[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA]

10-Hydroxycodeine

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Received October 16, 1953

Cold chromic acid oxidation of codeine has been shown previously to yield an hydroxycodeine, with the new hydroxyl group at position 9 or 10. The yield of this compound has been improved and evidence is presented which establishes its structure as 10-hydroxycodeine. This evidence consists primarily of degradation to a ketomethine in which the keto group (derived from the new hydroxyl) is conjugate with the aromatic ring. The chromic acid oxidation procedure is quite general and gives 10-hydroxydihydrocodeine from dihydrocodeine and 10-hydroxydihydrocodeinone.

Interest in the metabolic fate of morphine and codeine in the addict as compared to the non-addict has led us to examine various derivatives of the morphine alkaloids which appear to be reasonable for consideration as potential metabolites. In addition to the glucuronides,¹ certain oxidation products seem to be rational possibilities, since the metabolism of drugs very frequently involves oxidation.²

Such an oxidation product of considerable interest is hydroxycodeine, a compound differing from codeine (I) only in the presence of an additional oxygen atom and obtained from codeine by chromic acid oxidation. It was considered surprising that codeine, with its many sites vulnerable to oxidation, should give a single pure product with a rather indiscriminate oxidant such as chromic acid, and elucidation of the structure of hydroxycodeine might focus attention on a position especially susceptible to oxidation. Previous work³ has shown that the new hydroxyl group must be at position 9 or 10, and this report presents evidence that establishes 10hydroxycodeine (II) as the structure of this oxidation product.

Preparation of sufficient starting material for a structural investigation was the first problem. An early report^{3a} describes the preparation of hydroxycodeine in 10% yield "at most" with no mention of purity, and Holmes and Lee⁴ improved this to a 15% yield of crude from which we were able to isolate an 8% yield of pure material by chromatography. A method was finally developed, employing a much slower addition of chromic acid to the cold sulfuric acid solution of codeine, which resulted in a 32% yield. Since an appreciable amount of codeine remains unreacted, its separation from hydroxycodeine is an integral part of the preparation, and purification was most efficiently achieved by chromatography on alumina or solvent distribution, exploiting hydroxycodeine's large (as compared to codeine) water-benzene partition coefficient.

To remove any possible interference from the 7,8double bond during subsequent reactions, hydroxycodeine was hydrogenated to hydroxydihydrocodeine (III)⁵ and this latter compound was used for

(1) The preparation of the several glucuronides of morphine and codeine is currently being investigated in this Laboratory.

(2) R. T. Williams, "Detoxication Mechanisms," John Wiley and Sons, Inc., New York, N. Y., 1949.

(3) (a) L. Knorr and W. Schneider, Ber., **39**, 1414 (1906); (b) R.
Pschorr, *ibid.*, **39**, 3130 (1906); (c) L. Knorr and H. Horlein, *ibid.*, **39**, 3252 (1906); (d) R. Pschorr and H. Einbeck, *ibid.*, **40**, 1980 (1907);
(e) L. Knorr and H. Horlein, *ibid.*, **40**, 2042 (1907).

(4) H. L. Holmes and C. C. Lee, THIS JOURNAL, 69, 1996 (1947).

(5) It is interesting that the melting points of hydroxydihydroco-

the most part in the structural work. Hydroxydihydrocodeine also could be prepared directly from dihydrocodeine under the same conditions used for the oxidation of codeine.

Of the two possible positions (9 and 10) for the new hydroxyl group in hydroxycodeine, the 9hydroxy compound would be a carbinolamine (pseudobase), and Holmes and Lee⁴ have already indicated that hydroxycodeine does not exhibit typical carbinolamine reactions. This negative evidence, however, must be interpreted with caution, since those carbinolamine properties which depend on quaternary ammonium hydroxide formation might be absent in a carbinolamine such as 9hydroxycodeine (IIa) due to steric inability to form the doubly-bonded nitrogen structure IIb. For this reason we have sought additional data for or



against the carbinolamine structure by an examination of the apparent dissociation constant.

