[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES OF BROWN UNIVERSITY]

Chemical and Kinetic Studies on the Chugaev Reaction[1]

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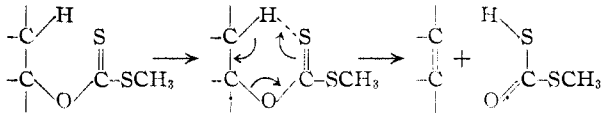
New evidence is presented which confirms the concerted mechanism postulated for the Chugaev reaction. The evidence was obtained by chemical and kinetic studies on the thermal decomposition of several cholestanyl and cholesteryl xanthates and carbonates. These xanthates were found to decompose by a first order process with negative entropies of activation and with energies of activation of 32–33 kcal./mole. Pyrolysis of the carbonates produces olefins in high yields at moderate temperatures.

Introduction

The thermal decomposition of xanthate esters to produce olefins, commonly referred to as the Chugaev reaction, has aroused considerable interest in recent years with regard to the mechanism and synthetic value of the reacton.[2–7] The reaction is particularly useful in the conversion of sensitive alcohols to the corresponding olefins without rearrangement of the carbon skeleton.[8,9]

The mechanisms postulated in the papers given above are for the most part similar in nature but differ in detail. All are based principally on the fact that the Chugaev reaction requires a *cis*-configuration of the eliminated groups. Alexander's picture is cited here as a typical example.



transition state complex

The thermal decomposition of carboxylic esters has been found to have the same stereochemical specificity, and an analogous mechanism has been proposed[10] for their pyrolysis.

Tarbell and Harnish[2] suggested that in the Chugaev reaction the xanthates first rearranged to the dithiolcarbonates, in which the much stronger hydrogen bonding to oxygen would then be available as a driving force for the reaction.

The suggestion has also been made that the xanthates can decompose by a chain process,[2,11] and that the so-called "stable" xanthates,[12] apparently identical with the ordinary xanthates in all respects except thermal stability, are due to removal of the chain initiator in the purification process.

In the case of xanthate and carboxylate esters which have no β-hydrogen atom, the products are suggestive of a free radical process. Bulmer and Mann[11] and Laakso and Nametkin[13] observed in this type of compound that the dithiolcarbonates were more stable to thermal decomposition than were the corresponding xanthates.

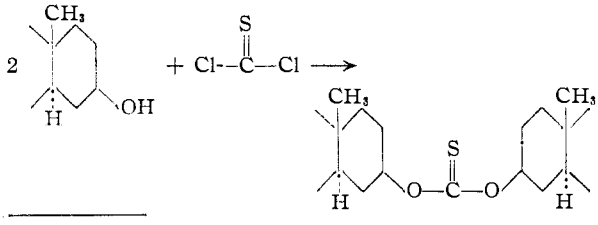
The purpose of this investigation was to obtain additional experimental evidence which might make possible a better understanding of the mechanism of the Chugaev reaction.

Preparation of Starting Materials and Determination of Products

Xanthates derived from sterols were used in the studies since they possessed the following advantages (1) the use of crystalline xanthates, thus avoiding the possibility of "stable" compounds[12] sometimes encountered in the purification of liquid xanthates; (2) ready isolation of crystalline products; and (3) ease of determination of products due to their optical activity.

β-Cholestanyl-S-methyl and S-benzyl xanthates were obtained in 65 and 87% yields, respectively, by treating the sodium salt of β-cholestanol (prepared with sodium hydride)[14] with carbon disulfide, followed by methyl iodide or benzyl chloride. Cholesteryl-S-methyl xanthate was prepared in 85% yield in the same manner. Attempts to prepare α-cholestanyl-S-methyl xanthate under the above conditions produced only the β-xanthate, apparently due to epimerization[15,16] of α-cholestanol. If air was carefully excluded no reaction was observed, and α-cholestanol was recovered unchanged.

Attempts were then made to prepare the xanthate esters by the use of thiophosgene to convert the stanol to the stanyl chlorothioncarbonate, followed by treatment with a mercaptan. The only product which could be isolated, however, even in the presence of a large excess of thiophosgene, was the distanylthioncarbonate.



(1) This paper is based on a portion of the thesis to be submitted by George L. O'Connor in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Brown University.

(2) D. S. Tarbell and D. P. Harnish, *Chem. Revs.*, **49**, 60 (1951).

(3) E. R. Alexander and A. Mudrak, THIS JOURNAL, **73**, 59 (1951); **72**, 3194 (1950); **72**, 1810 (1950).

(4) D. J. Cram, *ibid.*, **71**, 3883 (1949).

(5) D. H. Barton, *J. Chem. Soc.*, 2174 (1949).

(6) W. Hückel, W. Tappe and G. Legutke, *Ann.*, **543**, 191 (1940).

(7) P. G. Stevens and J. H. Richmond, THIS JOURNAL, **63**, 3132 (1941).

(8) W. Fomin and N. Sochanski, *Ber.*, **46**, 246 (1913).

