Summary

The thermal polymerization of the isomeric 9,-10-epoxystearic acids, m. p. 59.5° and 55.5°, derivable from oleic and elaidic acids, respectively, has been quantitatively studied. Both isomers can be polymerized to the gel stage, the high-melting isomer yielding a gel when about 75% of the carboxyl groups and 95% of the oxirane groups have disappeared, the low-melting isomer when about 85% of the oxirane groups and 90% of the carboxyl groups have disappeared. The main process appears to be the formation of linear polyesters by the reaction of the oxirane with the carboxyl group.

In the high-melting isomer, side reactions, which take place from the beginning of the reaction, cause the oxirane group to disappear at a more rapid rate than the carboxyl group, thereby preventing a kinetic analysis of the polymerization. In the low-melting isomer, the approximately parallel disappearance of both functional groups permits calculation of reaction rate constants as well as activation energy. This latter value is 18,600 cal. per mole. For both isomers, the reaction rate approximately doubles for each ten-degree rise in temperature.

The polymers just prior to the gel stage are highly viscous, colorless oils, soluble in many common organic solvents, and insoluble in water and in aliphatic hydrocarbons. At the gel stage they are insoluble at the boiling point in all the solvents tested.

Chemistry of Epoxy Compounds. VII.[2] Stereochemical Relationships between the 9,10-Epoxy-, Chlorohydroxy- and Dihydroxystearic Acids

BY DANIEL SWERN

The stereochemical relationships involved in the conversion of oleic and elaidic acids (cis- and trans-9-octadecenoic acids, respectively) to the 9,10-dihydroxystearic acids by way of the intermediate oxirane and chlorohydroxy compounds have been studied by King[3] and also by Atherton and Hilditch.[4] These investigators have proposed reaction schemes which not only differ on several fundamental points but which are at variance with accepted thinking on the Walden inversion[5] and double bond addition reactions[5] in some important respects.

A satisfactory reaction scheme must be in agreement with the following experimentally determined facts: (1) The 9,10-epoxystearic acid obtained from oleic acid by epoxidation with organic per-acids and that obtained by hypohalogenation and subsequent dehydrohalogenation are identical, and therefore have the same configuration; (2) the 9,10-epoxystearic acid obtained from elaidic acid by epoxidation and that obtained by hypohalogenation and dehydrohalogenation are also identical, and differ from the 9,10-epoxystearic acid described under (1) above; (3) the 9,10-dihydroxystearic acid obtained from oleic acid by oxidation with potassium permanganate and that obtained from elaidic acid by epoxidation and subsequent hydrolysis are identical; (4) the 9,10-dihydroxystearic acid obtained from

elaidic acid by oxidation with potassium permanganate and that obtained from oleic acid by epoxidation and hydrolysis are also identical and differ from the 9,10-dihydroxystearic acid described under (3) above; (5) the chlorohydroxystearic acids obtained from oleic acid by reaction with hypochlorous acid and those obtained by epoxidation of oleic acid and subsequent treatment of the 9,10-epoxystearic acid with hydrochloric acid are identical; (6) the chlorohydroxystearic acids obtained from elaidic acid by reaction with hypochlorous acid and those obtained by epoxidation of elaidic acid and treatment of the 9,10-epoxystearic acid with hydrochloric acid are also identical and differ from the chlorohydroxystearic acids described under (5) above; and (7) treatment of either 9,10-dihydroxystearic acid with hydrochloric acid, followed by dehydrohalogenation and hydrolysis, yields the other isomer.

For some time we have been studying the reactions discussed above, and in this paper we are suggesting a scheme which correlates configurational relationships involved, in harmony with accepted theories of the Walden inversion and double bond addition reactions. This reaction scheme is shown in Fig. 1 (the + and − signs do not refer to optical rotations but are employed to correlate configurational relationships and to demonstrate the inversions more clearly).

Although it is generally agreed that opening and closing of the oxirane ring is accompanied by inversion,[6,7,8,9] and this rule has been followed in re-

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(2) For paper VI of this series, see THIS JOURNAL, 70, 1228 (1948).

(3) King, J. Chem. Soc., 387 (1942).

(4) Atherton and Hilditch, ibid., 204 (1943).

(5) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940; Remick, "Electronic Interpretations of Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1943.

(6) Kuhn and Ebel, Ber., 58, 919 (1925).

(7) Böeseken and co-workers, Rec. trav. chim., 47, 683 (1928). Consult this paper for previous contributions.

(8) Esafov, J. Gen. Chem. (U. S. S. R.), 7, 1403 (1937).

