Anal. Calcd. for $C_{19}H_{18}N_4O_2$: C, 68.3; H, 5.4; N, 16.8. Found: C, 68.2; H, 5.2; N, 16.2.

3-Amino-5,6-diphenylpyrazinamide (XXIII).—A mixture of 2.0 g. of VI and 40 ml. of concentrated ammonium hydroxide was sealed in a glass bomb tube and heated at 185° for 16 hours. After cooling, the excess ammonium hydroxide was removed by evaporation under diminished pressure and the crystalline residue recrystallized from aqueous ethanol; yield 1.67 g. (94%). The product was obtained in the form of pale yellow needles after repeated recrystallizations from aqueous ethanol; m.p. 203.5–205°.

Anal. Calcd. for $C_{17}H_{14}N_4O$: C, 70.3; H, 4.9; N, 19.3. Found: C, 70.6; H, 4.9; N, 19.3.

Reaction of XXIII with Benzylamine.—A mixture of 0.3 g. of XXIII in 1 ml. of benzylamine was heated under reflux for 15 minutes, diluted with 10 ml. of ethanol and hot water added to incipient crystallization. Scratching caused the separation of 0.31 g. (76%) of light yellow needles which were recrystallized from absolute ethanol; m.p. 188.5–189°. A mixed melting point with an authentic sample of 3-amino-N-benzyl-5,6-diphenylpyrazinamide (VII) showed no depression.

Attempted Reaction of XXIII with Piperidine.—A mixture of 0.06 g. of XXIII, 5 ml. of piperidine and 2 ml. of dimethylformamide was heated under reflux for 16 hours. Removal of the piperidine and dimethylformamide under reduced pressure and crystallization of the residue from aqueous acetone gave 0.053 g. of yellow needles; m.p. 203.5–205°. A mixed melting point determination with a sample of XXIII showed no depression.

1-(*p*-Nitrophenyl)-3-(piperidino)-urea (XXV).—A mixture of 2.0 g. of *p*-nitrophenylurea[15] and 20 ml. of piperidine was heated under reflux for eight hours, the excess piperidine removed by evaporation under reduced pressure and the crystalline residue recrystallized from aqueous ethanol. The product was obtained as well-formed, light yellow needles, m.p. 165–166°, and showed no depression in melting point when mixed with an authentic sample of XXV prepared by the action of piperidine on *p*-nitrophenyl isocyanate; yield 2.43 g. (88%).

3-Amino-5,6-diphenylpyrazinoic Acid Hydrazide (XXVI).—A mixture of 1.0 g. of VI and 10 ml. of 85% hydrazine hydrate was heated under reflux for six hours. The reaction mixture was allowed to stand at 0° for three hours; the orange crystalline solid which had separated was filtered and washed thoroughly with ice-cold water. Recrystallization from absolute methanol gave 0.705 g. (73%) of long orange needles; m.p. 250–251°.

Anal. Calcd. for $C_{17}H_{15}N_5O$: C, 66.9; H, 4.9; N, 22.9. Found: C, 67.0; H, 4.8; N, 23.1.

The 3-Amino-6,7-diphenyl-2,4(1H,3H)-pteridinedione (XXVII).—The mother liquor from the reaction mixture above was evaporated to dryness, the residue washed well with water and dried. It was then extracted with 50 ml. of hot methylene chloride. Addition of 50 ml. of low-boiling petroleum ether caused the separation of a small amount of a colorless solid which was collected by filtration and recrystallized from methylene chloride–petroleum ether; m.p. (dec.) 259–260°.

Anal. Calcd. for $C_{18}H_{13}N_5O_2$: C, 65.2; H, 4.0; N, 21.1. Found: C, 65.0; H, 4.1; N, 21.1.

Evaporation of the methylene chloride–petroleum ether filtrates yielded an additional amount (*ca.* 0.015 g.) of 3-amino-5,6-diphenylpyrazinoic acid hydrazide (XXVI).

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[15] J. F. L. Reudler, *Rec. trav. chim.*, **33**, 35 (1914).

