

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF ETHICON, INC.]

Keto Fatty Acids Derived from Castor Oil. III. Acid Derivatives¹

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Amides and esters of C₁₈-keto fatty acids and several unsaturated C₁₈-acids were prepared by the mixed carbonic-carboxylic anhydride method. An extension of this procedure provided a novel route to the synthesis of long chain acid anhydrides.

In preceding papers the synthesis of a number of unsaturated and oxygenated keto fatty acids derived from castor oil was reported.¹ Although many of these materials were found to have considerable bactericidal and fungicidal activity, their potential usefulness was limited by their insolubility in aqueous media. To achieve greater solubility with possible enhancement of activity, the synthesis of amides and esters containing a basic side chain was undertaken. The preparation, by conventional methods, of several amino amides and amino esters of naturally occurring long chain fatty acids has been described in the patent literature.² The direct methods of esterification or amide formation were of little value, however, in the case of the keto fatty acids which were unstable toward base at elevated temperatures.

The formation of acid chloride intermediates of the keto fatty acids by means of thionyl chloride or phosphorus trichloride was not possible; decomposition and tar formation occurred to the exclusion of a product. 12-Oxo-*trans*-10-octadecenoic acid^{1a} could be converted into its acid chloride by the oxalyl chloride procedure of Bauer³ and the desired amino amide could be obtained on further reaction with β -diethylaminoethylamine. Unfortunately, this reaction sequence failed with the less stable keto fatty acids.

A universally applicable procedure for the synthesis of the keto fatty acid amides and esters was found in the use of the mixed carbonic-carboxylic anhydride method⁴ which hitherto had been employed primarily in the synthesis of peptide bonds and, in a few isolated instances, in the preparation of esters of unstable acids.⁵

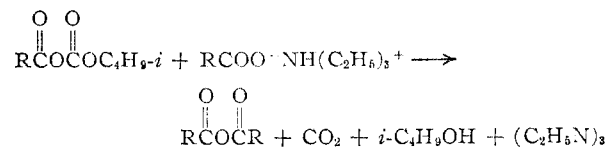
A number of basic and neutral amides of keto fatty acids which were synthesized by the mixed anhydride method are listed in Table I. The only limiting factors to the general applicability of this procedure were the solubility of the acid salt in the reaction solvent and the basicity of the amine. While aliphatic amines gave satisfactory results, certain aromatic amines whose basicity had been decreased by electrophilic groups in *o*- or *p*-position reacted poorly or did not react at all with the mixed anhydride. The major products formed in these

instances were neutral, non-nitrogenous materials which proved to be the symmetrical anhydrides of the fatty acids. Such anhydride formation had been proposed by Wieland and Bernhard⁴ as a possible side reaction of the mixed anhydride procedure, but no experimental data were supplied.

Ester formation by the mixed anhydride method proceeded in less satisfactory fashion than the corresponding amide synthesis. Side reactions such as the formation of symmetrical anhydrides became more prevalent and tended to decrease the yield of the desired esters and interfered with their isolation. The group of esters of keto fatty acids prepared in the course of this work is listed in Table II. When the mixed anhydride procedure was applied to the esterification of 12-oxo-10-octadecenoic acid with glycerol, a 1,3-diglyceride resulted.

In preliminary tests, many of the above amino amides and amino esters exhibited higher antimicrobial and antifungal potency than the corresponding acids. It was, therefore, of interest to prepare analogous derivatives of unsaturated naturally occurring acids which had previously been shown to possess bactericidal properties.⁶ A number of amino amides and amino esters derived from oleic acid, linoleic acid and linolenic acid were synthesized and these are listed in Tables I and II.

As a result of the observation that symmetrical anhydride formation accompanied some of the above amidations and esterifications, an attempt was made to make this mixed anhydride procedure a preparative method for the synthesis of otherwise difficultly accessible long chain fatty acid anhydrides. When in place of an amine or alcohol one equivalent of the triethylamine salt of the carboxylic acid was added to the mixed anhydride, the symmetrical anhydride was formed as the sole reaction product in yields ranging from 50 to 100%. The fatty acid anhydrides prepared are listed in Table III. The reaction leading to these anhydrides may be expressed as



Data on the antibacterial and antifungal activity of compounds described in this paper will be reported elsewhere.

