elution with petroleum ether–ether (39:1) afforded first the crude high melting epimer (XIVb), then a mixture, and finally the crude low melting epimer (XIVa). These fractions amounted to 1.80 g. (84%) of crystalline material, but because of the difficult separation there was obtained after recrystallization 585 mg. (27.5%) of XIVa, m.p. 116–120°, and 299 mg. (10.8%) of XIVb, m.p. 140–146°. In an earlier run the yields were 21.0 and 8.7%, respectively, so that the ratio was fairly constant.

The more abundant epimer (XIVa) was recrystallized from methanol for analysis, m.p. 120–121°; $[\alpha]^{28}D$ −67.0 ± 2° (*c* 1.0, chloroform); $\lambda_{max}$ 5.83–5.95, 6.10 μ.

*Anal.* Calcd. for $C_{27}H_{34}O_3$: C, 79.76; H, 8.43. Found: C, 79.57; H, 8.21.

The other epimer (XIVb) was recrystallized from methanol and from ether–petroleum ether, m.p. 146–148°; $[\alpha]^{28}D$ −60.0 ± 2° (*c* 1.0, chloroform); $\lambda_{max}$ 5.88, 6.10 μ.

*Anal.* Found: C, 79.94; H, 8.45.

**Hydroxylation of XIVa.**—To 200 mg. of epimer XIVa in 2 ml. of dry ether was added 138 mg. of osmium tetroxide. The mixture was kept at room temperature for 30 minutes during which time a dark brown granular deposit of osmate ester formed. This was dissolved by adding 9 ml. of ethanol and swirling; then a solution of 0.4 g. of sodium sulfite in 6 ml. of water was added and the mixture was shaken for 20 minutes. After filtering from the dark osmium compounds the colorless filtrate was concentrated *in vacuo* to a small volume, more water was added and it was extracted thrice with ether. Drying and concentration of the ether gave 211 mg. of colorless oil which could not be induced to crystallize. Chromatography on acid-washed alumina gave a small amount of starting material in the petroleum ether–ether (9:1) eluates and the (−)-2ξ,4b-dimethyl-2-(2-methyl-2,3-dihydroxypropyl)-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-7β-ol-1-one 7-benzoate in the petroleum ether–ether (2:8) eluates. The crude glycol amounted to 94 mg. and after recrystallization from ether–petroleum ether there was obtained 72 mg., m.p. 135–145°.

**Hydroxylation of XIVb.**—Two hundred milligrams of XIVb was dissolved in 4 ml. of ether and 138 mg. of osmium tetroxide added. After standing at room temperature for 80 minutes the resultant osmate ester was hydrolyzed and the isolation carried out essentially as described for epimer XIVa, yielding 161 mg. of oily crystalline residue. Chromatography on acid-washed alumina yielded 71 mg. of crystalline material in the petroleum ether–ether (9:1) eluates, then a mixture, and finally 38 mg. of crystalline material in the petroleum ether–ether (7:3 and 6:4) eluates. Recrystallization of the early fractions from methanol and ether yielded one isomer of (−)-2ξ,4b-dimethyl-2-(2-methyl-2,3-dihydroxypropyl)-1,2,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-7β-ol-1-one 7-benzoate, m.p. 220–221.5°; $[\alpha]^{27.5}D$ −48 ± 4° (*c* 0.5, chloroform); $\lambda_{max}$ 5.83 μ.

*Anal.* Calcd. for $C_{27}H_{32}O_4$: C, 77.11; H, 7.67. Found: C, 77.17; H, 7.81.

The later fractions were recrystallized from ether and methanol to give another isomer of the dilactol structure, m.p. 203–204°. (A mixed m.p. with the isomer above was 183–215°; $[\alpha]^{27.5}D$ −12 ± 4° (*c* 0.5, chloroform); $\lambda_{max}$ 5.84 μ). The infrared spectra of the isomers in chloroform were quite similar but had some notable differences in the 8 to 15 μ region.

Found: C, 76.18, 76.41, 77.24, 76.96; H, 7.67, 7.45, 8.55, 8.81.

RAHWAY, NEW JERSEY

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[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES, BROWN UNIVERSITY]

# Further Studies on the Chugaev Reaction and Related Reactions

BY GEORGE L. O'CONNOR[1] AND HAROLD R. NACE

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The pyrolysis of a series of cholesteryl xanthates has been studied. For the series, the first order rate constants have been determined, and from them, the Hammett parameter, ρ. In addition the pyrolyses of several closely related compounds, cholesteryl acetate, methyl trithiocarbonate, ethyl carbonate, phenyl carbamate and benzoate, have been studied. All showed first order rate constants, and the acetate and carbonate pyrolyses had negative entropies of activation and activation energies of 44.1 and 41.0 kcal./mole, respectively. On the basis of these studies it appears that all of these compounds decompose by way of a cyclic six-membered ring transition state similar to the one proposed for the Chugaev reaction. A correlation between the structure of these compounds and their thermal stability appears possible.

## Introduction

In a previous study[2] of the pyrolysis of several steroid xanthates it was observed that β-cholestanyl-S-benzyl xanthate decomposed almost twice as fast as the S-methyl xanthate.