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY,[1] PHILADELPHIA]

Chemistry of Epoxy Compounds. XIII.[2] Urea Complex Formation in Determining the Configurations of the 9,10-Dihydroxystearic Acids

BY DANIEL SWERN, LEE P. WITNAUER AND H. B. KNIGHT

In describing the stereochemical relationships in the conversion of oleic and elaidic acids to 9,10-dihydroxystearic acids by way of the intermediate oxirane and chlorohydroxy compounds, it has been necessary to make certain assumptions because at some of the reaction stages the configurations of the long-chain compounds are not known. Based upon the ability of low-melting 9,10-dihydroxystearic acid, m.p. 95° (prepared from elaidic acid by hydroxylation with potassium permanganate), to form a crystalline complex readily with urea in quantitative yield, and the reluctance of high-melting 9,10-dihydroxystearic acid, m.p. 131° (prepared from oleic acid by hydroxylation with potassium permanganate), to form a complex, it has been shown unambiguously that the hydroxyl groups in the high-melting isomer are on opposite sides of the chain whereas in the low-melting isomer they are substantially on the same side. Study of urea complexes prepared from the methyl esters of these hydroxy acids supports this conclusion. This information confirms the fact that hydroxylation with potassium permanganate proceeds by *cis* or normal addition, and that opening of the oxirane ring of the isomeric 9,10-epoxystearic acids involves an inversion.

Recently,[3] we described the stereochemical relationships in the conversion of oleic and elaidic acids to 9,10-dihydroxystearic acids by way of the intermediate oxirane and chlorohydroxy compounds. This scheme was self-consistent and in harmony with accepted theories of the Walden inversion and double bond addition reactions, but differed in some important respects from schemes proposed earlier by Atherton and Hilditch[4] and also by King.[5] Subsequently, King[6] modified his original scheme, and it is now fairly certain that our original formulation[3] is correct.

In devising reaction schemes for these higher molecular weight compounds, much of the reasoning is based upon similar reactions which have been carried out with simple related compounds of known configurations, because at some of the reaction stages the configurations of the long-chain compounds are not known. Of the various compounds investigated in the stereochemical studies just discussed, the configurations of oleic (*cis*-9-octadecenoic) and elaidic (*trans*-9-octadecenoic) acids,[7,8] and *cis*-9,10-epoxystearic acid, m.p. 59.5°, and *trans*-9,10-epoxystearic acid, m.p. 55.5°,[9] are known with certainty. It would be of great value for these

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[2] This paper was presented at the Spring Meeting of the American Chemical Society, Buffalo, N. Y., March, 1952. For paper XII, see THIS JOURNAL, **72**, 4315 (1950).

[3] Swern, *ibid.*, **70**, 1235 (1948).

[4] Atherton and Hilditch, *J. Chem. Soc.*, 204 (1943).

[5] King, *ibid.*, 387 (1942).

[6] King, *ibid.*, 1817 (1949).

[7] Rao and Daubert, THIS JOURNAL, **70**, 1102 (1948).

[8] Shreve, Heether, Knight and Swern, *Anal. Chem.*, **22**, 1261 (1950).

[9] Witnauer and Swern, THIS JOURNAL, **72**, 3364 (1950).

stereochemical and other studies if the configurations of all the compounds, and particularly those of the isomeric 9,10-dihydroxystearic acids, were also known.

Some evidence relating to the configurations of the isomeric 9,10-dihydroxystearic acids has already been published. Thus, low-melting 9,10-dihydroxystearic acid, m.p. 95° (prepared from elaidic acid by hydroxylation with alkaline potassium permanganate), is cleaved somewhat more rapidly with periodic acid[10] and lead tetraacetate[11] than is the high-melting isomer, m.p. 131° (prepared from oleic acid by hydroxylation with alkaline potassium permanganate). It was concluded from these studies that the hydroxyl groups are probably closer together in the low-melting than in the high-melting isomer. Comparative rate studies with open-chain compounds are not as clear cut, however, as those with cyclic compounds, in which ratios of velocity constants (k_{cis}/k_{trans}) of as much as 4×10^6 have been observed and, to the best of our knowledge, are always greater than 10.