(1) Preceding papers in this series (a) J. Nichols and E. Schipper, *THIS JOURNAL*, **80**, 5705 (1958); (b) J. Nichols and E. Schipper, *ibid.*, **80**, 5711 (1958).

(2) J. W. Bishop, U. S. Patent 2,574,954 (1951); M. De Groote, U. S. Patent, 2,602,087 (1952); German Patents, 464,142, 559,500 (1928), French Patent, 716,500 (1931).

(3) S. T. Bauer, *Oil and Soap*, **23**, 1 (1946).

(4) T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951); R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); J. R. Vaughan, Jr., and R. L. Osato, *THIS JOURNAL*, **73**, 5553 (1951).

(5) D. A. Johnson, *ibid.*, **75**, 3636 (1953); R. L. Barnden, R. M. Evans, J. C. Hamlet, B. A. Hems, A. B. A. Jansen, M. E. Trevett and G. B. Webb, *J. Chem. Soc.*, 3733 (1953).

(6) H. Humfeld, *J. Bacteriol.*, **54**, 513 (1947); E. Kodicek and A. N. Worden, *Biochem. J.*, **39**, 78 (1945); H. Spector, *Arch. Biochem.*, **11**, 167 (1946).

TABLE I
AMIDES, $C_8H_{13}COX(CH_2)_nCONHR$

X	R	Yield, %	Reaction solvent	Recrystn. solvent	M. p., °C.	Empirical formula	Carbon, % Calcd.	Hydrogen, % Calcd.	Nitrogen, % Calcd.
$CH_2=CHCH_2$	C_6H_5	70	Toluene	Ether	72-73	$C_{24}H_{37}O_2N$	77.55	77.74	9.99
$CH_2CH=CH$	C_6H_5	70	Tetrahydro-	Ether	86-87	$C_{24}H_{37}O_2N$	77.55	77.49	9.77
$CH-CHCO$ $-O-$	$o=CH_3OC_6H_4$	18	furan	95% ethanol	97-99	$C_{25}H_{37}O_3N$	69.57	69.90	8.61
$CH=CHCO$	1-Carboethoxycyclo-	71	Tetrahydro-	Ether	75-76	$C_{27}H_{45}O_3N$	69.94	69.97	9.78
CH_2CH_2CO	hexyl	56	furan	Ether	76-77	$C_{27}H_{47}O_3N$	69.64	69.74	10.17
$CH=CHCH_2$	$(CH_2)_2N(C_2H_5)_2$	15	Toluene	50% ethanol	42-43	$C_{24}H_{46}O_2N_2$	73.04	72.91	11.75
$CH=CHCH_2$	$(CH_2)_2N(C_2H_5)_2$	39	Toluene	Ether-petr.	38-39	$C_{25}H_{48}O_2N_2$	73.47	73.57	11.84
$CH=CHCH_2$	$p-C_6H_4N(C_2H_5)_2$	34	Toluene	Ether-petr.	65-66	$C_{25}H_{48}O_2N_2$	75.97	75.83	10.47
$CH=CHCH_2$	$(CH_2)_2N(CH_3)_2$	46	Toluene	Ether	49-50	$C_{22}H_{42}O_2N_2$	72.08	72.29	11.55
$CH=CHCH_2$	4-Pyridyl	83	Toluene	Ether	67-68	$C_{23}H_{43}O_2N_2$	74.15	73.98	9.74