(9) Wilson and Lucas, THIS JOURNAL, 58, 2396 (1936); Winstein and Lucas, ibid., 61, 1576, 1581 (1939); Lucas, Schlatter and Jones, ibid., 63, 22 (1941); Wilson and Gould, ibid., 63, 2541 (1941).
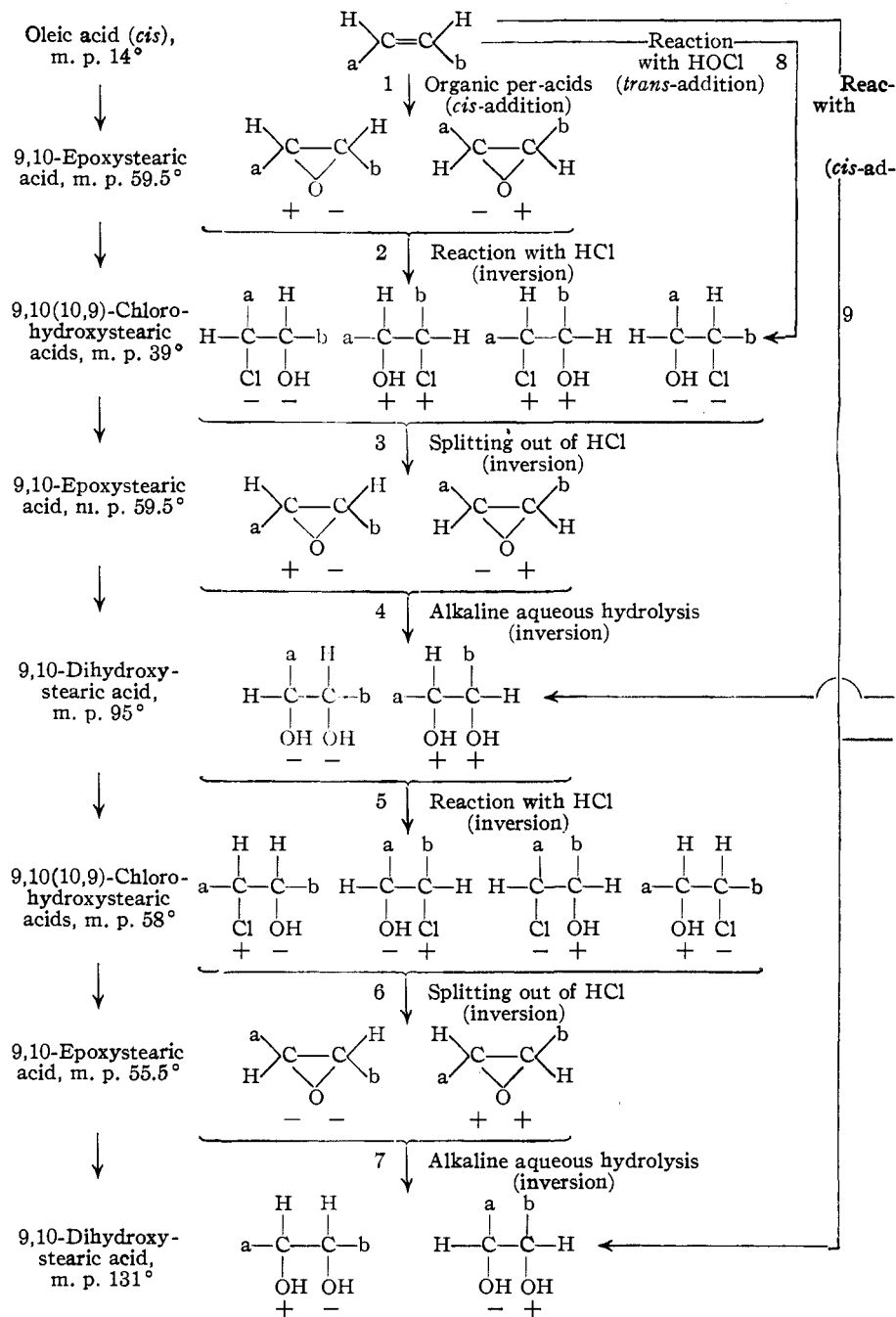
Fig. 1.

