Reactions of Isopropenyl Stearate with Diethyl Malonate, Acetoacetic Ester, and Related Keto Esters. Enol Esters. XVII[1]

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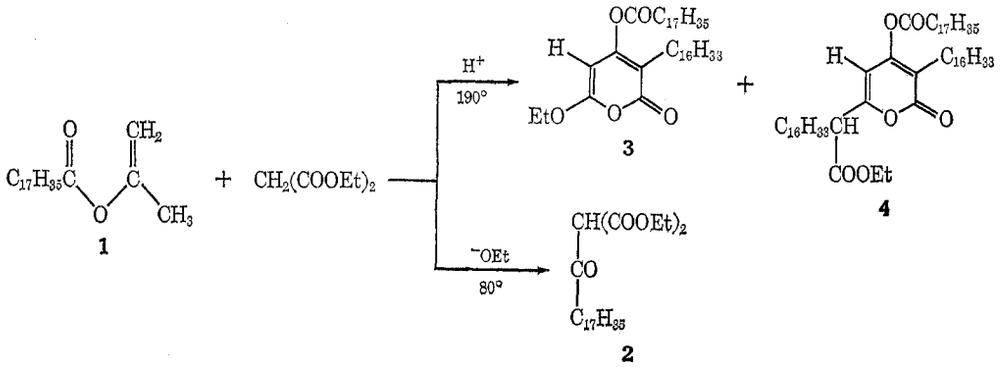
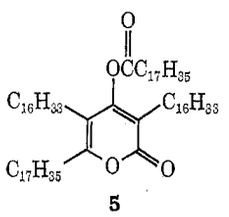
The major product from the acid-catalyzed reaction of isopropenyl stearate with diethyl malonate is identified as the α-pyrone, 6-ethoxy-3-hexadecyl-4-stearoyloxy-2*H*-pyran-2-one. Alcoholysis of the 6-alkoxy α-pyrone proceeds unusually easily without requiring catalysis. Acetoacetic ester and 3-oxoglutarate esters react analogously with isopropenyl stearate to form α-pyrones.

Isopropenyl esters of long-chain fatty acids are versatile acylation agents for the convenient preparation of a wide variety of O-, N-, S-, and C-acylated products.[3a-e] We had examined the base-catalyzed C-acylation of diethyl malonate using isopropenyl stearate (1) as a probe reagent and obtained the expected product, 2-stearoyl diethyl malonate[3d] (2).



At the temperature of the refluxing diethyl malonate solution and under conditions of acidic catalysis, however, a totally different substance was formed. We have been aware for some time[3e] that our previously assigned β-diketone structure[3f] for the latter substance was incorrect. The present paper deals with the elucidation of the structure of the major product of the acid-catalyzed reaction as a 6-ethoxy α-pyrone, namely, **3**. We have also detected traces of a minor α-pyrone companion product **4**. The synthesis and elucidation of the structure of product **4** materially aided the establishment of the correct structure of the major product **3**.

The ease of obtaining the reaction product **3** contrasted markedly with the difficulty of correctly assigning its structure. Technical difficulties hindering the solution of the problem included the facts that the ir spectra of very different structures have similar appearances because of the overpowering effect of the lengthy alkyl groups present. Similar considerations apply to the nmr, uv, and mass spectra; glc analysis is also precluded by the high molecular weight of the compounds, a feature also hindering mass spectral molecular ion determinations. In addition, melting points in this series tend to be deceptively similar; for example, the 6-ethoxy α-pyrone **3**, the 6-methyl α-pyrone **12**, and the hexadecylketene tetramer (3,5-dihexadecyl-6-heptadecyl-4-stearoyloxy-2*H*-pyran-2-one, **5**)[4,5] all melt at 76° and do not depress on admixture.



The carbon and hydrogen compositions given by elemental analyses are not very helpful in this series of compounds, nor is the attempted simplification of the problem by using a lower molecular weight enol ester reactant. For example, the reaction of isopropenyl octanoate with diethyl malonate gave a complex product mixture complicating rather than simplifying the structural elucidations.

