[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Synthesis of *dl*-Lichesterinic Acid Methyl Ester

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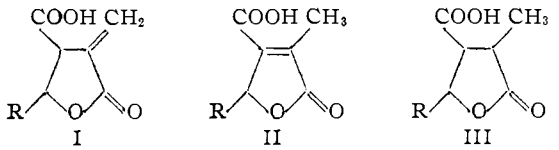
The methyl ester of *dl*-lichesterinic acid has been synthesized by the sulfuryl chloride dehydrogenation of methyl *dl*-dihydroprotolichesterinate, which was in turn obtained *via* the sodium borohydride reduction of methyl 2-methyl-3-carbomethoxy-4-ketoheptadecanoate. Various transformations encountered in the catalytic reduction of lichesterinic and protolichesterinic acids are presented, and the possible biogenetic origins of these substances are discussed.

In 1845, Schnedermann and Knop[2] isolated from the lichen *Cetraria islandica* (Iceland Moss) a substance $C_{19}H_{32}O_4$ which was termed by them lichesterinic acid. Subsequent workers confirmed this finding, but it remained for Zopf,[3] in 1902, to demonstrate that a different, but isomeric, acid could be obtained by a modified isolation procedure and that this new substance was transformed readily—even on mere heating in alcohol—into lichesterinic acid. This precursor was termed protolichesterinic acid. The nature and relationship of these two substances remained unknown until 1927, when the investigations of Asahina and Asano[4,5] culminated in the proposal of the currently accepted structures I and II for protolichesterinic

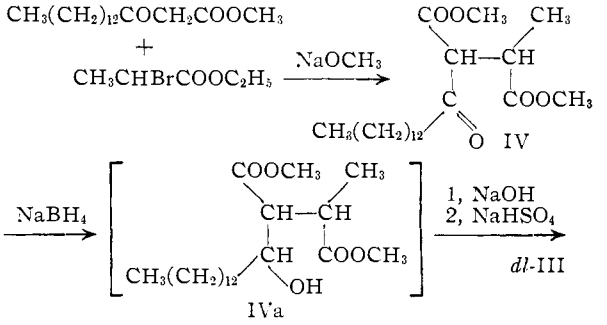


R = $CH_3(CH_2)_{12}$–

acid and lichesterinic acid, respectively. Recently there has been an expression of renewed interest in these two materials, since they, as well as the catalytic reduction product of I, dihydroprotolichesterinic acid (III), were found effective in inhibiting the growth of gram-positive bacteria.[6]

As part of a broader program dealing with the study of antibiotic materials, we undertook the problem of synthesizing these three substances. Although, because of its lability, a selective and separate route would probably be required for the proto-acid, it seemed to us that the remaining two might be available by a common path: namely, synthesis of the dihydroprotolichesterinic acid type followed by dehydrogenation. The latter objective now has been realized, and we are presently investigating methods for constructing structure I.

Of two routes investigated, the first outlined below proved successful. Methyl myristylacetate[7] was alkylated with ethyl 2-bromopropionate by allowing the reactants to stand in methanol solution for one week in the presence of sodium



methoxide; transesterification accompanied the main reaction, and the crystalline methyl 2-methyl-3-carbomethoxy-4-ketoheptadecanoate[8] (IV) was isolated in 65% yield. No solid product could be isolated when the reaction was attempted for shorter periods of time at 100°. Although the precedent[9] for direct attack at the 2-carbon of ethyl 2-bromopropionate rather than initial elimination to ethyl acrylate followed by Michael addition is convincing, the point nevertheless was checked by a Kuhn–Roth determination on the alkylated product—the value 1.67 demonstrates the two C-methyl groups in IV.

