 Raney nickel catalyst for 10 hr, analysis of the reaction mixture by glpc showed the presence of about 70% methyl 3-keto-5α-cholanoate (**3**), R_t 0.71; 20% methyl 3-keto-5β-cholanoate (**2**); R_t 0.61; and a third substance as a small peak, R_t 0.93, subsequently identified as methyl 3-keto-Δ^4-cholenoate[8] (**4**) by comparison with an authentic sample obtained by Oppenauer oxidation of methyl 3β-hydroxy-Δ^5-cholenoate. Isolation of **4** from the reaction mixture by plc, preparative layer chromatograpy, permitted characterization by uv, ir, and mass spectrometry.

The mass spectrum of **4** showed the molecular ion, *m/e* 386, as base peak, and the characteristic fragments of methyl esters of bile acids (*m/e* 371, M − 15; *m/e* 355, M − 31; *m/e* 271, M − 115) as well as those fragments derived from 3-keto Δ^4-steroids (*m/e* 344, M − 42; *m/e* 329, M − (42 + 15); *m/e* 301, M − 85; *m/e* 263, M − 123; *m/e* 229, M − (115 + 42); *m/e* 124). Shapiro and Djerassi[9] found similar fragmentation in the mass spectrum of 3-keto-Δ^4-androstene. The mass spectra of **2** and **3** showed the expected fragments *m/e* 373 (M − 15), *m/e* 318 (M − 70) and *m/e* (M − 115). The ratio of the relative intensities of the fragments *m/e* 318 (M − 70) from **2** and **3** was approximately 7:1 in accord with the observations of Budzikiewicz and Djerassi[10] on the more favorable loss of ring A from 3-keto 5β-steroids than the corresponding 5α derivatives.

Similar treatment of methyl deoxycholate (**5**) with Raney nickel in boiling *p*-cymene and analysis of the products by glpc showed the presence of about 20% methyl 3-keto-12α-hydroxy-5β-cholanoate (**6**), 60% methyl 3-keto-12α-hydroxy-5α-cholanoate[7] (**7**), and a small amount of 3-keto-12α-hydroxy-Δ^4-cholenoate (**8**). An attempt was made to prepare the reference compound **8** by the action of 2,3-dichloro-5,6-dicyanobenzoquinone on methyl 3-keto-12α-hydroxy-5β-cholanoate **6**, but the product was found to be a mixture of a small amount of **8** with a number of other compounds of very close polarity in tlc. A similar observation was recently reported by Turner and Ringold.[11] Consequently, **8** was prepared by the procedure of Riegel and McIntosh[12] from **6** by bromination at C_4 followed by dehydrobromination.

Since **8** is a 12-hydroxy derivative of **4**, the mass spectrum should exhibit certain similarities. The M − 15 fragment of **4** is replaced in **8** by the M − 18 fragment (*m/e* 384), and the M − 31 fragment common to both spectra is joined in **8** by an M − 32 fragment (*m/e* 370). Loss of a molecule of water from **8** results in the formation of a sequence of fragments, M − (42 + 18), M − (123 + 18) and M − (115 + 42 + 18), comparable to those fragments of **4**. The base peak of **8**, *m/e* 269, M − (115 + 18), contrasts to the molecular ion of **4**. Fragmentation *via* M − 85 is weak in **4** and insignificant in **8**; the fragment, *m/e* 124, of considerable intensity in **4** is very weak in **8**. The fragments, *m/e* 147 and 145, of **8** probably represent stabilized fragments from *m/e* 261 by loss of the C_{17} side chain and addition or loss of a proton.

Reversible Nature of the Reaction.—With sufficient quantities of **4** and **8** available each of these was refluxed with Raney nickel in boiling *p*-cymene and the products were analyzed by glpc. From **4**, both **2** and **3** were obtained in about 20 and 70% yield, respectively; from **8**, about 20% **6** and 60% **7** were obtained. In a similar experiment with 5α-cholestan-3β-ol (**9**) glpc analysis showed the presence of 74% 5α-cholestan-3-one (**10**), 11% 5β-cholestan-3-one (coprostanone) (**11**), and 15% Δ^4-cholestenone (**12**). Previous experiments[2] with several 3β-hydroxy Δ^5 derivatives showed the presence of 3-keto Δ^4-steroids and 5α-3-ketones but no quantitative experiments were conducted. These data suggest that Raney nickel promotes the formation of an equilibrium mixture of 5α- and 5β-steroids and that the 3-keto Δ^4 derivative is an intermediate in this transformation.

