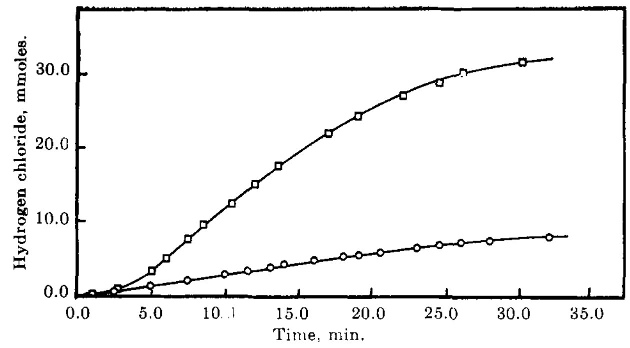

Fig. 2.—Rates of hydrogen chloride evolution in the reaction of (○) benzene and (□) biphenyl with aluminum chloride–cupric chloride in *o*-dichlorobenzene at 40°.

similar manner [metal halide, g. (mole), undissolved halide, g.]: cuprous chloride, 6.24 (0.063), 6.23; aluminum chloride, 8.40 (0.063), 0.92; aluminum chloride–cuprous chloride, 8.30:6.24 (0.063:0.063), 1.0.

Relative Rates. A. Benzene, Biphenyl, and *p*-Terphenyl at 80°.—The reactions were carried out according to the general procedure with the aromatic reactant (0.125 mole) in *o*-dichlorobenzene (1.5 moles). After the introduction of anhydrous aluminum chloride (0.063 mole), the mixture was heated to 79° with vigorous stirring under dry nitrogen (flow rate, 140 ml./min.). Anhydrous cupric chloride (0.063 mole) was added in a single portion and the reaction was followed at 80–81° by titration of the evolved acid gas with standard base. The rate data (average of two runs; deviation, ±7%) are summarized in Fig. 1.

B. Benzene and Biphenyl at 40°.—Rate data (average of two runs; deviation, ±2%) obtained at 40–41° in a similar manner are plotted in Fig. 2.

Authentic *p*-Sexiphenyl.—Synthesis of this compound was accomplished according to the procedure of Nozaki and coworkers,[6] m.p. 460–462° (sublimation and crystallization from 1,2,4-trichlorobenzene), lit.[30] m.p. 465°; infrared spectrum, absorption maximum, 811 cm.$^{-1}$; ultraviolet spectrum, λ_{max} 317 mμ.

Acknowledgment.—The authors wish to express their thanks to the National Science Foundation for partial support of this work.

Silicic Acid Chromatographic Study of the Catalytic Hydrogenation Products of 9,10-Epoxystearates[1]

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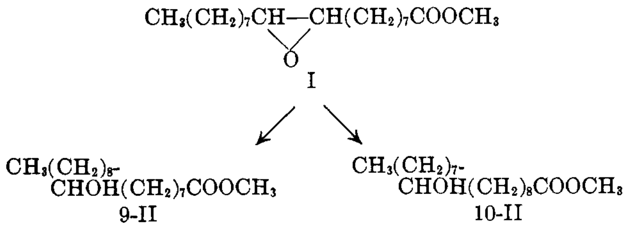
Received March 26, 1964

Hydrogenation of methyl *cis*-9,10-epoxystearate over palladium on charcoal in glacial acetic acid yields a mixture shown by silicic acid column chromatography to consist mainly of hydroxystearates, together with smaller amounts of stearate and ketostearates. Contrary to conclusions reached in earlier studies, degradation of the principal product (purification of the intermediate ketostearates, oximinostearates, and Beckmann-rearranged isomeric amido esters solely by adsorption chromatography assuring no discrimination between positional isomers) demonstrates that the 9- and 10-hydroxystearates are in fact formed in equal amounts.

Catalytic hydrogenolytic opening of the oxide ring of methyl 9,10-epoxystearates (I), (or of the free acids, readily obtained[2] by action of peracids on oleic and elaidic acids, would be expected *a priori* to yield equal amounts of DL-9- and -10-hydroxystearates (II), since the methyl and carboxyl termini of the oxide ring substituents are far too remote to impress any appreciable asymmetric reactivity on the site of reaction by inductive effects conducted along the long intervening polymethylene chains. Zook and Knight,[3] for example, have shown that a carboxyl group only two methylene groups away has very little influence on the randomness with which HBr adds to an olefinic center. Even more directly pertinent is the recent report[4] that catalytic hydrogenation of *cis*-6,7-epoxystearic acid yields equal amounts of DL-6- and -7-hydroxystearic acids.



$$\mathrm{CH_3(CH_2)_7\underset{\diagdown\,O\,\diagup}{CH{-}CH}(CH_2)_7COOCH_3}$$

I

$$\mathrm{CH_3(CH_2)_8\text{-}CHOH(CH_2)_7COOCH_3} \qquad \mathrm{CH_3(CH_2)_7\text{-}CHOH(CH_2)_8COOCH_3}$$

9-II 10-II

It is therefore difficult to rationalize the claims of a number of investigators[5-8] who have, without exception, indicated the predominant formation of 10-II[9] by hydrogenation of I. The patent improbability of such conclusions recommends careful examination of the evidence upon which they were based. In every case, samples of the product of interest were isolated by crystallization and identified solely (with a single exception[6]) on the basis of the melting behavior of the hydroxy acids, of the keto acids obtained from them by chromic acid oxidation, or of the corresponding semicarbazones. Following careful study of the phase properties of the 9- and 10-keto- and -DL-hydroxystearic acids, Cochrane and Harwood[10] have recently called attention to the strong possibility that these findings (together with a number of others bearing on the course of related reactions) were misinterpreted.