Earlier, McAlpine[3] observed that the menthyl-S-isopropyl and S-*p*-nitrobenzyl xanthates pyrolyzed more readily than the S-methyl compound.

On the basis of these observations a comprehensive study has been made of the effect of substitution on the stability of xanthates, and also of a number of analogous esters, with two purposes in mind. In the first place, less stable esters would allow lower pyrolysis temperatures, thus increasing the synthetic utility of the reaction, and, secondly, it was hoped that the study would shed more light on the mechanism of these decompositions.

Alexander[4] observed that in the pyrolysis of carboxylic esters the *cis*-β-hydrogen atom was preferentially eliminated. Hurd,[5] Barton,[6] and Alexander[4] have proposed that these esters decompose by a homogeneous unimolecular reaction involving a cyclic transition state of the type proposed for the Chugaev reaction. Fugassi, *et al.*,[7] investigated the kinetics of the decomposition of *t*-butyl acetate and propionate and obtained first order rates. The reactions appeared to be unimolecular processes with activation energies of 40.5 and 39.2 kcal./mole, respectively, thus supplying additional evidence for a cyclic transition state.

The close analogy between the pyrolysis of xanthate, carbonate and carboxylate esters is further supported by the results reported here based on a kinetic investigation of cholesteryl acetate, chloroacetate, ethyl carbonate, methyl trithiocarbonate, benzoate and phenyl carbamate.

(1) Jesse Metcalf Fellow, Brown University, 1951–1952.

(2) G. L. O'Connor and H. R. Nace, THIS JOURNAL, **74**, 5454 (1952).

(3) I. M. McAlpine, *J. Chem. Soc.*, 1114 (1931).

(4) E. R. Alexander and A. Mudrak, THIS JOURNAL, **73**, 59 (1951); **72**, 3194 (1950); **72**, 1819 (1950).

(5) C. D. Hurd and F. H. Blunck, *ibid.*, **60**, 2419 (1938).

(6) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 2459 (1949).

(7) C. E. Rudy and P. Fugassi, *J. Phys. Colloid Chem.*, **52**, 357 (1948); E. Warrick and P. Fugassi, *ibid.*, **52**, 1314 (1948).

### Preparation of Starting Materials and Determination of Products

The cholesteryl xanthates studied included the methyl, ethyl, benzyl, *p*-nitro-, *p*-chloro- and *p*-methoxybenzyl compounds, 2,4-dinitrophenyl, diphenylmethyl and triphenylmethyl. The cholesteryl xanthates were prepared by the action of carbon disulfide on the sodium salt of cholesterol (prepared with sodium hydride) followed by treatment with the appropriate alkyl halide. The yields were all good (70–90%) with the notable exception of the isobutyl compound. Attempts to prepare cholesteryl-S-isobutyl xanthate were unsuccessful even with much longer reaction times, cholesterol being recovered unchanged. The explanation for the unreactivity of isobutyl iodide likely lies in the fact that the back-side of the carbon atom carrying the iodine is hindered, preventing the attack of the bulky sodium cholesteryl xanthate.

Cholesteryl methyl trithiocarbonate was prepared in an analogous manner from the sodium salt of thiocholesterol, carbon disulfide, and methyl iodide. The configuration at carbon 3 in the cholesteryl xanthates is $\beta$ and the configuration of the trithiocarbonate is also very likely $\beta$. Thiocholesterol was prepared in 90% yield by a modification of Wagner-Jauregg's method[8] from cholesteryl thiocyanate by reduction with lithium aluminum hydride. Cholesteryl thiocyanate was obtained in 75% yield by reaction of $\beta$-cholesteryl chloride with alcoholic sodium thiocyanate. The cholesteryl thiocyanate (and hence the thiocholesterol) is assumed to have the $\beta$-configuration since nucleophilic replacement of groups at the 3-position of cholesteryl derivatives invariably leads to either the 3 $\beta$- or *i*-cholesteryl compounds[9] and lithium aluminum hydride reduction would not be expected to involve a change of configuration. The *i*-compounds are eliminated here since both the thiocyanate and thio compound react readily with dilute bromine solution indicating unsaturation. It is interesting that the thiocholesterol does not form an insoluble digitonide which is characteristic of the 3$\beta$-hydroxyl and 3$\beta$-amino compounds.[10]

The pyrolysis of the cholesteryl xanthates and methyl trithiocarbonate gave good yields (70–90%) of $\Delta^{3,5}$-cholestadiene. The lowest yields of $\Delta^{3,5}$-cholestadiene were obtained with the cho'esteryl diphenylmethyl and triphenylmethyl xanthates and part of the reaction product was found to contain sulfur. The high boiling point of diphenylmethyl and triphenylmethyl mercaptan prevented their removal and it seems likely that at the temperature of pyrolysis these could add to $\Delta^{3,5}$-cholestadiene since mercaptans are known to add to olefins under similar conditions.[11] These adducts, however, were not characterized. Although the formation of these addition compounds does not affect the results of the kinetic study, it does make the pyrolysis of these xanthates undesirable as a synthetic method for the preparation of olefins.