(9) P. G. Stevens, THIS JOURNAL, **54**, 3732 (1932).

(10) (a) C. D. Hurd and F. H. Blunck, *ibid.*, **60**, 2419 (1938). (b) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 2459 (1949).

(11) G. Bulmer and F. G. Mann, *ibid.*, 666 (1945).

(12) I. M. McAlpine, *ibid.*, 1114 (1931).

(13) (a) P. V. Laakso, *Suomen Kemistilehti*, **16B**, 19 (1943) (*C. A.*, **40**, 4687 (1946)); (b) S. S. Nametkin and D. Kursanov, *J. prakt. Chem.*, **112**, 164 (1926).

(14) The addition of a drop of ethanol was necessary to initiate the reaction of the hydride with the stanol.

(15) W. von E. Doering and T. Aschner, THIS JOURNAL, **71**, 838 (1949).

(16) H. R. Nace and G. L. O'Connor, *ibid.*, **73**, 5824 (1951).

α- and β-cholestanyl ethyl carbonate and cholesteryl ethyl carbonate were prepared from the sterol and ethyl chlorocarbonate in yields of 92, 96 and 98%, respectively. These compounds were prepared to study the possible effect on the pyrolysis of stronger hydrogen bonding to oxygen as compared to sulfur.

The pyrolysis of β-cholestanyl-S-methyl xanthate and of α- and β-cholestanyl ethyl carbonate yielded in each case an approximately 1:1 mixture of Δ^2- and Δ^3-cholestene. The olefin mixtures were analyzed by conversion to the dibromides, and measurement of the optical rotation of the dibromide mixtures. The 3,4-dibromide has a rotation of +6° and the 2,3-dibromide of +76°,[17] thus making them more suitable for analysis than the two olefins, whose rotations differ by only 12°. This olefin mixture is consistent with the predictions based on Barton's[17,18] concept of polar and equatorial bonds. Models show that for both the 3-α- and 3-β-xanthates and carbonates, the *cis*-hydrogens at the 2- and 4-positions are equivalent, and should lead to equal amounts of Δ^2- and Δ^3-cholestene.

It is interesting to note in this connection that the decomposition rates of α- and β-cholestanyl ethyl carbonates are practically the same. After 4 hours at 260° the α-compound was 86%, and the β-compound was 82% decomposed. In the α-compound the C–O bond is polar and the 2- and 4-*cis*-hydrogens are equatorial, while in the β-compound the situation is reversed. Therefore, it seems improbable that the rate determining step of the pyrolysis is the rupture of either the C–O or the C–H bond, since this should lead to different rates for the two isomers.[17,18]

The ethyl carbonates proved to be more stable than the xanthates, requiring a temperature of 300° for complete pyrolysis in 2.5 hours compared to 220° for complete decomposition of the xanthates in the same time. These results are summarized in Table III.

The pyrolysis of cholesteryl-S-methyl xanthate has been shown to give $\Delta^{3,5}$-cholestadiene.[19] The same product was obtained from cholesteryl ethyl carbonate, but a higher temperature and longer time was required for complete decomposition. No product other than $\Delta^{3,5}$-cholestadiene, such as the $\Delta^{2,5}$-cholestadiene, was detected in the product and its absence was presumably due, in part at least, to the lower energy realized in the conjugated 3,5-diene. Inspection of models shows no important differences in the configuration of the 2- and 4-*cis*-hydrogens.

The carbonate esters possess certain advantages over the corresponding xanthates, acetates and benzoates from the synthetic standpoint. They are readily prepared in high yield (90–98%) and offer no opportunity for epimerization of the sterol, as encountered in α-cholestanol. Pyrolysis gives excellent yields (90–95%) of pure olefins, at a lower temperature than is required for acetates or benzoates. The xanthates require lower temperatures than the carbonates but the olefins are frequently contaminated with sulfur compounds.[19]

The infrared absorption spectra of $\Delta^{3,5}$-cholestadiene, cholesteryl-S-methyl xanthate, and a sample of the xanthate decomposed 30% by heating at 176°, were examined in the 2.0–9.0 μ region. The only bands observed were those due to C—H (3.51 μ) and C=C (6.56 μ). No bands were observed which could be assigned to the C=O group, as might be expected from rearrangement of the xanthate to the dithiolcarbonate[20] as suggested by Tarbell and Harnish.[2]

An interesting photochemical decomposition of cholesteryl-S-methyl xanthate was observed during the course of this investigation. When a sample of this compound was irradiated with an intense ultraviolet light source for several hours at room temperature, the odor of mercaptan was evident, and the originally colorless sample turned brown. The infrared spectrum in the 2.0–9.0 μ region of this partially decomposed sample showed absorption only in the C—H and C=C regions.

Kinetic Investigation

Although it has been postulated[2] that the Chugaev reaction is unimolecular, no kinetic evidence on this score could be found. Accordingly, the decomposition of several sterol xanthates was studied, and the rates determined. All were found to give first order kinetics over the entire course of the reaction.