In support of the α-pyrone structure **3** for the principal product from the reaction of **1** and diethyl malonate we observed the molecular ion $C_{41}H_{74}O_5$, 646.5516 mass units[6] in the high-resolution mass spectrum. The ir spectrum showed enol ester absorption bands (1771 cm^{-1}), lactone carbonyl bands (1740 cm^{-1}), and a double-bond function (1640 cm^{-1}). The nmr spectrum (unaffected by attempted D_2O exchange) consisted of a singlet (1 H) at 5.30 ppm for

(1) Previous papers in this series: E. S. Rothman, S. S. Hecht, P. E. Pfeffer, and L. Silbert, *J. Org. Chem.*, **37**, 3551 (1972); E. S. Rothman, G. G. Moore, J. M. Chirinko, and S. Serota, *J. Amer. Oil Chem. Soc.*, **49**, 376 (1972).

(2) Agricultural Research Service, U. S. Department of Agriculture.

(3) (a) E. S. Rothman, S. Serota, and D. Swern, *J. Org. Chem.*, **29**, 646 (1964); (b) E. S. Rothman, G. G. Moore, and S. Serota, *ibid.*, **34**, 2486 (1969); (c) E. S. Rothman and G. G. Moore, *Tetrahedron Lett.*, 2553 (1969); (d) *J. Org. Chem.*, **35**, 2351 (1970); (e) *Tetrahedron Lett.*, 1065 (1971); (f) E. S. Rothman, *J. Org. Chem.*, **31**, 628 (1966).

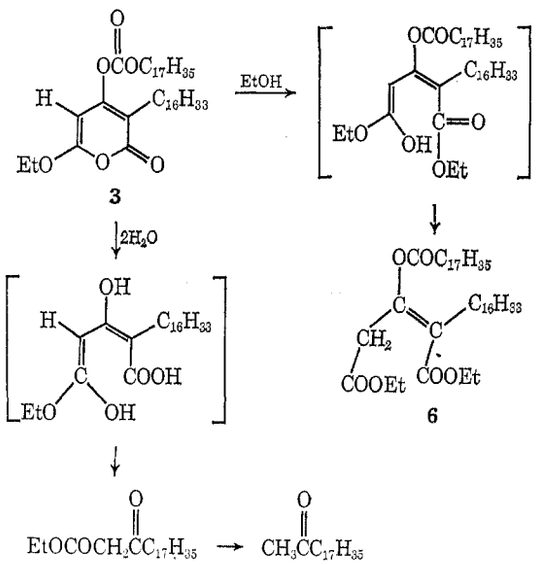
(4) E. S. Rothman, *J. Amer. Oil Chem. Soc.*, **45**, 189 (1968).

(5) In U. S. Patent 3,567,748 (March 2, 1971) it may now be established that the "unknown substance" in example 1 is the 6-ethoxy α-pyrone **3** and the compound in example 2 is the hexadecylketene α-pyrone tetramer **5**.

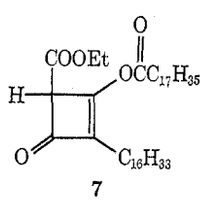
(6) The less precise method of molecular weight determination by thermistor technique gave a value of 714 g/mol.

the ring proton,[7] a quartet (2 H) at 4.25 ppm for ethoxy methylene protons, two overlapping triplets (2 H each) at 2.58 and 2.32 ppm, and the methylene envelope (1.8–0.8 ppm) corresponding to the remaining protons. The uv absorption maximum at 315 nm was in agreement with the α-pyrone structure assignment. The alternative γ-pyrone isomer was ruled out, since such structures absorb in the 250-nm range.[8]

A characteristic property of the alkoxy pyrone **3** is its facile, uncatalyzed reaction with 1 equiv of ethanol to form diethyl 2-hexadecyl-3-stearoyloxy-2-pentenedioate (**6**). Hydrolyses of **3** under controlled conditions enabled the isolation of stearoylacetic ester and of methyl heptadecyl ketone as shown in the following equation.