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[1] This paper is based on work performed under Contract AT(04-1)-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles.

[2] T. W. Findley, D. Swern, and J. T. Scanlan, *J. Am. Chem. Soc.*, **67**, 412 (1945).

[3] H. D. Zook and J. A. Knight, *ibid.*, **76**, 2302 (1954).

[4] S. P. Fore and W. G. Bickford, *J. Org. Chem.*, **26**, 2104 (1961).

[5] I. G. V. Pigulevskii and Z. Y. Rubashko, *J. Gen. Chem. USSR*, **9**, 829 (1939); *Chem. Abstr.*, **34**, 378^2 (1940).

[6] J. Ross, A. I. Gebhart, and J. F. Gerecht, *J. Am. Chem. Soc.*, **71**, 284 (1949).

[7] C. H. Mack and W. G. Bickford, *J. Org. Chem.*, **18**, 686 (1953).

[8] F. J. Julietti, J. F. McGhie, B. L. Rao, W. A. Ross, and W. A. Cramp, *J. Chem. Soc.*, 4517 (1960).

[9] Even, in one case,[7] to the exclusion of 9-II; cursory perusal of the literature has revealed occurrence of at least two instances in which this claim has led to preparation of "authentic" samples of 10-hydroxystearic acid by this procedure.

[10] C. C. Cochrane and H. J. Harwood, *J. Org. Chem.*, **26**, 1278 (1961).

It seems important to point out that in none of these studies of the course of hydrogenation of I (or of the corresponding free acids) was it established that isolation by crystallization is indiscriminate with respect to the isomers of II or of its derivatives. Moreover, in none were the structures of the products confirmed by unequivocal degradation techniques.

Interest in the 9- and 10-hydroxystearic acids in connection with other studies[11] thus led to the present reexamination of the catalytic hydrogenation products of the 9,10-epoxystearates, using silicic acid column adsorption chromatography (instead of crystallization or recrystallization) to isolate truly representative samples of the desired product and to purify intermediates in its systematic degradation to substances, the structure and relative yields of which would establish its composition conclusively.

Hydrogenation of chromatographically purified methyl *cis*-9,10-epoxystearate (*cis*-I, see Fig. 1a) under conditions essentially identical with those employed by Mack and Bickford[7] and chromatography of the total reaction product on a column of activated silicic acid disclosed (see Fig. 1b) that, in addition to the major product (hydroxystearate, peak C), two others (peaks A and B) of lower adsorption affinity are produced.

Substance A was identified by chromatographic behavior, melting point, and mixture melting point as methyl stearate. Although elimination of epoxide oxygen from certain specially substituted ethylene oxides by catalytic hydrogenation has been reported,[12] such an eventuality does not appear to have been recognized previously in the case of simpler epoxides.[13] Since the hydroxy esters are clearly not intermediates in the formation of stearate, it might be imagined that the deoxygenation involves essentially simultaneous addition of four hydrogen atoms to one side of the oxide ring, in which case the reaction would be expected, for steric reasons, to proceed more readily with the *cis* than with the *trans* epoxide. The latter (*trans*-I) was indeed found to give a smaller yield of stearate under the same conditions.[16]

On the basis of its chromatographic behavior alone, product B (Fig. 1b) might have been thought to be residual unchanged epoxy ester. It is considerably higher melting (42°) than the starting material (m.p. 17°), however, and was shown by infrared spectrophotometry to be methyl ketostearate (presumably an equimolar mixture of the 9- and 10-isomers; the mixture of ketostearates obtained by chromic acid oxidation of the major hydrogenation product C melts at 41°). Coleman and Swern[17] have also identified ketostearic acids among products of hydrogenation of the free acid corresponding to I under the conditions employed here. Although the mechanism of this isomerization has not been established, its occurrence suggests that to some extent the epoxide group, following attachment of the first ring-opening hydrogen atom, may, instead of adding a second to give the major product (hydroxystearate), return another to the catalyst, yielding a keto (or the tautomeric enol) group which is inert toward hydrogenation over palladium. It was established that the keto esters are neither present in the starting material nor produced by action of glacial acetic acid (solvent used during hydrogenation) on the epoxy esters.