The infrared spectrum of IV, possessing peaks at 5.75, 5.78 and 5.83 μ, indicates one additional carbonyl (the new ester grouping) over the starting methyl myristylacetate, which absorbs at 5.73 and 5.86 μ.

dl-Dihydroprotolichesterinic acid (VI) was obtained from IV by sodium borohydride reduction, carried out in methanol at room temperature. No attempt was made to isolate the presumed intermediate IVa, but rather it was hydrolyzed directly with methanolic potassium hydroxide to yield, after acidification of an insoluble potassium salt, VI in 40% yield. The *dl*-dihydro acid melted at 114–115° and formed, on treatment with diazomethane, the methyl ester VIa, m.p. 62–62.5°. Since the active dihydroprotolichesterinic acid was found to be sparingly soluble in chloroform or carbon tetrachloride, it was converted to its methyl ester IIIa, which did possess solubility properties rendering it suitable for infrared determination. The spectra of IIIa and VIa, measured in chloroform, were found to be indistinguishable.[10]

Along with *dl*-dihydroprotolichesterinic acid and the cleavage product lichesterylic acid (V), there

(1) Wisconsin Alumni Research Foundation Research Assistant, Feb.–June, 1953; du Pont Summer Research Assistant 1953 and 1954.

(2) G. Schnedermann and W. Knop, *Ann.*, **55**, 144 (1845).

(3) W. Zopf, *ibid.*, **324**, 52 (1902).

(4) Y. Asahina and M. Asano, *J. Pharm. Soc. Japan*, **539**, 1 (1927).

(5) The Japanese workers carried out their investigations on *l*-protolichesterinic acid, obtained from *C. tenuifolia*, whereas the earlier workers dealt with its enantiomer.

(6) C. J. Cavallito, D. McK. Fruehauf and J. H. Bailey, THIS JOURNAL, **70**, 3724 (1948).

(7) S. Ställberg-Stenhagen, *Arkiv Kemi, Mineral. Geol.*, **20A**, 19 (1945).

(8) M. Asano and T. Azumi, *Ber.*, **72B**, 35 (1939).

(9) C. A. Bischoff, *Ann.*, **214**, 53 (1882).

(10) Although both VI and VIa exhibited the expected lactone absorption (5.68 μ) in chloroform, the acid III absorbed in a mull at 5.77 μ. Since the latter value ordinarily indicates a six-membered lactone, this example serves to emphasize the caution which should be exercised when interpreting mull spectra.

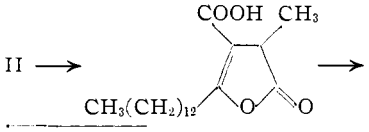
was formed in the reduction of IV an *isomer*,

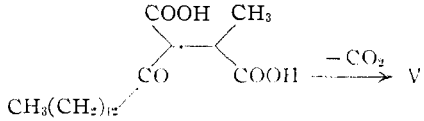
$$CH_3(CH_2)_{12}COCH_2CHCH_3COOH \quad (V)$$

dl-isodihydroprotolichesterinic acid, m.p. 135–136°, which was separated from VI and isolated easily because of the solubility in methanol of the potassium salt formed in the reduction–hydrolysis sequence. This acid, obtained in a yield averaging about 9%, may be identical with the sole product (m.p. 134–136°) obtained by Asano[8] in 0.36% yield by the sodium–alcohol reduction of IV.

An alternate approach to VI featured the condensation of methylmalonic ester with 2,3-epoxyhexadecanoic acid. The epoxide appeared promising for the present purpose because (1) glycidic esters have been opened by malonate anion[11] and (2) attack should occur at the 2-carbon since it is approximately sterically equivalent to the 3-carbon yet probably more susceptible to S_N2 attack because of the influence of the adjacent carbonyl group.[12] Accordingly 2-hexadecenoic acid was hypochlorinated[13] and subsequently esterified. Since it had been previously demonstrated that a 1,2-halohydrin normally reacts *via* the corresponding epoxide as an intermediate in the displacement reaction,[14] it was deemed sufficient to employ the chlorohydrin itself in the alkylation of diethyl methylmalonate. No well-defined product could be isolated, however, and the route was abandoned in favor of the one already described.

