Characterization of 2,4-Diphenylpyrimidine.—The viscous distillate, $n^{25}D$ 1.6543, slowly crystallized to a yellow solid, m.p. 58–59°. *Anal.* Calcd. for $C_{16}H_{12}N_2$: C, 82.8; H, 5.2; N, 12.0; neut. equiv., 232. Found: C, 83.0; H, 5.3; N, 11.7; neut. equiv., 249.

In comparing the ultraviolet spectrum of 2,4-diphenylpyrimidine with the spectra of the aliphatic pyrimidines, the former was found to have a greater absorption coefficient and the peak was shifted slightly to the longer wave length.

In another run, benzonitrile (125 g.) and potassium (2 g.) were treated with acetylene at a gage pressure of 10–15 atmospheres for 14 hours, while the temperature was maintained at 180–200°. There was recovered 25 g. of benzonitrile (b.p. 62–70° (7 mm.)). The 2,4-diphenylpyrimidine distilled at 190–194° (3 mm.) (57 g., 51% yield).

WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE PAINT DIVISION OF THE PITTSBURGH PLATE GLASS COMPANY]

Transesterification. II. Esters of Strong Organic Acids

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The transesterification of β-keto esters has been compared with that of esters of other strong organic acids. Malonates and oxalates, like acetoacetates, are transesterified under mild conditions, and it is suggested that the ease of transesterification of β-keto esters is due mainly to special structural features inherent in these esters, while that of oxalates is due to the inductive effect of the neighboring group.

In our first communication[1] we reported on the transesterification of β-keto esters which proceeds at steam-bath temperatures in the absence of catalysts. We have now completed a qualitative study of transesterifications of acids of strength similar and greater than that of acetoacetic acid to determine whether this facile transesterification is due to the inductive effect of the acetyl group, to intermolecular catalysis by active hydrogen or to structural features unique in β-keto esters. Table I lists the acids investigated, their ionization constants and the products obtained after heating representative primary and secondary alcohols with excess ester on the steam-bath without catalysts for 16 hours.

In any ester interchange one has the equilibria

$$R{-}COOR_1 + R_2OH \rightleftharpoons R{-}\overset{\displaystyle O^-}{\underset{\displaystyle HOR_2^+}{C}}{-}OR_1 \rightleftharpoons R{-}COOR_2 + R_1OH$$

the equilibrium constants of which are probably not greatly different from 1[2] and the reason for the ease of transesterification of acetoacetates at first considered most likely was the inductive effect of the acetyl group which removes electrons from the ester carbonyl, increases its electrophilic reactivity and thus the speed with which the equilibria are set up. A correlation is that acetoacetic acid is over ten times as strong an acid as acetic. Our qualitative data indicate, however, that the inductive effect can only be a mildly contributory factor in the ease of transesterification of β-keto esters because esters of some stronger acids do not react under our experimental conditions. Nor does it seem likely that the ease of transesterification of β-keto esters is due to an active hydrogen catalysis because we have found that when alcohols are heated in unreactive esters such as ethyl butyrate containing ethyl acetoacetate in a molar ratio of 10:1, the higher acetoacetate is the sole reaction product. Such experiments are, however, not entirely conclusive because one would expect the acetoacetate to be the more basic ester and its reaction might be the only one catalyzed.

TABLE I

Acid	$10^5 K_1$ at 25°	Products
Caprylic	1.44[a]	None
Butyric	1.50[b]	None
Crotonic	2.03[b]	None
Levulinic	.....	None
Benzoic	6.27[b]	None
Lactic	13.9[c]	None
Acetoacetic	26[d]	Acetoacetates
Benzoylacetic	.....	Benzoylacetates
Furoic	68[e]	None
Fumaric	95.7[f]	Small amt. fumarates
Tartaric	104[g]	None
Phthalic	112[h]	None
Malonic	177[f]	Mixed and symm. malonates
Ethyl-*n*-butylmalonic	.....	None
Maleic	1200[f]	None
Oxalic	5900[i]	Mixed and symm. oxalates

[a] C. G. Derrick, THIS JOURNAL, **33**, 1152 (1911). [b] J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939). [c] A. W. Martin and H. V. Tartar, THIS JOURNAL, **59**, 2672 (1937). [d] K. J. Pedersen, *J. Phys. Chem.*, **38**, 993 (1934). [e] W. L. German, G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 1604 (1937). [f] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 201. [g] I. Jones and F. G. Soper, *J. Chem. Soc.*, 1836 (1934). [h] W. J. Hamer, G. D. Pinching and S. F. Acree, *J. Research Natl. Bur. Standards*, **35**, 539 (1945); *C.A.*, **40**, 3044 (1946). [i] R. Gane and C. K. Ingold, *J. Chem. Soc.*, 2153 (1931).

