[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

Identity of Synthetic *trans*-11-Octadecenoic Acid

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The X-ray diffraction pattern of synthetic *trans*-11-octadecenoic acid[1] has recently been found to differ significantly from that of natural vaccenic acid.[2] Since the pattern found closely resembled that of elaidic acid, and since in addition the melting points of these two acids and of their high and low melting dihydroxy derivatives are closely similar, the question arose as to whether the synthetic acid might in fact be elaidic acid, formed perhaps during isomerization of the *cis*-11-octadecenoic acid with selenium at 180–200°. A further investigation of the identity of the synthetic *cis*- and *trans*-11-octadecenoic acids was therefore undertaken.

A newly synthesized batch of *cis*-11-octadecenoic acid was isomerized both with selenium at 180° and with nitrogen oxides at 60°. Both the low and high melting forms of the corresponding dihydroxy acids were prepared in high yields from the two *trans* samples and from the *cis* acid. Corresponding preparations from each of the three sources showed nearly the same m. p. and mixed m. p., while mixtures with the analogous 9,10-dihydroxystearic acids showed definite depressions (Table I).

TABLE I

COMPARISON OF VARIOUS DIHYDROXY ACIDS

No.	Acid hydroxylated	Dihydroxy derivatives M. p., °C.	Mixed m. p., °C.
1	*cis*-11-Octadecenoic	91–92	1 + 4, 91–92
2	*cis*-11-Octadecenoic	127–128	2 + 5, 128–128.5
3	*trans*-11-Octadecenoic[a]	128–128.5	3 + 2, 127–128
4	*trans*-11-Octadecenoic[a]	93–94	4 + 6, 92–92.5
5	*trans*-11-Octadecenoic[b]	128–129	5 + 3, 128–129
6	*trans*-11-Octadecenoic[b]	92–93.5	1 + 6, 90–92.5
7	Oleic	130–130.5[c]	7 + 5, 116.5–122
8	Oleic	93.5–94[c]	8 + 6, 83–87

[a] Isomerized with selenium at 180°. [b] Isomerized with nitrogen oxides at 60°. [c] Kindly supplied by Dr. Daniel Swern.

The dihydroxy derivative of the *trans* acid prepared with nitrogen oxides was cleaved with periodic acid, and the two aldehydes formed were separately oxidized with silver oxide. The two products were identified as *n*-heptanoic and hendecanedioic acids, respectively.

Both of the *trans* acids and the *cis* acid were subjected to a degradation procedure designed to reveal contamination with isomeric acids.[3] Briefly, the octadecenoic acids were oxidized as indicated above, with all material being carried through each step, and the aliphatic monocarboxylic acid (or mixture of acids) obtained was analyzed by partition chromatography. In each case 67–82% of the theoretical amount of monocarboxylic acid was formed, and 92–95% of the acid placed on the chromatographic column was recovered in the effluents.

Both visual observation and titration of successively collected fractions of the effluent revealed that the degradation acid from each sample moved through the column essentially as a single band. Mixed chromatograms with *n*-heptanoic acid merely increased the height of this band, whereas control experiments showed that both higher and lower homologs, *e. g.*, *n*-octanoic acid, formed distinctly separate bands. The presence of as little as 7% of such homologous acids was easily detected in known mixtures.

The results of the chromatographic analyses indicate that *n*-heptanoic acid was formed by oxidation of the *cis*-, selenium-isomerized *trans*-, and nitrogen oxides-isomerized *trans*- samples of 11-octadecenoic acid in yields of 78, 62 and 71%, respectively. Taken together with the isolation of *n*-heptanamide and hendecanedioic acid from one of the samples, these results show quite definitely that the bulk, at least, of the synthetic acids consisted of the Δ-11,12 isomer. Since, in addition, the chromatographic analyses definitely indicated that the *n*-heptanoic acid was not accompanied by appreciable amounts of homologous acids, the conclusion seems justified that the synthetic samples consisted almost entirely of *cis*- and *trans*-11-octadecenoic acid.

Since the X-ray diffraction patterns of *trans*-11,12-octadecenoic acid and natural vaccenic acid were found to be distinctly different,[2] it must be concluded that the two samples are not identical. This of course raises a question as to the structure of natural vaccenic acid, which must be left open at present. It may be possible that the natural vaccenic acid preparations submitted to X-ray examination consisted essentially of *trans*-11-octadecenoic acid, but were contaminated with small amounts of isomeric acids sufficient to produce an altered crystal structure.