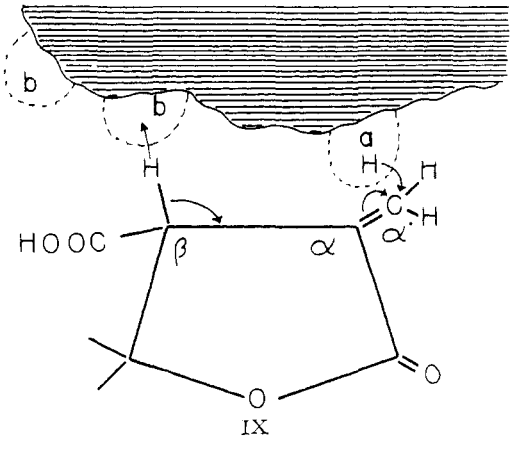
With the dihydro acid VI and its ester VIa available, we directed our efforts toward their transformation to *dl*-lichesterinic acid (VII). A selective dehydrogenating agent was required, and we found that but one of several tested was suitable, although not admirably so: sulfuryl chloride and a catalytic amount of benzoyl peroxide[15] converted VIa to the methyl ester VIII of *dl*-lichesterinic acid in 7–17% yield. The infrared and ultraviolet spectra of the synthetic methyl ester and those of the methyl ester derived from the natural source were respectively identical; furthermore, the melting point of the synthetic ester was not depressed on admixture with a sample of the methyl ester of the *dl*-product[16] obtained by mixing equal portions of the *d*- and *l*- materials derived from natural sources. Substantiating proof of structure was gained by basic hydrolysis of the *dl*-ester, which produced lichesterylic acid (V), derivable from the natural acid under similar conditions[4]—probably according to the mechanism





Bromine in polyphosphoric acid,[17] N-bromosuccinimide and maleic acid (as an acceptor in a palladium-catalyzed hydrogen transfer process) were even less promising in the production of VII or VIII from VI or VIa, although in some cases (see Experimental) the formation of *dl*-lichesterinic acid was evident from the ultraviolet absorption of the crude reaction products. We were not successful in obtaining the free *dl*-acid II through sulfuryl chloride treatment of VI.

In the course of repeating some of the early work, we had occasion to examine closely the catalytic reduction of I and II. Although there was little difficulty in procuring a fair yield of pure dihydroprotolichesterinic acid, m.p. 103.5–104.5°, the hydrogen uptake was erratic in that it slowed down decisively or stopped completely after roughly half of the theoretical amount had been absorbed. In one case, the hydrogenation process was interrupted at this point and the product isolated in the usual way. Infrared and ultraviolet analysis demonstrated the presence of a preponderant amount of *lichesterinic acid*, which therefore must arise by the palladium-catalyzed isomerization of protolichesterinic acid. It was shown that the mixture resulting from this incomplete hydrogenation process could be further reduced over platinum in glacial acetic acid, as could lichesterinic acid itself (*vide infra*). In an attempt to demonstrate directly a catalyzed isomerization, protolichesterinic acid was stirred for six hours over the catalyst in an aerial atmosphere; since only starting material was isolated, adsorbed hydrogen appears to be necessary for the isomerization. These observations can be accounted for by the operation of a catalyst with sporadic hydrogen-rich active centers ("a"), in a concerted hydrogen transfer reaction, represented pictorially by IX. We envision the



IX

approach of the hydrogen-bearing catalyst with transfer of hydrogen to α-methylene carbon and simultaneous abstraction of β-H by an adjacent hydrogen-poor, or "potential," active center ("b"); it would seem that the latter change *per se*, although

(11) G. V. Chelintsev and E. D. Osetrova, *J. Gen. Chem. (U.S.S.R.)*, **7**, 2373 (1937); *C. A.*, **32**, 2099 (1938).

(12) J. B. Conant and W. R. Kirner, THIS JOURNAL, **46**, 232 (1924).

(13) The relative positions of halogen and hydroxyl, a problem of no particular consequence for the present purpose, was not determined although precedent allows the tentative assignment as the 2-chloro-3-hydroxy isomer (*cf.* E. Erlenmeyer and A. Lipp, *Ann.*, **219**, 185 (1883)).

(14) E. E. van Tamelen, G. Van Zyl and G. D. Zuidema, THIS JOURNAL, **72**, 488 (1950).

(15) C. C. Price and M. Schwarcz, *ibid.*, **62**, 2891 (1940).

(16) We wish to thank Dr. S. Shibata for a sample of this *dl*-acid.

(17) E. E. Smissman, THIS JOURNAL, **76**, 5805 (1954).

