Summary

1. A series of ω-cyclohexyl acids containing from 1 to 13 carbon atoms in the side chain have been prepared.

2. Those with from three to nine carbon atoms in the side chain show bactericidal action toward *B. leprae.*

3. A number of hydroxy-substituted acids of the above-mentioned series, formed as intermediates, also show bactericidal action.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

SYNTHESIS OF CHAULMOOGRYLACETIC ACID. V

BY RUSSEL H. VANDYKE[1] AND ROGER ADAMS

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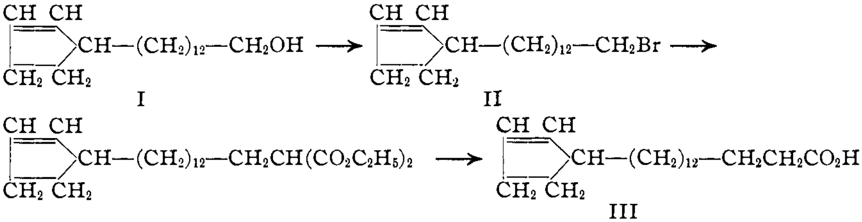
Although it has been known for several years that hydnocarpic and chaulmoogric acids have a specific action against *B. leprae,* very few derivatives or compounds closely related to these two acids have been synthesized and studied. This paper describes the salts of chaulmoogryl acetic acid. Incidentally, the intermediates necessary for this synthesis are valuable for producing other compounds in which the chaulmoogryl nucleus is present.

The procedure was to esterify pure chaulmoogric acid to the ethyl ester. This latter compound was reduced to chaulmoogryl alcohol I by means of sodium and alcohol. The alcohol was converted to the bromide II and the bromide to chaulmoogrylacetic acid III by a malonic ester synthesis.



Experimental Part

Ethyl Chaulmoograte.—This was prepared according to the method of Power and Gornall.[2]

Chaulmoogryl Alcohol.—The reduction of ethyl chaulmoograte was attempted under a variety of conditions. The best yield was obtained by following the general procedure of Grün and Wirth.[3]

A 2-liter, round-bottom, 3-neck flask, fitted with a mechanical stirrer and long condenser was used. A solution of 70 g. of ethyl chaulmoograte in 230 cc. of absolute al-

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[1] This paper is an abstract of a portion of a thesis submitted by R. H. VanDyke in partial fulfilment of the requirements for the degree of Master of Arts in Chemistry at the University of Illinois.

[2] Power and Gornall, *J. Chem. Soc.*, **85,** 838 (1904).

[3] Grün and Wirth, *Ber.*, **55,** 2206 (1922).

cohol (100%) was placed in a flask, warmed and then 23 g. of freshly cut sodium added as rapidly as possible to the stirred solution. The stirring was continued until all of the sodium was dissolved. About 300 cc. of water was added and most of the alcohol distilled from a steam-bath. The mixture was extracted with ether. After washing and drying, the solvent was removed and the chaulmoogryl alcohol distilled. It boiled at 222° at 16 mm. and melted at 36° (these constants agree with those of Power[2]). The yield was much better than obtained by Power, on the average 33 g. (55%).

Anal. Subs., 0.8167, made up to 15 cc. in $CHCl_3$ gave a rotation of. +3.18 in a 1-dcm. tube; $[\alpha]_D = +58.47°$.

Chaulmoogryl Bromide.—A solution of 10 g. of chaulmoogryl alcohol in 30 cc.. of dry toluene was placed in a small flask protected by a calcium chloride tube. The flask was set in an ice-bath and to it was added carefully 7 g. of phosphorus tribromide dissolved in 10 cc. of toluene. This was allowed to stand at 0° for about three hours, after which it was heated on a steam-bath for three to five hours, or until no more hydrogen bromide was evolved. The reaction mixture was extracted with petroleum ether (40–50°), the ether extracted, washed with water and then with 10% sodium hydroxide solution. After drying, the mixture was distilled to remove the toluene and petroleum ether and the resulting bromide fractionated under diminished pressure. It was a colorless oil boiling at 230° at 16 mm. and melting at 18.6°; n_D, 1.4846; d_{25}^{25}, 1.0461. The average yield was about 9 g. (70%).

Anal. Subs., 1.9890, made up to 15 cc. in $CHCl_3$ gave a rotation of 7.016 in a 1-dcm. tube; $[\alpha]_D = 52.92°$. Pure bromide in a 1-dcm. tube gave a rotation of 44.175°; $[\alpha]_D = 42.1°$

Subs., 0.2639, 0.2740; 8.02, 8.38 cc. of 0.09947 *N* $AgNO_3$. Calcd. for, $C_{18}H_{33}Br$; Br, 24.31. Found: 24.21, 24.35.

