[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, MASSACHUSETTS STATE COLLEGE]

Racemization of Chaulmoogric and Hydnocarpic Acids

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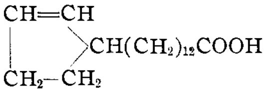
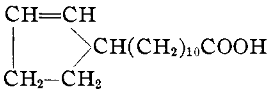
Chaulmoogric and hydnocarpic acids are optically active, occurring in nature, so far as known, only in the dextrorotatory form; chaulmoogric acid (I), $[\alpha]_D$ +62.2°, and hydnocarpic acid (II), $[\alpha]_D$ +68.3°.


I


II

Except for the clever synthesis of chaulmoogric acid and some of its derivatives by Perkins and Cruz,[1a] these acids and their derivatives have not previously been obtained in the optically inactive form. Attempts to racemize chaulmoogric acid have been unsuccessful. Thus prolonged heating in a closed tube to 250° with or without alkali did not affect the rotation[2] and repeated distillation of the acid or its derivatives causes no reduction in optical activity.

A comparatively easy method has been found for preparing the optically inactive nitriles of chaulmoogric and hydnocarpic acids and hence from these the optically inactive acids and other derivatives by the usual chemical reactions.

When the amide of chaulmoogric or hydnocarpic acid is mixed with phosphorus pentoxide and heated under a vacuum the nitrile which distils over is optically inactive. This optically inactive nitrile has been converted to the inactive acid and amide and in both cases the inactive forms were found to have melting points identical with the dextrorotatory forms and showed no appreciable depression or elevation in a mixed melting point as determined in an ordinary capillary melting point tube.

The nitrile prepared by dehydrating *d*-chaulmoogramide with thionyl chloride is dextrorotatory, $[\alpha]^{25}_D$ +55.2°, but if this nitrile is distilled from phosphorus pentoxide, the distillate is no longer optically active.

Chaulmoogric acid was not racemized, but destroyed, when attempts were made to distil it rapidly under vacuum from an intimate mixture with phosphorus pentoxide. Merely a drop or two of a green fluorescent liquid was obtained. Also the acid was not racemized when heated on the steam-bath with the trichloride, oxychloride or pentachloride of phosphorus nor even on heating to 150° with phosphorus pentachloride.

The mechanism of the racemization is not known. We could assume the formation of a weak addition product at the double bond by the phosphorus pentoxide and its subsequent breakdown as the cause for racemiza-

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(1) Present address 524 Sharrett Road, Princess Bay, S. I., N. Y.

(1a) Perkins and Cruz, THIS JOURNAL, **49**, 1070 (1927).

(2) Shriner and Adams, *ibid.*, **47**, 2727 (1925).

tion. However, Shriner and Adams[3] have shown that the chaulmoogric acid regenerated (maximum 22%), along with the isochaulmoogric acid, on removing hydrogen bromide from bromodihydrochaulmoogric acid is still dextrorotatory. There is no evidence here of a change similar to a Walden inversion which is frequently brought about by phosphorus compounds.

Besides chaulmoogric and hydnocarpic acids there are no commonly occurring optically active fatty acids which could be used to test further this method of racemization except those containing substituents affected by heating with phosphorus pentoxide.

The inactive chaulmoogric acid forms an apparently crystalline derivative with brucine and thus may offer a ready method for preparing l-chaulmoogric acid.

Experimental

The chaulmoogric and hydnocarpic acids used in this research were obtained from the mixed acids resulting from the hydrolysis of chaulmoogra oil by sodium hydroxide.[4]

The mixed acids were distilled under 4–5 mm. pressure following the method of Dean and Wrenshall.[5]

Hydnocarpic acid, m. p. 58–59°, $[\alpha]^{25}_{D}$ +68.0°, was obtained from the first and chaulmoogric acid, m. p. 68–68.5°, $[\alpha]^{25}_{D}$ +62.2°, from the third fraction using essentially the procedure of Adams and co-workers.[6]

***d*-Chaulmoogramide.**—This was prepared by Aschan's method which was used by Power,[7] first preparing a relatively pure chaulmoogryl chloride at 20–25° with phosphorus trichloride.[8] The crude amide melted at 106–107° and gave $[\alpha]^{25}_{D}$ +57.1°.

