a rise, virtually all of the acid has passed. Thus it is suggested that cuts be made when each step has remained constant for 4 cc.

With this technique of carrier separation a micro method is available for fatty acid separations and analyses. It appears that if the methyl esters of the acids in question are separable by displacement chromatography, the acids themselves can be measured by using their esters as carriers. This arrangement would appear to be preferable, for interposing small quantities of unsaturated acids in the saturated methyl ester series showed that oleic acid appeared in the methyl myristate zone, and linoleic acid appeared between methyl laurate, and methyl myristate. If a system can be worked out for displacement of both saturated and unsaturated methyl esters, the analysis of naturally occurring mixtures of saturated and unsaturated fatty acids should be possible. This technique of carrier displacement also provides a means of identifying small amounts of fatty acids or other types of compounds.

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The Cleavage of Cholesteryl and 7-Dehydrochloesteryl Ethers[1a]

BY DAVID H. GOULD,[1b] KURT H. SCHAAF AND WILLIAM L. RUIGH[1c]

A study has been made of the cleavage of cholesteryl and 7-dehydrocholesteryl ethers to the free sterols by means of sodium alkyls. In addition to sterols, unsaturated hydrocarbons are formed. Cholesteryl ethers give 3,5-cholestadiene. 7-Dehydrocholesteryl ethers give a new triene whose probable structure has been shown to be 3,5,7-cholestatriene, the configuration assigned by Eckhardt to his compound which, however, is probably the 2,4,6-cholestatriene. A mechanism is proposed for the reaction involving attack on a free β-hydrogen which accounts for the formation of the products of the reaction and the failure of methyl ethers to give the free sterols.

The methyl, ethyl and isopropyl ethers of 7-dehydrocholesterol have been prepared from the corresponding cholesteryl ethers.[2,3] Since on irradiation they gave products which were considerably less active than vitamin D_3, an investigation of their cleavage to the free sterol was undertaken. As 7-dehydrocholesterol is sensitive to strong acids, the method of cleavage was limited to basic reagents.[3] Of these the metal alkyls appeared most promising.

The cleavage of ethers by metal alkyls was first reported by Schorigin.[4] Ziegler[5] and also Gilman[6] have shown that various organoalkali metal compounds react with ethyl ether. Hückel and Bretschneider[7] cleaved alicylic ethers such as *l*-menthyl ethyl ether with ethylsodium, and obtained a 70% yield of *l*-menthol along with a hydrocarbon.

A consideration of the literature[8,9] led us to choose *n*-amylsodium, prepared from *n*-amyl chloride and sodium[10] although a number of other metal alkyls were also investigated. This reagent was successfully used to cleave the model cholesteryl ethers, as well as the 7-dehydrocholesteryl ethers to the free sterols.

To a hexane solution of the cholesteryl ether was added sodium sand and then *n*-amyl chloride. The formation of the reagent took place in the presence of the ether and the products of the reaction were separated chromatographically into a sterol and an ether–hydrocarbon fraction. The sterol fraction was essentially pure cholesterol. The other fraction contained unreacted ether together with a hydrocarbon shown to be 3,5-cholestadiene (XII, $\Delta^{3,5}$). In certain cases these were separated quantitatively by further chromatography; in others the estimation depended on the absorption spectra of the diene. The

TABLE I

CLEAVAGE OF CHOLESTERYL ETHERS WITH *n*-AMYLSODIUM

Ether	Benzene–methanol eluate, %[a]	Sterol, %[b]	Benzene eluate: Unreacted ether, %[c]	Benzene eluate: Diene, %[c]
Methyl	3[d]	Trace	46[e]	51[e]
Ethyl	74.1	100	15	10
Isopropyl	69.2	96.1	21	8
t-Butyl	32.2	99.7	61.3	3
Benzyl	Trace	Nil	51[e]	45[e]

[a] This chromatograph fraction contains crystalline sterol or tails of early fractions. [b] By digitonide determination on (*a*). [c] The 3,5-cholestadiene is usually determined by its absorption spectrum and the ether by difference. [d] This small oily fraction was probably a residue of methyl ether on the column. The methyl ether gives a positive digitonide. [e] Isolated by chromatography. See Experimental.

(1) (a) Presented before the Organic Division of the American Chemical Society at New York City, September, 1947. (b) Schering Corporation, Bloomfield, N. J. (c) Department of Microbiology, Rutgers University.

(2) W. L. Ruigh, D. H. Gould, H. Urist and K. H. Schaaf, to be published.