The rate constants were determined by following the loss in weight of a tared sample of xanthate due to the formation of volatile reaction products. The addition to the xanthate of glass wool, Δ^2- and Δ^3-cholestene, or radical chain inhibitors such as hydroquinone, diphenylamine or picric acid, had no measurable effect on the rate or the order of the reaction. These results are consistent with a unimolecular first order reaction, but are inconsistent with a chain process.

First-order rate constants were determined for β-cholestanyl-S-methyl and S-benzyl xanthate; the S-benzyl compound proved to be nearly twice as reactive as the S-methyl. Both β-cholestanyl and cholesteryl-S-methyl xanthate were studied at several temperatures and the energies and entropies of activation calculated. The experimental results are summarized in Figs. 1 and 2 in which the logarithm of per cent. unreacted xanthate is plotted against the time in minutes. The first-order rate constants (k) were determined graphically by the equation $k = -2.303 \times$ slope, where the slope is that of the plot of log concentration *vs.* time for a given compound and temperature. The first-order rate constants determined in this manner are given in Table I.

The frequency factor (s) and experimental activation energy (E_{exp}) were calculated from the Arrhenius theory $k = se^{-E_{exp}/RT}$ with the aid of Fig. 3 in which the log of k is plotted against $1/T$.

(17) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

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

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

(20) The possibility that the xanthate rearranges in a slow step to the dithiolcarbonate, which then decomposes in a fast step, seems unlikely in view of the greater stability of the dithiolcarbonates[11] and of the ethyl carbonates.

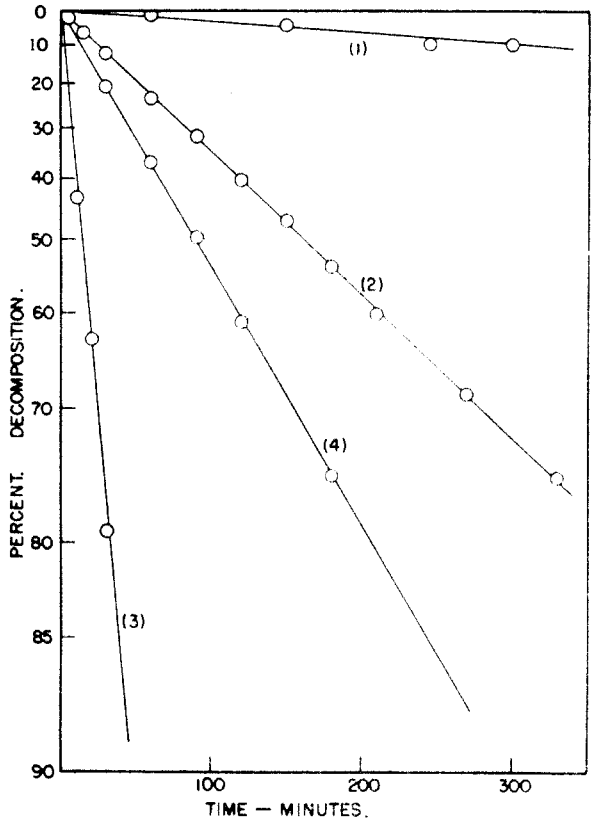


Fig. 1.—Typical first-order plots for the thermal decomposition of β-cholestanyl xanthates: (1), (2) and (3) are β-cholestanyl-S-methyl xanthate at 146, 176 and 206°, respectively, (4) is β-cholestanyl-S-benzyl xanthate at 176°.

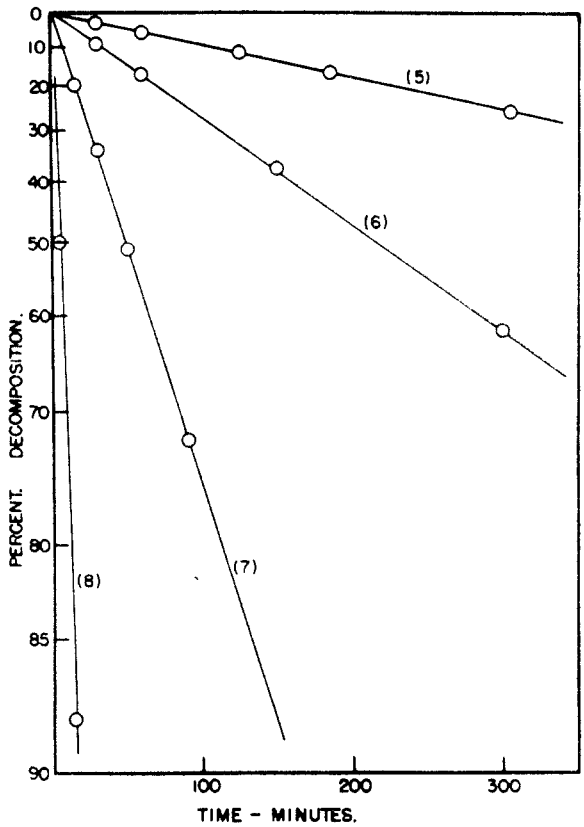


Fig. 2.—Typical first-order plots for the thermal decomposition of cholesteryl-S-methyl xanthate: (5), (6), (7) and (8) are at 146°, 161°, 176° and 206°, respectively.

TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE THERMAL DECOMPOSITION OF β-CHOLESTANYL AND CHOLESTERYL XANTHATES AND ETHYL CARBONATES AT VARIOUS TEMPERATURES

Expt. no.	Compound	Temp., °C.	$k \times 10^4$ min.$^{-1}$
1	β-Cholestanyl methyl xanthate	146	4
2	β-Cholestanyl methyl xanthate	176	44.4[a]
3	β-Cholestanyl methyl xanthate	206	497
4	β-Cholestanyl benzyl xanthate	176	78
5	Cholesteryl methyl xanthate	146	9.9
6	Cholesteryl methyl xanthate	161	32
7	Cholesteryl methyl xanthate	176	143[b]
8	Cholesteryl methyl xanthate	206	1420
9	β-Cholestanyl ethyl carbonate	176	0.0
10	α-Cholestanyl ethyl carbonate	176	0.0
11	Cholesteryl ethyl carbonate	176	0.0
12	Cholesteryl ethyl carbonate	206	<2

[a] The same value was obtained when the tube was packed with glass wool, 10% picric acid, diphenylamine, hydroquinone or 50% Δ^2- and Δ^3-cholestene. [b] Unpublished experiments in this Laboratory indicate that treatment of a benzene solution of menthyl-S-methyl xanthate with aqueous ferrous sulfate yields the "stable" xanthate observed by McAlpine.[12] Similar treatment of cholesteryl methyl xanthate gave $k = 140 \times 10^{-4}$ at 176°.

The E_{exp} were obtained by use of the equation $E_{exp} = -2.303\ R \times$ slope and are listed in Table II with the frequency factors (s) (in sec.$^{-1}$), which were calculated from the Arrhenius equation.

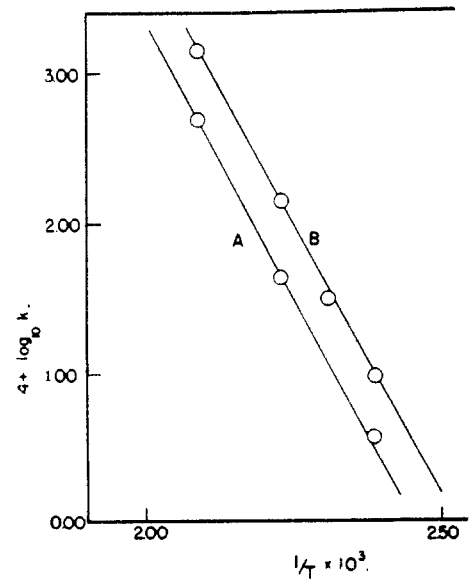


Fig. 3.—Activation energy plots for the decomposition of (A) β-cholestanyl-S-methyl xanthate and (B) cholesteryl-S-methyl xanthate.

The following equation is supplied by the theory of absolute reaction rates[21]

$$k = Ke^{\frac{k'T}{h}} e^{S^*/R} e^{-\frac{E_{exp}}{RT}}$$

(21) S. Glasstone, K. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 295.

By combining this equation with the Arrhenius equation and solving for S^* we obtain

$$S^* = 2.303\ R \log s - 2.303\ R \log \left(\frac{k'T}{Ke\ h}\right)$$

TABLE II

ENERGY AND ENTROPY OF ACTIVATION OF THE THERMAL DECOMPOSITON OF β-CHOLESTANYL- AND CHOLESTERYL-S-METHYL XANTHATES

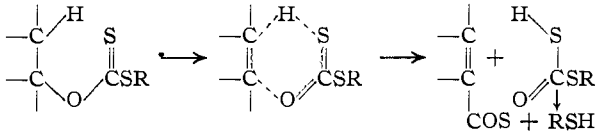
Compound	E_{exp}, cal.	$s \times 10^{-12a}$ sec.$^{-1}$	S^* e.u.[a]
β-Cholestanyl methyl xanthate	33,800	2.0	−5.0
Cholesteryl methyl xanthate	32,900	2.4	−4.7

[a] Calculated from the data obtained at 176°.

In this manner, entropies of activation of −5.0 and −4.7 e.u., respectively, for β-cholestanyl- and cholesteryl-S-methyl xanthate were obtained, calculated at 176°. The negative entropies of activation, obtained in the thermal decomposition of xanthate esters, indicate that several degrees of freedom are restricted in the transition state.

Stevens and Richmond,[7] Barton,[5] Cram[4] and Alexander[3] have all pictured the Chugaev reaction as a cyclic process involving a six-membered ring. The results reported here supply additional confirmation for a concerted cyclic process.[3-5] The negative entropies of activation indicate that this transition state is highly ordered.