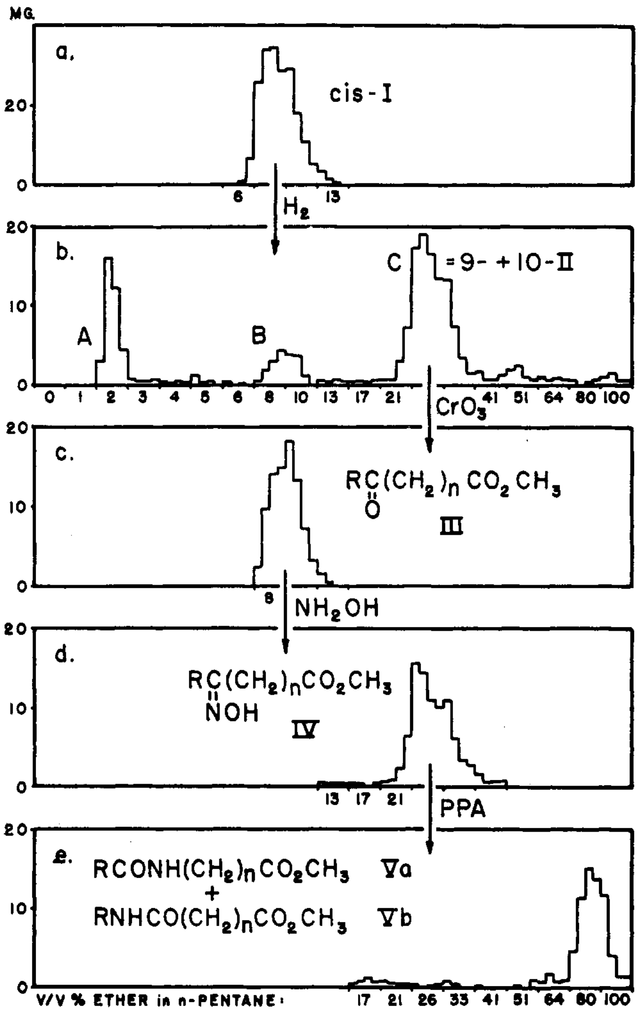

Fig. 1.—Silicic acid column chromatograms of *cis*-I, of its hydrogenation products, and of intermediates in the degradation of the major product. Weights of material eluted by half column-volumes of solvent are plotted against the compositions of the *n*-pentane–diethyl ether solvent mixtures employed in developing the chromatogram. The limited solubility of V in less polar solvent mixtures necessitated use in its chromatography (Fig. 1c) of six column-volumes of 13% ether in pentane in place of the usual (and essentially equivalent in elution efficacy) two volumes each of the 0–10% mixtures before continuing the development with the standard series, which is indicated in full on the Fig. 1b abscissa; PPA = polyphosphoric acid; R = C_8H_{17} or C_9H_{19}; *n* = 8 or 7, respectively.

That the major product (peak C, Fig. 1b) of the hydrogenation of *cis*-I is indeed a mixture is immediately ap-

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[11] D. R. Howton, *Radiation Res.*, **20**, 161 (1963).

[12] R. E. Lutz and J. L. Wood, *J. Am. Chem. Soc.*, **60**, 224 (1938); O. Gawron, T. P. Fondy, and D. J. Parker, *J. Org. Chem.*, **28**, 700 (1963).

[13] While the present work was in progress, Fore and Bickford[4] reported that catalytic hydrogenation of *cis*-6,7-epoxystearic acid also yielded some stearic acid. That such oxides may react in this way is of considerable interest in connection with the polemic of Walsh[14] and Robinson[15] over the former's "π-complex" depiction of the ethylene oxide group. One argument cited against the concept was that ". . .ethylene oxide is not reduced to ethylene. . ." It seems reasonable to suggest involvement of an olefinic intermediate (which may, of course, never escape the catalyst surface) in the reductions at hand.

[14] A. D. Walsh, *Nature*, **159**, 165, 712 (1947).

[15] R. Robinson, *ibid.*, **159**, 400 (1947); **160**, 162 (1948).

[16] The over-all rate of hydrogenation of the *trans* isomer is one-tenth that of the *cis*. In terms of the influence of the different configurations of these substances on their adsorption properties, this observation parallels that of the appreciably lower adsorption affinity of the *trans* ester for silicic acid (see Experimental).

[17] J. E. Coleman and D. Swern, *J. Am. Oil Chemists' Soc.*, **32**, 221 (1955).

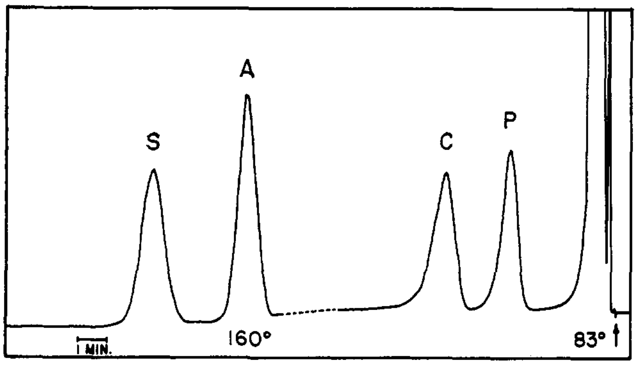

Fig. 2.—Gas chromatogram of neutral methyl esters obtained by methanolysis of amido esters (V). Reading from the right, the first peak following injection (arrow) is solvent (toluene), followed by pelargonate (P), and caprate (C). A portion of the graph (see dotted section) has been deleted, where the column temperature was increased rapidly (at 30°/min.) and the base line readjusted manually. The peaks of azelate (A) and sebacate (S) then follow.

parent from its melting point (44–45°; 9- and 10-II melt[10] at 50–51.5° and 54–55°, respectively). Its composition was established by application of the conventional degradation procedure outlined in Fig. 1 and by gas chromatographic determination of the relative amounts of both mono- and dicarboxylic esters obtained by action of boron trifluoride–methanol on the amido esters (V).

Each intermediate in the degradation was purified solely by chromatography on silicic acid, advantage being taken of the fact that differences in the adsorption affinities of close positional isomers are small, while those between the successive types of substances involved in the degradation sequence are large (Fig. 1).[18]

Oxidation of the hydroxy esters (II) by means of the chromic acid–pyridine reagent of Sarett[19] gave the keto esters (III), m.p. 41°, which were converted in the usual way to the oily oximino esters (IV). Beckmann rearrangement of the esters IV, induced by action of polyphosphoric acid,[20] gave a mixture of amido esters (V), m.p. 43–44°. In order to minimize differential loss of the relatively volatile monocarboxylic esters, a technique by which V could be methanolyzed in a sealed tube was devised, using N-*n*-heptylcaprylamide (derived from di-*n*-heptyl ketone by the same series of reactions used in converting III to V) as a model substance. As indicated in Diagram I below, methanolysis of the amido esters derived from 9-hydroxystearate yields methyl caprate (C) and dimethyl azelate (A), while those from 10-hydroxystearate give methyl pelargonate (P) and dimethyl sebacate (S).