Carbinolamines, because of the tautomeric quaternary ammonium hydroxide form, are usually strong bases with a $pK'_a \sim 11.^6$ However, when this tautomerism to the unsaturated quaternary ammonium structure cannot take place, the inductive effect of the hydroxyl on the same carbon as the nitrogen results in a base much weaker than the parent, non-hydroxylated amine.⁷ With hydroxycodeine, neither of these typical carbinolamine effects is the case. Its pK'_a is 7.12 while that of codeine is 8.04,⁸ a difference of only 0.92. This decrease in basicity is what would be expected from conversion of an amine to a β -hydroxyamine, and is much less

deine and hydroxycodeine are very similar ($202-203^{\circ}$ and $205-206^{\circ}$, respectively), there is no depression in m.p. on mixing ($205-206^{\circ}$), and the specific rotations in ethanol are very close (-129 and -132° , respectively). However, the X-ray powder patterns, for which we are indebted to Dr. D. H. Templeton, are clearly different, as are the hydro-chlorides.

(6) For example, cotarnine has $pK'_a > 11$, hydrastinine has $pK'_a = 11.38$, and berberine has $pK'_a = 11.53$ ("The Merck Index," 6th edition, Merck and Co., Inc., Rahway, N. J., 1952).

edition, Merck and Co., Inc., Rahway, N. J., 1952). (7) A good example is strychnine ($pK'_a = 7.37$) and its corresponding carbinolamine, pseudostrychnine ($pK'_a = 5.60$) [V. Prelog and O. Häfliger, *Helv. Chim. Acta*, **32**, 1851 (1949)].

(8) The pK_a' 's of codeine and hydroxycodeine were determined by titrating an aqueous solution of the hydrochloride with standard alkali using a Beckman Model G *pH* meter. Using the equation $pK_a = \log (a - x)/x + pH$, where x is the equivalents of alkali added at any point and a is the equivalents of alkali added at complete neutralization, determinations were made for twenty points between 10 and 90% titrated and agreed to $\pm 0.03 \ pK$ unit.

of an effect than would be expected on carbinolamine formation. Thus the pK'_a data is evidence for hydroxycodeine being the 10- rather than 9hydroxy compound.

Also, if hydroxycodeine is the 10-hydroxy compound, it is an α -hydroxy- α -phenyl- β -amino compound. Kindler, *et al.*,⁹ have studied the hydrogenation of such compounds in detail, and the conditions he found necessary for hydrogenolysis



of the hydroxyl group were also needed to convert hydroxydihydrocodeine (III) to dihydrocodeine. These conditions (palladium-on-carbon catalyst, glacial acetic acid solvent, and the presence of perchloric acid) are more drastic than ordinarily needed to replace the hydroxyl group of carbinolamines with hydrogen.¹⁰

Although the dissociation constant and hydrogenolysis data suggest the 10-hydroxy formulation, they are not in themselves sufficient to eliminate the 9-hydroxycarbinolamine structure. Definitive evidence was sought in an attempt to oxidize both hydroxyl groups of hydroxydihydrocodeine (III) to carbonyls. Using the Oppenauer procedure previously successful in oxidizing dihydrocodeine to dihydrocodeinone,¹¹ a 39% yield of a hydroxyketone was obtained. The infrared absorption peak at 5.82μ for this compound indicated that the 6-hydroxyl group had been the one oxidized since there was no absorption corresponding to a carbonyl conjugate with an aromatic ring. This was confirmed by preparation of the same compound. hydroxydihydrocodeinone (IV), by chromic acid oxidation of dihydrocodeinone. Failure to oxidize the new hydroxyl group under Oppenauer conditions could be considered support for the carbinolamine structure, but it also might be attributed to a trans relationship between hydroxyl and amino

(9) K. Kindler, B. Hedemann and E. Scharfe, Ann., 560, 215 (1948).
(10) However, in the case of pseudobrucine (a carbinolamine) similar conditions were also required [H. Leuchs and H. L. Louis, Ber., 72, 1483 (1939)].

(11) H. Rapoport, R. Naumann, B. R. Bissell and R. M. Bonner, J. Org. Chem., 15, 1103 (1950).

groups in the 10-hydroxy compound. Such a relationship might be expected to prevent oxidation.^{11,12}

Definitive proof of structure of hydroxydihydrocodeine was finally provided through degradation to the methine. It was found necessary to heat the methiodide with 30% potassium hydroxide for one hour to effect complete degradation¹³ and the hydroxydihydrocodeine methine was isolated in a 75% yield of pure crystalline material. Since the corresponding methine from hydroxycodeine had been shown previously^{8d,3e} to be a ketone, it was presumed that this methine was also a ketone,¹⁴ and there remained only to prove whether this newly formed carbonyl group was adjacent or onceremoved from the aromatic nucleus.