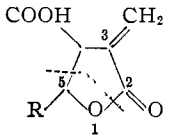
possible with a hydrogen-poor catalyst, is handicapped by a higher energy barrier than when coupled with hydrogen addition at the α'-carbon.

Contrary to the implications of earlier investigators,[4] we have found that lichesterinic acid will absorb hydrogen catalytically when Adams catalyst in glacial acetic acid is employed for the reduction process. Approximately a third more than the theoretical amount of hydrogen for one double bond was consumed, and the resulting mixture provided, through recrystallization from acetic acid, a 46% yield of pure material, m.p. 135.5–136.5°. The absence of significant ultraviolet absorption, an analysis indicative of a tetrahydro- rather than a dihydro- lichesterinic acid, and a neutral equivalent corresponding to a dibasic rather than a monobasic acid pointed to the structure X

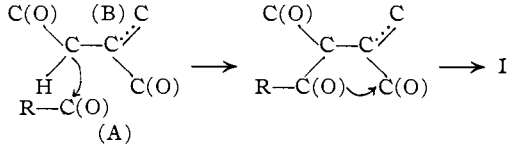
$$CH_3(CH_2)_{13}CH(COOH)CH(COOH)CH_3$$
X

which resulted from both hydrogenation and from allylic hydrogenolysis processes. Corroboration of the proposed structure was achieved by dehydration to the *anhydride*, which exhibited the carbonyl absorption bands (5.40 and 5.65 μ) anticipated for a five-membered anhydride. Although no direct comparison was made, it is pertinent to point out that the structure X was established for a product, m.p. 133–135°, obtained by the drastic reduction of dihydroprotolichesterinic acid with phosphorus–hydrogen iodide followed by dehalogenation with zinc and acetic acid.[18]

When considering the protolichesterinic acid structure in terms of its possible biogenetic origin, one readily recognizes the fruitfulness of dissection through the 1,2- and 4,5-bonds of the lactone ring, whereby two promising fragments result. The

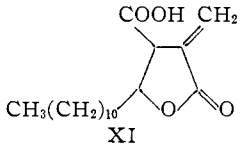


first of these (A), constituted by the normal 13-carbon chain and the 5-carbon with oxygen attached, belongs to the fatty acid type; the second (B), embodied by the remaining five carbons with an actual or incipient exocyclic double bond and with oxygen suitably disposed, conforms to the isoprenoid pattern. Both of these hypothetical



units would appear to be plausible, therefore, insofar as occurrence in a plant is concerned. Conjunction of these fragments, possibly *via* an aldol type reaction in which the (B) moiety plays the role of the active hydrogen component, can then occur, the subsequent changes required for the formation of I, *viz.*, lactonization and modifications in oxidation state, being considered trivial. Alternately, it is possible that the (B) moiety may arise through union of a 2- with a 3-carbon fragment after the introduction of (A); the process thereby becomes an alteration of isoprenoid biosynthesis as it is commonly viewed today.

This biogenetic scheme allows certain predictions, of which some can be brought to test. For example, although the arrangement of atoms in the lactone skeleton is considered inflexible, variation in oxidation state would not be unreasonable; this variation is realized in nephromopsinic acid, the stereoisomer of dihydroprotolichesterinic acid which occurs naturally in *Nephromopsis Stracheyi f. ectocarpisma.*[19] Further, it would be suspected that the (B) building block be incapable of modification in size of branching, whereas variations of (A) might parallel those in the natural fatty acid family and include different lengths of normal carbon chains, *even-numbered and varying by two carbon units.* In fact, Asahina has isolated from *Nephromopsis endocrocea* an acid termed nephrosterinic acid, which, exhibiting the typical reactions of protolichesterinic acid yet bearing *two carbons less*, appears to possess structure XI.[20] Thus the



XI

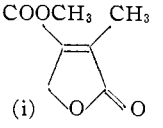
prediction may be made that yet uninvestigated lichens will yield acids of the protolichesterinic type with further variations in the side chain, possibly to the extent of including unsaturation and in any case consistent with the structures of naturally occurring fatty acids.