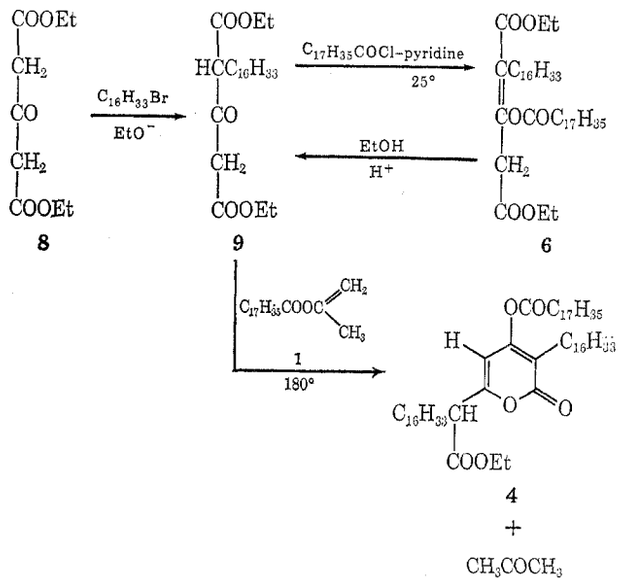


An alternative cyclobutenone structure **7** was considered and rejected. Although such a structure would



be expected to give **6** by an easy ring-opening reaction, cyclobutenones are reported to absorb near 250 nm[9] and not in the 315-nm region as we observed for **3**.

Since our conclusion on structure **3** rests directly on the correctness of the structure assignment **6** for the ring-opened product, we confirmed the latter structure by an independent synthesis. Alkylation of diethyl 3-oxoglutarate[10] (**8**) with hexadecyl bromide gave diethyl 2-hexadecyl-3-oxoglutarate (**9**). The latter was acylated with stearoyl chloride in pyridine to give a compound identical with the ring-opened product **6**. We were also able to hydrolyze selectively the enol ester–diester **6** to the diester **9**. Significantly, if the acylation of diester **9** was carried out, not with stearoyl chloride–pyridine, but rather with isopropenyl stearate (**1**) at elevated temperatures (conditions such as we routinely use to stearoylate substrate materials[3a]), we obtained good yields (as the sole product) of the α-pyrone **4**, "the companion substance." These interrelationships are clarified by the following sequence of equations.



Spectral data supporting the structure assignment **6** for the ring-opened product include the observation of the molecular ion $C_{43}H_{80}O_6$ (*m/e* 692.5970) in the high-resolution mass spectrum; bands in the ir spectrum at 1760 cm^{-1} attributable to enol ester carbonyl and at 1745 (saturated ester) and at 1629 cm^{-1} corresponding to olefinic unsaturation; and the nmr, which displays two overlapping quartets (4 H) at 4.17 and 4.12 ppm (CH_3CH_2O–), a singlet (2 H) at 3.72 ppm (C=CCH_2–COOEt–), overlapping triplets at 2.40 ppm (unlike pairs of α-CH_2 side chain units), and the usual methylene group envelope from 1.70 to 0.90 ppm. The ultraviolet spectrum shows only weak absorption at 220 nm.

The high-temperature transformation of the alkylated oxoglutarate **9** to the "companion pyrone" **4** deserves further comment. The structure proof of **4** includes observation of the molecular ion at *m/e* 912 (supported by the approximate value of 908 g/m determined by the thermistor method); the nmr spectrum shows a singlet at 6.13 ppm (ring proton), a quartet (2 H) at 4.24 ppm (CH_3CH_2OCO–), a triplet (1 H) at 3.45 ppm ($C_{16}H_{33}CHCOOEt$), and the composite absorption due to three lengthy alkyl chains. The ir spectrum has bands corresponding to enol ester, saturated ester, and the olefin function. The uv maximum at 297 nm is also in accord with the α-pyrone structure. Hydrolysis of **4** gave the carboxylic acid **10** with retention of the α-pyrone ring structure.[11] Analogously, for purposes of comparison, we used diethyl 3-oxoglutarate in reaction with **1** to prepare **11**. The carbethoxymethylene pyrone **11**, which resembles the "companion substance" **4** structurally in every way, except for the absence of the hexadecyl group from the

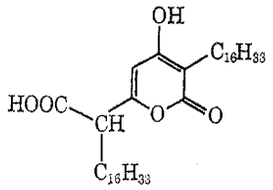
(7) This chemical shift of 5.30 ppm is almost 1 ppm further upfield than that observed for the 5 H in pyrones such as **4** where there is 6-alkyl instead of 6-ethoxy functionality. For nmr spectra of other 6-alkoxy α-pyrones, see A. Corbella, P. Garibaldi, G. Jommi, and G. Russo, *Gazz. Chim. Ital.*, **98**, 1096 (1968), and of ring protons in 6-alkylated cases, E. E. Kilbourn and M. C. Seidel, *J. Org. Chem.*, **37**, 1145 (1972).

