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

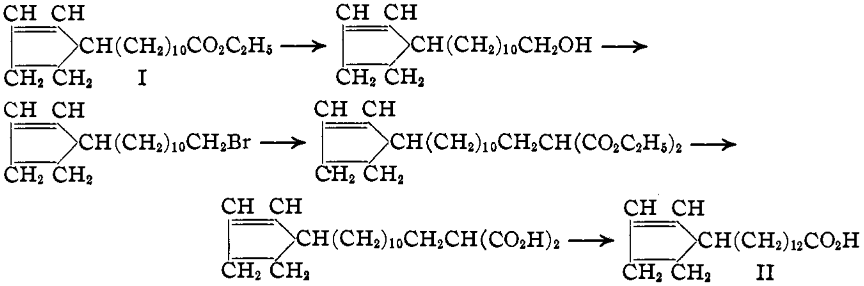
THE SYNTHESIS OF CHAULMOOGRIC ACID FROM HYDNOCARPIC ACID

BY W. M. STANLEY[1] AND ROGER ADAMS

RECEIVED DECEMBER 7, 1928 PUBLISHED MAY 6, 1929

In his early investigations on chaulmoogra oil and other oils of a similar character, Power[2] and his students isolated, in addition to chaulmoogric acid, hydnocarpic acid. This analyzed as a homolog of chaulmoogric acid. In order to confirm this conclusion, Power[3] oxidized hydnocarpic acid and isolated a di- and a tricarboxylic acid, the former of which proved to be *n*-decanedicarboxylic acid and the latter was assumed to be *n*-tridecane-α,α',γ-tricarboxylic acid. Since these oxidation products corresponded to those obtained from chaulmoogric acid, his conclusion was strengthened that the acids were homologs.

On account of the increasing importance of hydnocarpic acid and chaulmoogric acid, and on account of the fact that the correct structure for chaulmoogric acid, II, was found to be slightly different from that suggested by Power,[4] it seemed desirable to make further experiments to show the chemical relationship between these acids. This has been accomplished by conversion of hydnocarpic acid to chaulmoogric acid, II, through ethyl hydnocarpate, I, hydnocarpyl alcohol, hydnocarpyl bromide and hydnocarpylmalonic acid, successively.



No special comments need to be made concerning the well-known reactions involved. It should be stated, however, that the hydnocarpic acid used was not absolutely pure and consequently there was obtained in each step a certain amount of by-product which required careful fractionation for removal. No particular effort was made to purify completely each inter-

---

[1] This communication is a portion of a thesis submitted by W. M. Stanley in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] Power and Barrowcliff, *J. Chem. Soc.*, **87**, 884 (1905).

[3] Barrowcliff and Power, *ibid.*, **91**, 557 (1907).

[4] Shriner and Adams, THIS JOURNAL, **47**, 2727 (1925).

mediate step before conversion to the succeeding one, though each intermediate was purified for the determination of physical constants.

The hydnocarpylacetic acid obtained was contaminated with small amounts of other acids which were rather difficult to remove and required several fractional crystallizations. It was then possible to obtain a synthetic acid which had the same constants, melting point, rotation, etc., as the natural product (chaulmoogric acid). Moreover, the amides were compared and shown to be identical.

Perkins and Cruz[5] synthesized *dl*-chaulmoogric acid from simple organic compounds and showed that by oxidation the same decomposition products were obtained as from the natural, active form. The *dl*-form was not, however, resolved. Their investigation did not aid in the determination of the relationship of the natural hydnocarpic and chaulmoogric acids.

Experimental Part

Ethyl Hydnocarpate.—The hydnocarpic acid used in this investigation was kindly furnished by the Chemical Section of the Culion Leper Colony. The authors desire to express their appreciation for this material. The product had a melting point of 59.6° and a rotation of +69.4°.

A mixture of 250 g. of hydnocarpic acid, 400 g. of absolute ethyl alcohol and 7 g. of sulfuric acid was refluxed for two days. It was then cooled and poured into three times its volume of water containing 15 g. of sodium bicarbonate. The upper layer was separated and the slightly alkaline lower aqueous portion was extracted five times with ether and the ether extract washed twice with water. The ether extract was combined with the upper layer and again washed with water, dried over anhydrous magnesium sulfate, and distilled under diminished pressure. The yield was 246 g. (92%) of a product boiling at 160–165° (5 mm.) and having a rotation of +61.5° (0.5225 g. made up to 25 cc. in chloroform and used in a 1-dcm. tube). Twenty grams of hydnocarpic acid was recovered by acidifying the aqueous portion and extracting with ether. A 15-g. sample was fractionated and gave 9 g. of ethyl hydnocarpate, the physical constants of which did not change on further fractionation. The constants were: b. p., 143–144° (2 mm.); n_{D}^{25}, 1.4582; d_{4}^{25}, 0.9087; $[\alpha]_D$, +70.5° (0.5186 g. made up to 25 cc. in chloroform and used in a 1-dcm. tube).