After heating a sample of the mixed amido esters (V) with boron trifluoride–methanol in a sealed tube at 100° for 52 hr. (conditions calculated to result in 94% methanolysis), the reaction mixture was partitioned between water and toluene and samples of the dried toluene phase were analyzed by gas chromatography on a polyester column; a typical chromatogram is shown in Fig. 2.

DIAGRAM I

$$\underset{\text{9-II}}{CH_3(CH_2)_8CHOH(CH_2)_7COOCH_3}$$

$$\downarrow$$

$$CH_3(CH_2)_8NHCO(CH_2)_7COOCH_3 \longrightarrow CH_3(CH_2)_8NH_2 + \underset{\text{A}}{(CH_2)_7(COOCH_3)_2}$$

$$+$$

$$CH_3(CH_2)_8CONH(CH_2)_7COOCH_3 \longrightarrow NH_2(CH_2)_7COOCH_3 + \underset{\text{C}}{CH_3(CH_2)_8COOCH_3}$$

$$CH_3(CH_2)_7CHOH(CH_2)_8COOCH_3 \text{ 10-II}$$

$$\downarrow$$

$$CH_3(CH_2)_7NHCO(CH_2)_8COOCH_3 \longrightarrow CH_3(CH_2)_7NH_2 + \underset{\text{S}}{(CH_2)_8(COOCH_3)_2}$$

$$+$$

$$CH_3(CH_2)_7CONH(CH_2)_8COOCH_3 \longrightarrow NH_2(CH_2)_8COOCH_3 + \underset{\text{P}}{CH_3(CH_2)_7COOCH_3}$$

Data obtained from this and other chromatograms, including those given by known-composition mixtures of authentic esters, permitted evaluation of mole ratios P–C = 0.95 and S–A = 1.01, which represent the ratio of 10- to 9-hydroxystearate in the products of 9,10-epoxystearate hydrogenation and lead to the conclusion that opening of the epoxide ring in either of the two possible directions is essentially indiscriminate.[21]

Experimental

Melting points were obtained using open capillary tubes heated at 1°/min. (at the melting point) in a silicone oil bath or, for material melting below room temperature (only the temperature of disappearance of the solidus is reported for such samples), in water or acetone baths contained in an unsilvered cylindrical Dewar flask. All melting points are corrected.

Analyses were performed by the Elek Micro Analytical Laboratories, Los Angeles, Calif.

Adsorption chromatography was carried out as described in some detail elsewhere,[11] using 3.2 × 10 cm. columns of J. T. Baker Chemical Co. silicic acid powder, untreated except for activation *in situ* by prewashing with acetone, ether, and *n*-pentane (Phillips Petroleum Co. "Pure Grade"). With certain lots of this adsorbent, cutting with 5% (by weight) of Celite 545 was necessary to obtain satisfactory flow rates. Chromatograms were developed with *n*-pentane mixed with regularly increased amounts of ether, using two column-volumes of each of a standard series of mixtures (see abscissas of Fig. 1) unless otherwise indicated, and collecting one-half column-volume eluate fractions.

Oleic acid was obtained[22] from olive oil by saponification and removal of saturated fatty acids from the resulting mixture by low temperature crystallization from acetone.

Elaidic acid was prepared by selenium-catalyzed isomerization of oleic acid[23] followed by purification by repeated crystallization from acetone at −20° until the product was gas chromatographically pure. A sample of methyl elaidate obtained in the course of chromatographically purifying incompletely epoxidized elaidic acid (see below) melted at 10.2°, in agreement with an earlier report.[24]

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[18] Inasmuch as the yields in none of the four degradation steps is quantitative, it has been assumed that no appreciable discrimination between positional isomers occurs during the reactions involved; the final result supports the validity of this assumption.

[19] G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 427 (1953).

[20] E. C. Horning and V. L. Stromberg, *ibid.*, **74**, 2680 (1952).

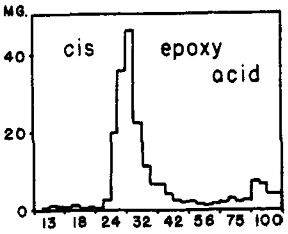
[21] Although some additional uncertainty is involved in quantitative comparison of gas chromatographic analysis of different types of substances (*e.g.*, mono- and dicarboxylic esters), the ratios S–P = 0.92 and A–C = 0.87 appear to suggest that the type Va amido ester may be formed in somewhat greater amount than type Vb; see Fig. 1e and Experimental.

[22] H. B. Knight, E. F. Jordon, Jr., E. T. Roe, and D. Swern, "Biochemical Preparations," Vol. 2, E. G. Ball, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 100.

[23] D. Swern, H. B. Knight, O. D. Shreve, and M. R. Heether, *J. Am. Oil Chemists' Soc.*, **27**, 17 (1950).

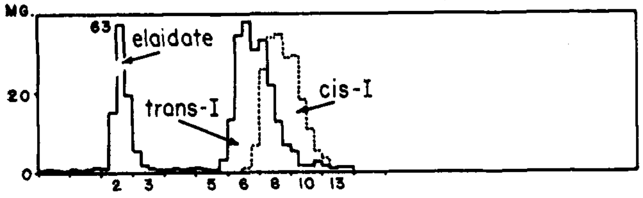
[24] H. Appel, H. Böhm, W. Keil, and G. Schiller, *Z. physiol. Chem.*, **282**, 225 (1947).