According to our reaction scheme, hydroxylation of oleic and elaidic acids with potassium permanganate proceeds by *cis* or normal addition. In the hydroxylation of oleic acid, assumption of the normal fatty acid zigzag structure by C–C rotation in the resulting 9,10-dihydroxystearic acid, m.p. 131°, causes the hydroxyl groups to remain relatively far apart, that is, on opposite sides of the chain, whereas in the hydroxylation of elaidic acid, no such rotation is required and the hydroxyl groups remain in substantially the same spatial position in the resulting 9,10-dihydroxystearic acid, m.p. 95°, as those in which they enter the molecule. This can be clearly seen with models built to scale.

We have now obtained unambiguous evidence for these conclusions by the use of the technique of urea complex formation discovered by Bengen[12] and amplified by Schlenk,[13] Zimmerschied, *et al.*,[14] Redlich, *et al.*,[15] and Schlenk and Holman.[16] Urea forms well-defined crystalline complexes with a wide variety of straight-chain organic compounds and, in some cases, with certain branched-chain compounds. The organic compound in the complex is held within a urea channel whose diameter is about 5.5 to 6 Å. The ease of formation and stability of urea complexes is dependent, in large part, on the size and shape of the organic compound whose complex is being made. Straight-chain aliphatic compounds, such as *n*-octadecane and other members of the homologous series, have a diameter of about 4.1 Å. and form complexes rapidly, usually in excellent yield. Compounds with a double methyl branch on one carbon atom, such as 2,2,4-trimethylpentane, require too large a channel for complex formation with urea, and no urea complex has yet been prepared from such doubly branched compounds under any of the presently known experimental conditions. Aliphatic hydrocarbons with a single methyl branch require a channel diameter of about 5.5 Å. If the straight-chain portion of such molecules is comparatively short, as in 3-methylheptane, complex formation apparently occurs only when they are mixed with straight-chain hydrocarbons. If the straight-chain portion is comparatively long, as in 3-methylhexadecane or -eicosane, complex formation occurs readily and rapidly.

Calculation of the channel diameter required for the formation of a urea complex from the 9,10-dihydroxystearic acid, m.p. 131°, employing interatomic distances reported by Pauling[17] and assuming that its hydroxyl groups are on opposite sides of the chain gives a value of about 6 Å. Similar calculation of the diameter of the 9,10-dihydroxystearic acid, m.p. 95°, on the assumption that the hydroxyl groups are in the "so-called" *cis* position, gives a diameter of about 5.4 Å. In view of the marked effect of the diameter of organic compounds on their complex-forming ability, it is evident, then, that the low-melting isomer should form a urea complex readily and in high yield, whereas the high-melting isomer should either be unable to form a urea complex or should be reluctant to form one. This conclusion is borne out experimentally. Low-melting 9,10-dihydroxystearic acid gives the urea complex readily in quantitative yield, whereas high-melting 9,10-dihydroxystearic acid does not yield any. That the diameter of the high-melting 9,10-dihydroxystearic acid is not too large to permit complex formation to occur under certain conditions is shown by the fact that in a 50:50 mixture of the two isomers, some high-melting 9,10-dihydroxystearic acid is obtained as complex. From such a mixture, however, the composition of the 9,10-dihydroxystearic acids[9] isolated from the urea complex is 75% low-melting and 25% high-melting isomer. It is evident, therefore, that the diameter of the high-melting 9,10-dihydroxystearic acid is significantly greater than that of the low-melting isomer.

Additional confirmatory evidence bearing on this point has been obtained by a study of the preparation of urea complexes of the methyl esters of the isomeric 9,10-dihydroxystearic acids, and determination of the dissociation temperatures[18] of the complexes obtained. The methyl esters were selected for several reasons. First, the additional carbon atom would be expected to facilitate complex formation with both isomers, since increase in length of chain increases ease of complex formation and stability of the resulting complex. Second, the methyl group would give additional opportunities for bonding of the long-chain compounds with urea, whereas in the free acids, which exist as dimers because of hydrogen bonding between carboxyl groups, the bonding potential with urea is much lower. Thus, one might expect to obtain urea complexes readily from both isomeric methyl esters. Third, if urea complexes could be obtained from

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[10] Wittcoff, Moe and Iwen, *ibid.*, **70**, 742 (1948).