actions 2, 3, 4, 6 and 7 of Fig. 1, Atherton and Hilditch[4] have suggested that inversion may not occur when the oxirane ring of 9,10-epoxystearic acid is hydrated. One of the reasons offered to explain this is the fact that hydrolysis of the oxirane ring by alkaline or by acidic hydrolytic agents yields the same isomeric form of dihydroxystearic acid, although the mechanisms of hydrolysis differ. Thus, in acid hydrolysis the oxirane compound is converted to the glycol by a two-step process in which a hydroxy-ester is an intermediate, whereas in alkaline hydrolysis the glycol is obtained directly in one step. We believe that the formation of the same 9,10-dihydroxystearic acid can be adequately accounted for on the assumption that in both types of hydrolysis only *one* inversion occurs, namely, at the time that the oxirane ring is opened. This is shown in Fig. 2, in which the conversion of 9,10-epoxystearic acid, m. p. 59.5°, to 9,10-dihydroxystearic acid, m. p. 95°, is em-
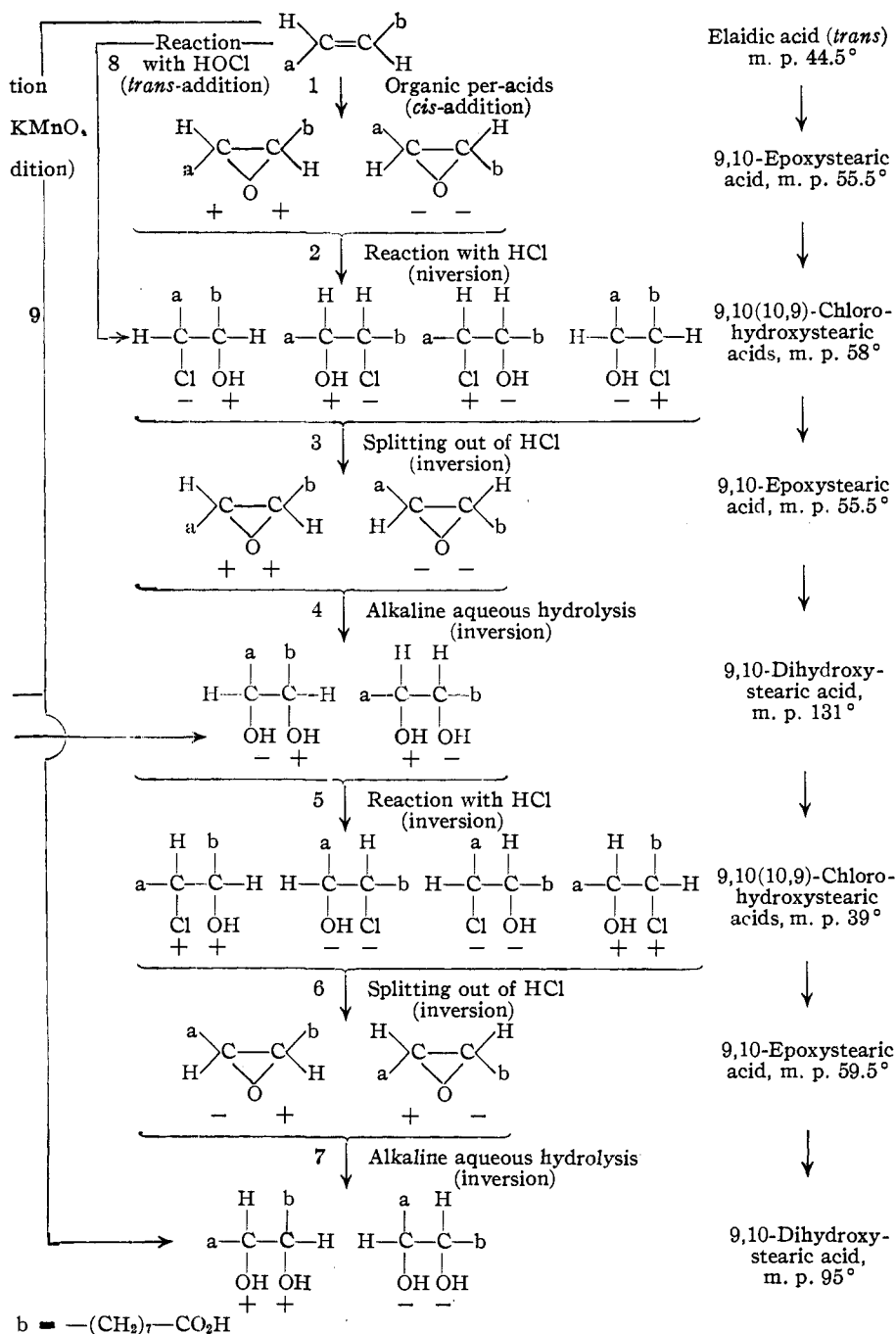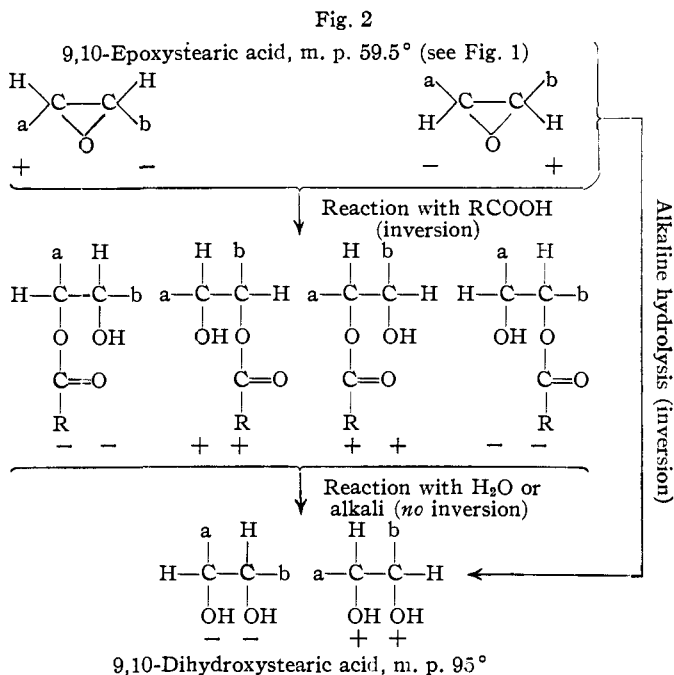
Fig. 1.