The pyrolyses of several sterol ethyl carbonates were studied previously[2] and gave excellent yields of olefins. Cholesteryl acetate and chloroacetate, prepared by the action of chloroacetyl chloride on cholesterol, also gave $\Delta^{3,5}$-cholestadiene in 60–75% yield. Cholesteryl phenyl carbamate was prepared from cholesterol and phenyl isocyanate, and on pyrolysis also gave $\Delta^{3,5}$-cholestadiene.

### Results of Kinetic Investigation

The kinetic studies reported here were carried out essentially as described previously[2] by following the weight loss of a tared sample due to loss of volatile reaction products. The rates of pyrolysis of the various cholesteryl xanthates and cholesteryl methyl trithiocarbonate were all determined at 176° and gave first order kinetics over the entire course of the reaction. With the methyl, ethyl and benzyl xanthates the weight loss corresponded to carbon oxysulfide and the mercaptan, while carbon disulfide and methyl mercaptan were lost in the case of the trithiocarbonate. In the remaining cholesteryl xanthates the high boiling point of the mercaptans prevented their removal and only carbon oxysulfide was lost. In each case the olefin remained.

Essentially the same procedure was used in determining the rates of pyrolysis of cholesteryl acetate, chloroacetate, ethyl carbonate and phenyl carbamate, although certain modifications were necessary in the study of cholesteryl acetate due to the relatively high temperature required for reaction (300°). The thermal decomposition of cholesteryl acetate, chloroacetate, phenyl carbamate and ethyl carbonate all gave first order kinetics. Cholesteryl acetate was studied in the

TABLE I

FIRST ORDER RATE CONSTANTS FOR THE THERMAL DECOMPOSITION OF VARIOUS CHOLESTERYL XANTHATES AT 176°

| Curve | Cholesteryl xanthate | $k \times 10^4$ min.$^{-1}$ |
|---|---|---|
| 1 | (Methyl trithiocarbonate) | 13 |
| 2 | Benzyl | 214 |
| 3 | *p*-Chlorobenzyl | 295 |
| 4 | *p*-Nitrobenzyl | 623 |
| 5 | Triphenylmethyl | 1430 |
| 6 | Ethyl | 120 |
| 7 | *p*-Methoxybenzyl | 220 |
| 8 | Diphenylmethyl | 495 |
| 9 | 2,4-Dinitrophenyl | 706 |
| 10 | Methyl | 143 |

TABLE II

FIRST ORDER RATE CONSTANTS FOR THE THERMAL DECOMPOSITION OF CHOLESTERYL ACETATE, CHLOROACETATE, ETHYL CARBONATE, PHENYL CARBAMATE AND BENZOATE

| Curve | Compound | Temp., °C. | $k \times 10^4$ min.$^{-1}$ |
|---|---|---|---|
| 1 | Cholesteryl ethyl carbonate | 241 | 13.2 |
| 2 | Cholesteryl ethyl carbonate | 261 | 59.8 |
| 3 | Cholesteryl ethyl carbonate | 281 | 236 |
| 4 | Cholesteryl acetate | 281 | 23.5 |
| 5 | Cholesteryl acetate | 306 | 128 |
| 6 | Cholesteryl acetate | 329 | 557 |
| 7 | Cholesteryl chloroacetate | 281 | 150 |
| 8 | Cholesteryl phenyl carbamate | 241 | 127 |
| 9 | Cholesteryl benzoate | 281 | 78.5 |

(8) T. Wagner-Jauregg and T. Lennartz, *Ber.*, **74B**, 27 (1941).

(9) S. Winstein, M. Brown, K. Schreiber and A. H. Schlesinger, THIS JOURNAL, **74**, 1140 (1952).

(10) (a) L. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 102; (b) D. P. Dodgson and R. D. Hayworth, *J. Chem. Soc.*, 67 (1952).

(11) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., London, 1948, p. 80.

temperature range 281–329° and a slightly lower temperature range was investigated (241–281°) in the case of the carbonate. The first order rate constants were determined graphically and are presented in Tables I and II.

It should be noted that there is a definite trend in the thermal stability of the xanthate esters, namely, the more *electronegative the ester group, the less stable is the xanthate.* This effect is shown nicely in Fig. 1 in which the rate constants for the pyrolysis of the various xanthate esters are plotted against the ionization constant of the correspondingly substituted acetic acid.[12] Within the experimental error, all of the points fall on a straight line. Hammett[13] has shown that such a linear relationship applies to a large number of side-chain reactions of benzene derivatives. The correlation of the pyrolysis rates with the corresponding ionization constants is quite good in this series, even with the purely aliphatic ethyl and methyl xanthates. The value of the Hammett parameter, rho, is +0.87 for the pyrolysis of the cholesteryl xanthates.