***cis-* and *trans*-9,10-epoxystearic acids** were prepared[2] from oleic and elaidic acids, respectively, by action of peracetic acid. Repeated recrystallization of the *cis* isomer from petroleum ether (60–70°), methanol, and acetone gave material melting as high as 57.0–58.4°, lit.[25] m.p. 58.1–58.7°, but chromatography of the corresponding methyl ester (*cis*-I, see below) disclosed the presence of about 20% of more strongly adsorbed substances. Chromatography of the free acid gave similar results, the purified material (81% recovery) showing m.p. 56.8°. (Note that development of this chromatogram was initiated with 13% ether in pentane and that a series of mixtures somewhat different from that ordinarily used was employed thereafter.)

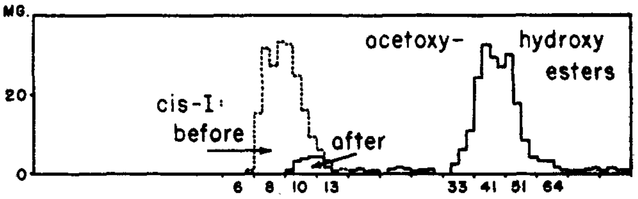


Methyl *cis*-9,10-epoxystearate (*cis*-I) was obtained by action of diazomethane (from N-nitroso-N-methylurea or from "Diazald," Aldrich Chemical Co., the corresponding *p*-toluenesulfonamide derivative) on solutions of the crude free acid in ether containing 10 vol. % methanol.[26] Chromatography gave a 75% yield of the pure ester, m.p. 17.3° (lit.[27] m.p. 18°, lit.[2] m.p. 15–16.5°), the major contaminating material being more strongly adsorbed on silicic acid. (The silicic acid adsorption chromatogram of *cis*-I is shown in Fig. 1a and, in comparison with the *trans* isomer, below.) Rechromatography results in an essentially quantitative recovery of the epoxy ester, accompanied by no additional appreciable quantity of material having altered chromatographic characteristics. Infrared examination of material from the leading edge of the epoxy ester peak (the isomeric keto esters III are slightly less strongly adsorbed than *cis*-I) showed no ketone carbonyl absorption. Chromatographic analysis of commercial "epoxy methyl stearate" (Metro Industries) revealed 33% of material, m.p. about 10°, showing chromatographic behavior of *cis*-I, 15% of less strongly adsorbed material (78.7% methyl palmitate, 15.6% stearate, 3.3% oleate by gas chromatography), and 47% of more strongly adsorbed material exhibiting strong OH absorption in the infrared.

Methyl *trans*-9,10-Epoxystearate (*trans*-I).—Treatment of a sample of the crude *trans* acid with diazomethane, followed by chromatography of the product, revealed presence of considerable residual unchanged elaidic acid, from which, however, the desired epoxy ester was readily separated; 302 mg. of acid yielded 104 mg. of methyl elaidate, m.p. 10.2°, having, as expected, essentially the same chromatographic behavior as methyl stearate (see peak A, Fig. 1b), and 187 mg. of the desired *trans*-I, m.p. 26.7° (in good agreement with the 25° figure given by Nicolet and Poulter,[27] but considerably below the 32–33.5° melting point cited by Bauer and Bähr.[28] This substance is appreciably less strongly adsorbed by silicic acid than the *cis* isomer.



Reaction of *cis*-I with acetic acid is of interest because of the possible importance of competitive opening of the oxide ring (giving stable acetoxyhydroxystearates) during hydrogenation, and in evaluation of acetic acid-induced isomerization[29] as a possible mode of formation of keto esters found in the hydrogenation mixture. A 192-mg. sample of chromatographed *cis*-I was dissolved in 4.8 ml. of glacial acetic acid and allowed to stand at room temperature (25 ± 1°) for exactly 1 week, the resulting solution was freed of solvent by lyophilization, the residual solid was treated with diazomethane in the usual way (there was no overt evidence of presence of free carboxylic acids), and the product was chromatographed on silicic acid. Unchanged starting material (8%, free of keto group absorption in the infrared) and 197 mg. of methyl 9(10)-acetoxy-10(9)-hydroxystearates, m.p. 41–42°, were obtained.



Recrystallization of the acetoxyhydroxy esters from *n*-pentane gave colorless needles, m.p. 40.7–41.0°.

Anal. Calcd. for $C_{21}H_{40}O_5$: C, 67.7; H, 10.8. Found: C, 67.5; H, 10.5.

Quantitative results of the chromatographic analysis permit evaluation of a rate constant, 8.6×10^{-4} l./mole hr., for the solvolysis of *cis*-I by acetic acid at 25°, in substantial agreement with approximate data reported by Findley, *et al.*,[2] and by King[30] with reference to reactivity of the corresponding free acid; the *trans* acid is reported[30] to be considerably less reactive. It is thus clear that little ring opening by solvent should occur in the short periods of time required to carry out these hydrogenations; this conclusion is borne out by the absence of more than traces of material more strongly adsorbed than II among the hydrogenation products obtained from either isomer of I (see Fig. 1b).

Hydrogenation of Epoxides.—Of the numerous hydrogenations of both isomers of I and of the *cis* free acid which were carried out, those described in detail here were representative with respect to results and serve best for direct comparison of behavior of the *cis* and *trans* epoxides. (The esters are preferred starting materials because they are more easily purified and yield a product mixture which may be chromatographed without further treatment; they are, however, disadvantageous from the standpoint that a fraction of the product is very strongly bound to the charcoal on which the catalyst is supported. The free-acid forms of the reduction products are more easily extracted from charcoal but are much less soluble in acetic acid and, although tending to supersaturate, occasionally crystallize from the hydrogenation mixture.)