TABLE I

ULTRAVIOLET ABSORPTION, mμ

log ε	210	220	230	240
Methyl 3-methylaconate[a] (i)	3.82	4.02	4.07	3.80
Lichesterinic acid[b]	3.87	4.01	4.04	3.88
Protolichesterinic acid[b]	3.95	3.86	3.65	3.40

[a] Formula (i), R. F. Rekker, P. J. Brombacher, H. Hamann and W. T. Nauta, *Rec. trav. chim.*, **73**, 410 (1954). [b] Measured in 95% ethanol solution with a Cary automatic spectrophotometer.



Experimental[21]

Methyl 3-Ketohexadecanoate.—The procedure of Ställberg-Stenhagen[7] was followed except that a more convenient purification method was used instead of the low temperature crystallization from acetone. Oily impurities first were removed from the crude product by thorough suction filtration with a rubber dam, whereby 82% of product was retained. By crystallization at 0° from 40–60° petroleum ether, including utilization of the filtrate as solvent for the new batch, a 40% over-all yield of ester, m.p. 38–39°, was isolated. A final recrystallization raised the melting point to 40.2–40.6°.

Methyl 2-Methyl-3-carbomethoxy-4-ketoheptadecanoate (IV).—Sodium (0.41 g.) was dissolved in 10 ml. of absolute methanol, and methyl 3-ketohexadecanoate (5.0 g.), sodium iodide (2.9 g.) and ethyl 2-bromopropionate (3.18 g.) were added in that order. After being swirled and heated for a few minutes on the steam-bath, the reaction mixture was stoppered well and allowed to stand at room temperature for 4–7 days. The resulting mixture was

(18) M. Asano and T. Azumi, *Ber.*, **68B**, 991 (1935).

(19) M. Asano and T. Azumi, *ibid.*, **68B**, 995 (1935).

(20) Y. Asahina and M. Yanagita, *ibid.*, **70**, 227 (1937).

(21) All melting points are corrected.

poured into water and acidified with sodium bisulfate. Thorough filtration of the waxy solid which precipitated followed by crystallization from 30 ml. of 60–68° petroleum ether afforded 4.35 g. (65%) of the desired alkylated ester, m.p. 48–50°. A second recrystallization from the same solvent gave, with about a 25% loss of material, colorless prisms melting at 49–50°.[8]

Anal. Calcd. for $C_{21}H_{38}O_5$: C, 68.07; H, 10.34. Found: C, 67.88; H, 10.60.

***dl*-Dihydroprotolichesterinic Acid (VI).**—Five grams of methyl 2-methyl-3-carbomethoxy-4-ketoheptadecanoate, previously dissolved in 50 ml. of absolute methanol by warming slightly on the steam-bath, was subjected to the action of 3.9 ml. of 1.0 *M* sodium borohydride in methanol for three days at room temperature. An additional 5.5 ml. of the borohydride solution then was added, and the reaction mixture was allowed to stand for three hours more. The flask contents then were poured into water, whereupon a white suspension formed, and the mixture was acidified to congo red with sodium bisulfate. The resulting oil was extracted with ether, and the extract dried over sodium sulfate. The oily precipitate obtained on evaporation of the ether was refluxed for 19 hours in a solution of 3.5 g. of potassium hydroxide in 55 ml. of 90% methanol. White needles separated during the hydrolysis, and these were filtered off, dissolved in water and acidified with 5% hydrochloric acid. After drying the crude acid which precipitated, it was extracted with petroleum ether; the insoluble residue was recrystallized from glacial acetic acid and melted then at 114–115°. The over-all yield of pure *dl*-dihydroprotolichesterinic acid was 1.70 g. (40%).

Anal. Calcd. for $C_{19}H_{34}O_4$: C, 69.88; H, 10.49. Found: C, 70.17; H, 10.91.

The filtrate of the hydrolysis mixture was poured into a large excess of water and acidified with sodium bisulfate. After removal of the crystalline precipitate and drying, it was extracted with boiling 60–68° petroleum ether to remove the lichesterylic acid which had formed (m.p. 84.5–85.0°, lit.[4] 84°). The residue from the extraction (m.p. 133–134°) was crystallized from glacial acetic acid and then melted at 135–136°; the average yield of *dl*-isodihydroprotolichesterinic acid was 9%.

Anal. Calcd. for $C_{19}H_{34}O_4$: C, 69.88; H, 10.49. Found: C, 69.46; H, 10.48.