After the completion of this work, our attention was drawn to a paper by Carroll[3] which independently describes the facile alcoholysis of acetoacetic and related esters. Carroll attempted to determine the rates of transesterification of acetoacetates by measuring the rates of distillation of lower alcohols evolved, and on the basis of these possibly inaccurate data concluded that the rate determining step is first order with respect to the ester when pri-

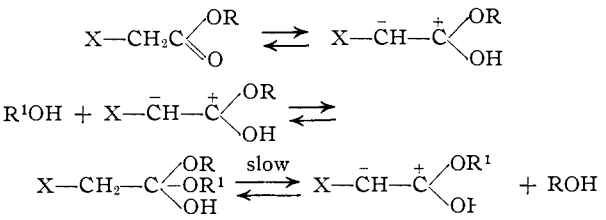
(1) A. R. Bader, L. O. Cummings and H. A. Vogel, THIS JOURNAL, **73**, 4195 (1951).

(2) P. R. Fehlandt and H. Adkins, *ibid.*, **57**, 193 (1935).

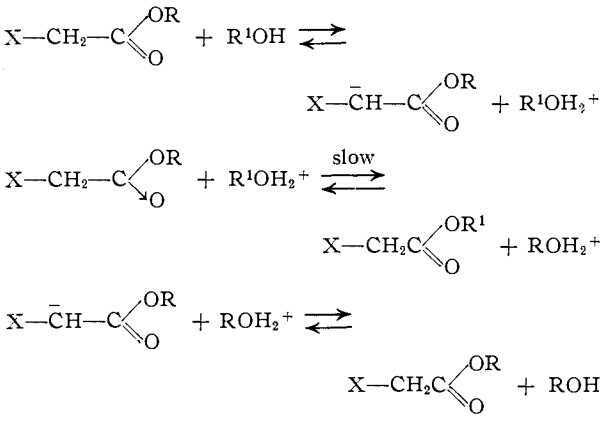
(3) M. F. Carroll, *Proc. XIth. Intern. Congr. Pure and Applied Chem.*, **2**, 39 (1947); *C. A.*, **45**, 7015 (1951).

mary and secondary alcohols are used, and second order when tertiary alcohols are used. For the unimolecular reaction, Carroll was undecided between two mechanisms:

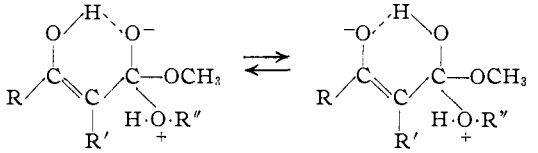
Mechanism A



Mechanism B



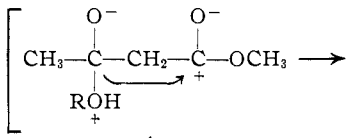
We do not believe that either mechanism could be operative and prefer a mechanism involving the cyclic intermediates Ia ⇄ Ib previously suggested.[1]



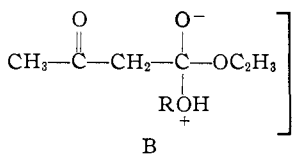
Ia Ib

Although these intermediates suffer from the loss of conjugate carbonyl resonance of the acetoacetate enol, they offer the distinct advantage of possessing stronger than normal hydrogen bonds because these involve the electrostatic attraction of the proton to a *real* negative charge.

An alternate mechanism considered was A → B. The presumed rate determining step (*viz.*, the



A



B

addition of the alcohol to the ester) should be facilitated by participation of the more electrophilic keto carbonyl, and is followed by a rapid intramolecular shift of the alcohol to the ester carbonyl. Shifts such as A → B are familiar from rearrangements of the pinacol–pinacolone type, and this mechanism is analogous to one proposed to account for the increased SN2 reactivity of positive halogens.[4]

The unambiguous way of distinguishing between this pinacolic and the enolic mechanism was to compare the complete non-reactivity of ethyl diethylacetoacetate[5] with that of a monoalkyl ester offering the same degree of steric hindrance. The dialkyl ester does not react with *l*-menthol even at 190°, while ethyl *s*-butylacetoacetate interchanges quite readily at 150°. Thus an active hydrogen appears to be a prerequisite for reaction, suggesting that the cyclic enol mechanism is operative.