$CH_2CH=CH$	$(CH_2)_2N(C_2H_5)_2$	73	Tetrahydro-	Ether-petr.	48-49	$C_{25}H_{48}O_2N_2$	73.47	73.22	11.84
$CH_2CH=CH$	$(CH_2)_2N(CH_3)_2$	46	furan	Ether	68-69	$C_{22}H_{42}O_2N_2$	72.08	72.11	11.55
$CH_2CH=CH$	$(CH_2)_2N(CH_3)_2$	60	Toluene	Ether	46-47	$C_{23}H_{44}O_2N_2$	72.58	72.31	11.65
$CH_2CH=CH$	$(CH_2)_2N(CH_3)_2$	73	Toluene	Ether-petr.	39-40	$C_{22}H_{42}O_2N_2$	72.08	71.92	11.44
$CH=CHCO$	$(CH_2)_2N(C_2H_5)_2$	22	Tetrahydro-	Ether	95-96	$C_{24}H_{44}O_2N_2$	70.54	70.54	10.86
CH_2CH_2CO	$(CH_2)_2N(C_2H_5)_2$	19	furan	Ether	88-89	$C_{24}H_{46}O_2N_2$	70.19	69.94	11.29
$CH-CHCH_2$ $-O-$	$(CH_2)_2N(CH_3)_2$	41	Toluene	Ether	53-55	$C_{23}H_{44}O_2N_2$	69.65	69.77	11.18
$CH-CHCH_2$ $-O-$	$(CH_2)_2N(C_2H_5)_2$	49	Toluene	Ether	42-44	$C_{24}H_{46}O_2N_2$	70.19	69.92	11.29
$CH-CHCH_2$ $-O-$	$(CH_2)_2N(C_2H_5)_2$	16	Toluene	Ether-petr.	44-45	$C_{25}H_{48}O_2N_2$	70.71	70.50	11.39
$CH-CHCH_2$ $-O-$	3-Pyridyl	77	Toluene	Ether	78-79	$C_{23}H_{46}O_2N_2$	71.10	70.98	9.34
$CH-CHCH_2$ $-O-$	$p-C_6H_4N(C_2H_5)_2$	21	Toluene	Ether	81-82	$C_{25}H_{48}O_2N_2$	73.32	73.59	10.11
$CH-CHCH_2$ $-O-$	$CH_2CHCH_2N(C_2H_5)_2$ OH	41	Toluene	Ether	39-40	$C_{25}H_{48}O_3N_2$	68.14	67.99	10.98
$CH-CHCO$ $-O-$	$(CH_2)_2N(C_2H_5)_2$	34	Methylene chloride	Ether	84-85	$C_{24}H_{46}O_2N_2$	67.88	67.76	10.44
$CH-CHCH_2$ OH	$(CH_2)_2N(CH_3)_2$	63	Toluene	EtAc	86-87	$C_{22}H_{44}O_2N_2$	65.96	66.01	11.07
$CH-CHCH_2$ OH	$(CH_2)_2N(C_2H_5)_2$	35	Toluene	EtAc	87-88	$C_{24}H_{46}O_2N_2$	67.25	67.09	11.29
$CH-CHCO_2$ OH	$(CH_2)_2N(C_2H_5)_2$	45	Tetrahydro-	Ether	71-73	$C_{24}H_{46}O_3N_2$	65.12	65.25	10.48
$CH-CHCH_2$ OH	furan	59	Toluene		208-211 ^{a,b}	$C_{24}H_{46}ON_2$	76.13	76.30	12.25
$CH-CHCH_2$ OH	N- β -Diethylaminoethyl linoleamide	48	Toluene		218-219 ^{a,c}	$C_{25}H_{48}ON_2$	76.47	76.75	12.32
$CH-CHCH_2$ OH	N- γ -Diethylaminoethyl linoleamide	20	Toluene		195-200 ^{a,d}	$C_{25}H_{48}ON_2$	75.80	76.02	11.50

^a B.p. at 0.04 mm. ^b Refractive index, 1.4770 at 24°. ^c Refractive index, 1.4777 at 27°. ^d Refractive index, 1.4880 at 27°.