b = —(CH₂)₇—CO₂H

ployed as the example, although the same reasoning applies to the conversion of its isomer, m. p. 55.5°, to 9,10-dihydroxystearic acid, m. p. 131°. It is important to note that inversion cannot occur in the hydrolysis of the intermediate hydroxyester obtained by treatment of the oxirane compound with acid because the carbon–oxygen bond of the alcoholic component, in this case 9,10-dihydroxystearic acid, is not ruptured.[5] Identical results are obtained when sulfuric acid is em-

ployed instead of organic acids, or when concentrated or dilute alkali is used.

As further evidence that the oxirane ring may be hydrated without inversion, Atherton and Hilditch[4] have referred to the work of Abderhalden and Eichwald,[10] but we believe that this work is inapplicable to the present problem. Thus, inversions may not occur during the opening or closing of an oxirane ring which is attached to a

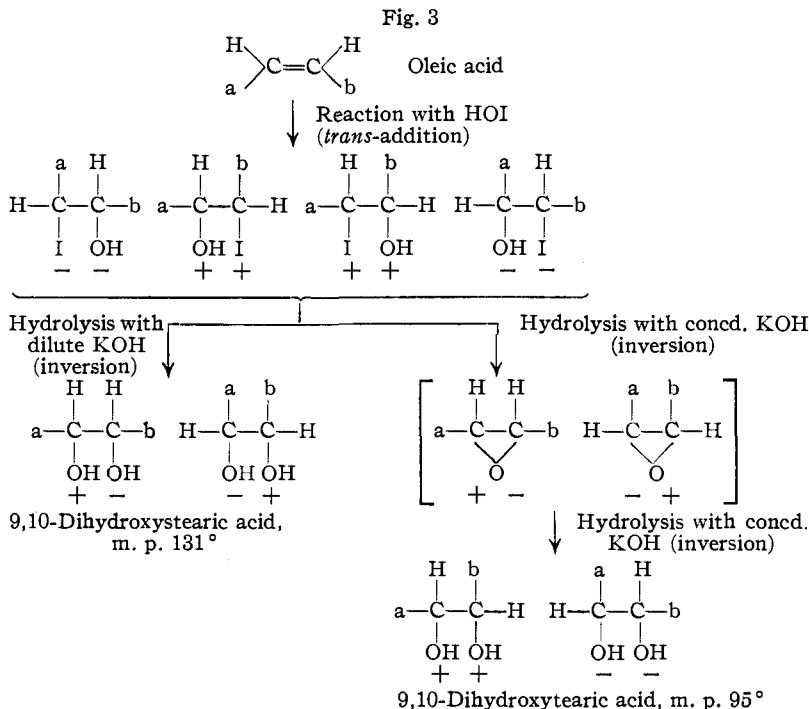(10) Abderhalden and Eichwald, *Ber.*, **48**, 1847 (1915).

