possessing approximately equally acid and basic properties which remain in the center compartment.

2. The method of transport was found to be applicable to the preparation of arginine and lysine in relatively large quantities.

Berkeley, California

[Contribution from the Chemical Section, Culion Leper Colony, Philippine Health Service]

THE OXIDATION OF CHAULMOOGRIC ACID BY PERMANGANATE[1]

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Derivatives of the peculiar fatty acids of chaulmoogra oil are being used for the treatment of leprosy with marked success. Bacteriological experiments have shown that these fatty acids have a strong selective toxic and growth-inhibiting action on acid-fast bacteria, and we have reason to believe that this accounts in part for the clinical effects.

Neverthless, the curative effects of the medicines now in use leave much to be desired, and work is in progress in this Laboratory to prepare, if possible, compounds which will be more bactericidal, less toxic to the patient, and more readily diffusible to the bacteria *in situ*. Chaulmoogric acid was chosen as one of the starting points for this work, and its oxidation products were among the first derivatives studied.[2]

The oxidation of chaulmoogric acid by permanganate was studied by Power and Gornall[3] and by Barrowcliff and Power[4] in the course of an extensive pioneer investigation of the structure of this interesting acid. The present study covers a portion of the field in greater detail, dealing especially with the structure and properties of the glycols formed in the first step of the reaction.

The Structure of Chaulmoogric Acid

The question of the structure of chaulmoogric acid is also here involved, but unfortunately the results to date are not decisive on this point. For this reason publication has been deferred for some time. Recently, however, Shriner and Adams[5] have brought the subject to general attention and, therefore, the data at hand may be of interest.

From the work of Barrowcliff and Power[4] one of the courses of oxidation

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[1] Published with the permission of the Director of Health upon recommendation of the Philippine Leprosy Research Board.

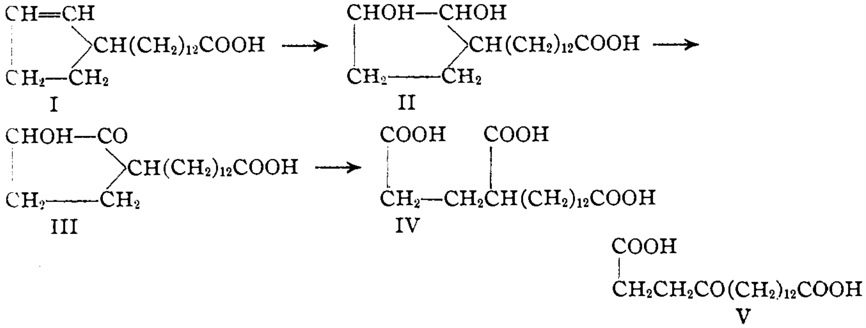
[2] The bacteriological testing of these products is being done by Dr. Otto Schöbl, Bureau of Science, Manila, and is to be reported in the *Philippine Journal of Science.*

[3] Power and Gornall, *J. Chem. Soc.*, **85**, 859 (1904).

[4] Barrowcliff and Power, *ibid.*, **91**, 557–8 (1907).

[5] Shriner and Adams, This Journal, **47**, 2727 (1925).

of chaulmoogric acid (I) appears clear. A dihydroxy-dihydrochaulmoogric acid (II) is formed, then an hydroxyketo-dihydrochaulmoogric acid (III), and eventually a tricarboxylic acid (IV). There is some doubt, however, concerning the origin of a keto-dicarboxylic acid (V), which is found among the products of oxidation in acetic acid solution.



The formation of the keto-dicarboxylic acid was explained by Barrowcliff and Power by the assumption of a second, tautomeric form of chaulmoogric acid in which the 1 and 3 carbon atoms of the ring are connected by a bridging bond. This explanation is so well reviewed and the theoretical objections to it are so well pointed out by Shriner and Adams[5] that the details need not be repeated here. The proposed tautomerism is without known parallel, either as to its causes or characteristics and, therefore, cannot be considered a satisfactory explanation of the experimental data.