In a quantitative hydrogenation apparatus employing mercury in the gas buret and operated at room temperature and atmospheric pressure, 400 mg. of 5% palladium on charcoal (Matheson Coleman and Bell) in 2.0 ml. of glacial acetic acid was saturated with hydrogen, and 180 mg. (0.517 mmole) of *cis*-I in 2.0 ml. of the same solvent was injected by hypodermic syringe into the vessel of the apparatus (a 15-ml. graduated centrifuge tube topped by a standard-taper joint). Hydrogen uptake was rapid and complete in about 10 min. The catalyst was centrifuged from the mixture and washed with four 1-ml. portions of acetic acid and the solvent was lyophilized from the combined supernates, leaving 132.2 mg. of solid residue; extraction of the catalyst with successive 5-ml. quantities of ether gave 15.0, 10.9, and 5.5 mg. of additional material, leaving about 17 mg. unrecovered. Chromatography (see Fig. 1b) of the product gave (in order of elution or increasing polarity) 34.6 mg. (20.1% based on starting material) of methyl stearate, m.p. 39.3–40.0°, 38.7–39.8° after mixing with the authentic substance, m.p. 38.6–39.3°; 14.7 mg. (8.1%) of III, m.p. 40.6–42.0°, identified additionally by infrared absorption and chromatographic behavior; 104.3 mg. (57.5%) of II, m.p. (of major fraction from center of peak) 43.2–43.8° (identified by degradation, see below); and 4.7 mg. (2.3%) of material tentatively identified by its chromatographic behavior as acetoxyhydroxystearate. In further confirmation of the identification of the products, the amount of hydrogen required to produce them is calculated to be 0.642 mmole (observed, 0.653).

Hydrogenation of 160 mg. (0.512 mmole) of *trans*-I under the same conditions resulted in uptake of 0.510 mmole of hydrogen, requiring about 131 min. Comparison of initial slopes of plots

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(25) L. P. Witnauer and D. Swern, *J. Am. Chem. Soc.*, **72**, 3364 (1950).

(26) H. Schlenk and J. L. Gellerman, *Anal. Chem.*, **32**, 1412 (1960).

(27) B. H. Nicolet and T. C. Poulter, *J. Am. Chem. Soc.*, **52**, 1186 (1930).

(28) K. H. Bauer and O. Bähr, *J. prakt. Chem.*, [2]**122**, 203 (1929).

(29) *Cf.* D. H. R. Barton, C. J. W. Brooks, and N. J. Holness, *J. Chem. Soc.*, 278 (1951).

(30) G. King, *ibid.*, 37 (1943).

of hydrogen uptake *vs.* time show that *cis*-I is reduced 10.0 times as rapidly as the *trans* isomer. Lyophilization of the original supernate from the centrifuged reaction mixture, together with three 5-ml. acetic acid washings, gave 115 mg. of white solid; 5-ml. washings of the catalyst with ether yielded 15.3, 6.2, and 6.3 mg. of additional product, leaving about 18 mg. still unaccounted for and presumably strongly adsorbed on the charcoal-supported catalyst. Chromatography of the product mixture gave 18.0 mg. (11.8%) of methyl stearate, 18.3 mg. (11.5%) of III, and 87.1 mg. (54.1%) of II, m.p. 43.7–44.7°.

Methyl Ketostearates (III).—Chromic oxide (93.1 mg., 0.93 mmole) was cautiously stirred into 0.9 ml. of reagent pyridine and 99.8 mg. (0.318 mmole) of II (chromatographically isolated from the hydrogenation products of *cis*-I) was added in another 0.9-ml. portion of pyridine. After the mixture had been stirred overnight at room temperature, 3.6 ml. of water was added and the product was extracted with three 5-ml. portions of ether. The extract was washed with 2-ml. portions of 1.5 *N* HCl until a strongly acidic aqueous phase was obtained (five were required) and then with 5 ml. of saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and freed of solvent. The residual solid was chromatographed on silicic acid (see Fig. 1c), giving 85.8 mg. (86.5%) of III, m.p. (of major fraction of peak) 40.8–41.3°.

Methyl Oximino Esters (IV).—A mixture of the above III (85.8 mg., 0.275 mmole), 2 mole equiv. each of hydroxylamine hydrochloride and anhydrous sodium acetate, and 1 ml. of absolute methanol in a 15-ml. centrifuge tube was boiled in steam with stirring until the solvent had evaporated. The residual mixture of solid and oil was partitioned between water and ether, the ether extract was dried over magnesium sulfate and freed of solvent, and the residual oil was chromatographed on silicic acid (see Fig. 1d), giving 87.8 mg. (97.5%) of IV, which failed to solidify on standing at 0°. Interestingly, II and IV exhibit essentially identical chromatographic behavior.

Methyl Amido Esters (V).—IV (85.0 mg.) was mixed with 2.9 g. of sirupy polyphosphoric acid (Matheson Coleman and Bell) in a 15-ml. centrifuge tube and the light brown frothy mixture was heated 20 min. on a steam bath with occasional stirring. After diluting the mixture with 14.5 ml. of water, the product was extracted with ether, the extracts were washed with three 5-ml. portions of water, dried over magnesium sulfate, treated with diazomethane (providing evidence that some hydrolysis of the carbomethoxy group had occurred), and the crude product was dissolved in a small amount of 13% ether in pentane and chromatographed on silicic acid (see Fig. 1e).[31] Pooled fractions eluted by 80% ether in pentane and by ether alone gave 61.0 mg. (71.8%) of V, buff-colored solid, m.p. 43.2–44.4°. (About 5 mg. of partially crystalline material eluted with 64% ether in pentane was rejected, perhaps unwisely, since this may account for the apparent slight asymmetry of oxime rearrangement indicated by analysis of the methanolysis products.) Carbon analyses of this mixture of substances were consistently high.