The structure of this methine was established beyond doubt as 10-ketotetrahydro- α -methylmorphimethine (V) in two ways. First, hydrogenation with a palladium-on-carbon catalyst in ethanol containing perchloric acid proceeded with absorption of two moles of hydrogen to give the known tetrahydro- α -methylmorphimethine. Thus the ketomethine must be an aromatic ketone. Second,



Fig. 1.—Ultraviolet absorption spectra of 10-ketotetrahydro- α -methylmorphimethine and dihydrocodeinone in 95% ethanol.

(12) L. M. Jackman, A. K. Macbeth and J. A. Mills, *J. Chem. Soc.*, 2641 (1949); W. von E. Doering and R. W. Young, THIS JOURNAL, **72**, 631 (1950).

(13) It is of interest to compare this behavior with that of dihydrocodeine methiodide which is degraded quantitatively in five minutes under such conditions. Since the Hofmann degradation proceeds by a bimolecular elimination mechanism [M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. I. Woolf, J. Chem. Soc., 2093 (1948)] the quaternary ammonium group must be trans to the hydrogen attached to the β -carbon, and the absence of such a configuration might explain the present difficult degradation. This would imply that the hydroxyl and amino group are trans, an inference similar to that drawn from the behavior on Oppenauer oxidation. However, these observations are far from sufficient to prove the steric relationship and more definitive evidence is being sought.

(14) Although an epoxide is a possible intermediate when an α_{β} aminoalcohol is degraded, isolation of the ketone eliminates this possibility since the epoxide would either survive or be converted to glycol under the present degradation conditions. examination of the infrared absorption spectrum of the ketomethine showed a strong peak at 5.98 μ , characteristic of a conjugated carbonyl. The ultraviolet absorption spectrum had three maxima (244 m μ , log ϵ 4.27; 284 m μ , log ϵ 4.06; 323 m μ , log ϵ 3.69), typical in position and intensity of methoxy and hydroxy aromatic ketones¹⁵ and distinctly different from non-conjugated types (Fig. 1).

Since the keto group in the methine has been proved to be at position 10, the hydroxyl group from which it was derived must also be at 10, and thus this chromic acid oxidation product of codeine must be 10-hydroxycodeine (II).

Experimental¹⁶

10-Hydroxycodeine (II).—Codeine (\cdot H₂O, 15 g., 0.047 mole), dissolved in a 2.5 l. of 1 N sulfuric acid, was cooled to 5° (and maintained at 5° throughout the addition) and a solution of 4.4 g. of chromic anhydride in 225 ml. of 10 N sulfuric acid was added with gentle stirring over a 6-hour period from an addition funnel, the capillary tip of which extended below the surface. Unreacted oxidant was then destroyed by the addition of 20 g. of sodium sulfite, solid sodium carbonate was added to about pH 4 followed by concd. ammonium hydroxide until the pH was approximately 11, and the solution was extracted with 100-ml. portions of chloroform until one ml. of the chloroform extract sulfuric acid.¹⁷ About ten portions were required.

The chloroform extract, concentrated to about 200 ml., was washed with three 60-ml. portions of 1 N hydrochloric acid, and the combined acid extracts were washed with three 10-ml. portions of chloroform and then with two portions of benzene. The *p*H was adjusted to 8 with sodium hydroxide and the solution was washed with ten 18-ml. portions of benzene. All the unreacted codeine was removed in this way from the aqueous layer, accompanied by only a small amount of 10-hydroxycodeine, and its separation and recovery is described below. The aqueous phase was now made 1 N in sodium hydroxide by addition of concd. sodium hydroxycodeine had been removed, as determined by the color test. Evaporation of the chloroform extracts and crystallization of the residue from acetone, gave the bulk of the 10-hydroxycodeine.

The above benzene solution of codeine was washed with ten 18-ml. portions of 1 N ammonium hydroxide to remove all the 10-hydroxycodeine, and evaporation of the benzene gave recovered codeine. The small amount of codeine removed by the ammonia washes was re-extracted with benzene, and the 10-hydroxycodeine was removed with chloroform. In this manner a total of 2.3 g. of codeine, m.p. 155-156°, was recovered, and there was obtained 4.0 g. of 10hydroxycodeine, m.p. 205-206° (yield, 27%, or 32% allowing for recovered codeine).

