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The Structure of Lactobacillic Acid, $C_{19}H_{36}O_2$

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The crystals of lactobacillic acid, $C_{19}H_{36}O_2$, are triclinic with two non-centrosymmetrically related molecules in the unit cell. The molecule is shown to be D- or L-*cis*-11,12-methyleneoctadecanoic acid by a two-dimensional crystal structure analysis. This result confirms the deductions from chemical evidence. The individual molecules have the same general stereochemistry and shape as in the corresponding racemate crystal structure, but the molecular packing and the hydrogen-bonding system for the carboxylic acid groups is more complex.

Introduction

Lactobacillic acid, $C_{19}H_{36}O_2$, is at present the only known naturally occurring fatty acid which contains the cyclopropane ring. It was isolated and recognized as such by Hofmann and Lucas[1] and Hofmann and Sax[2] in their work on the lipids of *Lactobacillus arabinosus* and *L. casei*. They also showed that this acid was identical with the phytomonic acid which had been obtained earlier[3,4] from the lipids of the plant pathogen *Agrobacterium* (*Phytomonas*) *tumefaciens*, but which had not previously been recognized as a cyclopropane acid.

Lactobacillic acid is believed to be D or L-*cis*-11,-12-methyleneoctadecanoic acid (*i.e.*, D or L-*cis*-10-(2-hexacyclopropyl)-decanoic acid) from chemical evidence.[5] Complete confirmation by chemical synthesis has not yet been achieved although the D, L-racemate and some closely related compounds have been synthesized.[6,7]

These compounds, together with the hydrogenation products of the two naturally occurring cyclopropene fatty acids, sterculic and malvalic, and some other related fatty acids have been studied by single crystal X-ray diffraction and the present status of this research is summarized in Table I.

In this paper a crystal structure analysis of lactobacillic acid is described. This analysis provides an independent proof by a physical method of the structure assignment based on the chemical evidence.

Crystal Data.—M.p. 29°; triclinic. $a = 5.64$, $b = 5.19$ and $c = 41.1$ Å.; $\alpha = 88.2°$, $\beta = 89.0°$, $\gamma = 56.6°$; U = 1005 Å.^{3}; $Z = 2$; $d_x = 0.96$ g./cm.^{3}; $d_m = 0.97$ g./cm.^{3}; space group P1, molecular symmetry 1.

The Experimental Measurements

Of all the fatty acid crystals studied in this series of investigations those of lactobacillic acid were the most difficult to grow in a form suitable for single crystal analysis. This probably is connected with the small quantities of material available and the difficulty in obtaining a specimen of the natural acid which is free from traces of structurally related impurities, since the crystallization behavior of fatty acids is notoriously sensitive to the purity of the specimen. Very thin and generally distorted soft plates developed on (001) were obtained from acetone–water mixtures. The unit cell dimensions were measured with Cu $K\alpha$ radiation from rotation, Weissenberg and precession photographs. The intensities of 210 reflections of the zero layer of the [110] axis were recorded on multiple films and their values were estimated by eye. No corrections were made for absorption.

The Structure Determination.—Although several attemps were made at intervals over a period of years, there was no success in solving the phase-problem for the projection data obtained on this structure until the crystallographically simpler structure of the D,L-*cis*-11,12-acid had been solved.[8] This synthetic compound, which gave much better single crystals, was believed from the chemical evidence to be the racemate of lactobacillic acid. The stereochemical information in regard to the general shape of the individual molecules obtained from this racemate structure played an important role in solving the structure of the enantiomorph by providing a basis for trial structures. The final result of this analysis, however, is independent of chemical evidence other than that lactobacillic acid is a C_{19} fatty acid. The racemate has a centered lattice, A2/*a*, with 8 molecules in a unit cell, $a = 8.93$, $b = 5.10$ and $c = 88.6$ Å.; $\beta = 98°$. For better comparison of the two structures the lactobacillic acid was referred to a C1 lattice with $a = 8.67$, $b = 5.64$ and $c = 41.1$ Å.; $\alpha = 89°$, $\beta = 91.5°$, $\gamma = 90°$, with 4 molecules in the unit cell. The projection data then refer to the *b* axis.