Resonance stabilization could be important in the transition state, since there are six π electrons available for distribution around the six-membered ring, as indicated by the dotted lines.



xanthate ester cyclic transition state products

The result is a hybrid of starting material and products, and the transition state can then decompose by a further shifting of atomic nuclei, accompanied by a redistribution of the non-localized electrons to give the products and the process is now energetically downhill. This redistribution of electrons need not occur by the shifting of electron pairs as is so often represented in concerted reactions of this type, but could occur equally well by the shifting of individual electrons (a cyclic free radical reaction). There is, however, no experimental evidence which indicates how the redistribution of electrons takes place.

In the cholesteryl compounds the 5–6 double bond could be in conjugation with such a system and hence the formation of the cyclic transition state would be expected to be favored in this case. The faster rates and lower activation energy for cholesteryl methyl xanthate as compared with the β-cholestanyl compound are in accord with this picture.

Acknowledgment.—The authors thank Professor Donald F. Hornig for valuable suggestions and criticisms.

Experimental[22]

β-Cholestanyl-S-methyl Xanthate.[23]—A mixture of 1.0 g. (2.6 millimoles) of β-cholestanol in 50 ml. of dry benzene and 500 mg. of sodium hydride was magnetically stirred 24 hours at the reflux temperature. If no hydrogen evolution took place, a trace of ethanol was added to start the reaction. The reaction mixture was allowed to cool to room temperature, 4 ml. of dry carbon disulfide added, and the resulting red mixture stirred under reflux 24 hours. The mixture was cooled to room temperature, 4 ml. of methyl iodide was added, and stirring under reflux continued for 24 hours. Water was then added dropwise to decompose excess sodium hydride, the organic layer was washed with water, dried over anhydrous sodium sulfate, and the solvent evaporated on a steam-bath to give a red oil. The oil was taken up in 10 ml. of petroleum ether (b.p. 30–60°) and chromatographed on 10 g. of aluminum oxide (Merck and Co., Inc., suitable for chromatographic adsorption) in a column 1 × 12 cm. The xanthate was easily eluted with 50 ml. of petroleum ether as a yellow oil which crystallized when solvent-free. Recrystallization from 2:1 acetone–alcohol gave 950 mg. of β-cholestanyl-S-methyl xanthate, m.p. 86–87°, $[\alpha]_D$ +5°. One additional recrystallization from 1:1 alcohol–acetone gave 800 mg. (65%) of xanthate with constant m.p. 87.5–88° and constant rotation $[\alpha]_D$ +2°.

Anal. Calcd. for $C_{29}H_{50}OS_2$: C, 72.74; H, 10.57. Found: C, 72.72; H, 10.42.

Cholesteryl-S-methyl Xanthate.—This xanthate was prepared from cholesterol by the above procedure in 85% yield with constant m.p. 127.5–128° (reported[24,25] 127°) and rotation $[\alpha]_D$ −53°.

β-Cholestanyl-S-benzyl Xanthate.—This compound was prepared from β-cholestanol and benzyl chloride by the above method in 87% yield with constant m.p. 102–102.5° and rotation $[\alpha]_D$ +9°.

Anal. Calcd. for $C_{35}H_{54}OS_2$: C, 75.75; H, 9.80. Found: C, 75.91; H, 9.88.

Attempted Preparation of α-Cholestanyl-S-methyl Xanthate.—The substitution of α-cholestanol in the above method yielded a product, m.p. 87–88°; $[\alpha]_D$ +2°, which gave no depression of melting point on mixing with a sample of β-cholestanyl-S-methyl xanthate. When the reaction was carried out in an atmosphere of dry oxygen-free nitrogen, the only product isolated by chromatography was α-cholestanol (85% recovery), m.p. 183–184°.

Attempted Preparation of β-Cholestanyl-S-ethyl Xanthate by the Use of Thiophosgene.—A mixture of 2.0 g. (5.2 millimoles) of β-cholestanol and 4 ml. of thiophosgene[26] was heated under reflux for 5 hours and then the excess thiophosgene was removed on a steam-bath under reduced pressure. The residue was taken up in 20 ml. of benzene, added dropwise to a mixture of 5 ml. of ethyl mercaptan, 500 mg. of sodium hydride and 20 ml. of benzene, and the resulting mixture heated under reflux for 5 hours. The excess sodium hydride was decomposed by the dropwise addition of water, the organic layer was washed with water, and then dried over anhydrous sodium sulfate. The solvent was removed and the residue in petroleum ether was chromatographed on 15 g. of aluminum oxide to yield two main fractions. Petroleum ether readily eluted a red oil which crystallized and on recrystallization from ethanol gave 320 mg. (15%) of di-β-cholestanyl thioncarbonate, m.p. 87–88° $[\alpha]_D$ +29°.

Anal. Calcd. for $C_{55}H_{94}O_2S$: C, 80.60; H, 11.56. Found: C, 79.74; H, 11.80.

Further elution with benzene gave, after recrystallization from ethanol, 1.24 g. of β-cholestanol, m.p. 141–142°.