TABLE II
 AMINOESTERS, $C_6H_{13}COX(CH_2)_7COOR$

X	R	Yield, %	Reaction solvent	B.p., °C.	n_D^{20}	t_g , °C.	Empirical formula	Carbon, % Calcd. Found	Hydrogen, % Calcd. Found	Nitrogen, % Calcd. Found
$CH^t=CHCH_2$	$(CH_2)_2N(C_2H_5)_2$	63	Toluene	195-200			$C_{24}H_{46}O_2N$	72.86 73.15	11.47 11.41	3.54 3.28
$CH^t=CHCO$	$CH_2CH(CH_3)N(Et)_2$	30	Tetrahydro-	230-235	1.4685	24	$C_{24}H_{46}O_2N$	70.88 70.78	10.71 10.80	3.31 3.30
$CH_2CH^t=CH$	$(CH_2)_2N(C_2H_5)_2$	49	furan	200-205	1.4629	24	$C_{24}H_{46}O_2N$	73.30 73.19	11.57 11.55	3.42 3.36
$CH^t=CHCH_2$	$(CH_2)_2N(n-C_4H_9)_2$	52	Toluene	220-230	1.4571	33	$C_{24}H_{46}O_2N$	74.78 74.77	11.90 12.09	3.01 2.70
$CH^t=CHCH_2$	$CH(CH_3)(CH_2)_2N(Et)_2$	36	Toluene	200-210	1.4623	28	$C_{27}H_{52}O_2N$	74.09 74.25	11.75 11.71	3.20 2.94
$CH-CHCH_2$ └─O─┐	$(CH_2)_2N(C_2H_5)_2$	24	Toluene	210-215	1.4601	24	$C_{24}H_{46}O_2N$	68.89 69.15	10.77 10.66	3.65 3.39
$CH-CHCH_2$ └─O─┐	$(CH_2)_2N(C_2H_5)_2$	61	Toluene	205-210	1.4626	27	$C_{24}H_{46}O_2N$	70.54 70.66	11.13 11.35	3.29 3.25
$CH_2CH^t=CH$	$(CH_2)_2N(C_2H_5)_2$	22	Toluene	^b			$C_{22}H_{40}O_2N$	71.88 71.54	11.24 11.25	3.81 3.66
$CH_2CH^t=CH$	$(CH_2)_2N(C_2H_5)_2$	38	Toluene	^b	1.5420	27	$C_{24}H_{46}O_2N$	72.86 73.14	11.47 11.52	3.54 3.25
$CH^t=CHCO$	$(CH_2)_2N(C_2H_5)_2$	15	Methylene chloride	^c			$C_{24}H_{46}O_2N$	70.37 70.67	10.58 10.60	3.42 3.54
CH_2CH_2CO	$(CH_2)_2N(C_2H_5)_2$	26	Tetrahydrofuran	^d			$C_{22}H_{40}O_2N$	68.89 68.96	10.77 10.75	3.65 3.58
β -Diethylaminoethyl oleate		37	Toluene	165-170	1.4540	31	$C_{34}H_{67}O_2N$	75.53 75.42	12.41 12.34	3.63 3.53
β -Diethylaminoethyl linoleate		40	Toluene	160-165	1.4630	28	$C_{34}H_{67}O_2N$	75.93 75.74	11.95 11.78	3.69 3.67
γ -Diethylaminopropyl lineoleate		61	Toluene	170-175			$C_{34}H_{67}O_2N$	76.28 76.51	12.04 12.00	3.59 3.29

^a The materials were evaporatively distilled at 0.04 mm. The temperature range given indicates the minimum outside bath temperature necessary for distillation rather than the actual boiling point. ^b The material could not be distilled without decomposition. The oil was purified by solution of the material in ether, decolorization with charcoal and crystallization from the ether solution at -50° . The material melted below 0° . ^c M.p. $37-38^\circ$ after recrystallization from petroleum ether. ^d M.p. $35-36^\circ$ after recrystallization from ether.