The configuration of the *cis*-11–12 acid molecules in projection in the racemate structure are shown in Fig. 1. Trial structures for the enantiomorph were assumed in which the individual molecules of the fatty acid had the same shape, with the characteristic bend at the cyclopropane ring. This assumption subsequently was confirmed by the results of the structure analysis.

Although the lactobacillic acid structure is non-centrosymmetrical, it seemed likely from the similarity in cell dimensions with the racemate that the general packing of the molecules with respect to the long axis would be similar. The line projection on the *c* axis therefore was used as the starting point for the structure determination. It was found that by assuming a center of symmetry in projection and a model based on the racemate structure, a set of *z* coördinates giving good qualitative agreement for the 001 reflections could be obtained. Considerable difficulty was experienced going from this stage to an approximate structure in projection down the *b* axis. Eventually a trial structure was tested in which one molecule was oriented with the bent chain in a plane parallel to (010), as in the racemate, and the other molecule was almost at right angles, perpendicular to (010), as shown in Fig. 2. This model was compatible with the large observed intensities in the 201 and 20$\bar{1}$ planes, and after ten cycles of structure factor and Fourier synthesis calculations refined satisfactorily to a reliability index of $R = 0.22$.

Only in the later cycles of refinement when the *x* coördinates were well determined were the *z* coördinates permitted to vary from those obtained from the centrosymmetric line projection data.

The electron density projection on (010) is shown in Fig. 2. Although the atoms are not all as clearly resolved as in the racemate structure, the position of the ring and its *cis* stereochemistry is unequivocally established. The atomic coördinates derived from this projection are given in Table II. The structure factors were computed with Berghuis, *et al.*,[15] scattering factors and the following isotropic temperature factors: oxygens $B = 4.5$ Å.$^{-2}$; molecule 1, C_1–C_{12}, C_{19} and molecule 2, C_{12}–C_{18}, $B = 3.0$ Å.$^{-2}$; molecule 1, C_{13}–C_{18}, molecule 2, C_1–C_{11}, C_{19}, $B = 5.0$ Å.$^{-2}$. The table of observed and calculated structure factors is available on request from the authors. The computations of

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(6) K. Hofmann, O. Tucker, W. R. Miller, A. C. Young and F. Tausig, *ibid.*, **76**, 1799 (1954).
(7) K. Hofmann, S. F. Orochena and C. W. Yoho, *ibid.*, **79**, 3608 (1957).

TABLE I

Acid	Formula	Source	M.p., °C.	Crystal symmetry	a	Å. b	c		Z	Crystal struct. anal.
Lactobacillic	$C_{19}H_{36}O_2$	Lipids of *lactobacillus arabinosus*	29	Triclinic P1	5.64	5.19	41.1	$\alpha = 88°$ $\beta = 89°$ $\gamma = 57°$	2	This work
Sterculic	$C_{19}H_{34}O_2$	Kernal oil of *sterculia foetida*								No work
Dihydrosterculic	$C_{19}H_{36}O_2$	Hydrogenat. of sterculic acid	40	Monoclinic A2/a					8	Identical with *cis* DL-(9,10)[8]
cis-DL-(9–10)	$C_{19}H_{36}O_2$		39	Monoclinic A2/a	8.93	5.10	88.6	$\beta = 98°$	8	Structure inferred from *cis*-DL-(11–12)
cis-DL-(11–12)	$C_{19}H_{36}O_2$	Synthetic[7]	37	Monoclinic A2/a					8	Structure analysis complete[9]
trans DL-(9–10)	$C_{19}H_{36}O_2$		35	Monoclinic $P2_1/a$	10.1	4.78	41.3	$\beta = 89°$	4	Structure analysis complete[10]
trans DL-(11–12)	$C_{19}H_{36}O_2$		37	Monoclinic $P2_1/a$					4	Structure inferred from *trans* DL-(9–10)
Malvalic[14]	$C_{18}H_{32}O_2$	Small plant *malva verticilata*	10							No work
Dihydromalvalic	$C_{18}H_{34}O_2$	Hydrogenat. of malvalic acid	40	Monoclinic A2/a	9.06	5.17	80.3	$\beta = 94°$	8	Structure analysis in progress. *cis*-DL-(8–9)[11]
Bombacic[12]	C_{18} ?	Kapok seed oil								No work
Erucic	$C_{22}H_{42}O_2$	Rape oil, mustard seed oil	33	Triclinic	9.88	5.17	47.8	$\alpha = 102°$ $\beta = 91°$ $\gamma = 87°$	4	Structure inferred from *cis*-cyclopropane acids[13]
cis-Nervonic	$C_{24}H_{44}O_2$	Human cerebroside	39	Triclinic	9.87	5.21	51.2	$\alpha = 102°$ $\beta = 91°$ $\gamma = 81°$	4	Structure inferred from *cis*-cyclopropane acids[13]