The methyl esters of both isomers were obtained through the agency of diazomethane. **Methyl *dl*-dihydroprotolichesterinate (VIa)** melted, after crystallization from methanol, at 62.0–62.5°.

Anal. Calcd. for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.07; H, 10.73.

Methyl *dl*-isodihydroprotolichesterinate was crystallized from methanol and melted at 67.0–67.5°.

Anal. Calcd. for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.55; H, 10.79.

Methyl *d*-Dihydroprotolichesterinate (IIIa).—*d*-Protolichesterinic acid was reduced in glacial acetic acid at room temperature and atmospheric pressure with 10% palladium-on-carbon as the catalyst. After allowing a sufficient length of time for the theoretical uptake of hydrogen, the product, obtained by dilution with water, was recrystallized from glacial acetic acid, whereby the m.p. 103.5–104.5° was attained. The yield was 60%. Treatment with diazomethane yielded the methyl ester, m.p. 54.5–55.5° (lit.[4] 52.5°).

The infrared spectra of the two esters IIIa and VIa, obtained in chloroform solution with a Perkin–Elmer infrared spectrophotometer, were identical in every detail. Although the spectrum of methyl isodihydroprotolichesterinate was very similar to those of IIIa and VIa, there was sufficient difference in the fingerprint region to make differentiation possible.

In one run, 1.8 g. of protolichesterinic acid was reduced under the conditions described above; after 56 of the theoretical 137 ml. of hydrogen had been absorbed, the uptake had essentially ceased. After filtration and dilution of the filtrate with water, the product precipitated and was recrystallized from acetic acid. The melting point, 109–116°, could not be improved by further crystallization; spectral analysis showed that this material was preponderantly lichesterinic acid. In an experiment identical except that no hydrogen was admitted to the system and the reaction time arbitrarily fixed at six hours, only recovered protolichesterinic acid, as indicated by melting point and mixed melting point, was obtained.

Hypochlorination of 2-Hexadecenoic Acid.—2-Hexadecenoic acid (8.8 g.) was dissolved in 500 ml. of water containing 18.5 g. of potassium hydroxide. After dissolution and on cooling to 0°, a fine suspension appeared which did not redissolve on warming to room temperature. While the mixture was stirred at room temperature, chlorine gas (from a measured amount of liquid chlorine, 2.50 g.), mixed with a stream of nitrogen, was passed in over a period of about four hours. On addition of an equivalent amount of dilute sulfuric acid, the suspension initially dissolved and, subsequently, a white solid coagulated. The precipitate was taken up in ether, and the extract was dried and evaporated down. The pale yellow oil remaining was taken up in 90 ml. of 60–68° petroleum ether; subsequent cooling at 0–5° for several days induced crystallization of 2.3 g. of chlorohydroxy acid. One recrystallization raised the melting point to 75–76° (1.7 g., 16%). For analysis the acid was crystallized once more from petroleum ether, and it then melted at 75.7–76.2°.

Anal. Calcd. for $C_{16}H_{31}ClO_3$: C, 62.62; H, 10.17. Found: C, 62.64; H, 10.28.

The ethyl ester, m.p. 50.8–51.5°, was obtained by Fischer esterification.

Dehydrogenation of Methyl *dl*-Dihydroprotolichesterinate.—A solution of 200 mg. of methyl *dl*-dihydroprotolichesterinate, 160 mg. of freshly distilled sulfuryl chloride, and 10 mg. of benzoyl peroxide in 0.5 ml. of carbon tetrachloride was refluxed for eighteen hours. After removal of the solvent by distilling *in vacuo* at room temperature, the product was taken up in a mixture of water and 20 ml. of ether; after separation of the ether layer, it was dried over anhydrous sodium sulfate. The product remaining on evaporation of the ether was dissolved in 1 ml. of ethanol and the resulting solution filtered to remove a small amount of an insoluble substance. On chilling, the filtrate deposited a white precipitate, which was filtered and dried. The yield of methyl *dl*-lichesterinate, melting at 47–49°, was 15–37 mg. (7–17%). After recrystallization from methanol, the ester melted at 49–50°.