In their investigation of the question Shriner and Adams obtained results which point definitely to Formula I for chaulmoogric acid. Their results invalidate that portion of Barrowcliff and Power's evidence for tautomerism which dealt with the addition of hydrobromic acid.[6] As for the keto-dicarboxylic acid (V), they propose the explanation that it is formed by the further oxidation of the dihydroxy acid (II). This explanation appears very reasonable in view of known analogous cases. A test experiment which suggests itself, however, is the oxidation of the pure dihydroxy acid. We have been unable to produce the keto-dicarboxylic acid in this manner.

[6] While congratulating Shriner and Adams on the clear cut results from the reactions reported by them, we nevertheless note that we have found some support, in preliminary experiments, for Barrowcliff and Power's postulate that two dihydrochaulmoogric acids are produced by their method. That is, although dihydrochaulmoogric acid as produced catalytically is a single, practically pure substance their method, through the hydrogen bromide addition product, does not give a pure product, even after complete reduction. As it is understood that another laboratory is investigating the field, work on this point has not been continued. In any event, abnormal addition or elimination of hydrobromic acid is so common that it could not be considered as evidence of tautomerism.

First-stage Oxidation Products

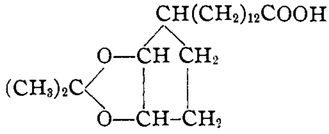
Barrowcliff and Power obtained dihydroxy-dihydrochaulmoogric acids, that is, glycols of chaulmoogric acid, by oxidation of the latter with somewhat more than twice the calculated quantity of permanganate in alkaline solution. The yields are not stated. In spite of improvements in the methods of separation and experimental variation of the conditions of oxidation, the writer has been unable to obtain more than 50% of the calculated yield.

The two glycols were isolated by several methods. It was found that the isomer more nearly corresponding to Barrowcliff and Power's α-dihydroxy-dihydrochaulmoogric acid, whether prepared by their method or otherwise, had a lower rotation ($[\alpha]_{\mathrm{D}}$, + 4.9°) and a slightly higher melting point (106°) than reported by these investigators ($[\alpha]_{\mathrm{D}}$, + 11.6°; m. p., 105°). This discrepancy is perhaps explainable by the observation that their method of separation of the isomers, namely, crystallization of the methyl esters, yields a product contaminated with a strongly rotating substance (ortho-acetone ether, see below) in case the methyl alcohol used contains acetone.

As for the other isomer, the fractional crystallization of the methyl esters (see experimental part; α-methyl ester) concentrates this in the most soluble portions, which were discarded by Barrowcliff and Power. The acid obtainable from these portions, and to which the designation β-dihydroxy-dihydrochaulmoogric acid is here applied, melts at 85° and shows $[\alpha]_{\mathrm{D}}$, —38.2°. The acid described by the previous investigators, m. p. 92–93°, $[\alpha]_{\mathrm{D}}$, —14.2°, was found to be a mixture, containing the alpha and beta isomers in nearly equal amounts. The two acids form a continuous series of mixed crystals from about this composition to that of the pure alpha isomer, and no evidence of a pseudo-racemic compound was found.

It is to be understood that alpha- and beta- are used here simply as arbitrary designations, and have no structural significance.

The glycols showed annoyingly inconsistent behavior in acetone solution. It was eventually found that in the presence of traces of mineral acid they react readily with acetone, giving products which are undoubtedly acetals, or more specifically, cyclic ethers of ortho-acetone (VI).



VI

The fact that the acetal from the β-glycol hydrolyzes more readily than that from the α-glycol was found to be useful in the separation of the isomers.

Furthermore, the acetals of the methyl esters can be separated by fractional crystallization much more sharply than the esters themselves.

According to the suggestion of Barrowcliff and Power one glycol (II) should give the tricarboxylic acid (IV) on oxidation, and the other (supposedly a 1,3-glycol) should give the keto-dicarboxylic acid (V). According to Shriner and Adams' explanation the glycols should be stereo-isomers (II), and each should give both the tricarboxylic acid (IV) and the keto-dicarboxylic acid (V) on oxidation. Experiment shows that they both yield practically pure tricarboxylic acid (IV). They may, therefore, be regarded as stereo-isomers, both having Formula II, but the keto-dicarboxylic acid (V) must be considered as arising from some other first-stage intermediate product as yet undiscovered.

Of the four stereo-isomeric glycols conceivably derivable from (*dextro*)-chaulmoogric acid we are led by the general behavior of permanganate to expect in this case only two, that is, those in which the hydroxyl groups have the *cis* relation to each other. The ready formation of acetals by the glycols in hand confirms their *cis* configuration[7] and incidentally the conclusion that the hydroxyl groups are on adjacent carbon atoms.