Power and Barrowcliff[2] report a boiling point of 211° (19 mm.) and a rotation of +51.6° on a 5-g. sample of ethyl hydnocarpate which they prepared. Sacks and Adams[6] report a boiling point of 217° (23 mm.) and n_{D}^{25}, 1.4577, on a 30-g. sample of ethyl hydnocarpate.

Hydnocarpyl Alcohol.—A total of 225 g. of ethyl hydnocarpate was reduced to hydnocarpyl alcohol in three separate reductions by the toluene method. In each experiment 75 g. of ethyl hydnocarpate, 500 cc. of absolute ethyl alcohol, 100 cc. of toluene and 70 g. of sodium were used.

A 5-liter, three-necked flask was fitted with a separatory funnel, a mechanical stirrer and an extra long condenser of large bore. In the flask were placed 70 g. of sodium and 100 cc. of toluene which had been dried over sodium, and the mixture was heated with a flame until the sodium melted. The stirrer was then started, the flame removed and the mixture allowed to cool until the molten sodium solidified into small

---

[5] Perkins and Cruz, This Journal, **49**, 1070 (1927).

[6] Sacks with Adams, *ibid.*, **48**, 2395 (1926).

pellets. A mixture of 75 g. of ethyl hydnocarpate in 300 cc. of absolute ethyl alcohol was immediately run into the flask as rapidly as possible, followed immediately by 200 cc. of absolute ethyl alcohol. The stirring was continued and the mixture heated with a flame of sufficient size to keep the alcohol refluxing vigorously until practically all of the sodium had disappeared. The stirrer was stopped and the contents of the flask poured into an ordinary 5-liter flask. This was repeated twice and the three runs combined in the flask were heated on a steam-cone for ten hours. While still hot the mixture was washed with five times its volume of hot water or until the wash water was free of soap. It was washed once with water, then with water containing a small amount of sulfuric acid and finally with water. The wash water was combined and extracted four times with ether, the ether extract washed with water and then added to the main alcohol portion. The alkaline wash water was acidified and 25 g. of crude hydnocarpic acid was recovered. The solvent was removed and the alcohol distilled under diminished pressure. The yield was 90 g. (46%) of a product boiling at 170–175° (8 mm.) and having a rotation of +73.6° (0.7996 g. made up to 15 cc. in chloroform and used in a 1-dcm. tube). Two high-boiling fractions consisting of 43 g. boiling at 185–210° (2 mm.) and 35 g. boiling above 210° (2 mm.) were obtained and probably consisted of dimolecular reduction products.

A 20-g. sample of the alcohol which was fractionated gave 15 g. of hydnocarpyl alcohol having the following constants: b. p., 144–145° (2 mm.); m. p., 23°; n_D^{25}, 1.4709; d_4^{25}, 0.8022; $[\alpha]_D$, +75.2° (0.8592 g. made up to 15 cc. in chloroform and used in a 1-dcm. tube). Further fractionation did not change these constants, although the high-boiling material from the first fractionation had a melting point of 27°, n_D^{27}, 1.4721, and $[\alpha]_D$, +59.5. Sacks and Adams[6] report the following constants on a 12-g. sample of hydnocarpyl alcohol which was not subjected to further fractionation: b. p., 199.5° (14 mm.); m. p., 23°; n_D^{25}, 1.4733; $[\alpha]_D$, +67.8° (0.8019 g. made up to 15 cc. in chloroform and used in a 1-dcm. tube).