(8) J. A. Berson, *J. Amer. Chem. Soc.*, **75**, 3521 (1953).

(9) R. B. Woodward and G. Small, Jr., *ibid.*, **72**, 1297 (1950).

(10) "Organic Syntheses," Collect. Vol. I, 2nd ed, H. Gilman and A. H. Blatt, Ed., Wiley, New York, N. Y., 1944, p 237.

(11) 6-Alkyl pyrones are far more resistant to attempted ring opening than are the highly sensitive 6-alkoxy pyrones.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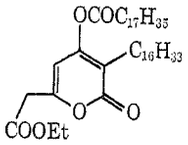
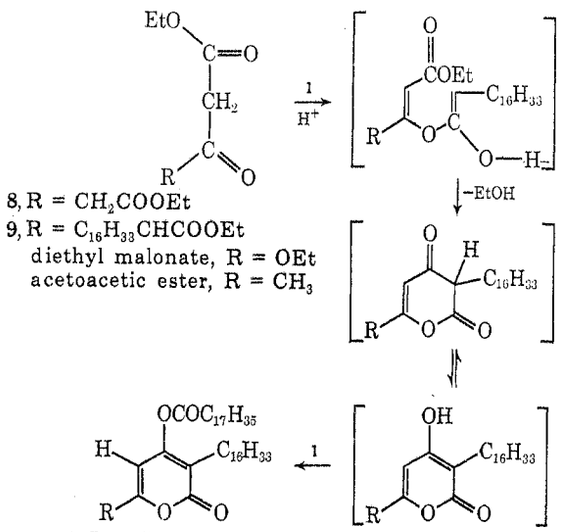

11

C-6 side-chain position, had the expected spectral properties (see Experimental Section).

The reaction of the 3-oxoglutarate **8** (or of the alkylated 3-oxoglutarate **9**) with isopropenyl stearate may be described in the scheme below as a sequence of steps involving an O-acylation, followed by the intramolecular C-acylation ring closure step, and, finally, enol O-acylation. Such a sequence also is in accord with the formation of the pyrone **3** from diethyl malonate and isopropenyl stearate, and also served to predict correctly formation of the pyrone product **12** from the reaction of acetoacetic ester with isopropenyl stearate.[12]


8, R = CH_2COOEt
9, R = $C_{16}H_{33}CHCOOEt$
diethyl malonate, R = OEt
acetoacetic ester, R = CH_3

3, R = OEt
4, R = $C_{16}H_{33}CHCOOEt$
11, R = CH_2COOEt
12, R = CH_3

In the initial O-acylation step, effected by means of isopropenyl stearate, reaction is probably favored by the irreversible elimination of acetone. In agreement with this view, we have found that *ethyl* stearate does *not* react with diethyl malonate under the same conditions.

The reactive 6-alkoxy pyrone system has received only scant attention in the literature. The single preparative procedure utilized by several researchers[13] uses fuming sulfuric acid to effect ring closure of "acetone dicarboxylic acid esters" to give low yields of mixtures of 2- and 6-alkoxy α-pyrones.

(12) The formation of the companion substance **4** in the reaction of isopropenyl stearate with diethyl malonate may result from the ethanolysis of **3** to **6** and then to **9** followed by reaction with isopropenyl stearate as shown in the generalized reaction scheme.

(13) G. Schroeter and C. Stassen, *Ber.*, **40**, 1604 (1907); G. Schroeter, H. Kesseler, O. Liesche, and R. F. Mueller, *ibid.*, **49**, 2697 (1916); G. Schroeter, *ibid.*, **59B**, 973 (1926).

Experimental Section

Melting points were determined on the Kofler stage but are otherwise uncorrected. Infrared spectra were recorded on a Perkin-Elmer[14] Model 457 grating instrument.

