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

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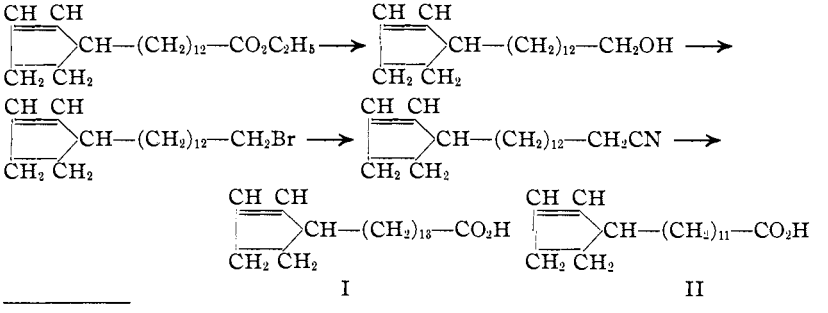
RECEIVED JUNE 7, 1926 PUBLISHED SEPTEMBER 4, 1926

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 acid and hydnocarpic acid, respectively, by the following general series of reactions, as illustrated by the formation of the homochaulmoogric acid:



I II

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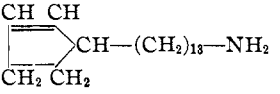
[1] This communication is an abstract of a portion of a thesis submitted by J. Sacks in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry in the Graduate School of the University of Illinois.

[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).

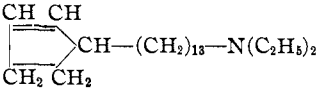
[3] Rogers, *Brit. Med. J.*, **1**, 147 (1919); *Indian Med. Gaz.*, **54**, 165 (1919). Walker and Sweeney, *J. Infectious Dis.*, **26**, 238 (1925).

[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).

In addition to these acids, chaulmoogrylamine III and chaulmoogryldiethylamine IV, respectively, were made by condensing chaulmoogryl bromide with potassium phthalimide and hydrolyzing the product, and by the condensation of the bromide with diethylamine.



III



IV

Besides these new synthetic derivatives just mentioned, the following substances were tested bacteriologically: cinnamic acid and its derivatives; *m*-nitro-, *m*-amino-, *p*-methoxy-cinnamic acids; *o*-coumaric acid and hydrocinnamic acid; the cyclopentane derivatives, Δ^1-cyclopentene-carboxylic acid, Δ^1-cyclopentenyl-acetic acid,[5a] and cyclopentanol-acetic acid;[5b] the cyclohexane derivatives, Δ^1-cyclohexene-carboxylic acid,[6] Δ^1-cyclohexenyl-acetic acid,[5] cyclohexanol-acetic acid[5] and cyclohexylidene-acetic acid;[5a] phenylpropiolic acid, cinnamylidene-acetic acid,[7] cinnamylidene-malonic acid,[8] furyl-acrylic acid and umbelliferone-β-acetic acid.

The hydnocarpic, homohydnocarpic, chaulmoogric, homochaulmoogric and chaulmoogrylacetic acids (the last was described by VanDyke and Adams[2d] in the preceding paper) present an interesting series for bacteriological testing since the difference in the individual compounds consists merely in the length of the side chain, varying from 11 to 15 carbon atoms. The tests have shown that the homo acids have very little effect. The chaulmoogrylacetic acid has practically no effect as compared with hydnocarpic and chaulmoogric acids.

Among the other compounds tested, cinnamic acid showed inhibitory power at a concentration of 1:1000, as has been previously demonstrated by Schöbl.[9] The cinnamic acid derivatives had no effect. Furyl-acrylic acid gave about the same results as cinnamic acid. Phenylpropiolic acid at a concentration of 1:1000 caused growth to be less rapid than in the controls. Cinnamylidene-acetic acid and umbelliferone-β-acetic acid showed rather marked inhibitory properties. The other compounds were without action.