Codeine and 10-hydroxycodeine also may be separated by chromatography on alumina, using 50% benzene–chloroform to elute the codeine and 85% chloroform–benzene to elute the 10-hydroxycodeine. Material obtained either by solvent distribution or chromatography, and sublimed (175° (0.05 mm.)) melted at 205–206° and had $[\alpha]^{25}$ D –132° (c0.53, ethanol).¹⁹

(15) R. F. Patterson and H. Hibbert, THIS JOURNAL, 65, 1862 (1943); Y. Naves, *Helv. Chim. Acta*, 32, 1351 (1949).

(16) All melting points are corrected and those above 210° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California.

(17) This color test, first reported by Ach and Knorr,¹⁸ was very useful in following the course of extraction of 10-hydroxycodeine and in detecting its presence, since 1 ml. of a chloroform solution containing 0.01 mg. of 10-hydroxycodeine gives a recognizable pink color with a drop of coned. sulfuric acid. The purest solid material (m.p. 205-206°) gives a deep violet color, and less pure samples give various shades of red.

(18) F. Ach and L. Knorr, Ber., 36, 3067 (1903).

(19) Since code ine is the chief impurity and it has $[\alpha]^{16}D - 136^{\circ}$ (ethanol) and $[\alpha]^{16}D - 112^{\circ}$ (chloroform) [Hesse, Ann., 176, 189

Anal. Caled. for $C_{18}H_{21}O_4N$: C, 68.6; H, 6.7. Found: C, 68.4; H, 6.5.

The hydrochloride was prepared with a solution of hydrogen chloride in absolute ethanol and recrystallized several times from absolute ethanol. After drying overnight at 100° (0.1 mm.), the anhydrous material melted at 254° dec. with preliminary softening from 180°; $[\alpha]^{25}D - 116°$ (c 0.97, water) (previously reported¹⁸ but no m.p., rotation, or analysis was given).

Anal. Calcd. for $C_{15}H_{22}O_4NCl$: C, 61.4; H, 6.3; Cl, 10.1. Found: C, 61.3; H, 6.2; Cl, 9.7.

The **diacetyl** derivative was prepared by heating under reflux with acetic anhydride for 20 hours, decomposing the reaction mixture with aq. ammonia, extracting with benzene, and recrystallizing the residue left on evaporation of the benzene from hexane and then from absolute ethanol, m.p. 157–158°, $[\alpha]^{25}$ D –108° (*c* 0.84, ethanol) (reported¹⁸ m.p. 160–161°).

10-Hydroxydihydrocodeine (III). A. By Hydrogenation of 10-Hydroxycodeine.—A solution of 3.14 g. (0.01 mole) of 10-hydroxycodeine in 50 ml. of methanol was hydrogenated at room temperature and 25 lb. pressure using 300 mg. of 5% Pd on barium sulfate as catalyst. In one hour, 1.15 moles of hydrogen was absorbed after which absorption ceased. Filtration, evaporation of the methanol, and crystallization from acetone afforded 2.93 g. (93% yield) of 10hydroxydihydrocodeine which was sublimed at 175° (0.05 mm.); m.p. 202–203°; $[\alpha]^{25}D = 129°$ (c 0.57, ethanol).

Anal. Caled. for $C_{18}H_{23}O_4N$: C, 68.1; H, 7.3. Found: C, 67.8; H, 7.2.

B. By Oxidation of Dihydrocodeine.—Using the same conditions as in the oxidation of codeine (above), 4.74 g. (0.016 mole) of dihydrocodeine was treated with chromie anhydride and the reaction product purified by distribution between benzene and water (pH8). From the benzene extracts there was recovered 1.96 g. of dihydrocodeine, and from the aqueous phase, by extraction with chloroform, evaporation of the chloroform, and crystallization of the residue from ethyl acetate, there was obtained 0.73 g. of 10-hydroxydihydrocodeine, m.p. 202–203° (yield 15%, or 25% allowing for recovered dihydrocodeine).

The **hydrochloride** was prepared with absolute ethanolic hydrogen chloride and recrystallized from absolute ethanol. After drying at 100° (0.1 mm.) overnight, it melted with decomposition at 265° after darkening from 250° ; $[\alpha]^{26}_{D}$ -84.6° (c 0.87, water).

Anal. Caled. for $C_{18}H_{24}O_4NCl$: C, 61.1; H, 6.8; Cl, 10.0. Found: C, 60.7; H, 6.9; Cl, 9.9.

Addition of methyl iodide to a methanolic solution of 10hydroxydihydrocodeine caused precipitation of the **methiodide**, which was recrystallized from methanol m.p. 242–246° dec. after drying at 100° (0.2 mm.) overnight; $[\alpha]^{25}$ D -79° (c 0.82, water).