Role of the Solvent.—In order to ascertain whether the solvent, *p*-cymene, plays a significant role in this reaction, glpc–mass spectrometric analysis of the solvent was undertaken after the reaction. Small quantities of the menthanes (*cis* and *trans*), *p*-xylene, ethyl toluene, and toluene were characterized. However, these materials were found in about the same quantities after boiling *p*-cymene and Raney nickel without steroid, suggesting that they represent minor products of action of the catalyst on the solvent. In subsequent experiments substantial quantities of di-*p*-cymene[13] were identified in the hexane eluent from column chromatography of the reaction mixture.

In order to define more clearly the role of the solvent in the reaction, methyl lithocholate (**1**) was treated with Raney nickel in boiling aromatic solvents (xylene, cumene, diisopropylbenzene) or nonaromatic solvents (1,4-dimethylcyclohexane, diisopropylcyclohexane, *n*-butylcyclohexane). The steroid residue obtained after separation of solvent and catalyst was analyzed by glpc on a column of 3% OV-17 on Gas Chrom Q (Table I). These results show that the alkyl cyclohexanes function as well or better than their corresponding aromatic analogs for the preparation of the 5α derivatives and suggest that a higher temperature of the reaction medium favors the formation of the latter. This behavior of the solvent may be due to a tendency of adsorbed hydrogen of Raney nickel to saturate the aromatic ring at the temperature of the reaction medium. This is supported by the observation that aromatic solvents recovered from Raney nickel with or without sterol invariably contain small amounts of the corresponding cyclohexanes as detected by glpc on Bentone 34. When the reaction was carried out in the presence of readily

(7) M. N. Mitra and W. H. Elliott, *J. Org. Chem.*, **33**, 2814 (1968).
(8) M. J. Haddadin and C. H. Issidorides, *ibid.*, **25**, 403 (1960).
(9) R. H. Shapiro and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 2825 (1964).
(10) H. Budzikiewicz and C. Djerassi, *ibid.*, **84**, 1430 (1962).
(11) A. B. Turner and H. J. Ringold, *J. Chem. Soc., C*, 1720 (1967).
(12) B. Riegel and A. V. McIntosh, Jr., *J. Amer. Chem. Soc.*, **66**, 1099 (1944).

(13) H. Pines, B. Kvetinskas, and V. N. Ipatieff [*ibid.*, **77**, 343 (1955)] reported mp 156° for di-*p*-cymene; R. Pappo, B. M. Bloom, and W. S. Johnson [*ibid.*, **78**, 6354 (1956)] reported mp 157–159°. The product obtained in these experiments showed mp 158° after crystallization from acetone; the structure was supported by uv, ir, and mass spectrometry.

TABLE I
REACTION OF METHYL LITHOCHOLATE AND RANEY NICKEL IN DIFFERENT SOLVENTS[a]

Exptl no.	Solvent	Bp, °C	Source[b]	R_t[c]	Methyl 3-keto-cholanoates, 5α	5β	Δ⁴
	Alkyl Benzene						
1	1,4-Dimethyl-	138	B	0.31	34	56	1
2	Isopropyl-	152–153	A	0.46	43	50	4
3	1-Methyl-4-isopropyl-	177	B	1.00	70	20	10
4	1,4-Disopropyl-	210	A	3.23	73	15	12
	Alkyl Cyclohexane						
5	1,4-Dimethyl-	120–124	A	0.07 0.09	65	31	1
6	Isopropyl-	154–155	A	0.27	78	18	4
7	*n*-Butyl-	178–180	A	0.71	74	21	5
8	1,4-Diisopropyl-	201–203	C	2.49	77	16	7
9	Menthone	207	D		2	60	
10	80% *p*-Cymene–20% cyclohexene		B		5	45	

[a] Recovered methyl lithocholate: 1, 10%; 2, 3%; 5, 4%; 9, 38%; 10, 50%. [b] Source: A, Aldrich Chemical Co., Inc., Milwaukee, Wis.; B, Fisher Scientific Co., St. Louis, Mo.; C, Chemical Samples Co., Columbus, Ohio; D, Matheson Coleman and Bell, Norwood, Ohio. [c] R_t = retention time relative to *p*-cymene (absolute time = 20 min) on 5% Bentone 34–5% diisodecylphthalate. S. F. Spencer, *Anal. Chem.*, **35**, 592 (1963).

reducible solvents such as cyclohexene or menthone, very little transformation from 5β- to 5α-steroid occurred as measured by glpc (Table I) in confirmation of the above conclusions.