 TABLE III
 ANHYDRIDES

Anhydride	Yield, %	Reaction solvent	Recrystan. solvent	M.p., °C.	Empirical formula	Carbon, % Calcd. Found	Hydrogen, % Calcd. Found
12-Oxo- <i>cis</i> -9-octadecenoic	63	Toluene	Ether-petr. eth. (1:10)	50-51	$C_{36}H_{72}O_8$	75.21 75.34	10.87 11.05
12-Oxo- <i>trans</i> -9-octadecenoic	80	Tetrahydrofuran	Ether	75-76	$C_{36}H_{72}O_8$	75.21 74.95	10.87 11.00
12-Oxo- <i>trans</i> -10-octadecenoic	65	Toluene	Petr. ether	52-53	$C_{36}H_{72}O_8$	75.21 75.31	10.87 10.73
9,12-Dioxooctadecanoic	50	Toluene	EtAc	104-105	$C_{36}H_{72}O_7$	71.28 71.16	10.23 10.09
9,12-Dioxo-10,11-epoxyoctadecanoic	97	Methylene chloride	EtAc	102-103	$C_{36}H_{72}O_8$	68.11 68.00	9.21 9.43
10,11-Epoxy-12-oxooctadecanoic	98	Methylene chloride	EtAc	70-71	$C_{36}H_{72}O_7$	71.28 71.53	10.23 10.14
9,12-Dioxo- <i>trans</i> -10-octadecenoic	90	Methylene chloride	EtAc	107-108	$C_{36}H_{72}O_7$	71.72 72.06	9.70 9.72
Oleic ^a	95	Toluene	Petr. ether	20-22			
Linoleic ^b	66	Toluene	Petr. ether	-1			

^a N. O. V. Sonntag, J. R. Trowbridge and I. J. Krems, *J. Am. Oil Chemists' Soc.*, **31**, 151 (1954). ^b D. Holde and R. Gentner, *Ber.*, **58**, 1067 (1925).

Experimental⁷

N- β -Diethylaminoethyl-12-oxo-*trans*-10-octadecenoamide.—A stirred solution of 25 g. of 12-oxo-10-octadecenoic acid^{1a} in 10 ml. of dry benzene was heated to 50° and 13 g. of oxalyl chloride was added slowly.⁸ The reaction mixture was stirred and maintained at $60-70^\circ$ for 3 hours. The solvent was removed under reduced pressure. The residual acid chloride was added dropwise to a stirred and cooled solution of 9.8 g. of β -diethylaminoethylamine in 130 ml. of dry benzene. The solution was allowed to stand at room temperature for one day and the solvent was removed under reduced pressure. The residue was dissolved in 200 ml. of water and the aqueous solution was passed dropwise through a column containing 200 ml. of ether. The washed aqueous solution was made basic with a concd. solution of potassium hydroxide and the oil was extracted with three 200-ml. portions of ether. The ether extracts were combined and dried over sodium sulfate. The solvent was removed and the residue was recrystallized from 50% ethanol; yield 8 g. (24%), m.p. $42-43^\circ$.

Anal. Calcd. for $C_{24}H_{46}N_2O_2$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.91; H, 11.75; N, 6.93.

Procedures Involving the Use of Mixed Anhydrides. Preparation of Amides.—To a stirred solution containing 0.01 mole of fatty acid, 0.01 mole of triethylamine and 100 ml. of an anhydrous solvent there was added dropwise 0.01 mole of isobutyl chloroformate. The reaction temperature was kept at -5° by means of an alcohol-Dry Ice-bath. Stirring was continued at this temperature for 30 minutes and 0.01 M of the amine or diamine, dissolved in a few ml. of solvent, was added. The stirred reaction mixture was rapidly

heated to boiling and refluxed for 10-20 minutes until carbon dioxide evolution ceased. The suspension was cooled and triethylamine hydrochloride was removed by filtration. The filtrate was evaporated to dryness under reduced pressure and the residual material worked up.

(a) **Neutral Amides.**—The material was taken up in 200 ml. of ether; the ether solution was washed with successive portions of 10% potassium carbonate and water. After drying the solution over sodium sulfate, the ether was removed and the residue was recrystallized from the appropriate solvent.