(3) H. Rosenberg and S. G. Turnbull [U. S. Patent 2,386,636] cleaved the trityl ether of 7-dehydrocholesterol with acetic acid, and also prepared the methyl and ethyl ethers. These ethers were prepared, however, only from 7-keto cholesterol. In general cholesteryl ethers cleaved by mild acids, *e.g.*, trityl, vinyl, etc., cannot be oxidized satisfactorily in the Windaus process.

(4) P. Schorigin, *Ber.*, **43**, 1931 (1910).

(5) K. Ziegler and A. Colonius, *Ann.*, **479**, 135 (1930).

(6) H. Gilman, E. A. Zoellner and W. M. Selby, THIS JOURNAL, **54**, 1957 (1932); A. H. Haubein, *Iowa State Coll. J. Sci.*, **18**, 48 (1943).

(7) W. Hückel and H. Bretschneider, *J. prakt. Chem.*, **151**, 61 (1938).

(8) A. A. Morton, *Chem. Revs.*, **35**, 1–45 (1944).

(9) J. Schmidt, "Organometallverbindungen," Vol. II, Wissenschaftliche Verlagsgesellschaft m. b. H., Stuttgart, 1934, p. 10.

(10) A. A. Morton and G. M. Richardson, THIS JOURNAL, **62**, 123 (1940); H. Gilman and H. A. Pacevitz, *ibid.*, **62**, 1301 (1940).

ether was then calculated by difference. No indications of other products were found in numerous chromatographic separations of the cleavage mixture. The results obtained in the cleavage of cholesteryl ethers are summarized in Table I.

In the cleavage of 7-dehydrocholesteryl ethers, essentially the same procedure was employed although conditions were much more critical and the course of the reaction less predictable. The results are shown in Table II.

TABLE II

CLEAVAGE OF 7-DEHYDROCHOLESTERYL ETHERS WITH *n*-AMYLSODIUM

Ether	Benzene–methanol eluate, %[a]	7-Dehydrocholesterol, %[b]	Sterol, %[c]	Benzene eluate Unreacted ether, %[d]	Triene, %[d]
Ethyl (1)	61.7	31.5[e]	38.8	16.6	11[e]
Ethyl (2)	29.2	20.2	22.6	3	65
Ethyl (3)	25.4	16.7[f]	17.1	56	19
Isopropyl	38.4	11.3	12	39	22.5

[a] This chromatograph fraction contains sterol and decomposition products. [b] Over-all yield by absorption spectrum of (*a*). [c] Over-all yield by digitonide determination on *a*. [d] The triene and ether are determined by absorption spectra. [e] Excess reagent decomposed with alcohol. Some reduction of 7-dehydrocholesterol is apparent, and 10% 4,6-cholestadiene was estimated from its absorption spectrum. [f] Yield equivalent to 38% on recycling unreacted ether.

Free 7-dehydrocholesterol, in contrast to cholesterol, is partially destroyed when treated with the cleavage reagent. In addition, there is formed a digitonin-precipitable sterol, spectroscopically transparent above 2200 Å., which is possibly γ-cholestenol, arising from the sodium and alcohol reduction of 7-dehydrocholesterol[11] when alcohol is added to decompose the excess reagent. Likewise, when the ethers are cleaved, the 7-dehydrocholesterol formed is partially reduced (Table II, Ethyl (1)). When alcohol is replaced by water, however, the digitonide value agrees closely with the yield of 7-dehydrocholesterol determined spectroscopically (Table II, Ethyl (2,3)).

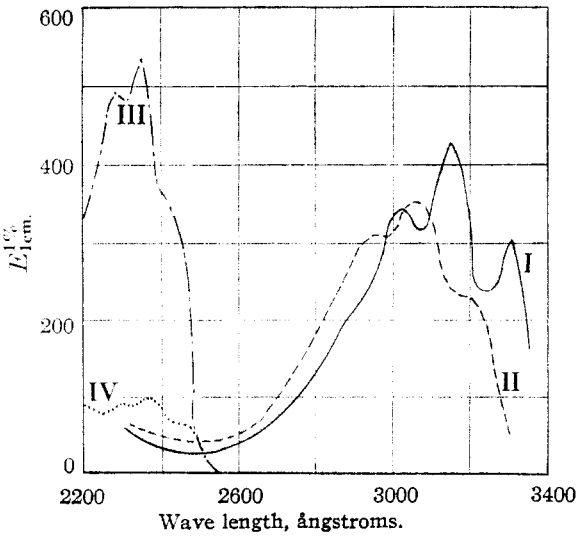


Fig. 1.—Ultraviolet absorption spectra in isopropyl alcohol: I (—), 3,5,7-cholestatriene; II (— — —), 2,4,6-cholestatriene (Eckhardt triene); III (—·—), 3,5-cholestadiene; IV (. . . . .), 4,6-cholestadiene (crude).