Role of the Steroid. A. Structure.—The structural requirements of the participating steroid were investigated initially with methyl 5β-cholanoate. After treatment with the reagents in the usual way, no methyl 5α-cholanoate[7] could be detected by glpc. In order to ascertain whether an oxygen function at position 7 instead of 3 could promote the transformation at 5, the following methyl esters were treated individually with Raney nickel in boiling *p*-cymene: 7α-hydroxy-5β- and -5α-cholanoates[6,14] and 7α,12α-dihydroxy-5β- and -5α-cholanoates.[6,15] In each case about 25% of the starting material was dehydrogenated to the corresponding 7-keto derivative, but no transformation at position 5 could be detected on QF-1 by glpc, since the major portion of the steroid was recovered unchanged.[6,7] These observations confirm earlier studies[6,7] in which 7-dehydro derivatives of the 5α and 5β series were identified, and demonstrate the importance of functional oxygen at position 3 for a favorable reaction.

B. Abstraction of Hydrogen.—Studies with **1**, and **5**, methyl cholate,[6] and methyl chenodeoxycholate[7] have shown that the reaction proceeds equally well with the corresponding 3-dehydro derivatives (*e.g.*, **2** or **6**). Thus, Raney nickel dehydrogenates the secondary steroidal alcohol to a ketone similar to that reported by Paul[16] for the preparation of hexanone-3 in 80% yield from hexanol-3.

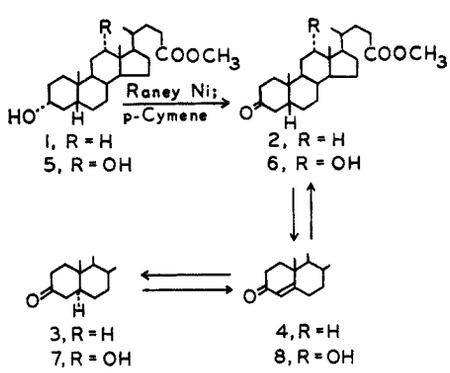
To gain insight into the mechanism of dehydrogenation of the 3-keto steroid this material was labeled at position 4. Methyl 3-keto-4β-bromo-5β-cholanoate was prepared from **2** and debrominated with zinc and tritiated acetic acid according to Corey and Sneen[17] to provide methyl 3-keto-4α-^{3}H-5β-cholanoate (**13**). Treatment of **13** with Raney nickel provided the expected yield of **3**, but the product contained less than 2% of the tritium. After separation of the recovered solvent into menthanes (R_t 0.45 and 0.50) and *p*-cymene (R_t 1.00) by preparative glpc on Bentone 34 and assay for radioactivity in these components, the tritium was found exclusively in *p*-cymene. Upon oxidation[18] of this material to *p*-toluic acid, approximately one-half of the tritium was retained in this moiety. These data suggest that the tritium was lost from the steroid preferentially to the solvent with approximately equal distribution between the toluic acid moiety and the isopropyl group of *p*-cymene.

Time of the Reaction.—Although these studies were carried out in accordance with earlier observations[2] regarding a reaction period of 10 hr, subsequent experiments have been conducted with **1**, **5**, and methyl cholate in *p*-cymene and Raney nickel in which aliquots of the reaction mixture were removed at various intervals and analyzed by glpc. These studies show that the reaction is complete within 1 hr, and that longer periods of heating provide no improvement in yield of the 5α-steroids.

Discussion

On the experimental evidence presented the course of the stereoisomerism of steroids at position 5 in the presence of W-2 Raney nickel[19] at the reflux temperature of various high-boiling solvents is represented in Chart I.

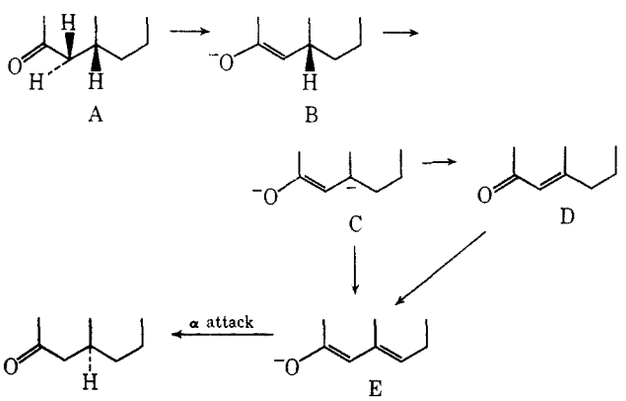
CHART I



Raney nickel enjoys three functions in this sequence: dehydrogenation of the C_3 hydroxyl, and dehydrogenation and rehydrogenation at C_4–C_5. The dehydrogenation at C_3 is not unexpected, since the formation of aldehydes and ketones from primary and secondary alcohols over finely divided metal at high temperature has been reported extensively.[16,20,21] To study the mechanism of the dehydrogenation of **2** to **4**, tritiated **2** was pre-