[11] Hilditch and Jasperson, *Nature*, **147**, 327 (1941).

[12] Bengen, German Patent Application O.Z. 12438, March 18, 1940.

[13] W. Schlenk, Jr., *Ann.*, **565**, 204 (1949).

[14] Zimmerschied, Dinerstein, Weitkamp and Marschner, *Ind. Eng. Chem.*, **42**, 1300 (1950).

[15] Redlich, Gable, Dunlop and Millar, THIS JOURNAL, **72**, 4153 (1950).

[16] H. Schlenk and Holman, *ibid.*, **72**, 5001 (1950).

[17] L. Pauling, "Nature of The Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940.

[18] To be published. The dissociation temperature of a complex is determined by heating a few transparent crystals on the hot stage of a microscope and observing the temperature at which opacity occurs.

both isomeric methyl esters, a determination of the dissociation temperatures[18] of the urea complexes would be a valuable clue to the structure of the organic component bound in the urea complex. The basis for this last assertion is the fact that the dissociation temperatures of urea complexes of isomeric substances are fairly sensitive guides to the tendency of the organic component to escape from the complex. With closely related isomeric pairs, which differ only in the spatial arrangement of groups (oleic acid–elaidic acid, methyl oleate–methyl elaidate, oleyl alcohol–elaidyl alcohol) the urea complex having the lower dissociation temperature is invariably the one obtained from the isomer which has the larger cross-section.

Experimentally, the methyl esters of both 9,10-dihydroxystearic acids formed urea complexes. Low-melting methyl 9,10-dihydroxystearate, m.p. 70°, formed the urea complex somewhat more rapidly than did high-melting methyl 9,10-dihydroxystearate, m.p. 103°, the yield of complex from the former was slightly higher and, of even greater significance, the dissociation temperatures of the complexes were 120 and 114°, respectively. All of these factors point toward a greater space requirement for the methyl ester of high-melting 9,10-dihydroxystearic acid.

Knowledge of the configuration of the isomeric 9,10-dihydroxystearic acids provides additional evidence that opening of the oxirane ring of the isomeric 9,10-epoxystearic acids involves an inversion. Thus, oleic acid yields *cis*-9,10-epoxystearic acid, m.p. 59.5°, by epoxidation with organic peracids (normal addition with no inversion). On hydrolysis of this product under alkaline or acidic conditions,[3] 9,10-dihydroxystearic acid, m.p. 95°, is obtained. If no inversion occurred during ring opening, the two hydroxyl groups would be present in the "so-called" *cis* position and, after assumption of the normal fatty acid zigzag formed by the product, high-melting 9,10-dihydroxystearic acid, m.p. 131°, would be obtained instead. Thus, by converting oleic acid to 9,10-dihydroxystearic acid by way of the intermediate *cis*-9,10-epoxystearic acid, the same 9,10-dihydroxystearic acid is obtained as that from elaidic acid by *cis* or normal hydroxylation with potassium permanganate. A similar line of reasoning applies to the sequence

$$\text{Elaidic acid} \xrightarrow[\text{peracids}]{\text{Organic}} \textit{trans}\text{-9,10-epoxystearic acid m.p. } 55.5^\circ \xrightarrow[\circ\ \text{Inversion}]{\text{Hydrolysis}} \text{9,10-dihydroxystearic acid, m.p. } 131^\circ$$

The melting points of the isomeric 9,10-dihydroxystearic acids are in line with the structural evidence presented. The isomer, m.p. 131°, with the hydroxyl groups on opposite sides of the long chain is able to form hydrogen bonds with adjacent chains throughout the whole crystalline mass, whereas the other isomer, m.p. 95°, can form only a limited number of hydrogen bonds with adjacent molecules. In the former, therefore, more energy is required to break the larger number of hydrogen bonds in going from the ordered crystalline state to the disordered liquid state, and this is reflected in a higher melting point.