Similarly, a diene (probably 4,6-cholestadiene (XIII) according to its absorption spectrum) is obtained by reduction of the by-product, 3,5,7-cholestatriene (XIII, $\Delta^{3,5,7}$), when alcohol is employed to stop the reaction. When water is used, the diene does not occur, and a corresponding increase in the amount of triene is found. Thus when the cleavage is carried out as described in the Experimental section, products are obtained according to Table II, Ethyl (3). If stronger conditions are used, *e.g.*, a large excess of reagent at 25°, there is little unchanged ether found, as in Table II, Ethyl (2).

The triene, m.p. 67–69°, $[\alpha]^{24}D$ −122.4°, E_{3150} 428 (Fig. 1), differs from the product obtained by Eckhardt[12] by the pyrolysis of the phosphate of 7-aminocholesterol to which he assigned the 3,5,7-structure. The Eckhardt triene, m.p. 67–69°, $[\alpha]D$ ± 0°, E_{3020} 320, has also been obtained by the pyrolysis of 7(α)-benzoxyepicholesteryl benzoate,[13] 7(β)-benzoxycholesterol,[14] and by dimethylaniline treatment of 7-benzoxycholesteryl ethers[15] (Fig. 1).

The new triene is formed in the cleavage of the 7-dehydrocholesteryl ether with alkylsodium by the elimination of the alkoxyl group at C-3. The primary product would thus have a 2,3- or 3,4-double bond. It is known, moreover, that basic conditions do not generally cause rearrangement of unactivated double bonds. We expect therefore to find a double bond attached to C-3 in the final product.

The behavior of the triene on reduction definitely proves the presence of a double bond attached to C-8. The first catalytic reduction product is α-cholestene with an inert double bond. The α-cholestene formed is rearranged by treatment with dry hydrogen chloride in chloroform to β-cholestene which is reduced catalytically to cholestane. This behavior is typical only of a double bond attached to C-8.[11,16]

The absorption spectrum demonstrates that the product contains three conjugated double bonds. An inspection of the possible conjugated trienes reveals that only one has both C-3 and C-8 double bonds. This is the 3,5,7-cholestatriene, and we therefore assign this structure to our product.

There is further evidence in support of this formulation. The positive Tortelli–Jaffe test of our product is further indication of the presence of a double bond attached to C-8. The high negative rotation suggests the presence of a C-5,6 double bond,[17] and this contrasts with the properties of the Eckhardt compound. Further substantiation is found in the indication that C-5,6 double bonds are catalytically reduced with

(11) F. Schenck, K. Buchholz and O. Wiese, *Ber.*, **69B**, 2696 (1936).

(12) H. J. Eckhardt, *ibid.*, **71B**, 461 (1938).

(13) A. Windaus and J. Naggatz, *Ann.*, **542**, 204 (1939).

(14) O. Wintersteiner and W. L. Ruigh, THIS JOURNAL, **64**, 2453 (1942).

(15) In the preparation of 7-dehydrocholesteryl ethers[8] we have obtained a triene of the properties given by Eckhardt.

(16) A. Windaus and R. Langer, *Ann.*, **508**, 105 (1933); A. Windaus, O. Linsert and H. J. Eckhardt, *ibid.*, **534**, 22 (1938); W. Bergmann and H. A. Stansbury, Jr., *J. Org. Chem.*, **9**, 281 (1944).

(17) H. E. Stavely and W. Bergmann, *ibid.*, **1**, 575 (1937).

platinum mainly to cholestanes, while coprostanes are formed from C-4,5 double bonds.[17]