Anal. Calcd. for $C_{20}H_{34}O_4$: C, 70.82; H, 10.12. Found: C, 70.79; H, 10.02.

The infrared spectrum of the synthetic *dl*-ester was indistinguishable from that of the *d*-ester derived from the natural source; the ultraviolet spectra, too, were identical.

Five milligrams of *dl*-lichesterinic acid, derived from equal parts of *d*- and *l*-lichesterinic acids,[16] was esterified in ether with diazomethane. The colorless product, m.p. 51–52°, obtained by recrystallization from aqueous methanol of the solid product remaining after evaporation of the ether, did not, on admixture, lower the melting point of the synthetic *dl*-lichesterinic acid methyl ester, m.p. 49–50°.

In an attempt to develop more efficient routes the following dehydrogenation experiments were attempted. (1) *dl*-Dihydroprotolichesterinic acid was heated for a short time with bromine in polyphosphoric acid at 120–140°; the halogenated, but unidentified product obtained, after being treated with collidine, yielded an inseparable mixture the ultraviolet of which indicated the possible presence of lichesterinic acid. (2) Treatment of the dihydro acid with N-bromosuccinimide with benzoyl peroxide under the usual conditions afforded crude material which, on the basis of ultraviolet analysis, contained about 7% of lichesterinic acid; no attempt was made, however, to isolate it. Treatment of the dihydroproto methyl ester with NBS was even less promising. (3) Use of the acid rather than the methyl ester in the sulfuryl chloride reaction yielded material which did not absorb in the ultraviolet. (4) Catalytic dehydrogenation studies in which were employed 10% palladium-on-charcoal in boiling toluene as well as 30% palladium-on-charcoal in boiling aqueous potassium maleate, led to no products with ultraviolet absorption.

Hydrolysis of Synthetic *dl*-Lichesterinic Acid Methyl Ester.—To synthetic *dl*-lichesterinic acid methyl ester (9.6 mg.), dissolved in 2 ml. of methanol, was added 1 ml. of 2.66×10^{-2} *M* aqueous sodium hydroxide; the resulting solution was allowed to stand at room temperature for five days. After acidification with sodium bisulfate, the reaction mixture was filtered; the precipitated material, after being

dried, was taken up in boiling petroleum ether (60–68°). Evaporation of the filtered solution left a colorless product (m.p. 74–76°) which, after one recrystallization, melted at 83–84°. A mixed melting point with authentic lichesterylic acid showed no depression. Ultraviolet analysis showed no evidence for simple hydrolysis to *dl*-lichesterinic acid.

Catalytic Reduction of *d*-Lichesterinic Acid.—The reduction of 540 mg. of *d*-lichesterinic acid was carried out in 200 ml. of glacial acetic acid over 200 mg. of platinum oxide catalyst. After 54.8 ml. of hydrogen (theoretical uptake for one mole, 40.7 ml.) had been consumed, the catalyst was removed by filtration, and the product isolated by dilution of the acetic acid solution with water. Extraction of the mixture with boiling petroleum ether (60–68°) followed by three recrystallizations from glacial acetic acid yielded 250 mg. (46%) of pure tetrahydroacid X, m.p. 135.5–136.5°.

Anal. Calcd. for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05. Found: C, 69.58; H, 11.20.

The anhydride, m.p. 34° (uncor.), was obtained in 57% yield by dehydration of the diacid (82 mg.) with acetyl chloride (0.4 ml.), a reaction carried out in a sealed tube at 100° for one hour. After removal of the acetyl chloride by evaporation, the product was crystallized at Dry Ice–acetone temperature from petroleum ether (60–68°). The infrared spectrum possessed bands at 5.40 and 5.65 μ, indicative of a five-membered cyclic anhydride.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Dehalogenative Decarboxylation[1]

BY WYMAN R. VAUGHAN AND ROBERT L. CRAVEN[2]