(22) Melting points are corrected. Rotations were determined on approximately 1% chloroform solutions at room temperature. Microanalyses by S. M. Nagy and associates at Massachusetts Institute of Technology.

(23) (a) The melts of the cholesteryl and cholestanyl xanthates, carbonates and acetates exhibit a curious behavior while cooling, becoming violet, proceeding through the spectrum to red, and finally becoming colorless in the crystal. A similar observation has been made on cholesteryl benzoate[b]; (b) C. Doree and J. A. Gardner, *Proc. Roy. Soc.*, (*London*), **B80**, 227 (1908).

(24) L. Tschugaeff and A. Gasteff, *Ber.*, **42**, 4631 (1909).

(25) A. C. Bose and W. Doran, *J. Chem. Soc.*, 2244 (1929).

(26) The thiophosgene was obtained from Rapter Laboratories, Argo, Illinois.

TABLE III

THE PYROLYSIS OF CHOLESTANOL XANTHATES AND CARBONATES

The procedures used in experiments 1–4 were essentially the same. The compound was heated at the given temperature in a potassium nitrate–sodium nitrite-bath for the required time under reduced pressure (20 mm.), and then the reaction product was chromatographed over alumina.

Compound	Wt., mg.	Time, hours	Temp., °C.	Yield of Δ^2- and Δ^3-cholestene,[a] %	[α]D of Δ^2- and Δ^3-cholestene[b]	Yield of Δ^2- and Δ^3-cholestene dibromides,[c] %	[α]D of dibromides[d]	Δ^2-Cholestene, %
β-Cholestanyl methyl xanthate	214	2.5	230	94	+62°	92	+42°	51
β-Cholestanyl benzyl xanthate	250	2.5	230	92	+60	98	+46	57
α-Cholestanyl ethyl carbonate	220	4	260	90[e]	+62	97	+40	48
β-Cholestanyl ethyl carbonate	146	4	260	94[f]	+62	95	+43	53
β-Cholestanol with H_3PO_4	1000	6	200	94[g]	+53	95	+45	56

[a] and [b] refer to the olefin as obtained by chromatography without further purification (the Δ^2- and Δ^3-cholestene were easily eluted with petroleum ether). In duplicate runs olefin was crystallized once from 1:1 alcohol–acetone; m.p., 68–69°, [α]D +64° in all runs. Further crystallizations did not affect the m.p. or [α]D. [c] and [d] refer to dibromide prepared by addition of an excess of bromine to a chloroform solution of the olefin which was allowed to stand overnight and purified by chromatography, the Δ^2- and Δ^3-cholestene dibromides being easily eluted with pet. ether. The m.p. of the dibromides after crystallization from 1:1 alcohol–acetone were 123–124° in all cases. The [α]D of crystallized samples was +48–50°. The rotation of the purified dibromides could not be used as a means of determining the per cent. of Δ^2- and Δ^3- present since the Δ^2-cholestene dibromide is more insoluble than the Δ^3-cholestene dibromide, which remains in the mother liquor, and hence the rotation of the material as it came from the column was used. [e] 30 mg. of undecomposed α-cholestanyl ethyl carbonate was recovered by chromatography. The yield is based on the carbonate decomposed, 86.4%. [f] 26 mg. of undecomposed β-cholestanyl ethyl carbonate was recovered by chromatography. The yield is based on carbonate decomposed, 82.2%. [g] In expt. 5 the β-cholestanol was heated under reflux with 20 ml. of 85% phosphoric acid, allowed to cool and 50 ml. of water added. The mixture was extracted with 3 × 25-ml. portions of benzene and dried over sodium sulfate, the solvent removed and the residue chromatographed yielding olefin and 160 mg. of unreacted β-cholestanol. Yield based on β-cholestanol decomposed. This procedure is based on suggestions of Dr. E. Schwenk, private communication.

Dicholesteryl Thioncarbonate.—A solution of 1.0 g. (2.6 millimoles) of cholesterol in 30 ml. of carbon tetrachloride and 4 ml. of thiophosgene was refluxed 12 hours and the solvent and excess thiophosgene removed by evaporation on a steam-bath. The dark residue was taken up in 25 ml. of petroleum ether and filtered through a column of 10 g. of alumina and then the column was washed with 50 ml. of petroleum ether. The filtrate was collected and evaporated to give a red oil which was extracted with 50 ml. of boiling alcohol. The volume of the alcoholic extract was concentrated to 20 ml., filtered and allowed to cool, allowing the crude dicholesteryl thioncarbonate to crystallize. Three crystallizations from alcohol gave 370 mg. (17.5%) dicholesteryl thioncarbonate, m.p. 90.5–91°, [α]D −33°.

Anal. Calcd. for $C_{55}H_{92}O_2S$: C, 80.80; H, 11.34. Found: C, 80.04; H, 11.25.

Di-β-cholestanyl Thioncarbonate.—This compound was prepared by the above method from β-cholestanol in 16% yield, m.p. 88–89°, [α]D +32°.