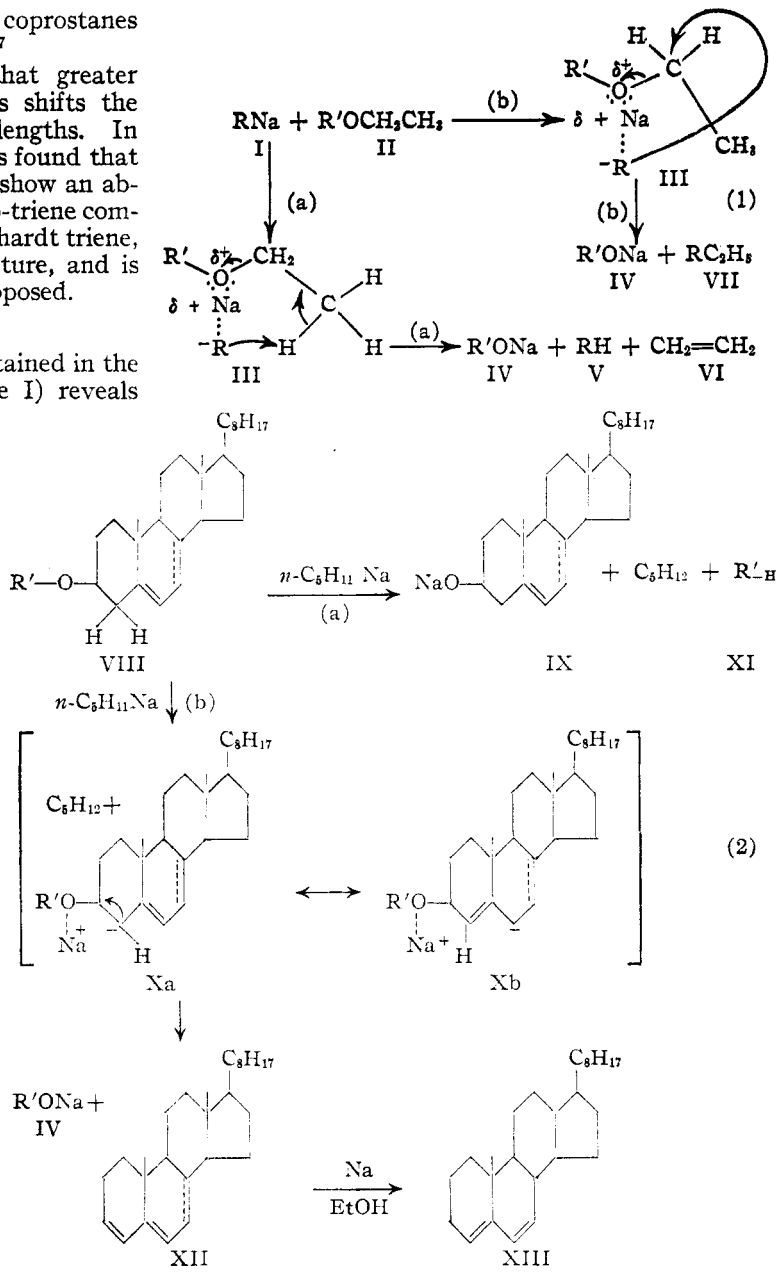
Finally, Woodward[18] has found that greater substitution on unsaturated systems shifts the absorption maxima to longer wave lengths. In accordance with these rules, Ross[19] has found that all derivatives of 3,5,7-cholestatriene show an absorption peak near 3150 Å., while 2,4,6-triene compounds absorb near 3050 Å. The Eckhardt triene, therefore, probably has a 2,4,6-structure, and is not the 3,5,7-compound originally proposed.

Discussion

An examination of the products obtained in the cleavage of cholesteryl ethers (Table I) reveals that the results fall into two groups. With the ethyl, isopropyl and *t*-butyl ethers, which contain a β-hydrogen atom in the alkoxyl group, the main product is cholesterol, along with minor amounts of 3,5-cholestadiene. In contrast, the methyl and benzyl ethers do not give cholesterol, but only 3,5-cholestadiene. In all our chromatographic separations of the reaction products, no trace has been found of compounds other than those mentioned.

On the basis of these results, we suggest that the mechanism of the sterol formation is represented as in equation 1a.[20] The first step is the formation of the coördination complex III.[21] This is accompanied by polarization of the carbon–sodium bond, and thus permits attack by the carbanion on a β-hydrogen. The reaction proceeds to give cholesterol (IV, R′ = $C_{27}H_{45}$), a hydrocarbon (V) and ethylene (VI), through a cyclic electronic shift as illustrated (IIIa).

The cleavage reaction bears a close resemblance to the Wurtz reaction, in which an intermediate alkylsodium attacks an alkyl halide. It might therefore be expected that the cleavage should occur according to 1b to form cholesterol (IV) and the coupling product (VII) through displacement of the $R'O^-$ group by rearward attack on the α-carbon, but this does not happen with the steryl ethers.[22] It has, however, been shown that *two* mechanisms are operative in the Wurtz reaction; in fact, "disproportionation," actually β-attack, may be the major result.[23] Products indicating β-attack have also been found in the cleavage of diisopropyl ether with *n*-amylsodium.[24]



(18) R. B. Woodward, THIS JOURNAL, **64**, 72 (1942).