Anal. Calcd. for $C_{19}H_{37}NO_3$: C, 69.7; H, 11.4; N, 4.3. Found: C, 71.1, 70.9; H, 11.2, 11.0; N, 4.7, 4.4.

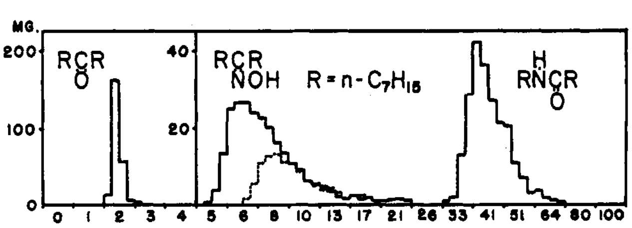
Methanolysis of Amido Esters (V).—A necked-down 6-in. Pyrex test tube was charged with 30.1 mg. of V and 0.5 ml. of boron trifluoride–methanol reagent (Applied Science Laboratories, Inc., presumably[32] 125 g./1 l.), sealed, and left in the chamber of an Abderhalden drying apparatus heated by boiling water vapors for 52 hr. After cooling in ice, the tube was opened, 0.3 ml. of toluene and 3 ml. of water were added, and the toluene phase was washed with four 0.5-ml. portions of water, dried over magnesium sulfate, and submitted to gas chromatographic analysis, using a Loenco Model 70 Hi-Flex apparatus fitted with a 3.3 ft. × 0.125 in. i.d. column of 17% ethylene glycol succinate on 60–80-mesh, acid-washed Chromosorb W. Helium was employed as the carrier gas, and the effluent was analyzed by thermal conductivity. Areas of peaks (see Fig. 2) were evaluated as the product of height times width at half-height (areas of the slightly skew monocarboxylate peaks were checked by weighing tracing cutouts). Area ratios were related to mass ratios by reference to data obtained from contemporary runs of mixtures of authentic esters of known composition closely matching that of the neutral methanolysate. In this way, it was determined that the ratio of methyl pelargonate (P) to caprate (C) was 0.95, while that of sebacate (S) to azelate (A) was 1.01. The ratios S–P = 0.92 and A–C = 0.87 appear to indicate appreciable differences in prevalence of the two possible routes of Beckmann rearrangement of the oximino esters (S and P, for example, being derived from the same oximino ester but from different amides arising from that precursor), although the possibility exists (see above) that a portion of the type Vb amido ester may have been omitted from the chromatographic sample submitted to methanolysis.

Di-*n*-heptyl ketone was prepared by dry distillation of calcium caprylate (*n*-octanoate). The crude product was washed with water, dried, redistilled, permitted to crystallize from the resulting light yellow oil, centrifuged free of noncrystalline material, chromatographed on silicic acid, and yielded a colorless solid, m.p. 41.0–41.6°, lit.[33] m.p. 41°, having chromatographic behavior essentially indistinguishable from that of monocarboxylic esters (see below and methyl stearate, peak A, Fig. 1b). Gas chromatography (Wheelco Model 10, argon carrier gas, Ra ionization detector, 40 × 0.25 in. ethylene glycol succinate on Chromosorb W column, 148°) of the ketone showed it to be free of homologs, and to have a retention time of 0.83 relative to that of methyl myristate, which contains the same number of carbon atoms.

Di-*n*-heptyl ketoxime was prepared from the ketone as described above (see preparation of IV). The chromatographically purified derivative (see graph below) was obtained in 89% yield, m.p. 20.9–21.2°, lit.[33] m.p. 20°. Chromatograms of this substance at two quite different loads (see graph below: broken tracing, 84 mg.; solid tracing, 222 mg.) serve to illustrate the fact that the leading edge of such peaks tends to be load dependent (substances which are able to function as hydrogen-bond donors appear particularly prone to exhibit this behavior), while the trailing edge remains little affected by load and hence is more reliably characteristic. Chromatograms of *cis*-I before and after diminishing to 8% of the original quantity by treatment with acetic acid (see above) also illustrate this effect.

N-*n*-Heptylcaprylamide.—As described in detail for conversion of IV to V, action of 4.0 g. of polyphosphoric acid on 216 mg. of diheptyl ketoxime gave an essentially quantitative yield of the isomeric amide, m.p. 58.1–58.3° (previously unreported), after chromatography on silicic acid and recrystallization from *n*-pentane at 0°. Six column-volumes of 13% ether in pentane were used in place of the more usual 0–10% mixtures in early development of the chromatogram of this amide. The magnitude of the adsorptivity contribution of the –NHCO– group manifest in the chromatographic behavior of this substance (and of V) is worthy of note.

Anal. Calcd. for $C_{15}H_{31}NO$: C, 74.6; H, 12.9; N, 5.8. Found: C, 74.5; H, 12.8; N, 5.8.



Boron Trifluoride Methanolysis of N-Heptylcaprylamide.—In order to delineate appropriate conditions for the methanolysis of V, a mixture of 11.9 mg. of methyl pelargonate (internal standard), 22.7 mg. of the amide, and 0.5 ml. of the boron trifluoride–methanol reagent was sealed in a Pyrex tube and heated at 100° for exactly 1 hr. Contents of the cooled tube were distributed between toluene and water, and the toluene phase (after washing with water and drying over magnesium sulfate) was submitted to gas chromatographic analysis to determine the extent (5.3%) to which methyl caprylate had been formed from

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[31] Because of the limited solubility of V in less polar solvent mixtures, six column-volumes of 13% ether were substituted in initial development of this chromatogram for the usual two volumes each of the 0–10% solvent mixtures. Experience with other substances has shown that this alternative development regime (which, incidentally, involves use of the same total amount of *ether*) has little effect on the emergence behavior of relatively strongly adsorbed solutes and saves time and pentane.