Chaulmoogrylmalonic Ester.—This was made by the usual procedure for condensing alkyl halides with malonic ester. The product was distilled under diminished pressure but no attempt was made to get a constant boiling point. The crude product was saponified directly.

Chaulmoogrylmalonic Acid.—A mixture of 5 g. of the crude chaulmoogrylmalonic ester was refluxed for four or five hours with 100 cc. of 10% potassium hydroxide solution. The alkaline solution was diluted and extracted with ether to remove the unsaponified ester. It was then made acid with dil. hydrochloric acid, and the chaulmoogrylmalonic acid extracted with ether. It was purified by crystallizing from benzene. It formed small, white, needle-like crystals melting at 94–95°.

Anal. Subs., 0.5191, made up to 15 cc. in $CHCl_3$ in a 1-dcm. tube gave a rotation of +1.557°; $[\alpha]_D = +45.0°$.

Subs., 0.1150; 6.76 cc. of 0.09618 *N* NaOH. Calcd. for $C_{21}H_{36}O_4$: neut. equiv., 176. Found: 176.8.

Chaulmoogrylacetic Acid.—A solution of 2 g. of pure chaulmoogrylmalonic acid in 20 cc. of xylene was refluxed for two to three hours. On cooling, a white crystalline product separated in the xylene which, after a few crystallizations from 80% alcohol and petroleum ether, came to a constant melting point at 72–73°.

Anal. Subs., 0.6705, made up to 15 cc. in $CHCl_3$ in a 1-dcm. tube gave a rotation of 1.9376°; $[\alpha]_D = 43.34°$.

Subs., 0.2024: 6.53 cc. of 0.1008 *N* KOH. Subs., 0.1012: CO_2, 0.2900; H_2O, 0.1047. Calcd. for $C_{20}H_{36}O_2$: neut. equiv., 308; C, 77.85; H, 11.77. Found: neut. equiv., 307.6; C, 78.1; H, 11.57.

Summary

Chaulmoogrylacetic acid has been prepared by converting ethyl chaulmoograte to chaulmoogryl alcohol, the alcohol to the bromide and finally by using a malonic ester synthesis on this last product.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

THE SYNTHESIS OF HOMOCHAULMOOGRIC ACID, HOMOHYDNOCARPIC ACID AND CHAULMOOGRYLAMINES. VI

BY J. SACKS[1] WITH ROGER ADAMS

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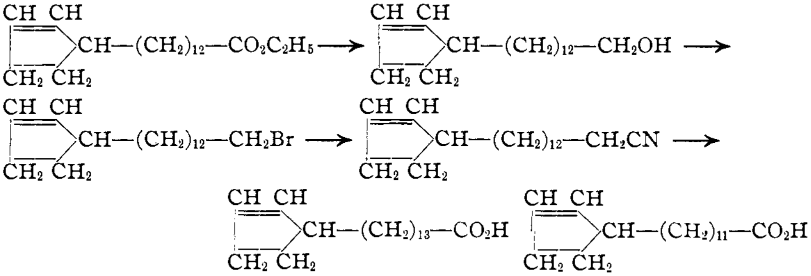
In continuation of the investigations[2] into the structure, synthesis and specificity[3] of the action of the fatty acids of chaulmoogra oil on *B. leprae*, a number of simple derivatives of chaulmoogric and hydnocarpic acids, the principal acids of chaulmoogra oil,[4] have been made and tested for their activity against certain acid-fast bacteria. A few other compounds containing a cyclic structure have also been tested. This report is a résumé of the chemical work and contains a brief statement of the bacteriological results. The detailed bacteriological results will be published elsewhere.

The homochaulmoogric acid I and homohydnocarpic acid II have been made from chaulmoogric and hydnocarpic acid, respectively, by the following general series of reactions, as illustrated by the formation of the homochaulmoogric acid:



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[1] This communication is an abstract of a portion of a thesis submitted by J. Sacks in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry in the Graduate School of the University of Illinois.

[2] (a) Shriner and Adams, THIS JOURNAL, **47**, 2727 (1925). (b) Noller with Adams, *ibid.*, **48**, 1074, 1080 (1926). (c) Hiers with Adams, *ibid.*, **48**, 1089 (1926); **48**, 2385 (1926). (d) VanDyke and Adams, *ibid.*, **48**, 2393 (1926).

[3] Rogers, *Brit. Med. J.*, **1**, 147 (1919); *Indian Med. Gaz.*, **54**, 165 (1919). Walker and Sweeney, *J. Infectious Dis.*, **26**, 238 (1925).

[4] (a) Power and Gornall, *J. Chem. Soc.*, **85**, 838, 851 (1904). (b) Power and Barrowcliff, *ibid.*, **87**, 884 (1905). (c) Barrowcliff and Power, *ibid.*, **91**, 557 (1907).