Fig. 2

9,10-Epoxystearic acid, m. p. 59.5° (see Fig. 1)

H—C—C—H   a—C—C—b
    O   O
+ −   − +

Alkaline hydrolysis (inversion)

Reaction with RCOOH
(inversion)

a H   H b   H b   a H
H—C—C—b a—C—C—H a—C—C—H H—C—C—b
  O OH   OH O   O OH   OH O
  C=O   C=O   C=O   C=O
  R   R   R   R
  − −   + +   + +   − −

Reaction with H₂O or
alkali (no inversion)

a H   H b
H—C—C—b a—C—C—H
  OH OH   OH OH
  − −   + +

9,10-Dihydroxystearic acid, m. p. 95°

terminal, non-asymmetric carbon atom,[11] as is the case in the three-carbon systems studied by Abderhalden and Eichwald, but inversions occur during ring opening and closure when the oxirane group is attached to a pair of asymmetric carbon atoms[6,9] as is the case in the isomeric 9,10-epoxystearic acids.

Halohydrins of the same configuration (see later discussion) may be prepared either by treating the oxirane compound with hydrogen chloride, hydrogen bromide or hydrogen iodide (reaction 2), or by treating the appropriate unsaturated acid with a hypohalous acid (reaction 8). The form of dihydroxystearic acid obtained by alkaline hydrolysis of these halohydrins is determined by the concentration of the alkali used, since oxirane compounds may be formed as intermediates when the concentration of alkali exceeds a certain value. Thus, Esafov[8] has shown that iodohydroxystearic acid, prepared from oleic acid, yields 9,10-dihydroxystearic acid, m. p. 131°, on hydrolysis with dilute potassium hydroxide, whereas the isomeric 9,10-dihydroxystearic acid, m. p. 95°, is obtained when concentrated potassium hydroxide is employed.

(11) Sowden and Fischer, THIS JOURNAL, **64**, 1291 (1942).

According to the scheme proposed in this paper, when dilute alkali is employed, the iodine atom is replaced directly by the hydroxyl group, with inversion,[5] and the 9,10-dihydroxystearic acid, m. p. 131°, is obtained. With concentrated alkali, the oxirane compound is formed as an intermediate, accompanied by inversion,[9] and this on hydrolysis also accompanied by inversion,[9] yields 9,10-dihydroxystearic acid, m. p. 95°. Thus, in the latter case two inversions must occur, whereas in the former only one takes place. This is shown in Fig. 3.

The chlorohydroxystearic acids obtained directly from the unsaturated acids by reaction with hypochlorous acid (reaction 8) and those obtained by treatment of the oxirane compounds with hydrogen chloride (reaction 2) have the same configuration, since they (the chlorohydrins) yield the same oxirane compound on ring closure. Since opening of the oxirane ring is accompanied by inversion,[6,7,8,9] it follows that hypohalogenation of the unsaturated acids must take place by *trans*-addition, as would be expected,[5] and epoxidation (reaction 1), therefore, must occur by *cis*-addition. That epoxidation occurs by *cis*-addition was also concluded by Braun[12] from a

Fig. 3

H—C=C—H   Oleic acid
  a   b

Reaction with HOI
(*trans*-addition)

a H   H b   H b   a H
H—C—C—b a—C—C—H a—C—C—H H—C—C—b
  I OH   OH I   I OH   OH I
  − −   + +   + +   − −

Hydrolysis with dilute KOH (inversion)

H H   a b
a—C—C—b H—C—C—H
  OH OH   OH OH
  + −   − +

9,10-Dihydroxystearic acid, m. p. 131°

Hydrolysis with concd. KOH (inversion)

H H   a b
a—C—C—b H—C—C—H
  O   O
  + −   − +

Hydrolysis with concd. KOH (inversion)

H b   a H
a—C—C—H H—C—C—b
  OH OH   OH OH
  + +   − −

9,10-Dihydroxytearic acid, m. p. 95°

study of the perbenzoic acid oxidation of crotonic and isocrotonic acids.

Furthermore, hydroxylation with potassium

(12) Braun, *ibid.*, **51**, 228 (1929).

permanganate (reaction 9) must also occur by *cis*-addition, which is in accord with accepted views on such oxidations,[6,7,13] and photochemical addition of hydrogen peroxide to the double bond, as well as the catalytic hydroxylation of the double bond with *t*-butyl hydroperoxide, must also take place by *cis*-addition.[14] The hydroxylation of maleic and fumaric acids to meso and racemic tartaric acids, respectively, by these reactions is excellent proof that a *cis*-addition mechanism is operative.