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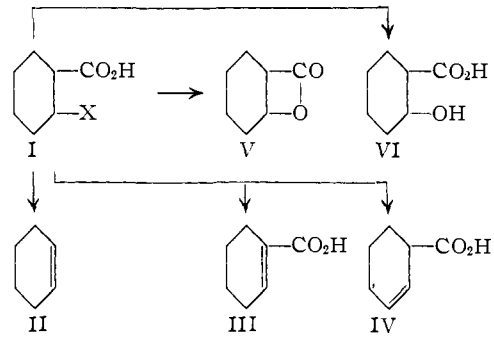
The dehalogenative decarboxylation reaction has been investigated with respect to the stereochemistry of the starting material. In agreement with previous findings *trans* elimination is encountered. It is shown further that where *trans* disposition of the halogen and carboxyl is prevented (and involvement of neighboring groups is avoided) the reaction will not occur. The present evidence indicates that dehalogenative decarboxylation is not effected by purely electrophilic attack on the halogen.

The suggestion[3] that halide ion and carbon dioxide are eliminated in a *trans* sense recently has been amply confirmed.[4–7] However, none of the work cited does more than imply that the elimination *must* be *trans*, only that *trans* elimination occurs to the virtual exclusion of *cis* elimination[5–7] in non-ionizing solvents (*e.g.*, acetone). In more polar solvents (*e.g.*, ethanol or water) the products of *cis* elimination are formed, owing to a proposed duality of mechanism. This observation is the more disturbing since one of us has observed that exclusively *cis* elimination is in fact possible. However, by invoking neighboring group participation the *trans* character of eliminations may be preserved in the instance cited.

In order to see to what extent *cis* elimination may occur (without neighboring group participation) in a system of known and rigid structure, four 2-halocyclohexanecarboxylic acids were prepared: *cis*- and *trans*-2-chloro- and *cis*- and *trans*-2-bromocyclohexanecarboxylic acids.[8] Since essentially the same reactions were observed for both epimeric pairs and since the chloro acids were distinctly less reactive, the arguments presented herewith will be based principally on the reactions of the bromo acids, with qualitative similarity implied for the related chloro acids. The various possible reaction products are illustrated in Chart I.

CHART I



The present investigation involves three sets of reaction conditions: (1) aqueous bases—essentially nucleophilic attack, (2) sodium bicarbonate suspended in acetone,[7] and (3) electrophilic attack by silver ion in non-aqueous media.

The expected course of reaction for the *cis*-halo acids with aqueous bases, if the dehalogenative decarboxylation is required to be *trans*, should lead primarily to cyclohexene-1-carboxylic acid (III) with some *trans*-2-hydroxycyclohexanecarboxylic acid formed by direct displacement of halogen (and possibly some cyclohexene-3-carboxylic acid (IV)). The analytical data presented in Table I support this hypothesis.

The *trans*-halo acids under similar conditions should afford chiefly cyclohexene II and 2-hydroxycyclohexanecarboxylic acid, the *trans* isomer where sodium bicarbonate is the base,[9] and the *cis* isomer where the *p*H is higher.[4]

The analytical data in Table I confirm the hypothesis that dehalogenative decarboxylation and hydroxy acid formation are the predominant reactions, and the identification of *trans*-2-hydroxycyclohexanecarboxylic acid from the *trans*-bromo acid and sodium bicarbonate confirms the alkyl–oxygen

(1) Abstracted from a portion of the Ph.D. Dissertation of Robert L. Craven, University of Michigan, 1954.

(2) American Brake Shoe Fellow 1951–1952; Albert B. Prescott Fellow, 1953.

(3) P. Pfeiffer, *Z. physik. Chem.*, **48**, 40 (1904).

(4) W. R. Vaughan and K. M. Milton, THIS JOURNAL, **74**, 5623 (1952).

(5) S. J. Cristol and W. P. Norris, *ibid.*, **75**, 632 (1953).

(6) E. Grovenstein and D. E. Lee, *ibid.*, **75**, 2639 (1953).

(7) S. J. Cristol and W. P. Norris, *ibid.*, **75**, 2645 (1953).

(8) W. R. Vaughan, R. L. Craven, R. Q. Little, Jr., and A. C. Schoenthaler, *ibid.*, **77**, 1594 (1955).

(9) A. R. Olson and R. J. Miller, *ibid.*, **60**, 2687 (1938); A. R. Olson and J. L. Hyde, *ibid.*, **63**, 2459 (1941); J. N. E. Day and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 693 (1941).