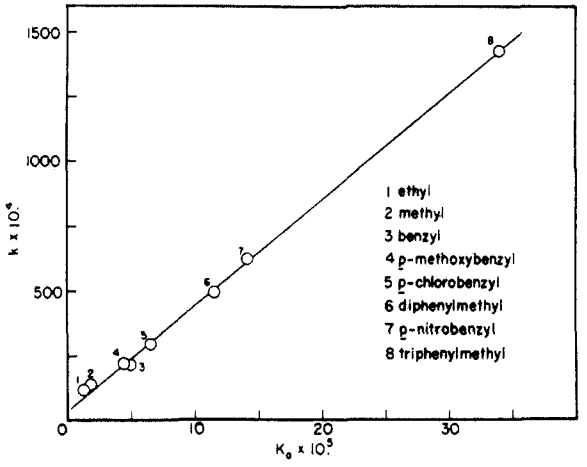



Fig. 1.—Hammett plot for the thermal decomposition of cholesteryl xanthates.

The frequency factors (s) and experimental activation energies ($E_{exp}$) for the decomposition of cholesteryl acetate and ethyl carbonate were calculated from the Arrhenius theory ($k = se^{-E_{exp}/RT}$) and are listed in Table III with the entropies of activation $S^*$ calculated from the theory of absolute reaction rates. The previously reported values for the decomposition of cholesteryl S-methyl xanthate are also included for comparison.

TABLE III

ENERGIES AND ENTROPIES OF ACTIVATION FOR THE THERMAL DECOMPOSITION OF CHOLESTERYL ACETATE AND ETHYL CARBONATE

| Compound | $E_{exp.}$, cal. | $s \times 10^{-12}$ sec.$^{-1}$ | $S^*$, e.u. |
|---|---|---|---|
| Cholesteryl acetate | 44,100 | 5.1 | −3.6 |
| Cholesteryl ethyl carbonate | 41,000 | 2.4 | −4.3 |
| Cholesteryl S-methyl xanthate | 32,900 | 2.4 | −4.7 |

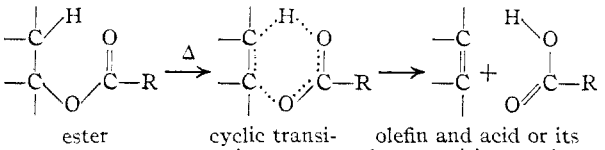
(12) (a) The ionization constants used were obtained from Dippy, *Chem. Revs.*, **25**, 151 (1939). (b) The ionization constant of triphenylacetic acid apparently has not been reported. From Fig. 1 its value is estimated to be $3.4 \times 10^{-4}$.

(13) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., 1940, Chap. VII.

## Discussion

The frequency factors and entropies of activation for cholesteryl acetate and ethyl carbonate are of the same order of magnitude as were found for the decomposition of cholesteryl S-methyl xanthate; however, the activation energies are much higher. The difference is +8.1 kcal./mole for the ethyl carbonate and +11.2 kcal./mole for the acetate. It appears, therefore, that the greater stability of the acetate and carbonate esters are due to the energy terms rather than the nonexponential terms.

The thermal decompositions of carbonate esters have not been shown to be of the *cis* type; however, it seems very likely that they are, in view of their close analogy to the pyrolysis of xanthate and carboxylic esters. This and the fact that these decompositions are unimolecular having negative entropies of activation indicate that all of these reactions proceed by a cyclic transition state such as the one previously discussed[2] for the Chugaev reaction. A number of thermal decompositions of this type may be considered as involving a similar transition state. For example, in the system




O = oxygen or sulfur
R = −R, −Ar, −SR, −OR, $-NHC_6H_5$ or −Cl

it appears that oxygen and sulfur may be interchanged in any or all of the possible positions and R may be hydrogen, alkyl, aryl, alkoxy, sulfide, amino or chlorine, without changing the mechanism of the elimination. The only change is the ease with which the elimination takes place. The reaction products are olefin and the acid or thioacid (which is unstable if R is alkoxy, sulfide, amino or chloro, and can further decompose, yielding in the case of the methyl xanthates, carbon oxysulfide and methyl mercaptan, and if the R is chlorine, hydrogen chloride and carbon dioxide). When the R is chlorine an additional reaction path is available yielding an alkyl chloride and carbon dioxide.[14]

Straus and Lemmel[15] reported that the phenyl carbamate of tetrahydronaphthol decomposed at 200° to give an olefin, aniline and carbon dioxide. Cholesteryl phenyl carbamate also decomposed readily giving the same type of products, thus affording another example of unstable carbamates.

The formation of ketene by the pyrolysis of acetic anhydride[16] can be pictured as arising from a similar transition as shown beyond.

The dehydration of alcohols by pyrolysis with boric acid[17] appears to be a further example of this type of reaction in which the unstable intermediate is the metaborate ester[18] (ROB = O) where a boron atom is substituted for the central carbon atom.

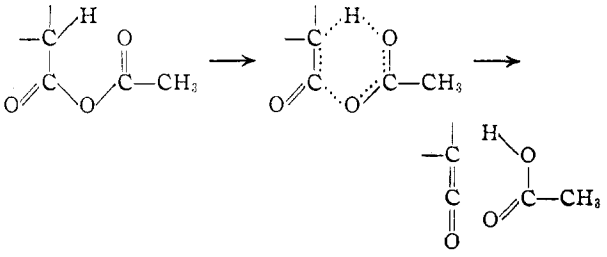
(14) A. R. Choppin and E. L. Compere, THIS JOURNAL, **70**, 3797 (1948).

(15) F. Straus and L. Lemmel, *Ber.*, **54**, 25 (1921).