[32] L. D. Metcalfe and A. A. Schmitz, *Anal. Chem.*, **33**, 363 (1961).

[33] A. D. Petrov and E. P. Kaplan, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 539 (1949); *Chem. Abstr.*, **44**, 1887*h* (1950).

the amide. From this information it was estimated that 94% methanolysis of amides of this type (*e.g.*, V) should require 52 hr. under these conditions.

Acknowledgment.—The authors wish to record their indebtedness to Mr. Robert W. Green for assistance in preparation of certain substances used in this study, to Dr. G. A. Dhopeshwarkar for a generous sample of elaidic acid, and to Mr. George Alexander for infrared absorption determinations. A summer fellowship granted by the National Foundation supported in part the contribution of the junior author (R. W. K., Jr.) to this study.

Transformations of N-Acyl-ε-caprolactams and the Synthesis of DL-Lysine

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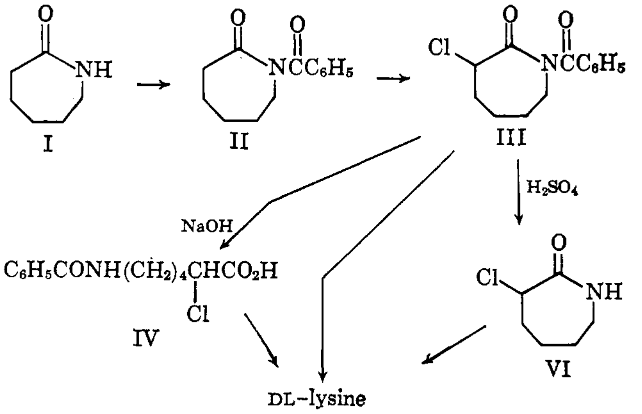
Received February 14, 1964

Unlike ε-caprolactam, N-benzoyl-ε-caprolactam undergoes monochlorination in the α-position to give N-benzoyl-α-chloro-ε-caprolactam. Alkaline hydrolysis of this acylated lactam furnishes ε-benzamido-α-chlorocaproic acid and cleavage of the benzoyl group with sulfuric acid provides α-chloro-ε-caprolactam. These cleavage products have been converted into DL-lysine in high over-all yield.

ε-Caprolactam has been an attractive starting material for the synthesis of lysine in recent years because of its availability and structural advantages. Introduction of the requisite amino group into ε-caprolactam by direct monochlorination in the α-position followed by ammonolysis has not been successful, the chlorination product being α,α-dichloro-ε-caprolactam.[1,2] The dichloro derivative, prepared by use of phosphorus pentachloride, has been converted into the monochloro compound and thence to lysine.[1] The monochlorocaprolactam has also been prepared from the N-chloro derivative.[3]

In contrast to the behavior of ε-caprolactam, N-benzoyl-ε-caprolactam (II) undergoes monochlorination smoothly through the agency of sulfuryl chloride to give N-benzoyl-α-chloro-ε-caprolactam (III).



The chlorination of N-benzoyl-ε-caprolactam, prepared by benzoylation in dimethylaniline, was subjected to intensive study. With chlorine only a small amount of N-benzoyl-α-chloro-ε-caprolactam could be isolated.[4] The best method consisted of chlorination with a slight excess of sulfuryl chloride in a mixture of carbon tetrachloride and cyclohexane at 40° for 24 hr. Under these conditions, N-benzoyl-α-chloro-ε-caprolactam (III) was produced in 89% yield.

Selective ring opening of N-benzoyl-α-chloro-ε-caprolactam (III) without loss of the benzoyl group or replacement of chlorine was accomplished by hydrolysis of III with sodium hydroxide in aqueous methanol. The product, ε-benzamido-α-chlorocaproic acid (IV), was found to be completely stable under the mild alkaline medium required for ring opening and was formed in 95% yield. The small amount of benzoic acid produced probably resulted from attack on the benzoyl group before ring opening. This undesired cleavage was minimized either by conducting the reaction in a solvent mixture in which III was slightly soluble or by slow addition of alkali to a hot solution of III.

The conversion of ε-benzamido-α-chlorocaproic acid into lysine was carried out by the conventional means of amination and hydrolysis.[5a,6] The over-all yield from ε-caprolactam was 73%.

Acidic hydrolysis of III provided another route to DL-lysine. In contrast to aqueous alkaline hydrolysis, concentrated sulfuric acid cleaved the benzoyl group with complete selectivity to α-chloro-ε-caprolactam (VI) in 95% yield simply by allowing a solution of III in sulfuric acid to stand at room temperature for 4 hr. The synthesis of DL-lysine was completed by ammonolysis of α-chloro-ε-caprolactam (VI) with fortified aqueous ammonia followed by hydrolysis of α-amino-ε-caprolactam (VII). These transformations have already been reported.[1a,b] Lysine was produced from VI in 72% yield or 60% from caprolactam.

Diacylamines, a class to which the N-benzoylcaprolactams belong, are known to be highly reactive toward nucleophilic and electrophilic reagents. A recent study[7] has shown in the case of N-acylbenzanilides that the stronger acid is liberated by alkaline hydrolysis and the weaker acid is liberated by cleavage in concentrated sulfuric acid. This pattern was followed upon treatment of III with these reagents.

N-Benzoyl-ε-caprolactam (II) behaved in the same manner as III toward sodium hydroxide but surprisingly underwent ring cleavage to the extent of 80% upon treatment with sulfuric acid, a reagent which effected cleavage of the benzoyl group in III.

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