Hydnocarpyl Bromide.—A solution of 70 g. of hydnocarpyl alcohol in 150 cc. of dry toluene was placed in a 600-cc. flask fitted with a thermometer, calcium chloride tube and a separatory funnel, and cooled to 0° by means of an ice-bath. An ice-cooled solution of 65 g. of redistilled phosphorus tribromide in 70 cc. of dry toluene was then added sufficiently slowly so that the temperature of the reaction mixture did not rise above 5°. The reaction mixture was kept at 0° for six hours, then at room temperature for twelve hours and finally on a steam-cone for six hours. It was cooled and extracted with petroleum ether, the ether extract washed first with water and then with a solution of sodium carbonate, and finally dried for twelve hours over anhydrous potassium carbonate. The solvent was removed and the bromide was distilled under diminished pressure. The yield was 62 g. (70.5%) of a product boiling at 165–170° (5 mm.) and having a rotation of +19.4° (0.7521 g. made up to 15 cc. in chloroform and used in a 1-dcm. tube). A 12-g. sample was fractionated to give 8 g. of hydnocarpyl bromide having the following constants: b. p., 156–157° (2 mm.); n_D^{25}, 1.4857; d_4^{25}, 1.0763; $[\alpha]_D$, +27.4° (0.7604 g. made up to 15 cc. in chloroform and used in a 1-dcm. tube). Further fractionation of the 8-g. sample did not cause any change in the constants. Sacks and Adams[6] report the following constants for hydnocarpyl bromide: b. p., 206–210° (14 mm.); m. p., 1°; n_D^{25}, 1.4871; $[\alpha]_D$, +40.0° (0.5859 g. made up to 15 cc. in chloroform and used in a 1-dcm. tube).

Monohydnocarpyl Diethyl Malonate.—The condensation of 50 g. of hydnocarpyl bromide with the sodium derivative of malonic ester was carried out in the usual way. The yield was 37 g. (59%) of a product having the following constants: b. p., 182–183° (2 mm.); n_D^{25}, 1.4601; d_4^{25}, 0.9519; $[\alpha]_D$, +25.6° (0.6717 g. made up to 15 cc. in chloroform and used in a 1-dcm. tube).

Anal. Subs., 0.3200: CO_2, 0.8506; H_2O, 0.3018. Calcd. for $C_{23}H_{40}O_4$: C, 72.57; H, 10.60. Found: C, 72.49; H, 10.48.

Hydnocarpylacetic Acid (Chaulmoogric Acid).—Without isolating the intermediate malonic acid, 27 g. of monohydnocarpyl diethyl malonate was hydrolyzed to the malonic acid and then converted to the corresponding monobasic acid by the usual procedure.[7] The yield was 18 g. (92%) of a product boiling at 184–186° (1.4 mm.), melting at 61° and having a rotation of +38.3°. By careful fractional crystallizations from 80% ethyl alcohol (ethyl acetate and petroleum ether were used once each to remove any trace of ethyl chaulmoograte which might be formed), impurities of lower-melting products were eliminated and the least soluble chaulmoogric acid obtained which melted at 68° and had a rotation of +54.2°. Cold chloroform was added (about 10 cc. per g. of acid) until about two-thirds of the solid acid dissolved on shaking for two or three minutes. The insoluble portion was filtered and the product obtained by evaporation of the filtrate was recrystallized from 80% ethyl alcohol. After a second similar treatment with chloroform, the product obtained in the filtrate had a melting-point of 68° and a rotation of +61.9° which did not change on further treatment. A mixed melting point with pure natural chaulmoogric acid showed no depression.

Fractions obtained during the crystallization of the synthetic chaulmoogric acid had a melting point as low as 59° and a rotation as low as +19.5°. Apparently small amounts of impurities, presumably acids, were converted in each step in the process in a similar manner to the hydnocarpic acid and were not so easily removed from the final product as might have been expected.

Anal. Subs., 0.3162, 0.1200: CO_2, 0.8965; H_2O, 0.3196; 4.25 cc. of 0.1007 *N* alcoholic NaOH. Calcd. for $C_{18}H_{22}O_2$: C, 77.07; H, 11.51; neut. equiv., 280.26. Found: C, 77.32; H, 11.23; neut. equiv., 280.3.

Chaulmoogramide.—The amide of the synthetic chaulmoogric acid was made by the method described by Aschan[8a] and later by Power and Gornall[8b] and also by the method described by Shriner and Adams.[4] The melting point was 104° and a mixed melting point with chaulmoogramide made from natural chaulmoogric acid showed no depression.

Summary

Hydnocarpylacetic acid was prepared from hydnocarpic acid through hydnocarpyl ester, hydnocarpyl alcohol, hydnocarpyl bromide, hydnocarpylmalonic ester, and hydnocarpylmalonic acid. It proved to be identical with natural chaulmoogric acid.

URBANA, ILLINOIS

---

[7] Adams, Stanley and Stearns, THIS JOURNAL, **50,** 1475 (1928).

[8] (a) Aschan, *Ber.*, **31**, 2344 (1898); (b) Power and Gornall, *J. Chem. Soc.*, **85,** 855 (1904).