6-Ethoxy-3-hexadecyl-4-stearoyloxy-2*H*-pyran-2-one (3).—Isopropenyl stearate[15] (8.03 g, 0.0248 mol), diethyl malonate (10 ml, 0.066 mol), and *p*-toluenesulfonic acid (0.1 g) were heated at the boiling temperature until acetone evolution ceased[3f] (30–40 min). On cooling to 25°, a crystalline product separated and was collected, washed with hexane, and recrystallized from hexane (yield 70%): mp 76.0–76.7°; ir (CS_2) 1771 (enol ester), 1740 (lactone), and 1640 (C=C), characteristic doublet at 1111 and 1128 cm^{-1}; uv max (C_2H_5OH) 227 nm (ϵ 5800), 315 (8700); nmr ($DCCl_3$) δ 5.32 (s, 1, ring proton), 4.25 (q, 2, ethyl), two unresolved triplets centered at 2.32 and 2.58 ppm (α-acyl protons and alkyl ring-adjacent methylene protons); mass spectrum *m/e* (rel intensity) 646 (28, molecular ion), 380 (100), 284 (27), 267 (33), 222 (25), and 169 (18).

Anal. Calcd for $C_{41}H_{74}O_5$: C, 76.11; H, 11.53. Found: C, 76.19; H, 11.72.

Diethyl 2-Hexadecyl-3-stearoyloxy-2-pentenedioate (6). Procedure A.—A sample of **3** (100 mg) was heated in 10 ml of C_2H_5OH on the steam bath for 20 min without catalyst. On evaporation of the solvent a residue of crystalline **6**, mp 33–34°, was obtained identical in ir with an authentic specimen.

Procedure B.—Attempted purification of **3** by slow partition chromatography on silica gel (10 g impregnated with 4 ml of C_2H_5OH) (98% CH_2Cl_2/2% C_2H_5OH moving phase) gave pure **6** quantitatively: mp 48°; ir (CS_2) 1760 (enol ester C=O), 1745 (saturated ester C=O), 1716 (α,β-unsaturated ester C=O), 1629 (C=C), and 1112 cm^{-1} (prominent peak); nmr ($CDCl_3$) δ 3.75 (s, 2), overlapping quartets centered at 4.20 and 4.43 (4), 2.0–2.7 ppm (4); uv max (C_2H_5OH) 222 nm (ϵ 10,250); mass spectrum *m/e* (rel intensity) 692 (8, molecular ion), 426 (80), 381 (70), 362 (100), 267 (70).

Procedure C.—Diethyl 3-oxoglutarate[16] (19 g, 0.062 mol) in 60 ml of dry C_2H_5OH containing 2 g of dissolved sodium, 2 g of sodium iodide, and 11.5 g (0.062 mol) of hexadecyl bromide was refluxed for 7 hr and let stand overnight. The mixture was acidified (dilute HCl), extracted with ether, and dried (Na_2SO_4). After removal of solvent, the product was purified by chromatography on silica gel. The product, eluted with CH_2Cl_2, after recrystallization from pentane, melted at 48.0–48.2° (lit. mp 47–48°),[16] yield 10 g of diethyl 2-hexadecyl-3-oxoglutarate. The alkylated glutarate (0.21 g, 0.5 mmol) in 1 ml of dry pyridine was added to a cold solution of stearoyl chloride (160 mg) in 2 ml of pyridine and the mixture was then stirred at room temperature for 3.5 hr. After dilution with water, acidification (HCl), extraction (CH_2Cl_2), and drying (Na_2SO_4), the product showed the same infrared spectrum as **6** prepared from **3**. Purification was effected by chromatography on silica gel (note: Florisil is destructive) to give a product, mp 47–48°, identical with **6** described in procedures A and B above (and different from 2-hexadecyl 3-oxoglutarate coincidentally melting at the same temperature). The analytical sample crystallized from pentane retained one molecule of (clathrated?) pentane removable by a single recrystallization from carbon tetrachloride.

Anal. Calcd for $C_{43}H_{80}O_6$: C, 74.51; H, 11.64. Found: C, 74.57; H, 11.72.

Selective Ethanolysis of 6 to Diethyl 2-Hexadecyl-3-oxoglutarate (9).—To a sample of **6** (114 mg) in 10 ml of absolute ethanol was added 1 drop of concentrated sulfuric acid. The mixture was stirred and refluxed for 16 hr, poured into 25 ml of water, and extracted with ether to give, after solvent removal, 90 mg of residue. Crystallization from pentane gave 30 mg of starting material. The mother liquor fraction gave 59 mg of diethyl 2-hexadecyl-3-oxoglutarate, mp 43–45°, identical in ir and tlc R_f value with an authentic specimen.