Experimental Part

Chaulmoogric and Hydnocarpic Acids.—The procedure for obtaining these acids was a very slight modification of that used by Shriner.[2a] The mixed fatty acids, after being heated under diminished pressure to remove water, were distilled at 3–7 mm. pressure and separated into three portions, A, B and C, of which the middle one, B, was somewhat larger than the end

[5] (a) Wallach, *Ann.*, **353,** 288 (1907); (b) **347,** 324 (1906).

[6] Aschan, *Ann.*, **271,** 265 (1893).

[7] Perkin, *J. Chem. Soc.*, **31,** 403 (1877).

[8] Stuart, *ibid.*, **49,** 365 (1886).

[9] Schöbl, *Phil. J. Sci.*, **23,** 533 (1923); **24,** 135 (1924).

portions. The low-boiling fraction, A, was worked up as follows. A fractional distillation of 600 g. was made at 3 mm. and four equal fractions were separated. The middle fractions were crystallized five times from two volumes of acetone, after which the product melted at 59–60°, the melting point of pure hydnocarpic acid. The yield was 33 g.

The high-boiling fraction, C, was crystallized once from 90% alcohol, twice from 80% alcohol and twice from ligroin, after which the melting point was 68–68.5°, the melting point of pure chaulmoogric acid. The yield was 400 g. from 8 kg. of oil.

Chaulmoogryl Cyanide.—A mixture of 15 g. of chaulmoogryl bromide[2] in 25 cc. of ethyl alcohol and 4 g. of potassium cyanide in 5 cc. of water was refluxed for 15 hours. Water was then added and the nitrile extracted with ether. After the ether solution had been dried, the solvent was removed and the nitrile distilled under diminished pressure. There was obtained 11 g. (87%) of a product boiling at 230° (16 mm.); m. p., 24.5°; n_D^{25}, 1.4691; d_{25}^{25}, 0.8928.

Anal. Subs., 0.9095 g., made up to 15 cc. in $CHCl_3$ gave a rotation of 3.00° in a 1-dcm. tube; $[\alpha]_D = 49.5°$.

Subs., 0.3912, 0.3182: 20.59, 15.48 cc. of 0.0714 *N* HCl. Calcd. for $C_{19}H_{33}N$: N, 5.09. Found: 5.03, 4.86.

Homochaulmoogric Acid, I.—A solution of 10 g. of chaulmoogryl cyanide in 50 cc. of alcohol was mixed with a solution of 1 g. of sodium hydroxide in 5 cc. of water. After refluxing for 16 hours, the solution was cooled, extracted once with ligroin, the free acid precipitated with hydrochloric acid and crystallized once from 80% alcohol and twice from ligroin. The pure substance was obtained in a yield of 6 g. and melted at 66–67°.

Anal. Subs., 0.5090, made up to 15 cc. in $CHCl_3$ gave a rotation of +1.84° in a 1-dcm. tube; $[\alpha]_D = +54.0°$.

Subs., 0.2513, 0.2613: 8.52, 8.83 cc. of 0.1 *N* NaOH. Calcd. for $C_{19}H_{34}O_2$: neut. equiv., 294.3. Found: 294.9, 295.9.

Chaulmoogrylamine Hydrochloride, III.—A mixture of 20 g. of chaulmoogryl bromide and 11.5 g. of potassium phthalimide was heated at 180° for 10 hours during mechanical agitation. After cooling, the reaction mixture was extracted with ether, the extract filtered and evaporated. The residue of crude chaulmoogryl-phthalimide was refluxed for 15 minutes with an excess of 10% potassium hydroxide solution, whereby it was converted to the potassium salt of the phthalamidic acid. The solution was then made strongly acid with hydrochloric acid and refluxed for 15 minutes to complete the hydrolysis. The acid solution was extracted with ether and then made alkaline. The chaulmoogrylamine was extracted with ether, the solution dried over solid potassium hydroxide, the solvent removed and the chaulmoogrylamine distilled under diminished pressure. The substance boiled at 206° (16 mm.). The yield was rather low, due possibly to the ease with which the amine absorbed carbon dioxide.