(16) (a) N. T. M. Wilsmore, *J. Chem. Soc.*, **91**, 1938 (1907); (b) Szwarc and Murawski, *Trans. Faraday Soc.*, **47**, 269 (1951).

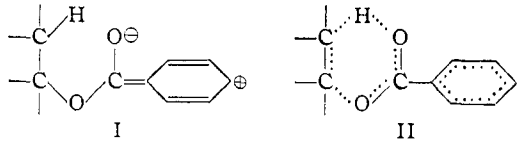
(17) W. Brandenberg and A. Galat, THIS JOURNAL, **72**, 3275 (1950).

(18) G. L. O'Connor and H. R. Nace, unpublished experiments.



There appear to be two important factors which influence the thermal stability of the compounds in this classification. The first is the nucleophilic character of the carbonyl oxygen or the thion sulfur. In general, the more nucleophilic these atoms are the more unstable will be the compound. For example, the xanthates and trithiocarbonates, having a more nucleophilic thion sulfur atom as compared to the carbonyl oxygen in the carbonate and carboxylic esters, are much less stable toward thermal decomposition. If R is varied in a series of these compounds, it affects the stability of the ester by changing the nucleophilic character of the thion sulfur or carbonyl oxygen. Thus the more electropositive is R the less stable is the ester. The xanthates are a special case which will be discussed later.

It should be noted from Table II that in the oxygen-containing esters the stability increases in the order phenyl carbamate, ethyl carbonate, benzoate and acetate. From this series it is evident that the more electropositive is R the less stable is the ester toward thermal decomposition with the possible exception of the benzoate which, perhaps, should follow the acetate. The results of Fugassi, *et al.*,[7] are also in accord with this view since it was found that *t*-butyl propionate where R is ethyl is somewhat less stable than *t*-butyl acetate, where R is the less electropositive methyl group. As a general rule, it has been found that acetate esters are more stable than benzoate esters apparently due to the more nucleophilic oxygen in the latter compounds due to resonance structures of the type (I)



I II

Also, the conjugated phenyl ring can aid resonance stabilization of the cyclic transition state (II). A similar effect was observed with a conjugated double bond in cholesteryl S-methyl xanthate as compared to the corresponding cholestanyl compound.[2]

The fact that cholesteryl chloroacetate is more reactive than the acetate appears to be anomalous at present. Fugassi[19] has also observed that *t*-butyl chloroacetate decomposes more easily than the acetate but states that some of this rapid decomposition might well have been caused by the catalytic activity of "uncoated" glass reaction vessels. It seems that the chloroacetates may be decomposing by an entirely different mechanism such as a free radical process, but the final decision on these compounds must await further investigation.

The stability of the xanthate esters is influenced by a second factor, which is not present in carboxylic and dithio esters. The arrangement of oxygen and sulfur in xanthate esters apparently gives maximum instability, cholesteryl S-methyl xanthate being one-tenth as stable as the cholesteryl methyl trithiocarbonate. The only difference here is substitution of sulfur for the ether oxygen. In the pyrolysis of xanthates an additional driving force is obtained from the net energy gained in going from an —O—C=S linkage to an O=C—S— linkage. In carboxylic and dithio esters a comparable driving force is not present since the same linkage is present before and after pyrolysis (—O—C=O or —S—C=S). It is interesting to note the effect of changing the R-group in the xanthates where it was found that the more electronegative the ester group the less stable was the xanthate. The effect is opposed to the one found in the other esters, which means that this second factor determines the stability of xanthates to a large extent, since the nucleophilic character of the thion sulfur is decreased but the instability is increased. This instability is presumably brought about by a decrease in the energy of activation rather than by a change in the frequency factor of the rate expression since the non-exponential terms of unimolecular thermal decompositions of this type are normally within a power of 10 of $10^{13}$ (see Table III and reference (4)). The exact manner in which this takes place is not entirely clear; however, it appears that an electron deficiency about the central carbon lowers the activation energy for the formation of the cyclic transition state by facilitating partial bond making with respect to bond breaking in the linkage —O—C=S. Thus, the more electronegative R is, the greater is the tendency for bond making to have proceeded further than bond breaking at the transition state. This will have the effect of supplying excess energy from the partial formation of the C=O bond as a driving force.[20] A somewhat analogous effect was also found in the Claisen rearrangement.[21]

## Experimental[22]

**Preparation of Cholesteryl Xanthates—General Procedure.**—A mixture of 3.0 g. of cholesterol in 100 ml. of dry benzene plus a drop of ethanol and 1.0 g. of sodium hydride was magnetically stirred 24 hours at the reflux temperature. If the drop of ethanol was omitted the formation of salt was very slow. The reaction mixture was allowed to cool to room temperature and 4 ml. of carbon disulfide was added, causing a red gelatinous precipitate of cholesteryl sodium xanthate. The resulting mixture was stirred 24 hours under reflux. The mixture was again cooled to room temperature, 3.0 g. of the appropriate alkyl halide added, and the stirring under reflux continued for 24 hours. The hot benzene

(19) P. Fugassi, private communication.