It is interesting to note the distinctions provided by the present case between the infrared spectra, X-ray patterns, and chemical evidence. The infrared spectra of synthetic *trans*-11,12-octadecenoic acid and Daubert's natural vaccenic acid were essentially identical,[1] but the X-ray patterns were distinctly different. Likewise, the synthetic acid and elaidic acid showed essentially identical X-ray patterns, although on the basis of chemical evidence they are certainly not the same substance.

Experimental

***cis*-11-Octadecenoic Acid.**—The previous synthesis[1] was repeated and confirmed in every respect except that the yield of 1-chloro-10-heptadecyne was only 68%. The *cis*

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(1) Ahmad, Bumpus and Strong, THIS JOURNAL, **70**, 3391 (1948).

(2) Benedict and Daubert, *ibid.*, **71**, 4113 (1949).

(3) Taylor and Strong, unpublished work.

acid was purified both by low-temperature recrystallization from acetone, and by the lead salt–alcohol procedure of Hilditch.[4]

***trans*-11-Octadecenoic Acid.**—The isomerization with selenium was carried out as previously described.[1] Isomerization with nitrogen oxides was carried out by the method of Teeter.[5] A mixture of 9.6 g. of *cis*-11-octadecenoic acid and a solution of 0.5 g. of sodium nitrite in 2 ml. of water was heated to 58–62° on a water-bath. A solution of 2.5 ml. of concentrated nitric acid and 2.5 ml. of water was then added, the mixture stirred for fifteen minutes, removed from the bath, and allowed to stand for one hour in a stoppered flask. The fatty acid was then taken up in ether, the ether solution washed free of mineral acids, dried, filtered, and cooled to −30°. A white crystalline product amounting to 4.5 g. was obtained. After one recrystallization from ether the m. p. was 42.5–43.5°.

11-12-Dihydroxystearic Acids.—The lower melting form was obtained from *cis*-11-octadecenoic acid by hydroxylation with formic acid and hydrogen peroxide according to the method of Swern, *et al.*,[6] and from the *trans* acid by oxidation with alkaline permanganate.[7] The higher melting form was prepared by the same methods applied to the opposite isomers. Melting points and mixed melting points are shown in Table I. The derivatives were purified by recrystallization from alcohol. The yields before crystallization were 82–94%.

Oxidative Degradation of *trans*-11-Octadecenoic Acid.—The *trans* acid obtained by isomerization with nitrogen oxides was converted to the dihydroxy derivative by Swern's method[6] in a yield of 91.6%. An amount of 0.1068 g. (0.337 millimole) of the crude dihydroxy acid was dissolved in 10 ml. of 95% ethanol and treated with a solution of 0.1139 g. (0.5 millimole) of periodic acid in 5 ml. of water. The mixture was shaken for two hours at room temperature, 5% aqueous sodium hydroxide solution added until the *p*H rose to 8.8, and the heptaldehyde formed was extracted with 100 ml. of ether used in six portions.

The ether extract was concentrated to 5 ml. and treated with 350 mg. of silver oxide, 5 ml. of water, and 10 ml. of a 10% solution of potassium hydroxide in 70% ethanol. This mixture was refluxed with continuous stirring for one hour, then made to *p*H 2.0 with sulfuric acid, and extracted with 100 ml. of petroleum ether ("Skellysolve B") in six portions. The extract was washed with saturated aqueous potassium chloride solution, dried over calcium chloride, evaporated to 4–5 ml., and then accurately diluted to 10 ml. Titration of an aliquot of this solution indicated the presence of a total of 0.286 milliequivalent of acid, 84.8% of the theoretical amount (77.5% based on the unsaturated acid). Other aliquots were reserved for partition chromatographic analysis, and the remainder converted via the acid chloride into the amide by standard procedures. The amide was twice recrystallized from aqueous alcohol, and then vacuum sublimed; m. p. 94.5–95.5°. When mixed with an authentic sample of *n*-heptanamide the m. p. was 94–95°.

Anal. Calcd. for $C_7H_{15}ON$: N, 10.8. Found: N, 10.0.

The aqueous solution remaining after extraction of the heptaldehyde was adjusted to *p*H 2.4 and the aldehydo-acid extracted with 100 ml. of ether in six portions. The extract was concentrated and oxidized with silver oxide in the manner described above. The dibasic acid was removed from the acidified reaction mixture with ether, and was recrystallized three times from hot water. The yield of pure product, m. p. 108.5–110°, was 49 mg., 67.2% of theory. Mixed with authentic hendecanedioic acid the m. p. was 108.5–109.5°.

