

A brown oil separated which was extracted with ether. The product distilled at 93–97° (12–13 mm.), giving 30.1 g. (91.2% yield); n_D^{25} 1.5114.²

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.17. Found: C, 81.26; H, 8.29.

This aldehyde gave positive tests with both Tollens and Schiff reagents. The semicarbazone was recrystallized from 50% water-ethanol, m.p. 178–179°.¹

α -Phenylisobutyric Acid.—Forty-six grams of α -phenylisobutyraldehyde was dissolved in 320 ml. of a 30% methanol-water solution containing 115 g. of silver nitrate. To this solution was added 50.6 g. of sodium hydroxide dissolved in 920 ml. of water. This slurry was boiled under reflux for 1.5 hours. The hot mixture was filtered and the cooled filtrate acidified with dilute nitric acid to produce a colorless, flocculent precipitate, wt. 27.8 g., m.p. 74–77°. An additional 10 g. of crude product was obtained by ether extraction of the filtrate. Recrystallization from aqueous methanol gave the pure product, m.p. 77–78°.⁴

α -Phenylisobutyryl Chloride.—Thirty grams of α -phenylisobutyric acid was heated under reflux for 45 minutes with 30 g. of thionyl chloride. The colorless product was fractionally distilled under vacuum; b.p. 94–96° (10 mm.);⁴ yield 17 g. (50%). A higher boiling fraction, b.p. 194–196° (7 mm.), which produced no acidic product on warming with sodium hydroxide followed by treatment with hydrochloric acid was not identified.

β' -Diethylaminoethyl- α -phenylisobutyrate Hydrochloride (β' -Diethylaminoethyl- α -methylhydratropate Hydrochloride).—A 13.5-g. (0.074 mole) sample of α -phenylisobutyryl chloride was added over a period of two minutes to 100 ml. of dry ether solution of 16.5 g. (0.148 mole) of β -diethylaminoethanol. After standing at room temperature for 17 hours the theoretical amount of β -diethylaminoethanol hydrochloride was removed from the reaction mixture by filtration. The ether solution, after washing with cold water, drying and treatment with dry hydrogen chloride gas, gave 15.0 g. of a colorless product, m.p. 134–136°.⁵ The melting point was unchanged after recrystallization from a mixture of dry ether and absolute ethanol. This product is very soluble in water.

Anal. Calcd. for $C_{18}H_{26}NO_2Cl$: C, 63.94; H, 8.74. Found: C, 64.01; H, 8.47.

γ,γ -Dimethyl- γ -phenylcrotonic Acid.—A mixture of 14.8 g. (0.10 mole) of α -phenylisobutyraldehyde, 11.4 g. (0.11 mole) of pure, dry malonic acid, 7.9 g. of dry pyridine and 0.5 ml. of piperidine was heated at 100° until the evolution of carbon dioxide had ceased (four hours). The cooled reaction mixture was diluted with 10 ml. of concd. ammonium hydroxide. The non-acidic layer was removed by ether extraction and distilled to return 12.2 g. of the starting aldehyde. Acidification of the basic solution with hydrochloric acid produced 0.45 g. (2.4% yield) of the crude acid, m.p. 84–86°. Recrystallization from aqueous ethanol or low boiling petroleum ether gave a colorless, crystalline product, m.p. 86.5–87.5°. This unsaturated acid readily reduced potassium permanganate in a 95% ethanol solution.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; neut. equiv., 190. Found: C, 75.71; H, 7.53; neut. equiv., 191, 192.

The employment of excess amounts of malonic acid and longer reaction times did not improve the yield.

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Acyl Migrations in Partially Acylated, Polyhydroxylic Systems¹

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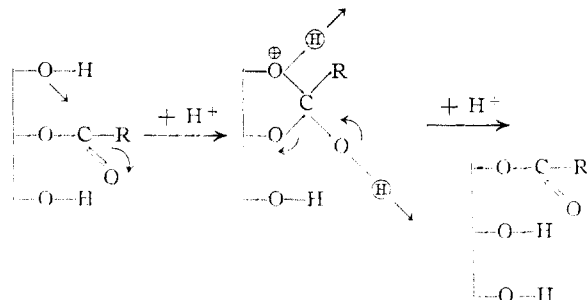
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Rearrangements involving acyl migrations under mild conditions are well known in a variety of par-