TABLE II

FRACTIONAL ATOMIC COÖRDINATES

Molecule 1 x	Molecule 1 z		Molecule 2 x	Molecule 2 z
0.375	0.017	O(1)	0.530	−0.019
.500	.027	O(2)	.675	− .029
.370	.033	C(1)	.585	− .033
.310	.065	C(2)	.570	− .055
.205	.082	C(3)	.700	− .069
.140	.111	C(4)	.645	− .104
.010	.129	C(5)	.790	− .122
− .070	.153	C(6)	.710	− .155
− .110	.180	C(7)	.810	− .173
− .185	.203	C(8)	.735	− .204
− .300	.225	C(9)	.860	− .225
− .305	.257	C(10)	.815	− .257
− .390	.284	C(11)	.905	− .274
− .450	.295	C(19)	.985	− .291
− .405	.314	C(12)	.875	− .314
− .325	.339	C(13)	.775	− .330
− .290	.363	C(14)	.820	− .363
− .200	.387	C(15)	.690	− .385
− .160	.419	C(16)	.795	− .415
− .090	.444	C(17)	.640	− .442
− .065	.474	C(18)	.740	− .468

Fourier syntheses and structure factors were carried out on an IBM 650 using programs devised by Shiono.[16]

Discussion of the Structure

The crystal structure analysis was carried to the stage of locating the carbon and oxygen atoms in one projection with sufficient precision to establish the general stereochemistry. Taken in conjunction with the chemical evidence[5] and the crystal structure analysis of the racemate,[9] the electron density map shown in Fig. 2 provides conclusive physical evidence that the structure is D or L-*cis*-11,12-methyleneoctadecanoic acid.

The *individual* molecules in the racemate and enantiomorph have the same stereochemistry, within the limits of the experimental errors, which is characterized by the bent chain configuration about the *cis* substituted cyclopropane ring. A similar stereochemistry also has been found in D,L-*cis*-8,9-methyleneheptadecanoic acid (dihydromalvalic acid),[11] oleic acid,[17] and has been postulated for erucic and *cis*-nervonic acids.[13]

In the crystal structures, however, the packing of the molecules is quite different in the enantiomorph and the racemate, being considerably less compact when the molecules all have the same sense, as is shown by the lower m.p. and density (29 *vs.* 37°, 0.97 *vs.* 1.005 g./cm.^{3}). In place of the hydrogen-bonded dimerization of the centro-symmetrically

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(15) J. Berghuis, *et al.*, *Acta Cryst.*, **8**, 478, 1955.
(16) R. Shiono, IBM 650 Programs for X-Ray Crystal Structure Analysis, Technical Reports Nos. 2, 9, Computation and Data Processing Center, University of Pittsburgh.
(17) Private communication, S. Abrahamsson.