The search for a first-stage oxidation product which could be oxidized into the keto-dicarboxylic acid (V) was instituted among the by-products accompanying the glycols. These appear to be condensation products, however, and none of the fractions obtained from the oxidation of chaulmoogric acid in alkaline solution gave the keto-dicarboxylic acid on further oxidation. Oxidation in acetic acid solution offers a more promising field, but so far the required intermediate has not been isolated. While awaiting further evidence, the writer is inclined to the supposition that in the series of reactions in question the tertiary hydrogen atom is attacked before the double bond.

Further Oxidation

The methyl ester of a hydroxyketo-dihydrochaulmoogric acid (III), which gave on hydrolysis a dicarboxylic lactone, was reported by Barrowcliff and Power. Shriner and Adams and also the present writer have been unable to duplicate the conditions necessary for the isolation of the methyl ester, but a substance believed to be the lactone was found to occur as a by-product of the glycols when the reaction mixture was heated before removal of the manganese dioxide.

In the isolation of Power's tricarboxylic acid (IV) the distillation of the methyl esters was not found to be advantageous. The by-products can be removed by fractional crystallization of the methyl esters, but more efficiently by crystallization of the glycols after the first stage of the oxida-

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[7] Compare van Loon, who made the ortho-acetone ether of cyclopentane-(1,2)*cis*-diol, *Diss. Techn. Hoogeschool,* Delft, **1919**, p. 81; *C. A.*, **17**, 1956 (1923). Also Hermans, *Ber.*, **57B,** 824 (1924).

tion. Further oxidation of the crystallized mixed glycols yields nearly pure tricarboxylic acid.

The isolation of the keto-dicarboxylic acid (V) is facilitated by its low solubility in ether. Approximately 11% of the calculated yield was obtained from chaulmoogric acid.

Experimental Part

The chaulmoogric acid used was obtained from the oil of *Hydnocarpus alcalae*,[8] a Philippine seed. The fatty acids from this oil were recrystallized several times from alcohol, yielding practically pure chaulmoogric acid (m. p., 67–68°; $[\alpha]_D$, + 61°).

Preparation of the Mixed Dihydroxy Acids.—Seventy-five g. of potassium permanganate and 25 g. of potassium hydroxide were dissolved in 4 liters of water, and about 2 kg. of cracked ice was added. A cold solution of 100 g. of chaulmoogric acid and 25 g. of potassium hydroxide in 2 liters of water was then added during rapid stirring. Enough ice was present to keep the temperature at about 2°. The addition required about one minute.

Within a few minutes the oxidation was complete and the manganese dioxide began to form a gel. The whole was warmed to about 30° and filtered through folded filters. The sludge was washed twice with water, which was filtered off by suction.

Although filtration is facilitated by warming, it was found that excessive heating at this point destroys the dihydroxy acids, with the formation of non-crystalline substances and a crystalline substance (m. p., 94°) difficultly soluble in ether. The latter appears to be identical with the lactone (m. p., 90°) obtained by Barrowcliff and Power from the methyl ester of hydroxyketo-dihydrochaulmoogric acid.

The combined filtrates were treated with dil. hydrochloric acid, which precipitated the dihydroxy acids as a voluminous curd. The curd was separated, and warmed with 1 liter of benzene. After removal of most of the water in a separatory funnel the solution was cooled to about 10° overnight, and filtered with suction. The crystals were recrystallized thrice at about 10° from a mixture of 100 cc. of benzene and 50 cc. of ether. Evaporation of the benzene-ether filtrates gave a slight, further yield of crystalline product, which was purified and added to the main portion.

The crystalline product from the above procedure weighed 57 g.; $[\alpha]_D$, —21°. Of this about one-third is estimated to be α-dihydroxy-dihydrochaulmoogric acid and two-thirds the beta isomer.