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tially acylated hydroxyamino systems and polyhydroxylic systems possessing the proper spatial relationships.³ The rearrangement of 1,2-diglycerides to 1,3-diglycerides has been used extensively in synthetic work.⁴ A mechanism proceeding through a cyclic orthoester intermediate has been suggested⁵ and a transition-state mechanism of the type:



is consistent with the facts that the benzoyl group does not migrate as readily as aliphatic acyl groups and that systems possessing R's that are strongly electron-attracting exist as cyclic orthoesters.^{6–8} The acyl group transfer in the rearrangement is postulated as intramolecular, in contrast to the intermolecular acyl group transfers observed in the catalyzed, directed, glyceride interesterification reactions.⁹

We have carried out the rearrangement of 2-monopalmitin¹⁰ in the presence of glycerol-1- C^{14} and have observed no incorporation of C^{14} into the 1-monopalmitin product. The counting tube sensitivity, geometry and background, the sample size and character, and the specific radioactivity relationships during the experiments were such that an incorporation of glycerol-1- C^{14} into the 1-monopalmitin on the part of 1% of the molecular rearrangements could have been measured and on the part of 0.3% easily detected. The results show that mechanisms involving hydrolysis and re-esterification play no part of consequence in this type rearrangement and suggest that the rearrangement reaction path is entirely intramolecular.

Experimental

331 mg. (1 mM.) of 2-monopalmitin¹¹ was added to 381 mg. (4.1 mM.) of glycerol-1- C^{14} , prepared from tartaric acid by oxidation to dihydroxymaleic acid, decarboxylation to hydroxyacetaldehyde, addition of $HC^{14}N$, hydrolysis, esterification, acetylation and reduction with lithium aluminum hydride¹² and containing a total radioactivity of 1.30×10^8 c.p.m. The mixture was dissolved in a minimum of warm ethanol containing 0.6 N HCl, allowed to remain for 36 hours at room temperature, and then cooled to -18° . The resulting crystals were dissolved in ethyl ether and the solution washed with water. The washed product after

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(11) The author wishes to express his appreciation to Prof. B. F. Daubert, Department of Chemistry, The University of Pittsburgh, for his generous gift of crystalline 2-mono-palmitin (m.p. 68.5°).¹³

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drying was recrystallized from ethyl ether, dried, and the crystals (m.p. 77.0°)¹² mounted directly on a sample pan and counted for C¹⁴ in a windowless, Q-gas flow counting tube operated in the Geiger-Müller region. No radioactivity could be detected within the limits of the precision of the measurements. A second determination yielded the same result.

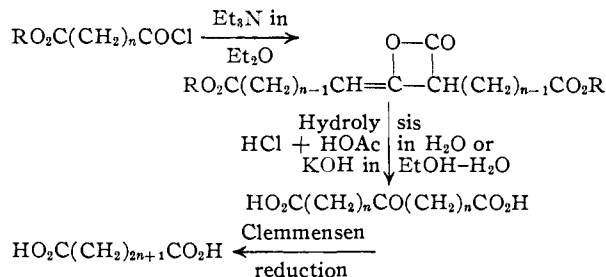
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Synthesis of Odd-numbered Keto Dibasic Acids and Corresponding Saturated Acids

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Odd-numbered keto dibasic acids of the type HO₂C(CH₂)_nCO(CH₂)_nCO₂H and related saturated acids, HO₂C(CH₂)_{2n+1}CO₂H, were desired as intermediates for syntheses of many-membered carbon rings. Recently Leonard and Goode¹ described the preparation of several acids of this kind *via* the dialkylation of acetonedicarboxylic ester with ω -halogen esters, a procedure first reported by von Pechmann and Sidgwick.² However, it seemed that the desired acids might be obtained in quantity more conveniently through application of the method used by Sauer in his preparation of 6-oxo-1,11-hendecanedioic acid from δ -carbethoxyvaleryl chloride through γ -carbethoxypropylketene dimer.³ The method in general terms is indicated in the following diagram.



By this method δ -ketoazelaic acid (I) was obtained as its diethyl ester in 42–52% yield from γ -carbomethoxybutyryl chloride. In this synthesis the best results were obtained by hydrolyzing the intermediate ketene dimer with hydrochloric acid in acetic acid–water, thus avoiding intramolecular condensation of the keto acid. The higher keto dibasic acids, 9-oxo-1,17-heptadecanedioic acid (II) and 10-oxo-1,19-nonadecanedioic acid (III), were obtained in excellent yield (85–95%) from the appropriate acid chlorides. The intermediate ketene dimers were best hydrolyzed by an ethanol–water solution of potassium hydroxide.³

Clemmensen reduction of II and III gave 1,17-heptadecanedioic acid and 1,19-nonadecanedioic acid in yields of 80 and 63%, respectively.