(19) W. C. J. Ross, *J. Chem. Soc.*, 737 (1946).

(20) The most stable configuration of an ethyl ether has the β-carbon oriented toward the open side of the oxygen as in III [Stuart, "Molekulstruktur," Julius Springer, Berlin 1934]. This places the β-hydrogen in the most favorable position for attack by the carbanion.

(21) The reactions of alkali metal alkyls can best be formulated as ionic when an effective polar group is present in the reactants. Thus in the metalation of benzene derivatives, the directed substitutions can only be due to the ionic character of the reagent, even when the reaction is carried out in non-polar solvents [see J. D. Roberts and D. Y. Curtin, THIS JOURNAL, **68**, 1658 (1946)]. It is also known that benzylsodium conducts an electric current in ether [W. Schlenk and J. Holtz, *Ber.*, **50**, 262 (1917)], presumably by coördination with the solvent. Similar complexes have been postulated in the "alfin" catalysts [A. A. Morton, E. E. Magat and R. L. Letsinger, THIS JOURNAL, **69**, 950 (1947)].

(22) A Wurtz mechanism, involving displacement through attack on the α-carbon, is excluded since (1) none of the coupling products, *e.g.*, 3-alkylcholestenes, is found; and (2) although methyl and benzyl groups in general react readily in displacements, in steryl ethers they are not split off to give cholesterol.

(23) F. C. Whitmore and H. D. Zook, THIS JOURNAL, **64**, 1783 (1942).

(24) In the case of ethers containing no β-hydrogen in either group, *e.g.*, dimethyl ether, cleavage presumably would not occur, or would proceed with difficulty through the α-attack mechanism Ib. Thus it has been found [A. Luttringhaus and v. Saaf, *Z. angew. Chem.*, **51**, 918 (1938)] that phenyl benzyl ether is cleaved with phenyllithium to give phenol and 1,1,2-triphenylethane. This apparently occurs through displacement of the phenoxyl group from the benzyl α-carbon, but is complicated by metallation of the reactants. In addition, Wittig and

Unfortunately, β-attack also occurs in the steryl nucleus at C-4, leading to steroid hydrocarbons (XII) by reaction 2b. With methyl (VIII, R′ = CH_3–) and benzyl (VIII, R′ = $C_6H_5CH_2$–) cholesteryl ethers, 3,5-cholestadiene (XII, $\Delta^{3,5}$) is the only steroid product since there can be no favorable cleavage 2a. The hypothetical C-4 carbanion (X), formed either transitorily or as part of a cyclic electronic shift, is stabilized by resonance with the 5,6-double bond (Xa, b). The alternative 2,5-cholestadiene is presumably not obtained since the C-2 hydrogens are not so activated. Other alkyl cholesteryl ethers are cleaved mainly to give cholesterol (IX), pentane, and an olefin (XI) according to equation 2a. Reaction 2b occurs to a minor extent only, probably due to the ease with which the smaller, sterically unfixed groups may assume the most favorable position for reaction.

The 7-dehydrocholesteryl ethers (VIII, $\Delta^{5,7}$) have the C-4 hydrogen strongly activated due to the increased possibility of resonance (X a, b, etc). As a result the undesired cleavage 2b occurs at least as readily as the cleavage 2a and the triene (XII, $\Delta^{3,5,7}$) is usually the major product. Finally, when alcohol is used to decompose the excess reagent, the triene is reduced to 4,6-cholestadiene (XIII), by the typical 1,6-reduction with sodium.

A further outcome of this work is confirmation of the ether configuration at C-3.[25] Since the cleavage occurs without α-attack (displacement), the configuration at C-3 is not affected; therefore the "Normal" ethers of both cholesterol and 7-dehydrocholesterol are "β" oriented.[26]

Experimental[27]

The Cleavage of Steryl Ethers.—A 500-cc., three-necked, creased round-bottom flask[28] is fitted with a high speed stirrer and gas inlet,[29] a dropping funnel, and a condenser attached to a mercury trap through a calcium chloride tube. Sodium (1.15 g., 0.05 atm.) is covered with 100 cc. of methylcyclohexane, and the apparatus flushed with nitrogen.[30] A slow stream of nitrogen is then continued throughout the reaction. The solvent is boiled, and the mixture stirred rapidly (7000 r.p.m.) to form sodium sand. In a nitrogen atmosphere, the solvent is siphoned off and replaced by 150 cc. of hexane. The steryl ether (0.0024 mole) is added and stirring is started. While the temperature is held at +10°, a solution of 0.6 cc. (0.53 g., 0.005 mole) of *n*-amyl chloride[31] in 60 cc. of hexane is added intermittantly over 4.5 hours and the mixture is stirred for 30 minutes more. The mixture first turns blue-gray and with the 7-dehydrocholesteryl ethers, it then becomes deep red.