β-Cholestanyl Ethyl Carbonate.—To 1.0 g. (2.6 millimoles) of β-cholestanol dissolved in 10 ml. of dry pyridine and cooled in an ice-bath, 4 ml. of ethyl chlorocarbonate was added dropwise and the resulting mixture was allowed to stand at room temperature for 20 hours. The reaction mixture was then poured into a cold solution of 20 ml. of acetic acid in 50 ml. of water. The crude ester soon crystallized, and after washing with water was recrystallized from 30 ml. of alcohol to give 1.15 g. (96.5%) of white needles, m.p. 105–105.5°, [α]D +9°. Recrystallization from ethanol gave β-cholestanyl ethyl carbonate, constant m.p. 105.5–106°, and rotation [α]D +10°.

Anal. Calcd. for $C_{30}H_{52}O_3$: C, 78.20; H, 11.38. Found: C, 78.32; H, 11.37.

α-Cholestanyl Ethyl Carbonate.—This compound was prepared from α-cholestanol as described above. In order to obtain high yields the reaction mixture was allowed to stand 48 hours at room temperature. A 92% yield of the carbonate was obtained with constant m.p. 102–102.5°, and rotation [α]D +15°.

Anal. Calcd. for $C_{30}H_{52}O_3$: C, 78.20; H, 11.38. Found: C, 78.25; H, 11.47.

Cholesteryl Ethyl Carbonate.—This compound was prepared as above from cholesterol in 98% yield, m.p. 83.5–84° (reported 83°[27]).

Pyrolysis of Cholesteryl-S-methyl Xanthate.—One gram of the xanthate was heated for 3 hours at 220° and 20 mm. The residue was taken up in petroleum ether, chromatographed over 10 g. of aluminum oxide and 720 mg. (93%) of $\Delta^{3,5}$-cholestadiene, [α]D −103°, obtained by elution with petroleum ether. Several recrystallizations from 1:1 acetone–alcohol gave 624 mg. (81%) of $\Delta^{3,5}$-cholestadiene, m.p. 79–80°, [α]D −122° (reported[19]: m.p. 79.5–80°, [α]D −123°).

Pyrolysis of Cholesteryl Ethyl Carbonate.—Two grams of the carbonate was heated for four hours at 280° and 20 mm. The colorless oil, which crystallized on cooling, was chromatographed as above to yield, after recrystallization from 1:1 acetone–alcohol, 1.52 g. (94%) of $\Delta^{3,5}$-cholestadiene, m.p. 79.5–80°, [α]D −123°.

Kinetic Investigation

Apparatus.—The constant temperature bath used was constructed from a 2500-ml. beaker in a 3000-ml. beaker, with the air space between packed with woolly asbestos. The unit was then placed in an earthenware crock having a diameter 4 inches larger than the outside beaker. The air space between was packed with glass wool, the bath was filled with heavy paraffin oil, and heated by means of a 25 × 200 mm. glass tube clamped vertically in the bath and wound with nichrome wire. The current to the heating coil was regulated by means of a Powerstat. The bath was equipped with a stirrer and a 76 mm. partial immersion A.S.T.M. 360° thermometer. Once thermal equilibrium was obtained, the temperature could be maintained to ±0.2° for any given temperature in the range 50–230°.

Method.—The compounds studied were prepared as described above and when several rate studies were made on the same compound at various temperatures, samples from the same batch of material were used to eliminate any differences between batches. The method used consisted in weighing out a sample of approximately 300 mg. in a tared 18 × 150 mm. Pyrex test-tube, the mouth of which was then loosely covered with aluminum foil to prevent entrance of foreign material. The sample tube was then clamped in the bath at the desired temperature, which remained unchanged. The temperature of the sample reached −0.5° of the bath temperature in 30 seconds. The time the sample was in the bath was recorded by a stopwatch and used without any correction for the "heat-up period" or the "cool-off period." At the end of a given time the sample tube was removed from the bath and the reaction was quenched by cooling the sample tube in cold benzene. The benzene served the dual purpose of cooling the sample and removing the bath oil from the outside of the tube. The outside of the tube was then thoroughly washed with ether and dried.

(27) V. Schadendorff and A. Verdino, *Monatsh.*, **65**, 338 (1935).

The tube was then weighed and the loss in weight of the sample recorded. The sample tube was then replaced in the bath and the process repeated until the desired amount of data had been obtained. The loss in weight for complete reaction corresponded to about 70 mg. for these compounds with the size sample used. The high boiling point of the compounds studied as well as of the olefins produced ensured that the loss in weight was due only to the gaseous reaction products and hence the loss in weight can be correlated to the extent of reaction.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RESEARCH DIVISION, SHARP AND DOHME, INC.]