The interconversion of the 9,10-dihydroxystearic acids[3,4] (reactions 5, 6 and 7) must proceed, therefore, as shown in Fig. 1. The postulation of an inversion when a hydroxyl group is replaced by a halogen atom, or when the reverse change occurs, is substantiated by extensive experimental evidence.[5]

Experimental

Preparation of the Isomeric 9,10-Epoxystearic Acids.—The high-melting isomer, m. p. 59.5–59.8°, was prepared in good yield by the epoxidation of pure oleic acid[15] with perbenzoic[16] or peracetic acids.[17] It can also be prepared by treating oleic acid with hypochlorous acid followed by dehydrohalogenation with alkali,[4,18] although the yields are poor.

The low-melting isomer, m. p. 55.5°, was similarly prepared[4,16,17,18] from pure elaidic acid.[19]

Preparation of the Isomeric 9,10-Dihydroxystearic Acids.—The high-melting isomer, m. p. 131°, was prepared in excellent yield from oleic acid by oxidation with alkaline potassium permanganate[20] or from elaidic acid by epoxidation,[16,17] yielding 9,10-epoxystearic acid, m. p. 55.5°, as an intermediate product, followed by alkaline aqueous hydrolysis.[18] It was also prepared in more than 95% yield by heating 5 g. of 9,10-epoxystearic acid, m. p. 55.5°, for several hours at 100° with 100 ml. of glacial acetic acid, removing the solvent by vacuum distillation and treating the residual hydroxyacetoxystearic acids with an excess of 1 to 6 *N* aqueous sodium hydroxide for one hour at 100° (or overnight at room temperature), followed by acidification with dilute hydrochloric acid. The high-melting isomer was also prepared under milder reaction conditions by allowing 9,10-epoxystearic acid, m. p. 55.5°, to stand overnight at room temperature in anhydrous formic acid solution or in glacial acetic acid solution containing 1 to 5% of 95% sulfuric acid, or by allowing it to stand for several weeks at room temperature in glacial acetic acid solution, followed by removal of the solvent and aqueous hydrolysis. The best over-all procedure for preparing the high-melting isomer, which does not require isolation of the intermediate oxirane compound, involves oxidation of elaidic acid with 25 to 30% hydrogen peroxide in formic or acetic acid solution.[21] Yields are over 95%.

The low-melting isomer, m. p. 95°, was prepared in excellent yields from elaidic acid by oxidation with alkaline potassium permanganate,[20] from oleic acid by epoxida-

tion[16,17] and hydrolysis,[18] from 9,10-epoxystearic acid, m. p. 59.5°, as described above, or from oleic acid by oxidation with 30% hydrogen peroxide in formic or acetic acid solution.[21]

Preparation of the Isomeric 9,10(10,9)-Chlorohydroxystearic Acids.—Although the 9,10(10,9)-chlorohydroxystearic acids can be prepared from oleic and elaidic acids by reaction with hypochlorous acid (prepared from gaseous chlorine and sodium hydroxide and utilized *in situ*,[4,18,22]) in our experience the yields may be low and the products are usually contaminated with polychlorinated materials. The best procedure for their preparation is to dissolve 2.98 g. (0.01 mole) of 9,10-epoxystearic acid (either isomer) in 100 ml. of a 0.2 *N* solution of anhydrous hydrogen chloride in absolute ether[22,23] contained in a 250-ml. separatory funnel, and allow the solution to stand at room temperature for three hours. The ether solution is washed with cold water until acid-free, dried over anhydrous calcium sulfate and filtered. Distillation of the ether yields 3.30 to 3.35 g. (99 to 100% yield) of 9,10(10,9)-chlorohydroxystearic acids as a non-volatile residue. Neutralization equivalent, calcd., 334.5; found, 334 to 335. 9,10-Epoxystearic acid, m. p. 59.5°, yields 9,10(10,9)-chlorohydroxystearic acids, m. p. 39–40° (lit.[22] 35°), which are reconverted to 9,10-epoxystearic acid, m. p. 59.5°, on treatment with concentrated alkali.[4,18] The chlorohydroxystearic acids, m. p. 39–40°, are identical with those obtained by the hypochlorination of oleic acid, since they both yield 9,10-epoxystearic acid, m. p. 59.5°, on dehydrohalogenation.[4] 9,10-Epoxystearic acid, m. p. 55.5°, yields 9,10(10,9)-chlorohydroxystearic acids, m. p. 58.0–58.8° (lit.[4] 58°), which are reconverted to 9,10-epoxystearic acid, m. p. 55.5°, on treatment with concentrated alkali.[4] The chlorohydroxystearic acids, m. p. 58–58.8°, are identical with those obtained by the hypochlorination of elaidic acid, since they both yield 9,10-epoxystearic acid, m. p. 55.5°, on dehydrohalogenation.[4]

Acknowledgment.—The author wishes to thank Thomas W. Findley and John T. Scanlan for thought-provoking discussions which helped to clarify some of the ideas presented in this paper.