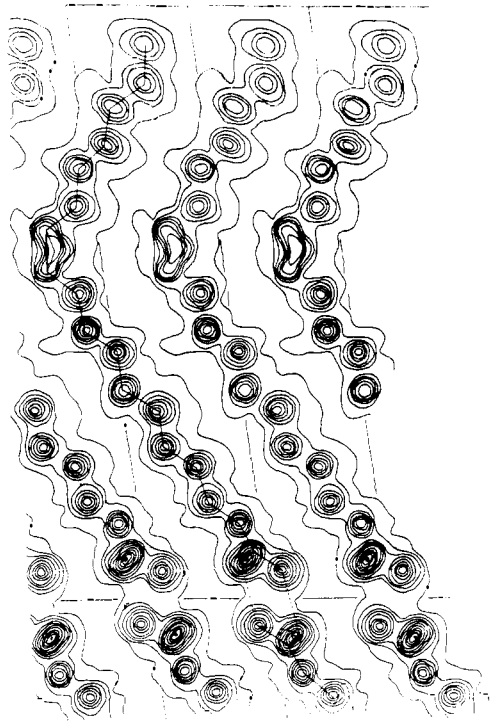

Fig. 1.—Projection on (010) of the electron density distribution of D,L-*cis*-11,12-methyleneoctadecanoic acid. (*i. e.*, racemate of lactobacillic acid).

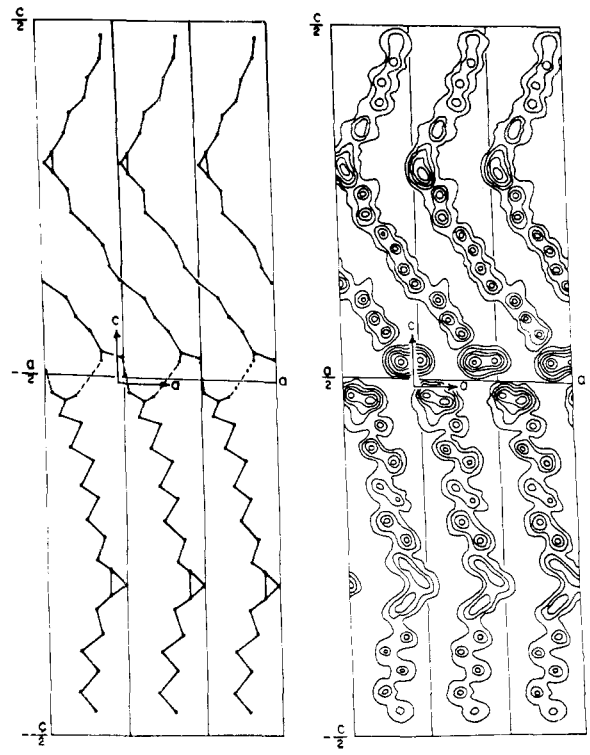

Fig. 2.—Projection on (010) of the electron density distribution of lactobacillic acid. (D or L, *cis*-11,12-methyleneoctadecanoic acid).

related left and right handed molecules in the racemate, an infinite sheet system of hydrogen bonds links the carboxylic acid groups in the lactobacillic acid. This is illustrated in Fig. 2.

While the atomic positions in projection are compatible with reasonable inter- and intra-molecular distances, no details of the stereo-chemistry or molecular packing can be obtained from this analysis. For this information a complete three-dimensional analysis would be necessary since the other projections do not give sufficient data for a reliable analysis owing to the large number of independent parameters. Despite many attempts at recrystallization of the comparatively small quantities of this compound which were available, no crystals of a quality which would justify an extensive three-dimensional analysis have hitherto been obtained.

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Synthesis of B-Trisubstituted Borazines by Reaction of B-Trichloroborazine with Grignard Reagents[1]

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The reaction of $B_3Cl_3N_3H_3$ with Grignard reagents in diethyl ether serves as a convenient method for the preparation of B-trisubstituted borazines. B-Trimethylborazine can be isolated by fractionation of the volatile solvent-product mixture from the reaction of $B_3Cl_3N_3H_3$ with CH_3MgI. A similar procedure did not lead to isolation of B-triethylborazine, but this compound can be obtained in good yield by vacuum pyrolysis of the solids remaining after removal of solvent ether from the reaction mixture. B-Triphenylborazine and the BN-substituted compounds hexamethylborazine and hexaethylborazine have been prepared by this pyrolysis technique. Some data on the stability of borazine, B-trimethylborazine and B-triethylborazine are reported.

The reaction of B-trichloroborazine with Grignard reagents or other organometallic compounds presents an attractive method for the synthesis of B-trisubstituted borazines. R. Schaeffer[2] demon-

(1) Presented in part at the 132nd Meeting of the American Chemical Society, New York, N.Y., September, 1957.

(2) Final Report on Contract N6ori-20, August 1950–June 30, 1951, p. 2 (University of Chicago).