(20) For a more detailed discussion of these effects see C. G. Swain and W. P. Langsdorf, THIS JOURNAL, **73**, 2813 (1951).

(21) E. G. Foster, A. C. Cope and F. Daniels, *ibid.*, **69**, 1893 (1947).

(22) All melting points are corrected. Rotations were determined on approximately 1% chloroform solutions at room temperature. Microanalyses by S. M. Nagy and associates at the Massachusetts Institute of Technology. The analytical samples were crystallized to constant melting point and constant rotation.

TABLE IV

CHOLESTERYL XANTHATES

| Compound | M.p., °C. | [α]D | Alkyl halide | Yield, % | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|
| Methyl | 127.5–128 | −53° | Methyl iodide | 85 | $C_{29}H_{49}OS_2$ | | | | |
| Ethyl | 143.5–144 | −42 | Ethyl bromide | 80 | $C_{30}H_{50}OS_2$ | 73.75 | 73.59 | 10.27 | 10.34 |
| Benzyl | 142.5–143 | −30 | Benzyl chloride | 92 | $C_{35}H_{52}OS_2$ | 76.03 | 75.98 | 9.48 | 9.53 |
| *p*-Nitrobenzyl | 147.5–148 | −29 | *p*-Nitrobenzyl chloride | 85 | $C_{35}H_{51}O_3S_2N$ | 70.29 | 70.09 | 8.60 | 8.60 |
| *p*-Chlorobenzyl | 142.0–142.5 | −29 | *p*-Chlorobenzyl chloride | 85 | $C_{35}H_{51}OS_2Cl$ | 71.57 | 71.60 | 8.79 | 8.91 |
| *p*-Methoxybenzyl | 124.5–125 | −28 | *p*-Methoxybenzyl chloride | 70 | $C_{36}H_{54}O_2S_2$ | 74.19 | 74.39 | 9.34 | 9.51 |
| 2,4-Dinitrophenyl | 142–144 dec. | Yellow solid | 2,4-Dinitrochlorobenzene | 80 | $C_{34}H_{48}O_5S_2N_2$ | 64.78 | 65.25 | 7.77 | 7.98 |
| Diphenylmethyl | 170.5–171.5 | −25 | Diphenylmethyl chloride | 80 | $C_{41}H_{56}OS_2$ | 78.29 | 77.90 | 8.97 | 9.12 |
| Triphenylmethyl | 156.0–156.5 | −21 | Triphenylmethyl chloride | 72 | $C_{47}H_{60}OS_2$ | 80.09 | 79.96 | 8.58 | 8.74 |

solution was then filtered to remove inorganic salts and any unreacted cholesteryl sodium salt. The residue was washed with 25 ml. of dry benzene and the filtrates combined, washed with water, and dried over anhydrous sodium sulfate. The benzene was then removed by evaporation on a steam-bath yielding the crude xanthate as a reddish oil which usually crystallized when allowed to cool. The crude xanthate was crystallized from 1:1 ethanol-ethyl acetate. If the product was colored at this point it was decolorized by dissolving it in 50 ml. of petroleum ether and washing through 10 g. of aluminum oxide (Merck and Co., Inc., suitable for chromatographic absorption) in a column 1 × 12 cm. The column was then washed with 100 ml. of petroleum ether. The combined filtrates were evaporated on a steam-bath and the residue crystallized twice from 1:1 ethanol–ethyl acetate. The yields and physical properties of the cholesteryl xanthates are summarized in Table IV. All the cholesteryl xanthates crystallized as long, colorless needles except as noted.

**Cholesteryl Thiocyanate.**—A mixture of 20 g. (0.049 mole) of cholesteryl chloride and 150 g. (1.85 moles) of sodium thiocyanate in 1000 ml. of ethanol was refluxed 48 hours. The reaction mixture was filtered hot and allowed to cool whereupon crude cholesteryl thiocyanate crystallized. It was recrystallized from 200 ml. of a 1:1 ethanol-ethyl acetate mixture yielding 16 g. (75%) of cholesteryl thiocyanate m.p. 126–128°, [α]D −10° (reported[8] m.p. 129°, [α]D −11°).

**Thiocholesterol.**—A solution of 5.0 g. (0.012 mole) of cholesteryl thiocyanate in 50 ml. of dry ether and 50 ml. of dry benzene was added dropwise over a two-hour period to a magnetically stirred mixture of 1.0 g. of lithium aluminum hydride in 50 ml. of dry ether, whereupon the salt of thiocholesterol precipitated. The reaction mixture was stirred overnight and then decomposed by the dropwise addition of 50 ml. of 6 *N* hydrochloric acid. The organic layer was separated and washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation on a steam-bath and the residue was crystallized from 75 ml. of ethanol and 25 ml. of ethyl acetate yielding 4.2 g. (95%) of thiocholesterol, m.p. 96–97°, [α]D −23° (reported[8] m.p. 99.5°, [α]D −24°). When equal volumes of a saturated alcoholic solution of thiocholesterol and a 1% alcoholic solution of digitonin were mixed and allowed to stand several days no insoluble digitonide was formed.