Water is carefully added to decompose the excess reagents. The organic layer is washed neutral, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The resin is then chromatographed from benzene on alumina,[32] and eluted with benzene, giving a fraction containing unreacted ether and hydrocarbons. Elution with 10% methanol in benzene gives a fraction containing the desired sterols, reduced sterols and colored decomposition products. The two fractions are treated as described below. Typical results are collected in Tables I and II.

(A) **The Sterol Fraction.**—The sterol fraction usually gave pure sterol on crystallization from alcohol. A digitonide determination on this fraction showed the purity as sterol.[33] Cholesterol, m.p. 145–146°, showed no depression with an authentic sample, m.p. 146–147°. The acetate, m.p. 113–113.5°, showed no depression with cholesteryl acetate, m.p. 114–115°. 7-Dehydrocholesterol, obtained by crystallization or through decomposition of the digitonide, m.p. 147.5–148° in CO_2 (known 148°), was at least 85% pure by its absorption spectrum. The 3,5-dinitrobenzoate, m.p. 208–209° (dec.) in CO_2, was 95% pure by its absorption spectrum, E_{2930} 127. An authentic sample had m.p. 209° (dec.) in CO_2, E_{2930} 135. Reduced sterol and decomposition products were determined by difference.

When the reaction mixtures were irradiated under conditions with which 20–25% conversion to vitamin D occurs,[2] the antirachitic activity was found to correspond to that expected from the estimated amounts of 7-dehydrocholesterol and any unreacted ether.

(B) **The Ether Fraction.**—In the case of the ethers which cleaved to cholesterol, the unreacted ether was easily obtained pure by crystallization from alcohol or acetone and identified by mixed melting point. The unreacted 7-dehydrocholesteryl ethers could usually be isolated by crystallization from acetone, and were estimated in the ether fraction by their absorption spectra.[2]

(a) **3,5-Cholestadiene.**—When large amounts of diene were obtained, as in the cleavage of cholesteryl methyl ether, the ether fraction was chromatographed from hexane on alumina, giving two essentially pure fractions, the second being unchanged ether. One crystallization of the first from acetone–methanol gave 3,5-cholestadiene, needles, melting point 79–80°, E_{2350} 535 (Fig. 1), showing no depression with an authentic sample. The literature gives melting point 80–80.5°, *E* 440.[34] The diene gives a red Rosenheim test with trichloroacetic acid.

(b) **4,6-Cholestadiene.**—This is apparently a reduction product of the triene and was found only when alcohol was used to decompose the excess reagent. Chromatography gave a fraction of melting point 62–63°, estimated as 25% pure, E_{2375} 124 with inflections at 2300 and 2450 Å. (Fig. 1). Reported constants are melting point 90–91°, $\lambda_{max.}$ = 2380 Å.[35] The material gave a negative Tortelli–Jaffe test for C-8 double bonds, and a red Rosenheim test with trichloroacetic acid. The spectrum differed from that of 3-ethoxy-4,6-cholestadiene, prepared for comparison.

(c) **3,5,7-Cholestatriene.**—This product was isolated as the first fraction in chromatographing the 7-dehydro ether fractions from hexane on alumina. Crystallization from acetone gave needles, melting point 67–69° in CO_2, $[\alpha]^{24}D$ −122.4°. The product has three sharp maxima, *E* = 342, 428, 303 at λ=3025, 3150 and 3300 Å., respectively (Fig. 1). The wave length of the highest maximum checks with the value given for 3,5,7,22-ergostatetraene, *E* 495 at 3160 Å.[36] The product gives a red Rosenheim test with trichloroacetic acid, and a positive Tortelli–Jaffe test. Per-

Lohmann [*Ann.*, **550**, 260 (1942)] have found that certain benzyl ethers do not cleave in the usual sense. Treatment of benzyl methyl ether with phenyllithium leads to the rearranged 1-phenylethanol, while dibenzyl ether gives 1,2-diphenylethanol. It is noteworthy, however, that benzyl ethyl ether, in which β-hydrogen is available, cleaves normally to give benzyl alcohol and ethylene.