A solution of the amine in dry ether was treated with dry hydrogen chloride. The hydrochloride immediately separated. It was filtered and washed with ether. The chaulmoogrylamine hydrochloride was readily soluble in chloroform. It can be crystallized from hot water, and when pure melts at 114°.

Anal. Subs., 1.2655, made up to 15 cc. in $CHCl_3$ gave a rotation of +3.73° in a 1-dcm. tube; $[\alpha]_D = +44.2°$.

Subs., 0.2256, 0.2008: 14.82, 13.25 cc. of 0.05 *N* $AgNO_3$. Calcd. for $C_{18}H_{36}NCl$: Cl, 11.84. Found: 11.62, 11.71.

Chaulmoogryldiethylamine, IV.—A mixture of 10 g. of chaulmoogryl bromide

with 9 g. of diethylamine was allowed to stand at room temperature for two days. Water was then added and the solution made alkaline with sodium hydroxide. The amine was taken up in ether, the ether washed well with water and dried over solid potassium hydroxide. After filtration, dry hydrogen chloride was passed into the solution and the solid hydrochloride separated. This was purified by dissolving in chloroform and precipitating with ligroin. It melts at 99°.

Anal. Subs., 1.103 g., made up to 15 cc. in $CHCl_3$ gave a rotation of +2.53° in a 1-dcm. tube; $[\alpha]_D$ = +34.5°.

Subs., 0.1719, 0.1989: 10.03 cc., 11.37 cc. of 0.05 *N* $AgNO_3$. Calcd. for $C_{22}H_{44}NCl$: Cl, 9.92. Found: 10.10, 10.03.

Ethyl Hydnocarpate.—This was prepared by the procedure described by Power and Barrowcliff.[4c] The yield was 82%; it boiled at 217° (23 mm.) (Power reports 211° at 19 mm.); n_D^{25}, 1.4577.

Hydnocarpyl Alcohol.—A reduction of 30 g. of ethyl hydnocarpate with sodium and absolute alcohol was carried out in a manner similar to that of the reduction of ethyl chaulmoograte.[2c] The product was isolated in the same way. The yield was 12 g. (50%) of product boiling at 199.5° (14 mm.); m. p., 23°; n_D^{25}, 1.4733.

Anal. Subs., 0.8019 g., made up to 15 cc. in $CHCl_3$ gave a rotation of +3.52° in a 1-dcm. tube; $[\alpha]_D$ = +67.8°.

Subs., 0.1206, 0.1058: CO_2, 0.3574, 0.3092; H_2O, 0.1358, 0.1188. Calcd. for $C_{16}H_{30}O$: C, 80.59; H, 12.69. Found: C, 80.85, 80.34; H, 12.60, 12.60.

Hydnocarpyl Bromide.—From 10 g. of hydnocarpyl alcohol by the method used for chaulmoogryl bromide (VanDyke and Adams), 8.5 g. (70%) of product boiling at 206–210° (14 mm.) was obtained; m. p., 1°; n_D^{25}, 1.4871.

Anal. Subs., 0.5859, made up to 15 cc. in $CHCl_3$ gave a rotation of +1.56° in a 1-dcm. tube; $[\alpha]_D$ = +40.0°.

Subs., 0.1597, 0.1960: 11.03, 12.69 cc. of 0.05 *N* $AgNO_3$. Calcd. for $C_{16}H_{29}Br$: 26.56. Found: 26.38, 26.27.

Homohydnocarpic Acid, II.—A mixture of 6 g. of hydnocarpyl bromide in 20 cc. of alcohol and 1.5 g. of potassium cyanide in 2 cc. of water was refluxed for 15 hours. Water was added and the nitrile extracted with ether. No attempt was made to purify the nitrile on account of the small quantity of material available. It was hydrolyzed by refluxing overnight with 10% aqueous alcoholic sodium hydroxide. Water was added, the solution acidified with hydrochloric acid and the resulting acid crystallized from 80% alcohol. A yield of 2 g. of pure product melting at 56–57° was obtained.