**Cholesteryl Methyl Trithiocarbonate.**—This compound was prepared in 92% yield using the general method described for preparing xanthates with thiocholesterol in place of cholesterol, and methyl iodide as the alkyl halide. Cholesteryl methyl trithiocarbonate crystallized as long, bright yellow needles m.p. 126–128°.

*Anal.* Calcd. for $C_{29}H_{48}S_3$: C, 70.69; H, 9.62. Found: C, 70.89; H, 9.88.

**Cholesteryl Chloroacetate.**—A mixture of 10 g. of cholesterol, 10 ml. of benzene and 10 ml. of chloroacetyl chloride was heated on a steam-bath for one hour. Then the benzene and excess chloroacetyl chloride were removed by evaporation and the residue was crystallized from ethyl acetate containing a little ethanol yielding 11.0 g. (90%) of white ester, m.p. 164–165°. The product was recrystallized from ethyl acetate yielding 9.0 g., m.p. 164.5–165.5°, [α]D −35°.

*Anal.* Calcd. for $C_{29}H_{47}O_2Cl$: C, 75.21; H, 10.24. Found: C, 75.11; H, 10.23.

**Cholesteryl Phenyl Carbamate.**—A mixture of 2.0 g. of cholesterol in 20 ml. of carbon tetrachloride and 2 ml. of phenyl isocyanate was heated under reflux for 3 hours. The solvent was removed by evaporation on a steam-bath and the residue crystallized from ethanol yielding 2.5 g. (95%) of the phenyl carbamate, m.p. 168.5–169° (reported[23] m.p. 168°).

TABLE V

PYROLYSIS OF CHOLESTERYL XANTHATES, CARBONATES AND ACETATES

The procedure used in all the pyrolyses was essentially the same. About 0.5 g. of the compound in a 6-inch Pyrex test-tube was heated at the given temperature under reduced pressure (20 mm.) for the stated time in a potassium nitrate-sodium nitrite bath. The residue was then taken up in 50 ml. of ether and washed with sodium hydroxide solution followed by water. The ether layer was dried over anhydrous sodium sulfate and then the ether was removed and the residue chromatographed over alumina. The $\Delta^{3,5}$-cholestadiene was eluted readily with petroleum ether. The optical rotation of the diene as it came from the column was −90 to −110°. The diene was then crystallized from a 1:1 ethanol-acetone mixture; m.p. 78–80°.[a]

| | Cholsteryl compound | Time, hours | Temp., °C. | Yield of 3,5-cholestadiene, % |
|---|---|---|---|---|
| 1 | Methyl xanthate | 3 | 220 | 81 |
| 2 | Ethyl xanthate | 3 | 220 | 86 |
| 3 | Benzyl xanthate | 3 | 220 | 90 |
| 4 | *p*-Nitrobenzyl xanthate | 3 | 220 | 90 |
| 5 | *p*-Chlorobenzyl xanthate | 3 | 220 | 88 |
| 6 | *p*-Methoxybenzyl xanthate | 3 | 220 | 84 |
| 7 | 2,4-Dinitrophenyl xanthate | 3 | 220 | 65[b] |
| 8 | Diphenylmethyl xanthate | 3 | 220 | 72[b] |
| 9 | Triphenylmethyl xanthate | 3 or 1 | 220 | 65[b] |
| 10 | Methyl trithiocarbonate | 3 | 220 | 80 |
| 11 | Ethyl carbonate | 4 | 280 | 94 |
| 12 | Acetate | 4 | 320 | 75 |
| 13 | Chloroacetate | 4 | 320 | 60 |
| 14 | Benzoate | 3 | 300 | 85 |
| 15 | Phenyl carbamate | 3 | 220 | 90 |

[a] Reported in Ref. 10a, p. 252 [α]D −104 to −123°, m.p. 79.5–80°. [b] Sulfur compounds were removed by allowing the ether solution of olefin to stand over sodium amalgam.

## Kinetic Investigation

**Apparatus.**—The constant temperature bath has been described previously.[2] However, the heavy paraffin oil which formerly was used was unsatisfactory at the higher temperatures required in this investigation. Sunvis 150[24] heavy heat transfer oil was tried and found to be satisfactory up to 330°. Once thermal equilibrium was obtained the temperature could be maintained to ±0.2° for any given temperature in the range 50–330°.

**Method.**—The method used in determining the rate of decomposition of the cholesteryl xanthates was essentially

(23) A. Verdino and V. Schadendorff, *Monatsh.*, **65**, 141 (1935).

(24) Obtained from Sun Oil Company.

the same as previously described. The difference in volatility of the various mercaptans did not introduce any complications with this method. The weight lost with the methyl, ethyl and benzyl xanthates corresponded to loss of mercaptan and carbon oxysulfide while only carbon oxysulfide was volatile in the case of the remaining xanthates. Methyl mercaptan and carbon disulfide were lost in the case of the trithiocarbonate.

The rather high temperatures required for the decomposition of cholesteryl ethyl carbonate, acetate and chloroacetate caused slight charring when carried out at atmospheric pressure, and it was found desirable to make these runs under reduced pressure (20 mm.). The rates were the same at either pressure. The weight loss for the acetates corresponded to the acid, for the carbonate to ethanol and carbon dioxide and for the carbamate, to carbon dioxide and aniline.