(25) E. C. Ford and E. S. Wallis, THIS JOURNAL, **59**, 1415 (1937), prepared epicholesterol methyl ether and reviewed the literature on the ether configurations.

(26) This supports the contention that replacements at C-3, *e.g.*, the formation of ethers from tosylates, take place in cholesterol without inversion; *cf.* C. W. Shoppee, *J. Chem. Soc.*, 1147 (1946); S. Winstein and R. Adams, THIS JOURNAL, **70**, 838 (1948); R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948); P. L. Julian, A. Magnani, E. W. Meyer and W. Cole, THIS JOURNAL, **70**, 1834 (1948).

(27) All melting points are corrected. The absorption spectra were taken on a Beckman instrument and extinction coefficients are given as $E^{1\%}_{1\ cm.} = (1/cd) \log I_0/I$. ($c$ = g./100 cc., d = cm.) in isopropyl alcohol. Rotations are taken in chloroform in approximately 1% solution.

(28) A. A. Morton, B. Darling and J. Davidson, *Ind. Eng. Chem., Anal. Ed.*, **14**, 735 (1942).

(29) A. A. Morton, *ibid.*, **11**, 170 (1939); A. A. Morton and D. M. Knott, *ibid.*, **13**, 649 (1941).

(30) Commercial nitrogen is purified by passing through a red hot Vycor tube filled with copper gauze, and through drying tubes of phosphorus pentoxide.

(31) The *n*-amyl chloride must not be admixed with other isomers or the yield of reagent will be low. Under the given conditions a 50% yield of *n*-amylsodium is obtained.

(32) Harshaw Chemical Co. activated alumina brand 2-350, acetic acid washed and dried at 180°C.

(33) The sterol must first be isolated by chromatography since we have found methyl ethers give digitonides.

(34) E. L. Skau and W. Bergmann, *J. Org. Chem.*, **3**, 166 (1938).

(35) J. C. Eck and E. W. Hollingsworth, THIS JOURNAL, **63**, 107 (1941).

(36) K. Dimroth, *Angew. Chem.*, **52**, 545 (1939).

benzoic acid titration showed 2.24 double bonds suggesting a resistant double bond.[37] A sample of 195 mg. (0.000527 mole) of the triene was mixed with 200 mg. of previously reduced platinum oxide in 25 cc. of ethyl acetate. On shaking, the mixture rapidly took up 24.1 cc. (S.T.P.) of hydrogen, corresponding to 2.04 double bonds, showing a hindered double bond. The filtered solution was evaporated to dryness. The oily residue was crystallized from acetone–methanol to give 125 mg. of needles, melting point 51–55°. Perbenzoic acid titration showed 1.1 double bonds. The product gave no Tortelli–Jaffe or Rosenheim tests but gave a red Liebermann–Burchard test and absorbed bromine. α-Cholestene melts at 53–54°.[38] The product, presumably α-cholestene, was isomerized as usual with anhydrous hydrogen chloride in chloroform at 0°. The solution was washed neutral, dried and evaporated to dryness, giving a residue which was chromatographed on alumina from hexane. The product was crystallized from acetone–methanol but was not obtained pure, melting point 43–46°, known for β-cholestene, 73–74°.[38] The crude material was reduced catalytically as before and took up hydrogen corresponding to 1.2 double bonds. The crude residue was treated to remove unsaturated material[39] and the resulting product chromatographed from hexane on alumina. Crystallization from benzene and nitro-ethane gave cholestane, m.p. 76–77.5°, $[\alpha]^{23.5}D$ + 23.2° which showed no depression when mixed with an authentic sample.

Preparation of 3,5-Cholestadiene and Cholestane.—3,5-Cholestadiene was prepared for comparison by the usual method[40] of heating cholesteryl methyl xanthate (m.p. 126–127°) to 200° *in vacuo*. Crystallization from ether and acetone gave needles, melting point 75–77°, with E = 495 at 2350 Å. and secondary peaks at 2275 and 2425 Å.