The availability of ω -carbalkoxy acid chlorides and the ease with which they may be transformed *via* the ketene dimers to the corresponding keto di-

basic acids, recommends Sauer's method as a useful one for preparing the odd-numbered symmetrical keto dibasic acids. The Clemmensen reduction of these keto acids to saturated odd-numbered dibasic acids is also a satisfactory process.

Experimental⁴

Materials.—Thionyl chloride, anhydrous ether and triethylamine were purified as previously described.⁵ Acid chlorides of mono esters of dibasic acids were prepared by treating the carbalkoxy acids with thionyl chloride. Those used showed the following properties: γ -carbomethoxybutyryl chloride, b.p. 105–110° (20 mm.), n_D^{20} 1.444–1.446; ω -carbomethoxycaprylyl chloride, b.p. 127.5–130° (3.3 mm.); ω -carbethoxypelargonyl chloride, b.p. 174–176° (15 mm.).

δ -Ketoazelaic Acid (I).—The procedure used was similar to that described by Sauer for the preparation of 6-oxo-1,11-hendecanedioic acid³ but some important modifications were made. γ -Carbomethoxybutyryl chloride (330 g., 2 moles) was added rapidly to a cooled, well stirred solution of 242 g. (2.4 moles) of triethylamine in 2 l. of anhydrous ether, all under an atmosphere of purified nitrogen. After completion of the addition, stirring of the mixture under nitrogen was continued for 24 hr. at room temperature. Then 40–50 ml. of a solution of 350 ml. of concentrated hydrochloric acid in 490 ml. of glacial acetic acid was added with stirring, followed by the addition of 300 ml. of water. The ether layer was separated and the aqueous layer extracted with four 300-ml. portions of ether. Tarry material, which separated during the acidification and which was insoluble both in ether and in water, was dissolved in acetone and combined with 100 ml. each of concentrated hydrochloric acid and acetic acid. This mixture was evaporated on the steam-bath and the resulting residue combined later with the main hydrolysate. The combined ether solutions were added to ca. 800 ml. of the hydrochloric acid–acetic acid solution described above and, after distillation of the ether, the residue was refluxed 6 hr. This residue, combined with the hydrolyzed tars mentioned previously, was evaporated on the steam-bath. A mixture of 200 ml. each of concentrated hydrochloric acid and acetic acid was added to the non-volatile residue and the whole evaporated again on the steam-bath. Subsequently 200 ml. of water was added to the residue and the mixture again evaporated on the steam-bath. After repeating this last treatment and finally heating the residue on the steam-bath for 12 hr. there was obtained 225–235 g. of crude I suitable for esterification.

Pure I was obtained by extracting the crude acid with chloroform, adding petroleum ether to the extract, and recrystallizing the precipitated acid from water: m.p. 109–109.6°; neut. equiv., 100.5; phenylhydrazone deriv., m.p. 149–151.1°.^{1,2,6}

Diethyl δ -ketoazelaic acid was prepared following the procedure of Leonard and Goode¹ using the crude I described above. The crude I obtained from 330 g. (2 moles) of γ -carbomethoxybutyryl chloride gave 110–135 g. of the ester: b.p. 137–155° (0.5 mm.). This 42–52% yield for the two steps from the acid chloride is based on twenty preparations. A sample of this diester redistilled showed the following properties: b.p. 142° (0.3 mm.); n_D^{20} 1.4459; d_4^{20} 1.0545; sapon. no. 126.8, 125.4; semicarbazone deriv., m.p. 78.5–79° from chloroform–ligroin.¹

9-Oxo-1,17-heptadecanedioic Acid (II) and 10-Oxo-1,19-nonadecanedioic Acid (III).—Following essentially the procedure of Sauer,³ ω -carbomethoxycaprylyl chloride and ω -carbethoxypelargonyl chloride were dehydrochlorinated to give the corresponding crude ketene dimers. These dimers were then hydrolyzed using a solution of potassium hydroxide in ethanol–water, also as described by Sauer.³

The unrecrystallized III obtained (98.5% yield) showed m.p. 117–119.5°.⁷ II after one recrystallization from ethanol showed m.p. 113–115°.⁸

(4) Boiling points are uncorrected. Melting points are corrected.

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