Because their enolization is so slight, we are undecided whether malonates exchange by a mechanism involving a similarly chelated enol, or whether their reactions are largely inductively facilitated as are those of fumarates and oxalates.

These facile transesterifications provide convenient methods for the esterification of alcohols under mild, neutral conditions in the absence of catalysts, and in addition to the β-keto esters reported,[1] we have prepared the acetoacetates of ergosterol and cortisone. With esters of the monobasic acids the yields are usually quantitative, while with malonates and oxalates the mixed esters formed predominantly are easily separated from the much more insoluble symmetrical products.

Experimental

Materials.—Cholesterol was recrystallized from a mixture of isopropyl ether and methanol, m.p. 148.9–149.4° (cor.), $\alpha^{25}D$ −35° (hexane), saponification number 0.0.

Octadecyl alcohol (Eastman Kodak Co. white label) was recrystallized from methanol, m.p. 58.4–58.8° (cor.), saponification value 0.0.

All esters except methyl furoate were products of the Eastman Kodak Co. or the Matheson Co. and were redistilled before use. Methyl furoate prepared from furoic acid (Fischer method) boiled at 181–182°.

Method.—Except where stated otherwise, 5.0 g. of cholesterol and 5.0 g. of octadecyl alcohol were each heated under an air condenser on the steam-bath with 25 g. of the esters for 16 hours. The unreacted lower esters were then removed by distillation *in vacuo*, and the residues were triturated with methanol, filtered and dried. When no transesterification had taken place, the identity of the residues with cholesterol and octadecyl alcohol, respectively, was ascertained by m.p., mixed m.p. and determination of the saponification number.

Results.—Cholesterol and octadecyl alcohol, each of saponification number less than 10, were recovered from methyl caprylate, ethyl butyrate, methyl crotonate, methyl levulinate, methyl benzoate, ethyl lactate, methyl furoate, ethyl tartrate, methyl phthalate, ethyl ethyl-*n*-butylmalonate and ethyl maleate.

The reaction product of cholesterol with ethyl fumarate had a saponification number of 12 after 18 hours and of 40 after 56 hours; the reaction product of octadecyl alcohol had a saponification number of 60 after 18 hours.

17-Hydroxy-11-dehydrocorticosterone-21-acetoacetate hydrate prepared from cortisone[6] by the standard procedure[1] and crystallized from aqueous ethanol and chloroform melts at 107–109°.

Anal. Calcd. for $C_{25}H_{32}O_7 \cdot H_2O$: C, 64.92; H, 7.41. Found: C, 64.93, 64.94; H, 7.42, 7.50.

Ergosteryl acetoacetate[7] prepared similarly forms shiny platelets from aqueous ethanol, m.p. 124–125°; λ_{max}^{EtOH}

(4) J. W. Baker, *Trans. Faraday Soc.*, **37**, 643 (1941).

(5) A. McKenzie, *J. Chem. Soc.*, **89**, 381 (1906).

(6) We wish to thank Dr. M. Tishler of Merck and Co. for a generous sample of cortisone.

(7) Thanks are due to Dr. H. Bolker for a generous sample of ergosterol.

271.5 mμ (log ε 4.09), 281.5 mμ (log ε 4.10), 292.0 mμ (log ε 3.86); $\alpha^{25}D$ −79.3° (chloroform).

Anal. Calcd. for $C_{32}H_{48}O_3$: C, 79.95; H, 10.06. Found: C, 79.80, 79.60; H, 10.12, 10.10.

Twenty-five g. of *l*-menthol and 10 g. of ethyl *s*-butylacetoacetate[8] were heated at 145–150° for five hours; the unreacted starting materials were removed by distillation *in vacuo* and the almost water white flask residue (9.0 g.) was distilled to yield 7.5 g. of water-white *l*-**menthyl** *s*-**butylacetoacetate**, b.p. 108–111° (0.3 mm.), $n^{25}D$ 1.4582.

Anal. Calcd. for $C_{18}H_{32}O_3$: C, 72.92; H, 10.88. Found: C, 73.01, 72.96; H, 11.08, 11.02.

Malonates.—Ten grams of cholesterol and 100 cc. of ethyl malonate were heated on the steam-bath for 15 hours, the excess ethyl malonate was removed by distillation *in vacuo*, and the product chromatographed on Fisher adsorption alumina, 80–200 mesh. There were isolated from the hexane eluate 7.8 g. of white flakes, m.p. 60–63° which after crystallization from ethanol yielded 6.5 g. of pure **ethyl cholesteryl malonate** melting at 63.5–64.0°, $\alpha^{25}D$ −31° (chloroform), and 0.7 g. of the much less soluble **dicholesteryl malonate** which after crystallization from isopropyl ether melts at 178°, $\alpha^{25}D$ −33° (chloroform).