(14) H. B. Kagan and J. Jacques, *Bull. Soc. Chim. Fr.*, 871 (1960).
(15) A. S. Jones, M. Webb, and F. Smith, *J. Chem. Soc.*, 2164 (1949).
(16) R. Paul, *C. R. Acad. Sci., Paris*, **208**, 1319 (1939).
(17) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956).
(18) W. F. Tuley and C. S. Marvel, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 822.
(19) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 181.
(20) R. P. A. Sneeden and R. B. Turner, *J. Amer. Chem. Soc.*, **77**, 190 (1955), and references cited therein.
(21) E. Lieber and F. L. Morritz, *Advan. Catal.*, **5**, 417 (1953).

pared and formulated as the 4α-tritio derivative in accord with the arguments of Corey and Sneen.[17,22] If dehydrogenation of this 4α-^{3}H-3-keto ester occurred solely *via cis* elimination of the 4β and 5β hydrogen atoms, the steroid should retain the tritium; if a *trans* diaxial elimination occurred, the steroid should be devoid of tritium. Since the steroid did in fact contain very little tritium, *cis* elimination need not be considered. Elimination of the 4α,5β-diaxial protons by direct combination with the catalyst is difficult to visualize. However, if polarization or enolization of 2 occurred in the reaction medium to form the enolate (B), the axial tritium would be removed from the steroid and could appear in the solvent by exchange, in a manner analogous to that reported by Horner and Mayer[23] between deuterium and the hydrogens of alkyl benzenes. The tertiary allylic proton at C_5 of the enol (B) could be abstracted by the catalyst from the β side of



the molecule to form the dianion (C), which then proceeds to the α,β-unsaturated ketone (D). This mechanism is essentially the reverse of that suggested by Barton and Robinson[24] for the reduction of α,β-unsaturated ketones by metals in liquid ammonia, and in effect supports a *trans*-diaxial elimination.[25] Support for the involvement of the 3-oxo group in the above is found in the inability to detect isomerization of methyl 5β-cholanoate under comparable conditions. Additional studies to clarify this subject are now in progress.

The course of hydrogenation of 3-keto Δ^4-steroids has been reviewed by Fieser and Fieser,[26] Shoppee,[27] and McQuillin,[28] and reinvestigated by Augustine[29-31] McQuillin, *et al.*,[32] Nishimura, *et al.*,[33] and Combe, *et al.*[34] Reduction in the presence of palladium under nonequilibrating conditions provides varying amounts of the 5β or 5α isomers, and is dependent on the acidity, alkalinity, or polarity of the solvent. McQuillin, *et al.*,[32] point out that polarization of the 3-keto Δ^4-steroid will assist deformation and permit the absorbed molecule to assume the preferred *trans*-decalin type configuration. Whereas the β face of the α,β-unsaturated ketone is less hindered than the α side, inspection of Dreiding models of the enolate or polarized form reveals axial interaction on the α side of the molecule only at positions 2 and 9, as opposed to hinderance at positions 1, 7, and 10 on the β side. Inhoffen and coworkers[35] showed in 1950 that cholestenone enol ether was reduced on the α side by palladium and hydrogen. 4-Methyl-3-keto Δ^4-steroids provide the more stable 4α-methyl 5α derivatives on catalytic reduction in the presence of palladium.[28,36] Nishimura, *et al.*,[33] have projected structures for enolic derivatives of 3-keto Δ^4-steroids in which fixation of the metallic catalyst at the 5β position enables ring A to assume a conformation almost at right angles to the remainder of the structure and assures β attack; a similar structure with the catalyst affixed on the α side assures a more planar configuration and α attack. Each of these cases is concerned with reduction in a nonequilibrating system. Although the experiments reported here were generally conducted for a period of 10 hr, equilibration is reached within 1 hr. Since conditions for catalytic reduction (*i.e.*, room temperature and generally cessation after uptake of 1 mol of hydrogen) differ appreciably from these experiments, the mechanistic interpretations of the former cases may not apply *in toto* here.