β-Phenylserine

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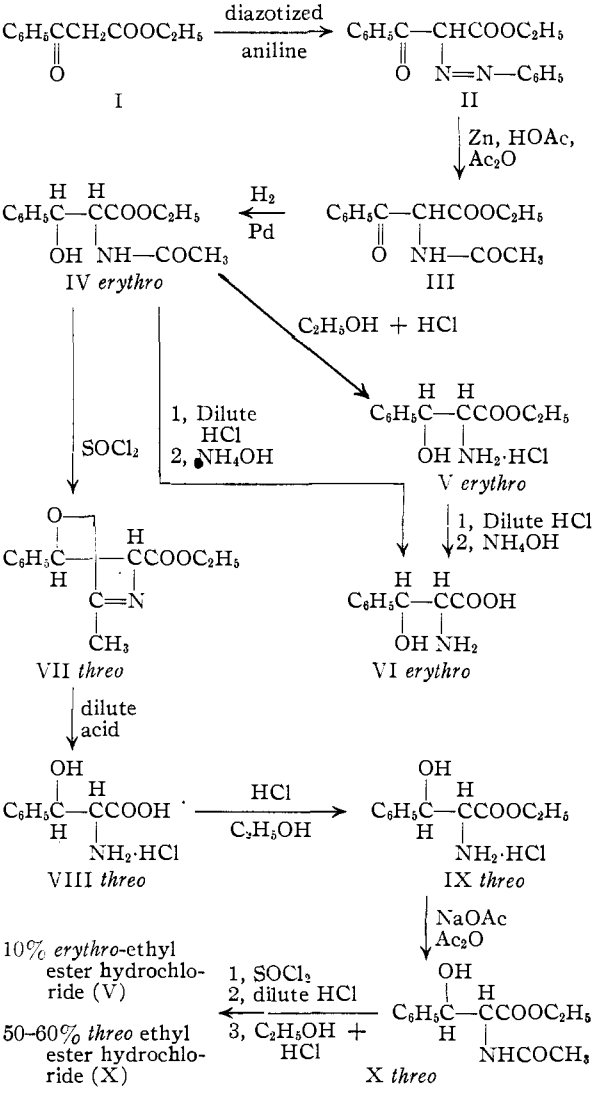
erythro-β-Phenylserine (VI) was prepared from ethyl benzoylacetate. The configuration of an intermediate, *erythro*-N-acetyl-β-phenylserine ethyl ester (IV), could be inverted by oxazoline formation with thionyl chloride. Hydrolysis of the oxazoline yielded *threo*-β-phenylserine hydrochloride (VIII). The configuration of *threo*-N-acetyl-β-phenylserine ethyl ester (X) was for the most part unchanged on treatment with thionyl chloride. No crystalline oxazoline was obtained from X.

The two diasteroisomers of β-phenylserine were required in connection with a biological investigation and a study of their preparation was undertaken. When the synthetic work was initiated, none of the published syntheses of β-phenylserine appeared promising as methods of preparing both diastereoisomeric forms. However, the synthesis of threonine and allothreonine from ethyl acetoacetate[1] provided an example of a successful preparation of both isomers of a β-substituted serine. Therefore, a new synthesis was devised in which *threo*- and *erythro*-β-phenylserine were synthesized from ethyl benzoylacetate. Hayes and Gever[2] attempted to use this method for the preparation of β-(2-furyl)-serine from ethyl 2-furoylacetate but were unable to separate one of the intermediates from the acetanilide that was formed as a by-product.

In this Laboratory, ethyl α-phenylazobenzoylacetate (II) was obtained by treating ethyl benzoylacetate (I) with benzenediazonium chloride by the method of Bulow and Neber.[3] Reductive acetylation of the phenylazo compound (II) yielded ethyl α-acetamidobenzoylacetate (III) with acetanilide as a by-product.

The removal of this by-product by ordinary recrystallization procedures was extremely difficult but repeated water extraction of a benzene solution of the mixture readily eliminated all the acetanilide. Reduction of the ketone (III) was carried out by a catalytic hydrogenation. Palladium catalyst (5% on charcoal) was used and the reduction ceased completely when one mole of hydrogen had been absorbed. The product (IV) had a sharp melting point and appeared to consist of a single diastereoisomer.

Treatment of the N-acetyl-β-phenylserine ethyl ester (IV) with hydrogen chloride in absolute ethanol yielded *erythro*-β-phenylserine ethyl ester hydrochloride (V). *erythro*-β-Phenylserine (VI) could be prepared indirectly by acid hydrolysis of the ester hydrochloride (V) and directly by acid hydrolysis of the *erythro*-N-acetyl-β-phenylserine ethyl ester



(IV). The yields were higher by the latter route, but intermediate isolation of the ester hydrochloride, possessing a characteristic melting point, gave an added check on the stereochemical purity of the final product.

(1) K. Pfister, C. A. Robinson, A. C. Shabica and M. Tishler, THIS JOURNAL, **71**, 1101 (1949).

(2) K. Hayes and G. Gever, *J. Org. Chem.*, **16**, 269 (1951).

(3) C. Bulow and P. Neber, *Ber.*, **45**, 3732 (1912).