Anal. Calcd. for $C_{32}H_{52}O_4$: C, 76.75; H, 10.47. Found: C, 76.76; H, 10.71. Calcd. for $C_{57}H_{92}O_4$: C, 81.37; H, 11.02. Found: C, 81.30, 81.37; H, 10.90, 11.13.

Five grams of octadecyl alcohol and 50 cc. of ethyl malonate were heated on the steam-bath for 18 hours, the unreacted ethyl malonate was removed as above, and the residue dissolved in hot acetone. On cooling, white shiny platelets of **dioctadecyl malonate** (250 mg.) deposited which after recrystallization from acetone melt sharply at 64°. The combined mother liquors were evaporated to dryness, dissolved in hexane and chromatographed. The first eluates yielded 4.3 g. of a waxy solid, **ethyl octadecyl malonate**, m.p. 30–32°.

Anal. Calcd. for $C_{23}H_{44}O_4$: C, 71.82; H, 11.53. Found: C, 71.54; H, 11.76. Calcd. for $C_{39}H_{76}O_4$: C, 76.91; H, 12.58. Found: C, 77.28, 77.10; H, 12.74, 12.81.

Oxalates.—Ten grams of β-sitosterol, 75 cc. of ethyl oxalate and 25 cc. of toluene were heated on a steam-bath for 16 hours, the solvent and unreacted ethyl oxalate were removed by distillation *in vacuo*, and the residue was separated by solubility in a mixture of ethanol and acetone into the sparingly soluble **di-β-sitosteryl oxalate** (0.7 g.) and the more soluble **ethyl β-sitosteryl oxalate** (9.2 g.). The symmetrical ester crystallized from a mixture of toluene and ethanol in flat, shiny needles, m.p. 195–196°, while the mixed ester, crystallized from a mixture of ethanol and acetone, melts at 65–66°.

Anal. Calcd. for $C_{33}H_{54}O_4$: C, 77.00; H, 10.57. Found: C, 77.03; H, 10.70. Calcd. for $C_{60}H_{98}O_4$: C, 81.57; H, 11.18. Found: C, 81.87; H, 11.20.

Cholesterol treated similarly yielded corresponding amounts of **dicholesteryl oxalate**[9] which forms fine needles from a mixture of ethanol and toluene, m.p. 220–222°, and **ethyl cholesteryl oxalate** which after crystallization from a mixture of ethanol and acetone melts at 94.5–95.5°, $\alpha^{25}D$ −33° (chloroform).

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 77.00, 76.94; H, 10.70, 10.54.

Ethyl octadecyl oxalate prepared similarly and crystallized from ethanol melts at 36.5–37.0°.

Anal. Calcd. for $C_{22}H_{44}O_4$: C, 71.30; H, 11.43. Found: C, 71.18, 71.20; H, 11.51, 11.47.

Competitive Reactions.—Ergosterol (1.0 g.) dissolved in a mixture of 58 g. (0.5 mole) of redistilled ethyl butyrate and 6.5 g. (0.05 mole) of redistilled ethyl acetoacetate was heated on the steam-bath for three hours. The solvent mixture (42 g.) was then removed quickly by distillation *in vacuo*, and the residual water-white solution was diluted with 50 cc. of hot ethanol and 30 cc. of water. On cooling the solution deposited shiny white platelets (0.80 g., m.p. 122–124°) which after two crystallizations from aqueous ethanol yielded similar crystals (0.7 g.) which melted at 124–125° and did not depress the m.p. of authentic ergosteryl acetoacetate. Their infrared spectra in chloroform were identical.

Anal. Calcd. for $C_{32}H_{48}O_3$: C, 79.95; H, 10.06. Found: C, 79.79; H, 10.09.

Similar treatment of cholesterol and β-sitosterol with methyl acetoacetate in large molar excesses of methyl benzoate and methyl phthalate also yielded only the corresponding acetoacetates.

Acknowledgment.—The authors wish to thank Professor Martin G. Ettlinger and Dr. E. E. van Tamelen for many helpful suggestions and Drs. H. L. Gerhart and S. W. Gloyer for their kind interest.

(8) Prepared by the general procedure of "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 243.

(9) I. H. Page and H. Rudy, *Biochem. Z.*, **220**, 304 (1930).

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