In reduction of substituted naphthalenes[37] under equilibrating conditions several *trans*-decalins were obtained. Siegel[38] earlier interpreted the formation of *trans*-dimethylcyclohexanes as *cis* addition to a newly migrated double bond generated by the "half-hydrogenated" state. Whether the interpretations of Siegel and Weitkamp need to be invoked in this case (*e.g.*, intermediate E above) awaits results of additional experiments. However, these interpretations offer an explanation for the formation of 20–30% **7** or **3** by the action of Raney nickel in boiling *p*-cymene on methyl cholate or methyl chenodeoxycholate,[7] respectively. After the 7α-hydroxy analog of **8** or **4** has been formed, the allylic hydroxyl is eliminated to form the conjugated 3-keto Δ^{4,6} system, which is then reduced to **7** or **3**. Although small quantities of 12-keto derivatives have been noted in these reactions, in no case has a 12-deoxy derivative been detected from **5** or methyl cholate.

The failure of the 7-keto-5β-cholanoates to undergo dehydrogenation at position **5** from the β side may be

(22) It should be noted that the specific activity of the tritiated steroid was lower than that of the tritiated acetic acid by a factor of 11, in support of the assignment of structure. If inversion did not take place in the formation of the tritiated steroid and the product was indeed the 4β derivative, tritium should be eliminated from the steroid whether or not enolization occurred. Further studies on this inversion are in progress.

(23) L. Horner and D. Mayer, *Ann. Chem.*, **680**, 1 (1964), cited from *Chem. Abstr.*, **63**, 9765 (1965).

(24) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(25) Concerning the composition of the catalyst, V. N. Ipatieff and H. Pines [*J. Amer. Chem. Soc.*, **72**, 5320 (1950)] reported an analysis of W-6 catalyst as 21% alumina, 1.4% metallic aluminum, 0.5% sodium aluminate, and 77% nickel. No comparable analysis has been reported for W-2 catalyst. However, the latter is prepared over a longer period of time than the W-6 catalyst, and is washed copiously with water *after* it has been washed to neutrality; the catalyst is finally washed several times with *p*-cymene before use. It should be noted that the allomerization proceeds equally well with catalyst which is 3 months old, but fails with the triacetate of methyl cholate (unpublished observations).

(26) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 272.

(27) C. W. Shoppee, "Chemistry of the Steroids," Butterworth and Co., Ltd., London, 1964, p 50.

(28) F. J. McQuillin in "Elucidation of Structures by Physical and Chemical Methods," A. Weissberger, Ed., Part I, Interscience Publishers, New York, N. Y., 1963, p 498.

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attributed to axial hindrance by the C_{10} methyl group and the C_8 hydrogen. On the other hand, dehydrogenation of the more planar 7-keto 5α-steroid is hindered by axial interaction of hydrogen at C_9, C_1, and C_{14}. Reduction of Δ^5-7-keto steroids is reported to proceed primarily by α attack,[39,40] although both 5β and 5α derivatives are formed.[41] Evidently the catalyst reached the axial 7α-hydroxy group to a limited extent, since about 25% of the 7-keto derivative was formed in each case.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are corrected. Infrared spectra were recorded on a Model 21 Perkin-Elmer double-beam spectrophotometer as Nujol mulls. The ultraviolet absorption spectrum was obtained with a Hitachi Perkin-Elmer uv spectrophotometer, Model 139.

Analytical tlc was carried out on 20 × 20 cm plates coated with 0.25 mm of silica gel G (Brinkmann Instruments Inc., Westbury, N. Y.); the different steroids were located on the plate after development in specified mixtures of acetone and benzene by spraying with 10% phosphomolybdic acid in 95% ethanol. Preparative layer chromatography (plc) was carried out with plates coated with 0.5 mm of silica gel H; the steroids were located on the plate after development by spraying with water.