Ethanolysis of 3 to Ethyl Stearoylacetate.—A sample of **3** (0.25 g) was refluxed for 2.5 hr with sodium ethoxide (from 0.06 g of Na) in 20 ml of absolute ethanol. After acidification (HCl), extraction (CH_2Cl_2), drying the organic layer, and removal of solvent, the residue was chromatographed on Florisil to give

(14) Reference to brand or firm name does not constitute endorsement by the U. S. Department of Agriculture over others of a similar nature not mentioned.

(15) E. S. Rothman and S. Serota, *J. Amer. Oil Chem. Soc.*, **48**, 373 (1971).

(16) E. Graf and K. C. Liu, *Arch. Pharm. (Weinheim)*, **300** (1), 348 (1967).

ethyl stearate, methyl heptadecyl ketone, and ethyl stearoylacetate, identical in ir and melting point with an authentic sample.[17]

Hydrolysis (Complete) of 3 to Methyl Heptadecyl Ketone.—A solution of **3** (0.14 g) in 9 ml of methanol and 1 ml of water containing 0.36 g of sodium hydroxide was refluxed for 2.3 hr, cooled, acidified (HCl), extracted into methylene chloride, and dried (Na_2SO_4), the solvent was evaporated, and the residue was purified by chromatography on silica gel. The 70% CH_2Cl_2–30% pentane eluate gave quadrilateral crystals, 30 mg, from cold methanol, identical in ir, glc retention time, and mass spectrum (molecular ion 282 g/m) with an authentic specimen. Stearic acid, 60 mg, mp 69–70°, was found in the later eluates.

6-(α-Carbethoxyheptadecyl)-3-hexadecyl-4-stearoyloxy-2*H*-pyran-2-one (4).—Diethyl 2 hexadecyl-3-oxoglutarate (**9**) (2.3 g, 5.4 mmol) and isopropenyl stearate (3.2 g, 0.01 mol) were heated with 5 mg of *p*-toluenesulfonic acid to 190° for 25 min, during which time acetone was evolved. Chromatography of the cooled reaction mixture on Florisil using warm 5% CH_2Cl_2–95% hexane as the eluting agent (to prevent crystallization on the column) gave a good yield of **4** in the earliest cuts. Recrystallization from hexane gave the analytical sample, mp 71–72°, identical in ir, nmr, and melting point with a sample laboriously isolated from mother liquors from the isopropenyl stearate–diethyl malonate reaction mixture described above. The product showed the following spectra: nmr ($CDCl_3$) δ 6.15 (s, 1), 4.23 (q, 2), 3.45 (t, 1), 2.5 (two overlapping α-methylene triplets); ir (CS_2) 1770 (enol ester C=O), 1730 (lactone C=O), 1648 (C=C), 1109 cm^{-1} (characteristic peak); mass spectrum *m/e* (rel intensity) 912 (1, molecular ion), 647 (13), 646 (20), 629 (10), 602 (16), 435 (16), 435 (6), 422 (6), 336 (100) ($C_{21}H_{36}O_3$), 112 (25); uv max (C_2H_5OH) 210 nm (ε 9000), 300 (10,300).

Anal. Calcd for $C_{59}H_{108}O_6$: C, 77.57; H, 11.92. Found: C, 77.88; H, 12.16.

6-(α-Carboxyheptadecyl)-3-hexadecyl-4-hydroxy-2*H*-pyran-2-one. Hydrolysis of 4 to 10.—A sample of **4** (0.1 g) in 6 ml of ethanol containing 0.17 g of potassium hydroxide was refluxed for 3 hr and let stand for 24 hr. After acidification (HCl), extraction (CH_2Cl_2), drying (Na_2SO_4), and solvent evaporation, the residue was chromatographed on silica gel. Elution with methylene chloride removed impurities. Elution with ether gave the product acid, mp 109–110°, unchanged by recrystallization from pentane: uv max (C_2H_5OH) 210 nm (ε 12,900), 292 (9000); ir ($CHCl_3$) broad band 3450–2400 (OH), broad band 1660–1710 (C=O), 1582 cm^{-1}.