Anal. Caled. for C₁₉H₂₆O₄NI: C, 49.7; H, 5.7. Found: C, 49.7; H, 5.8.

10-Hydroxydihydrocodeinone (IV). A. By Oppenauer Oxidation of 10-Hydroxydihydrocodeine.—10-Hydroxydihydrocodeine (950 mg., 3 mmoles) was subjected to the same Oppenauer oxidation conditions that had successfully oxidized dihydrocodeine to dihydrocodeinone,¹¹ and 1 g. of potassium and 11 g. of benzophenone were used. The acid extracts (50 ml.) of the reaction mixture were washed with chloroform, basified to ρ H 9, and extracted with benzene. The residue from evaporation of the benzene was chromatographed on alumina using first 20% chloroform in benzene. Eluate was collected in 40-ml. portions and, after the 28th portion, the solvent was changed to 40% chloroformbenzene and then to 70% chloroformbenzene. Since all the fractions after the fourteenth appeared to contain the same substance, they were combined and the solid was crystallized first from isopropyl alcohol and then from benzene. The 10-hydroxydihydrocodeinone thus resulting (370 mg., 39% yield) sublimed at 190° (0.01 mm.) and melted at 202-203° [mixed m.p. 170-175° with 10-hydroxydihydrocodeine (m.p. 202-203°)], [α]³⁵D - 132° (c 1.0, ethanol).

(1875)] whereas 10-hydroxycodeine has $[\alpha]^{26}D - 132^{\circ}$ (ethanol) and $[\alpha]^{22}D - 115^{\circ}$ (chloroform),⁴ the rotation is unreliable for characterization. However, the melting point is useful since it is repro-

(cf. ref. 4).

ducible and the presence of 10% codeine lowered it to 201-202°

Anal. Calcd. for $C_{18}H_{21}O_4N$: C, 68.6; H, 6.7. Found: C, 68.4; H, 6.8.

B. By Oxidation of Dihydrocodeinone.—Dihydrocodeinone was oxidized with chromic anhydride under the general conditions described above. Purification was effected by chromatography on alumina, using benzene to elute the large amount of unchanged dihydrocodeinone and 60 to 80% chloroform in benzene to elute the 10-hydroxydihydrocodeinone. Recrystallization from benzene gave material of m.p. 200-202°.

The methiodide was prepared in and crystallized from methanol; m.p. 240-244° dec., $[\alpha]^{25}D - 78°$ (c 0.98, water).

Anal. Caled. for $C_{19}H_{24}O_4NI$: C, 49.9; H, 5.3. Found: C, 50.1; H, 5.4.

10-Hydroxydihydrocodeine Methine (10-Ketotetrahydro- α -methylmorphimethine) (V).—To 1.37 g. (3 mmoles) of 10hydroxydihydrocodeine methiodide dissolved in 7 ml. of water was added 7 ml. of 60% aqueous potassium hydroxide and the mixture was heated under reflux (nitrogen atmosphere) for one hour. The mixture was extracted thoroughly with ether, the ether was evaporated, and the residue (0.92 g.) was crystallized several times from ether to give 0.75 g. (75% yield) of methine, m.p. 114–115°, $[\alpha]^{25}$ -45° (c 0.81, ethanol).

Anal. Caled. for $C_{19}H_{25}O_4N$: C, 68.9; H, 7.6. Found: C, 68.8; H, 7.7.

The **methiodide** was prepared in methanol and crystallized from ethanol; m.p. $259-260^{\circ}$ after drying at 100° (1 mm.); $[\alpha]^{25}$ D -35.2° (c 0.93, water).

Anal. Caled. for $C_{20}H_{23}O_4NI$: C, 50.7; H, 6.0; I, 26.8. Found: C, 50.4; H, 5.4; I, 27.2.

The semicarbazone was prepared in the usual fashion in aqueous solution. Basification with concd. ammonium hydroxide followed by extraction with chloroform and evaporation of the chloroform left a residue which was crystallized from butanone, m.p. $129-132^{\circ}$.

Anal. Calcd. for $C_{20}H_{28}O_4N_4$: N, 14.4. Found: N, 14.0.