Summary[24,25]

A reaction scheme is described which correlates the configurational relationships in the conversion of oleic and elaidic acids (*cis*- and *trans*-9-octadecenoic acids, respectively) to 9,10-dihydroxystearic acids by way of the intermediate oxirane

(13) Böeseken and Cohen, *Rec. trav. chim.*, **47**, 839 (1928); King, *J. Chem. Soc.*, 37 (1943).

(14) Milas, Kurz and Anslow, Jr., THIS JOURNAL, **59**, 543 (1937); Milas and Sussman *ibid.*, **58**, 1302 (1936); Milas, *ibid.*, **59**, 2342 (1937); Milas, Sussman and Mason, *ibid.*, **61**, 1844 (1939).

(15) Brown and Shinowara, *ibid.*, **59**, 6 (1937); Wheeler and Riemenschneider, *Oil and Soap*, **16**, 207 (1939).

(16) Swern, Findley and Scanlan, THIS JOURNAL, **66**, 1925 (1944).

(17) Findley, Swern and Scanlan, *ibid.*, **67**, 412 (1945).

(18) Ellis, *Biochem. J.*, **30**, 753 (1936).

(19) Bertram, *Chem. Weekblad*, **33**, 3 (1936).

(20) Lapworth and Mottram, *J. Chem. Soc.*, **127**, 1628 (1925).

(21) Swern, Billen, Findley and Scanlan, THIS JOURNAL, **67**, 1786 (1945).

(22) Nicolet and Poulter, *ibid.*, **52**, 1186 (1930).

(23) Swern, Findley, Billen and Scanlan, *Anal. Chem.*, **19**, 414 (1947).

(24) NOTE ADDED IN PROOF: In the recent paper by McKay and Bader, *J. Org. Chem.*, **13**, 75 (1948), it was assumed that oxidation of oleic and elaidic acids with alkaline potassium permanganate proceeds by a *trans* hydroxylation mechanism. This was based on infrared absorption studies of the isomeric methyl 9,10-dihydroxystearates, Davies, *J. Chem. Phys.*, **8**, 577 (1940), and on the difference between the rates of reaction of the 9,10-dihydroxystearic acids with lead tetraacetate, Hilditch and Jasperson, *Nature*, **147**, 327 (1944). In these papers no conclusions regarding the absolute configuration of the dihydroxystearic acids and their relationship to oleic and elaidic acids were made. It is our belief, based upon the information presented in our paper and also in literature references 3, 6 and 13 cited therein, that the conclusions drawn by McKay and Bader regarding the configurations of the dihydroxy and tetrahydroxystearic acids are unjustified [see also Wittcoff and Miller, THIS JOURNAL, **69**, 3138 (1947)]. Furthermore, the terms *cis* and *trans*, employed by McKay and Bader and some earlier investigators, should not be applied to the hydroxy acids since these compounds are diastereoisomers and not geometric isomers, for which the terms are intended.

(25) This paper was presented at the meeting of the American Chemical Society held in New York, N. Y., on Sept. 15–19, 1947.

and chlorohydroxy compounds. This scheme is self-consistent and is in harmony with accepted theories of the Walden inversion and double bond addition reactions.

According to this scheme, epoxidation of the unsaturated acids with organic per-acids, or oxidation with alkaline potassium permanganate, takes place by cis-addition, whereas reaction with hypochlorous acid proceeds by trans-addition. Furthermore, it is postulated that opening (either in alkaline or acidic media) and re-forming of the oxirane ring, as well as replacement of a hydroxyl group of 9,10-dihydroxystearic acid by halogen, are each accompanied by an inversion. An inversion is also postulated when halogen is replaced by hydroxyl in the 9,10(10,9)-halohydroxystearic acids, and an explanation is offered for the formation of high- or low-melting 9,10-dihydroxystearic acid when 9,10(10,9)-iodohydroxystearic acids (from oleic acid) are treated with dilute or concentrated alkali, respectively.
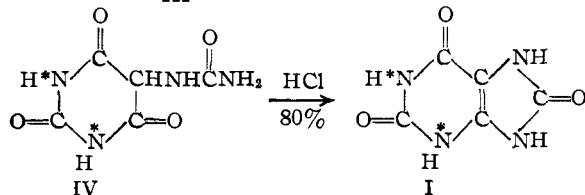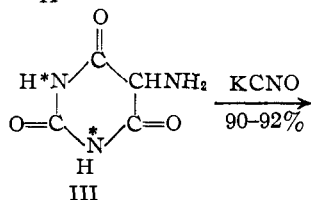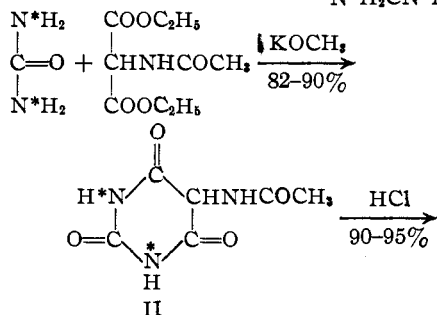