Gas chromatography of steroids was carried out on an F & M Model 402 gas chromatograph with a U-shaped glass column (6 ft × 0.25 in. o.d.) packed with 3% OV-17 on Gas Chrom Q (Applied Science Laboratories, State College, Pa.) under the following conditions: flash heater, 280°; column, 260°; detector, 280°; helium, 40 psi at a flow rate of 80 cc/min. Quantitation of the steroids by glpc was carried out by multiplying the height of the peak by the width at half-height. Glpc of the hydrocarbons (Table I) was carried out in the same apparatus with a column of 5% Bentone 34–5% diisodecylphthalate on Gas Chrom Q (100–120 mesh) prepared according to Spencer;[42] flash heater, 100°; column, 60°; detector, 75°; helium, 40 psi at a flow rate of 65 cc/min. Glpc analysis of *p*-cymene was carried out on a column of 3% OV-1 on Gas Chrom Q (100–120 mesh); flash heater, 100°; column, 70°; detector, 105°; helium, 40 psi at a flow rate of 25 cc/min.

Mass spectrometry was carried out with an LKB Model 9000 single-focusing gas chromatograph mass spectrometer fitted with molecule separators of the Becker–Ryhage type. For the analysis of *p*-cymene and companions a coiled glass column (8 ft × 0.25 in. o.d.) packed with 3% OV-1 on Gas Chrom Q (100–120 mesh) was used with the following conditions: flash heater, 85°; column, 54°; molecule separator, 104°; ion source, 250°; accelerating voltage, 3.5 kV; ionizing energy 70 eV; trap current, 60 μA. Mass spectra of bile acids were determined with the direct inlet probe.

Radioactivity was measured in a Model 3314 Tricarb liquid scintillation spectrometer. Aqueous scintillator[43] was used as the medium for assay of tritium. The effluent from glpc was passed directly into the aqueous scintillator; the flame jet of the detector was replaced with a heated tube 18 in. × 1/16 in. o.d.

Raney Nickel Catalyst.—W-2 catalyst was prepared from Raney catalyst powder (No. 2813, W. R. Grace and Co., Chattanooga, Tenn.) according to the method of Mozingo.[19]

Action of Raney Nickel on Methyl Lithocholate.—The procedure described here is typical and can be applied to other steroids referred to earlier. *p*-Cymene used in this experiment can be replaced by other solvents described earlier. Methyl lithocholate (1.5 g, mp 128–129°) was mixed with freshly prepared Raney nickel catalyst (*ca.* 3.0 g) and freshly distilled *p*-cymene (15 ml). The Raney nickel was washed with *p*-cymene just before addition to remove adherent liquid. After the mixture was refluxed for 10 hr, the product was filtered and the filtrate was distilled in steam. From the distillate *p*-cymene was separated from water, dried over anhydrous sodium sulfate, and analyzed by glpc. The solid residue (1.39 g) in the distillation flask was taken up in ether and the ether layer dried. After evaporation of the ether, the product was purified by plc with 5% acetone in benzene and crystallized from aqueous methanol. An aliquot of the solid residue (500 mg) by this procedure yielded (i) methyl 3-keto-5α-cholanoate[7] (**3**) [280 mg, mp 113–114°, R_t 0.71, R_f 0.60 (5% acetone in benzene)]; (ii) methyl 3-keto-5β-cholanoate[44] (**2**) (90 mg, mp 119–120°, R_t 0.61, R_f 0.62); and (iii) methyl 3-keto-Δ^4-cholenoate[8] (**4**) [40 mg, mp 125–126°, R_t 0.93, R_f 0.41, uv max (C_2H_5OH) 241.5 mμ (log ε = 4.22), ir 1730, 1666, 1607, 1207, 1184, 1165, 1040, 869 cm^{-1}].

Oppenauer Oxidation of Methyl 3β-Hydroxy-Δ^5-cholenoate.—Methyl 3β-hydroxy-Δ^5-cholenate,[8] mp 143–144° (1.7 g), was oxidized by the Oppenauer method.[45] The crude oxidation product (1.65 g) was purified by chromatography on a column of silica gel followed by crystallization from aqueous methanol. Methyl 3-keto-Δ^4-cholenoate thus obtained had mp 125–126°; R_t 0.93; R_f 0.41 (5% acetone in benzene).

Action of Raney Nickel on Methyl Deoxycholate.—Methyl deoxycholate (1.0 g, mp 82°) on treatment with Raney nickel (*ca.* 2 g) in *p*-cymene (12 ml) in the usual way yielded a product (890 mg) which was purified by plc using 20% acetone in benzene followed by crystallization from acetone–hexane. An aliquot of this product (500 mg) by this procedure yielded (i) methyl 3-keto-12α-hydroxy-5α-cholanoate[7] (**7**) [270 mg, mp 145°, R_t 1.41, R_f 0.49 (20% acetone in benzene)]; (ii) methyl 3-keto-12α-hydroxy-5β-cholanoate[15] (**6**) (84 mg, mp 141–142°, R_t 1.17, R_f 0.40); and (iii) methyl 3-keto-12α-hydroxy-Δ^4-cholenoate[12] (**8**) (18 mg, mp 151–152°, R_t 1.87, R_f 0.33).