Anal. Calcd. for $C_{11}H_{20}O_4$: neut. equiv., 108.14. Found: neut. equiv., 108.1, 107.2.

Partition Chromatography of Degradation Acids.—Petroleum ether ("Skellysolve B") was equilibrated against 90% methanol, and the upper and lower layers used as the mobile and stationary phases, respectively, for a partition chromatographic column. The stationary phase was supported by Celite 545[8] and was mixed with sufficient brom cresol green indicator to render the acid bands easily visible. Additional details will be presented elsewhere,[3] but the general procedure was similar to that of Ramsey and Patterson.[9]

An aliquot of the solution of monobasic acid (or acids) obtained by the degradation of 11-octadecenoic acid described above was passed through this column. One main

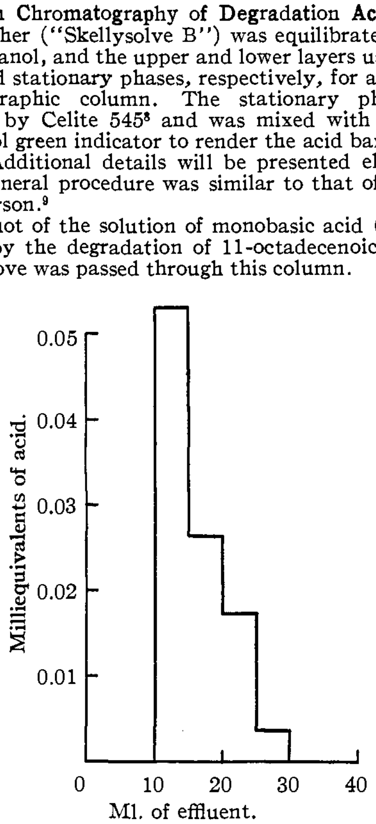

Fig. 1.—Partition chromatogram of degradation acid from *trans*-11-octadecenoic acid: acid placed on column, 0.1095 meq.; recovered, 0.1010 meq., 92.2%.

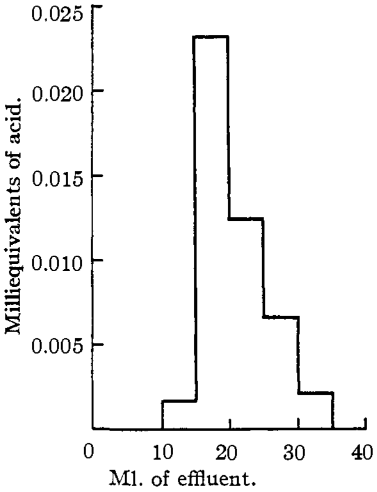

Fig. 2.—Mixed partition chromatogram of degradation acid from *trans*-11-octadecenoic acid plus *n*-heptanoic acid: acids placed on column, *n*-heptanoic 0.0197 meq., degradation acid 0.0286 meq.; recovered, 0.0464 meq., 96%.

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[4] Hilditch, "The Chemical Constitution of Natural Fats," John Wiley and Sons, New York, N. Y., 1941, p. 371.

[5] H. M. Teeter, personal communication.

[6] Swern, Billen, Findley and Scanlan, THIS JOURNAL, **67**, 1786 (1945).

[7] Robinson and Robinson, *J. Chem. Soc.*, **127**, 175 (1925).

[8] Johns-Manville Company, Chicago, Illinois.

[9] Ramsey and Patterson, *J. Assoc. Off. Agr. Chem.*, **31**, 139 (1948).

yellow band was observed to pass down the column, and was preceded by a very slight second band. When the leading band was about 2 cm. from the bottom of the column, collection of the effluent in 5-ml. portions was started. Titration of the effluent fractions gave the values plotted in Fig. 1. The minor band evidently was formed by too small an amount of acid to be detected by the titration procedure used, which in control experiments[3] has been found adequate to reveal the presence of 7% or more of a second acid. Total recovery of the acid placed on the column was 92.2%, which corresponds to an over-all yield of 71.4% of *n*-heptanoic acid.

In a second experiment a similar solution of degradation acid from another portion of the above crude dihydroxy acid was used for a mixed chromatogram. An aliquot containing 0.0286 milliequivalent of acid was mixed with 0.0197 milliequivalent of *n*-heptanoic acid, and the mixture subjected to partition chromatography as before. The results are given in Fig. 2. Total recovery from the column in this case was 96%, and only one band could be detected.