Anal. Subs., 0.5033 g., made up to 15 cc. in $CHCl_3$ gave a rotation of +1.87° in a 1-dcm. tube; $[\alpha]_D$ = +56.7°.

Subs., 0.2345, 0.2111: 8.78, 7.89 cc. of 0.1 *N* NaOH. Calcd. for $C_{17}H_{30}O_2$; neut. equiv., 266.3. Found: 267.1, 267.6.

Summary

1. Homohydnocarpic acid and homochaulmoogric acid have been prepared by converting the hydnocarpyl alcohol and chaulmoogryl alcohol into the corresponding bromides, then into the cyanides and finally hydrolyzing the latter products.

2. Chaulmoogrylamine has been prepared by the condensation of chaulmoogryl bromide with potassium phthalimide and hydrolyzing the condensation product, and chaulmoogryldiethylamine has been prepared by condensing the bromide with diethylamine.

3. These substances and chaulmoogrylacetic acid have been tested for bactericidal action against *B. leprae.*

4. A number of cyclopentane, cyclohexane and cinnamic acids and benzene derivatives have been tested for bacteriological effect on *B. leprae.*

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

THE MECHANISM OF REACTION BETWEEN THIONYLANILINE AND ORGANOMAGNESIUM HALIDES

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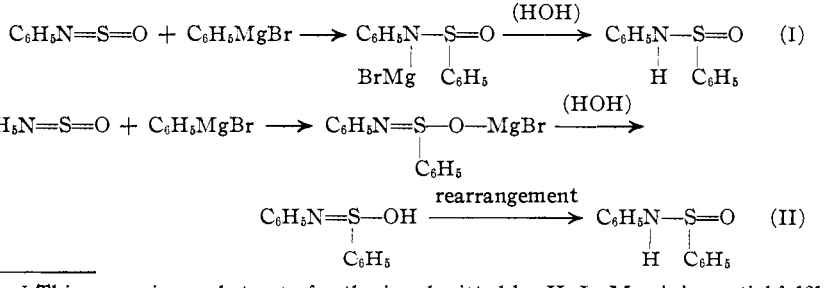
RECEIVED JUNE 10, 1926 PUBLISHED SEPTEMBER 4, 1926

Introduction

Thionylamines (RN=S=O) are related structurally to ketenes (R_2C=C=O), isocyanates (RN=C=O) and isothiocyanates (RN=C=S). These different classes of compounds have a pair of terminal cumulated unsaturated groups and take part in a number of reactions in common. It has been proved that the ketenes,[2] isocyanates[3] and isothiocyanates[3] react under ordinary conditions with but one molecular proportion of RMgX compound. Addition is restricted exclusively to the terminal unsaturated group, the R of the RMgX compound attaching itself to carbon and the —MgX to oxygen and to sulfur, respectively.

When thionylaniline, C_6H_5NSO, the most representative of thionylamines, is treated with typical organomagnesium halides but one molecule of the latter adds under ordinary conditions and anilides of sulfinic acids result. These sulfinanilides may have resulted by either of two mechanisms, depending on whether addition took place at the —N=S— (I) or at the =S=O (II) group, as follows.



[1] This paper is an abstract of a thesis submitted by H. L. Morris in partial fulfilment of the requirements for the degree of Master of Science in Chemistry at Iowa State College in 1922. A preliminary account of the work was presented at the Birmingham, Alabama, meeting of the American Chemical Society, April 5–6, 1922 and abstracted in *Science*, **56**, 54 (1922).

[2] Gilman and Heckert, THIS JOURNAL, **42**, 1010 (1920).

[3] Gilman and Kinney, *ibid.*, **46**, 493 (1924).