Anal. Calcd for $C_{39}H_{70}O_5$: C, 75.68; H, 11.40. Found: C, 75.59; H, 11.29.

6-Carbethoxymethylene-3-hexadecyl-4-stearoyloxy-2*H*-pyran-2-one (11).—A mixture of diethyl 3-ketoglutarate (**8**) (2.0 g, 0.01 mol), isopropenyl stearate (4.5 g, 0.013 mol), and *p*-toluenesulfonic acid (160 mg) was heated at 160° for 23 min. After cooling, the mixture was dissolved in pentane and cooled to deposit 1.05 g of the α-pyrone **11**. One pass through a short column of Florisil using 25% methylene chloride in pentane as eluting agent gave, after isolation and recrystallization, analytically pure material: mp 72–73°; nmr ($CDCl_3$) δ 6.3 (s, 1), 4.35 (q, 2), 3.61 (s, 2); ir (CS_2) 1770, 1730, 1648, 1109 cm^{-1}; mass spectrum *m/e* (rel intensity) 688 (0.5, molecular ion), 422 (25), 335 (6), 211 (100), 165 (50).

Anal. Calcd for $C_{43}H_{76}O_6$: C, 74.95; H, 11.12. Found: C, 75.13; H, 11.41.

Reaction of Ethyl Acetoacetate with Isopropenyl Stearate. 6-Methyl-3-hexadecyl-4-stearoyloxy-2*H*-pyran-2-one (12).—Isopropenyl stearate (30 g, 0.094 mol) and dry ethyl acetoacetate (37 g, 0.26 mol) were refluxed with 0.05 g of *p*-toluenesulfonic acid for 0.5 hr. Pentane was added to the product and the mixture was cooled in a freezer and then filtered cold. The precipitate and the filtrate were separately chromatographed on silica gel. Elution of the precipitate fraction with pentane containing methylene chloride gave stearic anhydride, ethyl stearate, and **12** (14.6 g, 25%), which melted at 75–76° after recrystallization from pentane: ir (CS_2) 1770, 1729, 1651, 1109 cm^{-1}; nmr ($CDCl_3$) δ 5.98 (s, 1), 2.6 (two overlapping triplets, 4), 2.22 (s, 3), 1.9–0.7 (m, 64); uv max (C_2H_5OH) 292 nm (ε 7000).

Anal. Calcd for $C_{40}H_{72}O_4$: C, 77.86; H, 11.76. Found: C, 78.28; H, 11.87.

The filtrate fraction was eluted with pentane and methylene chloride to give ethyl stearate and 6.0 g (17%) of the enol stearate of ethyl acetoacetate (ethyl 3-stearoyloxy-2-butenoic acid): mp 42.7–43.4°; ir (CS_2) 1768, 1729, 1670, 1220, 1144, 1108, 1055 cm^{-1}; nmr ($CDCl_3$) 5.68 (s, 1), 4.22 (q, 2), 2.58 (t, 2), 2.07 (s, 3), 1.9–0.7 (m, 36); uv max (C_2H_5OH) 218 nm (ε 9000).

Anal. Calcd for $C_{24}H_{44}O_4$: C, 72.68; H, 11.18. Found: C, 72.42; H, 11.28.

Registry No.—**3**, 40317-84-8; **4**, 40110-40-5; **6**, 40110-41-6; **8**, 105-50-0; **9**, 14251-08-2; **10**, 40110-44-9; **11**, 40110-45-0; **12**, 40110-46-1; isopropenyl stearate, 6136-89-6; diethyl malonate, 105-53-3; hexadecyl bromide, 111-82-3; stearoyl chloride, 112-76-5; ethyl acetoacetate, 141-97-9; ethyl 3-stearoyloxy-2-butenoic acid, 40110-47-2.

Acknowledgment.—The authors are grateful to Dr. Charles Hignite of the Massachusetts Institute of Technology and Mr. Calvin Dooley for mass spectrographic data on unusually difficult compounds; to Mrs. A. Kravitz and L. Scroggins for elemental analyses; and to Mr. J. M. Chirinko for technical assistance.

(17) F. Bergel, A. Jacob, A. R. Todd, and T. S. Work, *J. Chem. Soc.*, 1375 (1938).