The rate of decomposition of cholesteryl benzoate was determined by placing 300 mg. of the ester in a closed vial and placing it in the bath for 30 min. After the vial had been removed from the bath it was washed with benzene and ether, then opened, and its contents dissolved in 30 ml. of hot benzene. Water (50 ml.) was added and the acid was titrated with 0.05 *N* sodium hydroxide using phenolphthalein indicator.

PROVIDENCE 12, RHODE ISLAND

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[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE AND COMPANY]

# The Conjugate Addition of Ethyl Malonate to 3,5-Cholestadien-7-one

BY JACK W. RALLS

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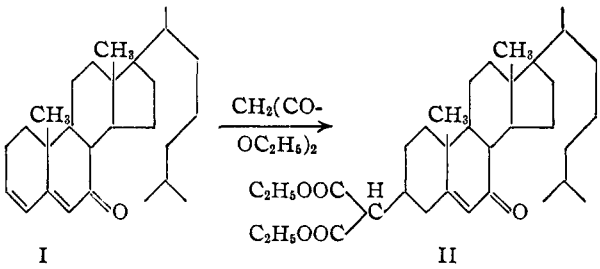
Conditions for the conjugate addition of ethyl malonate to 3,5-cholestadien-7-one are described. The adduct is demonstrated to be ethyl 7-keto-3β-cholesterylmalonate. Several transformation products of the adduct have been prepared.

The stereospecific 1,6-addition of ethyl mercaptan to 3,5-cholestadien-7-one (I) has been described.[1] To examine the generality of this unusual reaction, we have studied the conjugate addition of ethyl malonate to the dienone system of I.

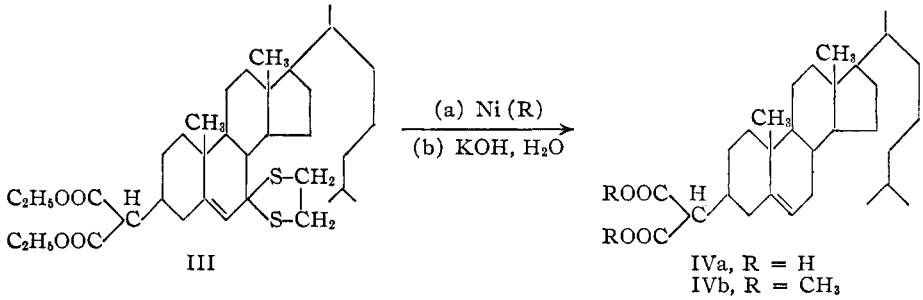



I II

There are several examples of the addition of malonic esters to α,β,γ,δ-bis-unsaturated esters.[2] The reaction of malonic esters with conjugated dienones has not been reported.

Reaction of ethyl malonate and 3,5-cholestadien-7-one (I) does not take place readily employing the milder conditions used for Michael condensations.[3] For example, a 95-hour refluxing of an equal molar mixture of ethyl malonate and I in benzene solution with piperidine as a catalyst gave no reaction. The addition proceeded at a slow rate when an ethanolic solution of the reactants containing catalytic amounts of sodium ethoxide was kept at room temperature. The most successful conditions found consisted of heating an ethanolic solution of the dienone and the active methylene compound in the presence of a molar equivalent of sodium ethoxide. In this way a 50% yield of the adduct was obtained.

The addition product (II) melted at 105–106° and had a rotation of −78°. The ultraviolet absorption spectrum ($\lambda_{max}^{alc}$ 238 mμ, $E_m$ 14,700) was excellent evidence for the structure as formulated. Confirmatory data for the assignment of structure II to the adduct and information on the stereochemical course of the reaction was obtained by converting II to the known[4,5] 3β-cholesterylmalonic acid (IVa). The ethyl 7-keto-3β-cholesterylmalonate-7-ethylenemercaptole (III) was prepared and desulfurized with Raney nickel in boiling dioxane. The intermediate ethyl 3β-cholesterylmalonate was not isolated but was saponified to 3β-cholesterylmalonic acid (IVa) melting at 199–203° and having a rotation of −30.5°. Kaiser and Svarz report,[4]




III

IVa, R = H
IVb, R = $CH_3$

m.p. 202–206°, $[\alpha]^{25}D$ −22.5° for this compound. The methyl ester (IVb) was also prepared and agreed with the properties described for the original preparation.

The adduct II was saponified to give 7-keto-3β-cholesterylmalonic acid (V). Thermal decarboxylation of V afforded 7-keto-3β-cholesterylacetic acid (VIa) which was characterized as the methyl ester (VIb).

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(1) J. W. Ralls, R. M. Dodson and B. Riegel, THIS JOURNAL, **71**, 3320 (1949).

(2) C. F. H. Allen and A. H. Blatt in H. Gilman, "Organic Chemistry, An Advanced Treatise," 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 698.

(3) R. Connor and W. R. McClellan, *J. Org. Chem.*, **3**, 570 (1939).

(4) E. Kaiser and J. J. Svarz, THIS JOURNAL, **67**, 1309 (1945).

(5) R. H. Baker and Q. R. Petersen, *ibid.*, **73**, 4080 (1951).