# The Synthesis of Uric Acid Containing Isotopic Nitrogen

BY LIEBE F. CAVALIERI, VIRGINIA E. BLAIR AND GEORGE BOSWORTH BROWN

The existing procedures[1,2,3,4,5,6] for the synthesis of uric acid involve many steps and the over-all yields are low, based upon the urea used. For the introduction of isotopic nitrogen a modified synthesis has been developed in order to insure optimum utilization of the isotope. This synthesis introduces N^{15} in the pyrimidine ring (positions 1 and 3) (I) as shown in the following equations:

$$N^*H_4NO_3 \longrightarrow N^*H_3 \xrightarrow[50-60\%]{(C_6H_5O)_2CO} N^*H_2CN^*H_2 + 2C_6H_5OH$$

$$\begin{matrix} N^*H_2 \\ | \\ C{=}O \\ | \\ N^*H_2 \end{matrix} + \begin{matrix} COOC_2H_5 \\ | \\ CHNHCOCH_3 \\ | \\ COOC_2H_5 \end{matrix} \xrightarrow[82-90\%]{KOCH_3}$$

II

III

IV   I

(1) Baeyer, Ann., 127, 1 (1863).
(2) Grimaux, Bull. soc. chim., [2] 31, 535 (1879).
(3) Fischer, Ber., 30, 559 (1897).
(4) Horbaczewski, Monatsh., 8, 201 (1887).
(5) Behrend and Roosen, Ann., 251, 235 (1889).
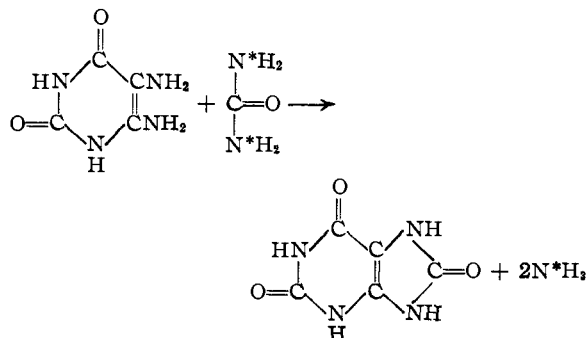(6) Behrend, ibid., 441, 215 (1925).
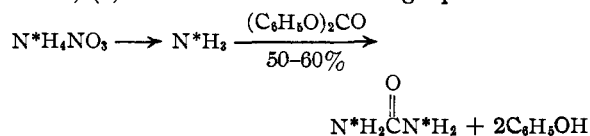
The over-all yield in this synthesis was 55%, based upon the urea used. The yields afforded by the older procedures can be estimated to be about 27%.

A second synthesis of uric acid (V) incorporating N^{15} presumably in position 9 was carried out according to the method of Grimaux.[2]

V
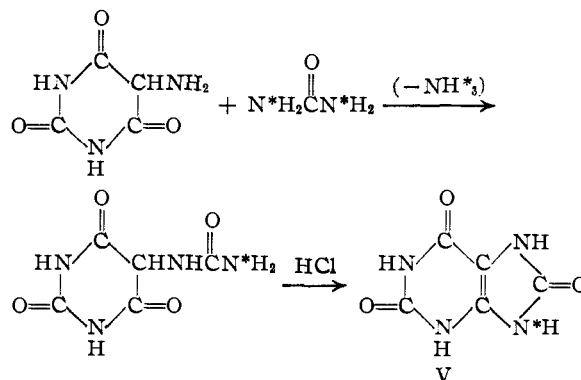
It will be noted that one amino group of the urea molecule was eliminated in the initial reaction. Cyclization with hydrochloric acid produced uric acid (V) containing about 1 atom of isotopic nitrogen. Since in the analogous reaction of 2,6-dioxy-4,5-diaminopyrimidine with urea[7] both of the amino groups of the urea were eliminated and no isotopic nitrogen was introduced into the uric

(7) Levene and Senior, J. Biol. Chem., 25, 618 (1916).