***dl*-Chaulmoogronitrile.**—Fifteen grams of powdered chaulmoogramide, dried in a vacuum over sulfuric acid, was mixed intimately with 6.5 g. of phosphorus pentoxide and rapidly heated in a metal bath to the temperature of distillation under 3–4 mm. pressure. The nitrile distilled at 158–164° as a colorless oil; yield 6.9 g., or 55%. If large quantities, requiring a longer time of heating, are used the yields are considerably smaller. Less phosphorus pentoxide allows some amide to distil with the nitrile.

To ensure complete removal of chaulmoogramide 21.0 g. of the nitrile was fractionally redistilled from 2.0 g. of phosphorus pentoxide at 2.5 mm. pressure. The middle fraction of 9.0 g. was collected at 155–158° and again redistilled, collecting 4.5 g. at 156–158° (2.5 mm. pressure); n^{25}_{D} 1.4692, d^{25}_{25} 0.8856. The nitrile was optically inactive.

Anal. (Kjeldahl) Calcd. for $C_{18}H_{31}N$: N, 5.36. Found: N, 5.28, 5.32.

Hydrolysis of *dl*-Chaulmoogronitrile.—Twenty-five grams of *dl*-chaulmoogronitrile boiling at 155–158° (2–3 mm.) was hydrolyzed by refluxing with excess aqueous alcoholic potassium hydroxide for thirty hours. The solution was diluted with water, extracted with ether to remove unchanged material and then acidified with dilute hydrochloric acid. The precipitated acid was taken up in ether, washed and the solution dried, after which the ether was removed and the acid distilled at 3–4 mm. pressure. The distillate solidified immediately to a white solid. This was crystallized twice from

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[3] Ref. 2, p. 2730.

[4] The mixed crude acids were kindly supplied by Drs. T. B. Johnson and R. J. Anderson of Yale University.

[5] Dean and Wrenshall, THIS JOURNAL, **42**, 2626 (1920).

[6] Sacks and Adams, *ibid.*, **48**, 2396 (1926).

[7] Power and Gornall, *J. Chem. Soc.*, **85**, 855 (1904).

[8] Hinegardner and Johnson, THIS JOURNAL, **51**, 1506 (1929).

80% alcohol and then twice from ethyl acetate, when pure white flakes were obtained which melted at 68.5°. The acid was optically inactive and showed no depression and apparently no elevation in a mixed melting point with chaulmoogric acid which melted at 68.5°. This behavior is similar to that of the synthetic *dl*-chaulmoogric acid obtained by Perkins and Cruz[9] though these investigators report a possible slight elevation in the mixed melting point.

Anal. Subs., 0.3096 g. requires 11.00 cc. of 0.1 *N* NaOH. Calcd. for $C_{18}H_{32}O_2$: neut. equiv., 280.3. Found: 280.9.

***dl*-Chaulmoogramide.**—One gram of the *dl*-chaulmoogric acid was converted into the amide by the method previously described. The amide was optically inactive and after one crystallization from alcohol melted at 106° and showed no depression in a mixed melting point with *d*-chaulmoogramide that melted at 105–106°.

***d*-Chaulmoogronitrile.**—Fifteen grams of *d*-chaulmoogramide and 15.0 g. of thionyl chloride in 50 cc. of dry benzene were refluxed for four hours. The benzene and excess thionyl chloride were distilled off under reduced pressure, the nitrile taken up in ether and the solution washed with sodium carbonate followed by water and dried. After removal of the ether 8.4 g. of nitrile remained which distilled at 5 mm. pressure as a colorless oil from which a fraction of 6.2 g. was collected at 176–178°. This fraction was redistilled at 3–4 mm. pressure where a 4.2 g. fraction distilled at 158–160°; n^{25}_{D} 1.4666, d^{25}_{25} 0.8820.

Optical Activity. Subs., 0.3001 g., made up to 10 cc. in chloroform gave a rotation of +1.656° in a 1-dm. tube; $[\alpha]^{25}_{D}$ +55.2°.

Anal. (Kjeldahl) Calcd. for $C_{18}H_{31}N$: N, 5.36. Found: N, 5.37.

Hydrolysis of *d*-Chaulmoogronitrile.—Eight grams of *d*-chaulmoogronitrile was hydrolyzed by the procedure used for the inactive nitrile. The acid melted at 67.5–68° and showed no depression in a mixed melting point with *d*-chaulmoogric acid, melting at 67.5–68°.