Action of 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) on Methyl 3-Keto-12α-hydroxy-5β-cholanoate (6).—A mixture of **6** (600 mg) and DDQ (350 mg) dissolved in 60 ml of dioxane was refluxed for 6 hr.[46] The solution was cooled and the dark brown residue left after evaporation of solvent was treated with benzene. The benzene solution was passed through a column of neutral Woelm alumina deactivated with 12% water. The residue from the benzene eluate (520 mg) containing a number of compounds was separated by plc into four fractions of different polarity. The fraction (107 mg) with a mobility just less than that of **6** was purified by repeated plc followed by crystallization from acetone–hexane to provide shining needles, mp 170–171°. On glpc two distinct peaks appeared, one amounting to about 70% of the mixture corresponded to methyl 3-keto-12α-hydroxy-Δ^4-cholenoate, R_t 1.86.

Methyl 3-Keto-12α-hydroxy-Δ^4-cholenoate. A.—Methyl 3-keto-12α-hydroxy-5β-cholanoate (**6**, 1.79 g) in 20 ml of acetic acid was brominated with a solution of 0.257 ml of bromine in 12 ml of acetic acid according to the procedure of Riegel and McIntosh.[12] Purification of the crude brominated product by plc in 15% acetone in benzene provided a residue, 1.55 g, which, however, failed to crystallize from acetone–hexane or benzene–hexane.

B. The brominated residue (1.55 g) was dried and refluxed in 20 ml of dry pyridine for 4 hr. The solution was poured into dilute hydrochloric acid. The resulting precipitate was extracted with ether–benzene and the extract washed with dilute hydrochloric acid, sodium bicarbonate solution, and finally with water. After evaporation of the solvent, the residue (0.97 g) was purified by plc in 25% acetone in benzene. The major compound thus obtained (470 mg) on crystallization from acetone–hexane yielded stout needles of methyl 3-keto-12α-hydroxy-Δ^4-cholenoate: mp 151–152°; R_t 1.87; R_f 0.33 (20% acetone in benzene); ir 3472, 1721, 1669, 1612, 1453, 1208, 1179, 1160, 1096, 1055, 866 cm^{-1}; uv max (C_2H_5OH) 241 mμ (log ε = 4.2).

Methyl 3-Keto-4β-bromo-5β-cholanoate.—Methyl 3-keto-5β-cholanoate[44] **2**, mp 121–122°; 1.0 g) in 15 ml of acetic acid was mixed with 0.16 ml of bromine in 1.5 ml of acetic acid. The mixture was allowed to stand 4 hr and then poured on ice. The resulting solid was filtered and purified by plc using 3% acetone in benzene and crystallized from acetone–methanol. This afforded methyl 3-keto-4β-bromo-5β-cholanoate[47] (820 mg):

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mp 99–100°; R_f 0.61 (3% acetone in benzene; R_f of methyl 3-keto-5β-cholanoate, 0.37, and methyl lithocholate, 0.16).

Acetic Acid-t[48,49].—Acetic anhydride (3.5 g), water (0.5 g), and tritiated water (0.1 g) with an original activity of 10 mC were mixed together and refluxed for 1 hr. The product was cooled, left overnight at room temperature, and distilled. After rejecting the first fraction, the second fraction was collected as tritiated acetic acid.

Methyl 3-Keto-4α-^{3}H-5β-cholanoate (13).—Methyl 3-keto-4β-bromocholanoate (300 mg) was dissolved in 10 ml of dry ether which was added directly into the reaction flask by distillation from lithium aluminum hydride. Tritiated acetic acid (0.3 ml) and zinc dust (0.6 g), previously dried *in vacuo*, were added to the ether solution which was maintained at 15° and magnetically stirred for 1 hr in an atmosphere of nitrogen. Ether was added and the mixture was filtered. The ethereal filtrate was washed with sodium bicarbonate solution and then with water, and finally dried over anhydrous sodium sulfate. On evaporation of ether a residue of 249.4 mg was obtained which on tlc had the same mobility as methyl 3-keto-5β-cholanoate,[7] R_f 0.62 (5% acetone in benzene). On crystallization of the residue from acetone–hexane short needles of methyl 3-keto-4α-^{3}H-5β-cholanoate,[17] mp 121–122°, were obtained: specific activity, 2.36×10^4, 2.38×10^4 dpm/mg.