Cholestane was prepared for comparison by catalytic reduction of 3,5-cholestadiene. The product was chromatographed and crystallized from benzene and nitroethane to give needles, melting point 79–80°, $[\alpha]^{27}D$ + 25.2°. The properties are given as melting point 79–80°, $[\alpha]D$ +24.5°, +24.8°.[41]

The Action of *n*-Amylsodium on Sterols.—Cholesterol is recovered quantitatively when subjected to the cleavage reagent. 7-Dehydrocholesterol, however, gave a reaction mixture only 94% precipitable by digitonin, indicating some decomposition. The use of alcohol to decompose the excess reagent gave only a 72% recovery of 7-dehydrocholesterol as indicated by the absorption spectrum. The remaining 22% sterol is probably a sodium and alcohol reduction product, *e.g.*, 7-cholestenol.

Other Cleavage Reagents and Conditions.—*n*-Butylsodium gives somewhat lower yields (30–50% of cholesterol), as does *n*-hexylsodium. Satisfactory results can be obtained with cholesteryl ethers at room temperature, using more reagent, or with low speed stirring. High speed stirring, however, permits shorter reaction periods, lower temperatures and less reagent, causing less decomposition of 7-dehydrosteroids. Unsatisfactory results are found with ethyl and *t*-butyl chlorides or alkyl bromides. Other reagents giving little or no cleavage are sodium, sodium–potassium alloys, potassium, alkyllithiums (less than 10% sterol) and alkylpotassiums or mixtures (tendency to form unsaturated hydrocarbon). The alkali amalgams are useful in preparing the alkylalkalies, but are not necessary. Temperatures below 0° or above 25° are not advisable. Ether, pyridine and methylcyclohexane were tried as solvents, but the most satisfactory results were only obtained with saturated hydrocarbons (b.p. 100° or less).

Acknowledgment.—Grateful acknowledgment is expressed to Mr. A. E. Briod and Dr. Kenneth Morgareidge for their interest and encouragement during the course of this research. Thanks are due for the able technical assistance of Miss Edith Greenfield and Mrs. Grace Barrett. Absorption spectra were performed by Mr. William McGarry.

(37) The material was extremely sensitive to air oxidation. Storage at −15° in an infrequently opened desiccator filled with CO_2, was not satisfactory. A sample so stored, whose m.p. had lowered to 50–55° was analyzed and as expected had a low carbon value. Found: C, 85.07; H, 11.82. Calcd.: C, 88.44; H, 11.56. There was insufficient material for repurification.

(38) J. C. Eck and E. W. Hollingsworth, THIS JOURNAL, **63**, 2986 (1941).

(39) R. J. Anderson and F. Nabenhauer, *Org. Syntheses*, **17**, 46 (1937).

(40) J. C. Eck, R. L. van Peursem and E. W. Hollingsworth, THIS JOURNAL, **61**, 171 (1939).

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Syntheses with *cis*-Hexahydrophthalic Anhydride

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Condensation between *cis*-hexahydrophthalic anhydride and anisole in the Friedel–Crafts reaction yielded three products, *cis*- and *trans*-2-(*p*-anisoyl)-cyclohexane-1-carboxylic acid and 2,2-bis-(*p*-methoxyphenyl)-hexahydrophthalide. *cis*-Hexahydrophthalic anhydride underwent the Perkin reaction but in low yield. Three phenolic estrogens were converted to the corresponding carbinols by high pressure catalytic hydrogenation.

As part of a synthetic program in search of non-steroidal compounds with hormonal activity, *cis*-hexahydrophthalic anhydride was considered a promising intermediate because of its availability and potential application to the various synthetic methods developed for phthalic anhydride. In the Friedel–Crafts reaction, *cis*-hexahydrophthalic anhydride has been found to react readily with benzene to give 2-benzoylcyclohexane-1-carboxylic acid.[1] The results of further studies are presented in this paper.

Depending upon the conditions selected, the Friedel–Crafts reaction between *cis*-hexahydrophthalic anhydride and anisole could be directed to give any one of three products. Two of these products were *cis*- and *trans*-2-(*p*-anisoyl)-cyclohexane-1-carboxylic acids (I). The low-melting *cis* isomer was obtained when the reaction was conducted in nitrobenzene with equimolar quantities of anhydride and anisole. The *trans* isomer was isolated as an artifact as a result of the lability of the *cis* form in hot aqueous alkali. This isomerization occurred when the alkaline reaction mixture was subjected to steam distillation for removal of nitrobenzene. Assignment of the *cis* configuration to the low-melting acid was based on the following considerations: the anhydride used as starting material is known to have the *cis* configuration; on refluxing with aqueous alkali, the low-melting acid was transformed to the high-melting acid; and, on further treatment with anisole and aluminum chloride, the

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