Optical Activity. Subs., 0.3172 g., made up to 10 cc. in chloroform gave a rotation of +1.950° in a 1-dm. tube; $[\alpha]^{25}_{D}$ +61.4°.

Distillation of *d*-Chaulmoogronitrile from Phosphorus Pentoxide.—6.2 g. of *d*-chaulmoogronitrile was mixed with 4.0 g. of phosphorus pentoxide and rapidly distilled at 3–4 mm. pressure; 2.6 g. of a practically colorless, optically inactive liquid distilled from the charred mass; n^{25}_{D} 1.4710. Due to the small quantity it was not hydrolyzed.

***d*-Hydnocarpamide.**—This was prepared by the procedure used for preparing chaulmoogramide; m. p. 111–112°, $[\alpha]^{25}_{D}$ +69.4°.

***dl*-Hydnocarponitrile.**—Six grams of the powdered and thoroughly dried amide was mixed with 3 g. of phosphorus pentoxide and rapidly heated under 2–3 mm. pressure when 1.9 g. of a colorless liquid distilled at 155–156°; n^{25}_{D} 1.4559; d^{25}_{25} 0.8580. The nitrile was optically inactive.

***dl*-Hydnocarpic Acid.**—Two grams of the inactive hydnocarponitrile was hydrolyzed as described for chaulmoogronitrile. After repeated crystallization from petroleum ether, the acid melted at 58.5–59° and showed no change in a mixed melting point with *d*-hydnocarpic acid. The acid was optically inactive.

Summary

1. The distillation of the amides of *d*-chaulmoogric and *d*-hydnocarpic acids with phosphorus pentoxide produces the corresponding *dl*-nitriles.

2. The *dl*-nitriles of chaulmoogric and hydnocarpic acids have been hydrolyzed to the corresponding optically inactive acids.

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[9] Perkins and Cruz, THIS JOURNAL, **49**, 1076 (1927).

3. *d*-Chaulmoogramide is converted into the *d*-chaulmoogronitrile by means of thionyl chloride.

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The Molecular Weight of Erythrocruorin

BY THE SVEDBERG AND INGA-BRITTA ERIKSSON

The stable native proteins so far studied in this Laboratory by means of the ultracentrifugal methods can with regard to molecular weight be divided into two large groups: the hemocyanins with molecular weights of the order of millions and all other proteins with molecular weights from about 35,000 to about 200,000. A few preliminary determinations which we had the opportunity to carry out some time ago on the respiratory protein chlorocruorin from the blood of the marine worms *Spirographis spallanzanii* and *Pomatoceros triqueter* indicated that chlorocruorin, like the hemocyanins, has a molecular weight of the order of millions. Unfortunately, owing to the difficulty of procuring enough material of this comparatively rare and very unstable protein, a complete investigation has not yet been possible.

The very high molecular weight of chlorocruorin shows that proteins of molecular mass of the order of millions are not restricted to the hemocyanins as was previously believed. The enormous weight, therefore, is not conditioned by the presence of the copper-containing active hemocyanin group in the protein molecule. As a working hypothesis we adopted the idea that a very high molecular weight might be a characteristic of the respiratory proteins dissolved in the blood of the invertebrates. From this point of view an ultracentrifugal study of the red respiratory pigment in solution in the blood of many invertebrates suggested itself. This protein has hitherto been considered as identical, or almost identical, with the hemoglobin in the erythrocytes of the blood of the vertebrates. As a matter of fact it closely resembles hemoglobin with regard to its absorption spectrum and its oxygen-binding capacity.[1] These two properties, however, are connected with the hemin group and not with the protein part of the molecule. It is not impossible that there might exist respiratory pigments resembling hemoglobin very closely as far as light absorption and oxygen-binding go but differing completely in the chemical and mass-properties of the molecule. A few preliminary runs on the red blood proteins of *Arenicola marina* and *Lumbricus terrestris* fully confirmed this supposition.[2] The molecular weight is of the order of millions and the

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[1] Barcroft, *Proc. Roy. Soc.* (London), **B96**, 28 (1924).

[2] Svedberg and Eriksson, *Nature*, **130**, 434 (1932).