(b) **Basic Amides.**—The residue was taken up in 100-500 ml. of 3 N hydrochloric acid (depending on the solubility of the amino amide in aqueous acid) and the solution or emulsion was dripped through a column containing 250 ml. of ether. The washed aqueous layer was made basic with 10% potassium hydroxide. If a precipitate appeared at this stage it was filtered off and recrystallized. If the material oiled out, the oil was extracted with three 100-ml. portions of ether. The combined ether extracts were dried and after removal of the solvent the residue was recrystallized from the proper solvent or was distilled under reduced pressure. Reactions which involved the use of 2,5-dichloroaniline, *o*-chloroaniline, *p*-nitroaniline, 2,4-dinitroaniline and N-methyl-*p*-nitroaniline did not lead to the desired amides. Instead there were obtained in small yields (10-20%) the anhydrides of the corresponding acids employed in the reaction; the major reaction products were oily mixtures which could not be purified.

Preparation of Aminoesters.—The general method for the preparation of amides was followed except that two equivalents of an amino alcohol and one equivalent of triethylamine were added to the mixed anhydride in place of the one equivalent of amine. The reaction mixture was worked up according to the method given for the preparation of the amino amides. In most cases when the reaction residue was

(7) The authors are indebted to Mr. Erik Hoffmann and Miss Mary Grace Comfort for the analytical data reported in this paper. All melting points are uncorrected.

taken up in the 3 *N* hydrochloric acid solution a considerable amount of acid-insoluble material appeared which proved to be identical with the symmetrical acid anhydride.

α, α' -Di-(12-oxo-*trans*-10-octadecenoyl)-glyceride.—The above esterification procedure was applied to 2.96 g. (0.01 mole) of 12-oxo-*trans*-10-octadecenoic acid using toluene as solvent and glycerol as the alcohol component. The solid reaction residue was taken up in 100 ml. of ether and the ether solution was washed with successive portions of 200 ml. of 10% potassium carbonate and water. The ether layer was dried over sodium sulfate and the ether was removed under reduced pressure. The residue was taken up in 50 ml. of hot ethanol. The solution was cooled to 0° and a precipitate was filtered off which after several recrystallizations from petroleum ether melted at 52–53°; it proved to be identical with 12-oxo-*trans*-10-octadecenoic anhydride; yield 1.2 g. When the filtrate was cooled to –20°, 1 g. of a material was obtained which was recrystallized from petroleum ether; m.p. 52–53°. This material gave a marked m.p. depression when admixed with the anhydride fraction.

Anal. Calcd. for $C_{39}H_{68}O_7$: C, 72.18; H, 10.56. Found: C, 72.03; H, 10.43.

β -Diethylmethylammoniummethyl 12-Oxo-*trans*-10-octadecenoate Iodide.—A solution containing 0.26 g. of β -diethylaminoethyl 12-oxo-*trans*-10-octadecenoate, 0.2 ml. of methyl iodide and 5 ml. of dry ether was allowed to stand overnight. The yellow precipitate was collected and recrystallized from acetone and ethyl acetate; yield, 0.3 g. (83%); m.p. 70–71°.

Anal. Calcd. for $C_{25}H_{46}INO_3$: C, 55.85; H, 9.00; N, 2.61. Found: C, 56.01; H, 9.07; N, 2.42.

Preparation of Anhydrides.—The anhydrides were prepared by the general method outlined for the preparation of the amides except that in place of an amine, one equivalent of the triethylamine salt of the carboxylic acid dissolved in 100 ml. of the reaction solvent was added to the mixed carbonic-carboxylic acid anhydride. The reaction product was worked up in a manner identical with that described above for the isolation of neutral amides.

SOMERVILLE, N. J.