Experimental

Starting Materials.—The isomeric 9,10-dihydroxystearic acids, m.p. 95° and 131°, were prepared from oleic and elaidic acids, respectively, as previously described.[3] The methyl esters, m.p. 70 and 103°, were prepared by refluxing the acids with a large excess of methanol (naphthalene-2-sulfonic acid catalyst).[19]

Preparation of Urea Complexes.—Five grams of 9,10-dihydroxystearic acid, m.p. 95°, and 25 g. of urea were dissolved in 100 ml. of methanol with heating. The solution was allowed to stand overnight at room temperature and the precipitate, consisting of glistening needles, was filtered off and dried. It weighed 9.5 g.; acid number 46.8; content of 9,10-dihydroxystearic acid in complex, 2.5 g. The filtrate was cooled to 0°, yielding 10.4 g. of complex; acid number 46.3; content of 9,10-dihydroxystearic acid in complex, 2.6 g. Recovery of 9,10-dihydroxystearic acid was quantitative. In a control experiment, consisting of 5 g. of 9,10-dihydroxystearic acid, m.p. 95°, in 100 ml. of methanol (urea omitted), no precipitate was obtained at room temperature.

The weight content of 9,10-dihydroxystearic acid, m.p. 95°, in the complex is approximately 26 ± 1%. This value is significant and is good evidence that complex formation has occurred, since we have found that in preparing complexes from about forty long-chain fatty acids, esters and alcohols,[20] the content of fatty component is almost invariant at 25% of the total weight of complex.

Repetition of the experiment, but replacing the low-melting 9,10-dihydroxystearic acid with the other isomer, m.p. 131°, yielded fairly pure 9,10-dihydroxystearic acid as the precipitate at room temperature, and urea as the precipitate at 0°. Increasing the content of urea to 90 g. and the methanol to 400 ml. gave only urea as a precipitate.

A solution consisting of 2.5 g. of each of the isomeric 9,10-dihydroxystearic acids and 25 g. of urea in 100 ml. of methanol was allowed to stand at room temperature for 1.5 hours and then filtered. The precipitate weighed 8.2 g.; acid number 46.7; content of 9,10-dihydroxystearic acids in complex, 2.1 g. The complex (7.0 g.) was well-mixed with 200 ml. of water at 60° and filtered. The urea-free precipitate was washed with five 200-ml. portions of hot water and dried under vacuum, giving 1.7 g. (95% yield) of mixed 9,10-dihydroxystearic acids: composition by X-ray diffraction,[9] 75% low-melting, 25% high-melting isomer.

The methanol filtrate from which the complex had been separated was diluted with four volumes of hot water and filtered. The precipitate was washed with several liters of hot water and dried under vacuum, giving 2.7 g. (93% yield) of mixed 9,10-dihydroxystearic acids: composition by X-ray diffraction,[9] 70% high-melting, 30% low-melting isomer.

Five grams of methyl 9,10-dihydroxystearate, m.p. 70° and 25 g. of urea were dissolved in 100 ml. of methanol with heating. The solution was allowed to stand for three hours at room temperature and the precipitate of glistening needles was filtered off and dried. It weighed 14.9 g.; saponification number, 47.0 (corrected for slight interference of urea); content of methyl 9,10-dihydroxystearate in complex, 4.1 g.; dissociation temperature of complex, 120°. The filtrate was cooled to 0°, yielding 4.3 g. of complex; saponification number, 46.3 (corrected); content of methyl 9,10-dihydroxystearate in complex, 1.0 g. Recovery of methyl 9,10-dihydroxystearate was quantitative.

Repetition of the experiment, but replacing low-melting methyl 9,10-dihydroxystearate with the other isomer, m.p. 103°, yielded 13.7 g. of complex at room temperature, [saponification number, 47.1 (corrected); content of methyl 9,10-dihydroxystearate in complex, 3.8 g.; dissociation temperature of complex, 114°], and 4.3 g. at 0° [saponification number, 46.2 (corrected); content of methyl 9,10-dihydroxystearate, 1.0 g.]. Recovery of methyl 9,10-dihydroxystearate was 95%.

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(19) Swern and Jordan, THIS JOURNAL, **67**, 902 (1945).

(20) To be published.