A sample of *trans*-11-octadecenoic acid obtained by selenium isomerization of the *cis* acid at 180° was carried through an exactly similar degradation process, and the monocarboxylic acid fraction, which was obtained in 62% over-all yield, was shown by mixed chromatogram to be *n*-heptanoic acid. In this case also no trace of a second band could be seen on the column or detected by titration of the effluent fractions. Degradation of the *cis*-acid and chromatographic analysis was carried out in the same manner with similar results.

Summary

Since the X-ray diffraction pattern of synthetic *trans*-11-octadecenoic acid has been reported to differ from that of natural vaccenic acid and to resemble that of elaidic acid, the structure of the synthetic acid was re-examined. The identity of the synthetic product as a $\Delta^{11,12}$-octadecenoic acid was definitely established.

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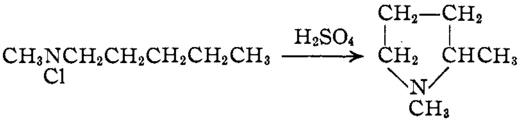
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

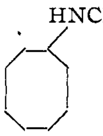
Preparation of N-Methylgranatanine

BY STANLEY WAWZONEK AND PAUL J. THELEN[1]

N-Haloamines are converted by heat in sulfuric acid solution into N-substituted pyrrolidines.[2] N-Chloroamines have been found by Coleman and co-workers[3] to be more applicable under these conditions than the N-bromoamines and to be suitable for preparing bicyclic compounds like tropane.[4]



The cyclization of the N-chloroamine (II) derived from N-methylcyclooötylamine (I) has now been studied in order to determine whether N-methylgranatanine (III) or 9-azabicyclo[4,2,1]-nonane (IV) would be produced. The reaction leading to the latter (IV) would be similar to that involved in the formation of pyrrolidines, whereas a reaction leading to the former (III) would constitute a new cyclization method for bridged piperidine structures (III) and would be a new synthesis of N-methylgranatanine (III). Fisher–Hirschfelder models favored the formation of N-methylgranatanine (III). During the course of this work sufficient evidence was obtained to propose a mechanism for the reaction.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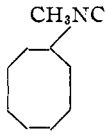
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III


IV

N-Chloro-N-methylcyclooöctylamine (II) was converted in sulfuric acid into varying yields of N-methylgranatanine (III) under conditions which are summarized in Table I. The cyclization was found to proceed consistently in best yields in sulfuric acid at 0–8° in the presence of ultraviolet light and chlorine. The structure of the product was demonstrated by the formation of a picrate and a chloroplatinate which did not

TABLE I

RING CLOSURES OF N-CHLORO-N-METHYLCYCLOOÖCTYLAMINE (55.7 MILLIMOLES)

					Yield, %	
Run	Chlorination, %	H_2SO_4 concn., %	Temp., °C.	Time, hours	Granatanine picrate	II° Amine recovered as sulfonamide
1	97	84	65	0.5	15	64
2	97	84	65	0.25	22	55
3	91.5	84	65	0.25	10	42.8
4	46.5	84	65	0.5	23	54.5
5	91.7	84[a]	25	22.0	15.3	34
6	87.8	84[b]	25	22.0	3.3	50.4
7	93.5	84[a]	65	.5	10.4	45.4
8	83.6	87[c]	5–8	22.0	24.4	35.8
9	94.2	84[d]	5–8	8.0	11.9[e]	23.7
10	79.7	84[c]	0–8	18.0	22.6	33.3

[a] Irradiated with ultraviolet light. [b] Carried out in complete darkness. [c] Irradiated with ultraviolet light in the presence of chlorine. [d] Carried out in complete darkness in the presence of 6.6 ml. of 30% H_2O_2. [e] 19.1% of the N-chloroamine was recovered.

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[1] Abstracted from a thesis by Paul J. Thelen presented to the Graduate College of the State University of Iowa in partial fulfillment of the requirements for the Ph.D. degree, January, 1948.

[2] Britton, U. S. Patent 1,607,605; *C. A.*, **21**, 249 (1927).

[3] (a) Coleman and Goheen, THIS JOURNAL, **60**, 730 (1938); (b) Coleman, Nichols and Martens, *Org. Syn.*, **25**, 14 (1945); (c) Coleman, U. S. Patent No. 2,285,413 (1942).

[4] Coleman and Carnes, *Proc. Iowa Acad. Sci.*, **49**, 288 (1942) [Abstract].