Hydrogenolysis Experiments. A. Dihydrocodeine from 10-Hydroxydihydrocodeine.—A solution of 317 mg. (1 mmole) of 10-hydroxydihydrocodeine in 15 ml. of glacial acetic acid containing 0.5 ml. of 60% aqueous perchloric acid and 200 mg. of 5% palladium on carbon was hydro-

genated at 40 to 50° and 30 lb. pressure. After several hours, hydrogen absorption ceased, the solution was filtered, and the filtrate was basified with sodium hydroxide and extracted with chloroform. Sublimation of the residue left on evaporation of the chloroform gave 230 mg. (76% yield) of dihydrocodeine, m.p. $105-107^{\circ}$. There was no depression in m.p. on admixture with an authentic sample of dihydrocodeine.

B. Tetrahydro- α -methylmorphimethine from 10-Ketotetrahydro- α -methylmorphimethine.—The keto methine (331 mg., 1 mmole), dissolved in 15 ml. of absolute ethanol to which 1 ml. of 60% aqueous perchloric acid had been added, was hydrogenated at room temperature and atmospheric pressure using 100 mg. of 5% palladium-on-carbon as catalyst. Hydrogen absorption ceased after exactly 2 moles of hydrogen had been consumed in two hours. Water (25 ml.) was added to dissolve the crystalline precipitate that had appeared in the hydrogenation mixture, the solution was filtered, and the filtrate was extracted with five equal volume portions of chloroform. Evaporation of the chloroform extracts left 340 mg. (81%) of crude tetrahydro- α -methylmorphimethine perchlorate. The aqueous alcohol was then basified and again extracted with chloroform from which 40 mg. (12%) of the oily free base was obtained.

Crystallization of the crude perchlorate above from absolute ethanol and drying at 100° (1 mm.) gave material of m.p. $224-225^{\circ}$ (reported²⁰ m.p. $218-219^{\circ}$).

Anal. Calcd. for $C_{19}H_{25}O_7NC1$: C, 54.6; H, 6.8. Found: C, 54.3; H, 6.7.

The **methiodide** was prepared from the free base in methanol and recrystallized from absolute ethanol; m.p. 225-227°, mixed m.p. with an authentic sample of tetrahydroa-methylmorphimethine methiodide (m.p. 226-227°), 225-227°.

The hydrochloride was prepared by adding absolute ethanolic hydrogen chloride to an isopropyl alcohol solution of the free base. After crystallization from isopropyl alcohol and drying at 100° (1 mm.), the hydrochloride had m.p. 226-227°, $[\alpha]^{25}D - 31.2°$ (c 0.90, water) [reported²¹ for tetrahydro- α -methylmorphimethine hydrochloride, m.p. 228°, $[\alpha]^{15}D - 31.9$ (c 0.97, water)].

(20) H. Wieland and M. Kotake, Ann., 444, 69 (1925).
(21) E. Speyer and K. Koulen, *ibid.*, 438, 34 (1924).

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[FROM THE BIOCHEMISTRY DEPARTMENT, UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE]

On the Structure of Lactobacillic Acid^{1,2}

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A method is presented for the isolation of dihydrosterculic acid from the kernel oil of *Sterculia foetida*, and synthetic procedures are described for the preparation of methyleneoctadecanoic acids possessing a *trans* configuration. A comparison of the infrared absorption spectra of lactobacillic and dihydrosterculic acid with those of synthetic *trans*-9,10- and 11,12methyleneoctadecanoic acids offer strong support to the previously assigned cyclopropane structure for the naturally occurring acids.

The lipides of *Lactobacillus arabinosus*^{3,4} and *Lactobacillus casei*⁵ contain significant amounts of a novel fatty acid of the composition $C_{19}H_{36}O_2$ for which we have chosen the name lactobacillic acid. The chemical behavior of lactobacillic acid (stability toward oxidation and lability on hydrogenation)

(1) Supported by grants from the American Cancer Society, upon recommendation of the Committee on Growth of the National Research Council, the Rockefeller Foundation in New York, and Ciba Pharmaceutical Products, Inc., Summit, N. J.

(2) A preliminary report of some of this work has appeared in the Record of Chemical Progress, 14, 7 (1953).

(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 and S. M. Sax, ibid., 205, 55 (1953).

and the presence in its infrared absorption spectrum of a maximum at 9.8 μ pointed to the presence of a cyclopropane ring. Based on these findings we have postulated the structure of a methyleneoctadecanoic acid (I) for lactobacillic acid.^{3,4}



The occurrence of fatty acids of the general structure I is not limited to the above mentioned lactobacilli. The kernel oil of the tropical tree