[CONTRIBUTION FROM THE BIOCHEMISTRY AND CHEMISTRY DEPARTMENTS, UNIVERSITY OF PITTSBURGH]

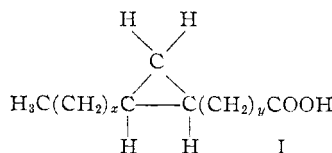
Studies on the Structure of Lactobacillic Acid. II. Position of the Cyclopropane Ring^{1,2}

BY KLAUS HOFMANN, GINO J. MARCO AND GEORGE A. JEFFREY

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A micromethod is described for the degradation of long-chain cyclopropane fatty acids. The procedure provides valid information regarding the position of the cyclopropane ring in this class of compounds. The cyclopropane ring of lactobacillic acid was shown to occupy the 11,12-position on the octadecanoic acid chain. X-Ray diffraction methods were used in the identification of the degradation products. Undecanedioic acid was found to be dimorphic, and X-ray diffraction data for both forms are presented. In addition to furnishing information regarding the ring position, the present degradation method provides a means to selectively remove the methylene bridge-carbon from the rest of the carbon chain of cyclopropane fatty acids. The biochemical implications of this finding are discussed.

Previous investigations from this Laboratory^{3–5} have led to the conclusion that lactobacillic acid, a lipid constituent of various microorganisms, is a methyleneoctadecanoic acid of the general structure I



The results of chemical and physical studies and a comparison with synthetic methyleneoctadecanoic acids of known structure established the cyclopropane nature of lactobacillic acid, but the position of the cyclopropane ring and the stereochemistry of the molecule remained to be determined. In the present communication we wish to present results of degradative studies, on a micro scale, which locate the methylene bridge in lactobacillic acid between positions 11 and 12 on the octadecanoic acid chain.

(1) Supported by Grants from the American Cancer Society, upon recommendation of the Committee on Growth of the National Research Council; Ciba Pharmaceutical Products, Inc., Summit, N. J., and the U. S. Public Health Service.

(2) A preliminary communication reporting some of the results of this investigation has appeared: G. J. Marco and K. Hofmann, *Federation Proc.*, **15**, 308 (1956).

(3) K. Hofmann and R. A. Lucas, *THIS JOURNAL*, **72**, 4328 (1950).

(4) K. Hofmann, R. A. Lucas and S. M. Sax, *J. Biol. Chem.*, **195**, 473 (1952).

(5) K. Hofmann, O. Jucker, W. R. Miller, A. C. Young, Jr., and F. Tausig, *THIS JOURNAL*, **76**, 1799 (1954).

In 1952,⁴ it was observed that treatment of lactobacillic acid with hydrogen bromide in glacial acetic acid resulted in formation of an oily acidic product arising from addition of the elements of hydrogen bromide to the cyclopropane ring. This method of opening the ring now has been repeated with larger samples of lactobacillic acid, and also was applied to three other acids of the cyclopropane series, namely, *trans*-DL-9,10- and *trans*-DL-11,12-methyleneoctadecanoic acids and dihydrosterculic acid (*cis*-DL-9,10-methyleneoctadecanoic acid). The ring position and stereochemistry of the latter three acids is known with certainty.^{5,6} Bromine analyses of the crude reaction products demonstrated a practically quantitative reaction with hydrogen bromide of all the acids studied. Dehydrobromination in boiling *s*-collidine under nitrogen converted the hydrobromination products from each acid into a mixture of monoethenoid fatty acids. Iodine number determinations performed with the dehydrobrominated materials indicated the following olefinic acid percentage content: lactobacillic acid, 59.0; dihydrosterculic acid, 70.6; *trans*-9,10-methyleneoctadecanoic acid, 67.3; *trans*-11,12-methyleneoctadecanoic acid, 89.7. (These figures are based on a theoretical iodine number of 85.7 for a monoethenoid nonadecanoic acid.) The crude dehydrohalogenated materials derived from each acid then were subjected to hydroxylation with performic acid, and the ensuing

(6) H. Hofmann, S. F. Orochena and C. W. Yoho, *ibid.*, **79**, 3608 (1957).