Action of Raney Nickel on Methyl 3-Keto-4α-^{3}H-5β-cholanoate.—A mixture of compound **13** (152 mg), Raney nickel catalyst (*ca.* 400 mg), and *p*-cymene (10 ml) was refluxed in the usual way. After separation of the catalyst and the solvent, the product (120 mg) was purified by plc in 3% acetone in benzene. The major compound (96 mg) on crystallization from aqueous methanol yielded shining plates of methyl 3-keto-5α-cholanoate: mp 115–116°; specific activity 4.3×10^2, 4.6×10^2 dpm/mg.

***p*-Toluic Acid-^{3}H.**—*p*-Cymene-^{3}H (specific activity 1.24×10^2 dpm/mg, 5 ml), obtained by steam distillation of the product from the previous reaction, was oxidized by dilute nitric acid by the procedure of Tuley and Marvel.[18] The crude *p*-toluic acid-^{3}H (1.5 g, mp 173–174°) was purified by extraction with toluene in a Soxhlet and chilling the product. *p*-Toluic acid-^{3}H was separated, dissolved in sodium hydroxide solution, precipitated by hot dilute hydrochloric acid, and crystallized from toluene: mp 177–178°; specific activity 0.57×10,[2] 0.59×10^2 dpm/mg after two crystallizations.

Action of Raney Nickel on Cholestanol.—A mixture of cholestanol (510 mg), 20 ml of *p*-cymene, and Raney nickel catalyst (*ca.* 1.2 g) was heated for 10 hr under reflux in the usual way. After separation of the catalyst and the solvent, the product (440 mg) was separated by plc in 5% acetone in benzene into the following compounds: (a) 5α-cholestan-3-one [270 mg, mp 128°, R_f 0.80 (R_f of cholestanol 0.30, methyl 3-keto-5α-cholanoate 0.60), R_t 0.41 (R_t of cholestanol 0.35)]; (b) 5β-cholestan-3-one [32 mg, mp 62°, R_f 0.84, R_t 0.35]; (c) Δ^4-cholestenone [36 mg, mp 82°, R_f 0.56 (R_f of methyl 3-keto-Δ^4-cholenoate 0.41), R_t 0.53]. No cholestanol was detected in the above reaction product.

Registry No.—**2**, 1173-32-6; methyl 3-keto-12α-hydroxy-Δ^4-cholenoate, 19684-72-1; *p*-toluic acid-^{3}H, 19689-62-4; 5β-cholestan-3-one, 601-53-6; Δ^4-cholestenone, 601-57-0.

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Neighboring Group Participation in Reactions of Alcohols with Lead Tetraacetate

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The participation of the neighboring group in two related steroidal α-methoxy alcohols has been studied. 3β-Acetoxy-5α-methoxycholestan-6β-ol, **2a**, and 3β-acetoxy-6β-methoxycholestan-5α-ol, **5a**, were prepared by cleavage of the corresponding 5β,6β- and 5α,6α-epoxides, **1a** and **1b**, in methanol in the presence of acetic acid or boron trifluoride. The course of the lead tetraacetate oxidation of these alcohols was strongly influenced by the adjacent methoxyl group. The structures of the products isolated have been established and mechanisms for their formation are discussed.

Since the discovery, in 1959, that CH_3, CH_2, and CH groups δ, and sometimes ε, to a secondary alcohol group could be oxidized by lead tetraacetate[1] to give rise to cyclic ethers, reactions of this type have been extensively studied.[2] Much of this work has been done with steroids[3] which are convenient models on which to study the geometrical factors involved in this interesting reaction. However, alcohols in diterpene,[4] bridged bicyclic,[5] and aliphatic[6–8] systems have also been shown to form cyclic ethers as well as other products. Conditions for this reaction vary; in the work described here the alcohol was treated with lead tetraacetate and irradiated in refluxing cyclohexane or benzene in the presence of iodine.[9]

Certain correlations have been made[2b] regarding the favorable internuclear distance between the oxyradical and the carbon atom carrying hydrogen atoms which can be abstracted intramolecularly. When a molecule has more than one alkyl group appropriately situated for hydrogen atom abstraction, other factors may influence the preferential abstraction of one hydrogen

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