In the filtrates about 37 g. of material was found variously divided, in different experiments, between the benzene filtrate and the benzene-ether filtrates. Petroleum ether extracted from the benzene-soluble portion about 1 g. of crystalline material evidently containing unchanged chaulmoogric acid. The remainder of the benzene-soluble fraction was indistinguishable from the portions recovered from the benzene-ether filtrates. They were light brown, sirupy, gradually becoming pasty at 25°, and evidently mixtures. Repeated attempts to isolate substances from these residues proved unsuccessful (except for the lactone previously mentioned, and small amounts of degradation products of low molecular weight).

Variations of the oxidation procedure were tried. Addition of the soap solution to the oxidizing mixture, as above described, gave as good results as any method. It is comparatively convenient and rapid, and has the

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[8] Perkins and Cruz, *Philippine J. Sci.*, **23**, 545, 562 (1923).

advantage that the mixture can be kept in non-viscous condition until the reaction is practically complete. Most of the experiments, however, were made in the more usual manner, by adding the oxidizing agent to the soap solution. Good results were obtained as follows:

One kg. of chaulmoogric acid was melted in 5 liters of hot water and a solution of 300 g. of potassium hydroxide stirred in. After cooling somewhat, the solution was diluted with 25 liters of water, and further cooled to 10° by direct addition of ice. An ice-cold solution of 500 g. of potassium permanganate in 30 liters of water was added gradually during two hours, the soap solution being meanwhile violently agitated by a mechanical stirrer and kept at 9–11° by the addition of ice.

This proportion (one half-part by weight) of permanganate, while one-third more than the calculated requirement, was found to be the minimum advisable. When less permanganate was used, considerable chaulmoogric acid could be recovered unchanged. When more permanganate was used the dihydroxy acids proved surprisingly resistant to it at low temperatures. Even with four times the calculated quantity of permanganate considerable quantities of dihydroxy acids were found in the reaction product.

The concentration of alkali affected the results somewhat. In nearly neutral solution (100 g. of chaulmoogric acid, 20 g. of potassium hydroxide, 50 g. of permanganate, 8 liters of water) the oxidation proceeded very rapidly, leaving about 16 g. of the chaulmoogric acid unoxidized. Only 17 g. of hydroxy acids ($[\alpha]_D$, —20°) was obtained in this case. A similar mixture with thrice as much permanganate gave traces of an acid identified with the keto-dicarboxylic acid produced by oxidation in acetic acid solution.

An excess of alkali tends to slow down the reaction and to increase the yield of dihydroxy acids. Too much alkali, however, prevents the oxidation of all the chaulmoogric acid, and interferes with filtration, by causing the manganese dioxide to remain gelatinous. The relative yield of alpha acid is considerably less in very strongly alkaline solutions. A strongly alkaline reacting mixture (100 g. of chaulmoogric acid, 200 g. of potassium hydroxide, 50 g. of potassium permanganate, 6 liters of water) gave about 37 g. of unchanged chaulmoogric acid, and 27 g. of mixed dihydroxy acids, $[\alpha]_D$ —28°.

Isolation of β-Dihydroxy-dihydrochaulmoogric Acid

The reaction product from 100 g. of chaulmoogric acid (either purified as above described, or simply crystallized once from 100 cc. of benzene and 50 cc. of ether) was dissolved in 100 cc. of boiling acetone. A few drops of concd. hydrochloric acid were added. Immediate and vigorous spontaneous boiling was noted. The solution was allowed to cool for a few minutes and 200 cc. of petroleum ether was then added. The mixture was washed, in a separatory funnel, thrice with 500cc. portions of water. The main part of the product remained in the upper clear petroleum ether solution. Between this and the aqueous layer a resinous (or sirupy) layer formed, the amount of which depended on the degree of previous purification of the sample in hand. This middle layer was again treated with acetone, hydrochloric acid, and petroleum ether, to remove any unchanged dihydroxy acid.

The combined clear petroleum ether solutions were shaken with 200 cc. of concd. hydrochloric acid in a 2-liter Erlenmeyer flask. Sufficient β-dihydroxy-dihydrochaulmoogric acid was precipitated within a few minutes to stabilize an emulsion of the whole. One hundred cc. of water was then added, and the emulsion was shaken occasionally during 48 hours.

One liter of water and 100 cc. of benzene were added. The crystalline product was filtered off with suction and washed with several liters of water. It was recrystallized from a mixture of 100 cc. of benzene with 50 cc. of ether and again washed with water; yield about 20 g.; m. p., 77°; $[\alpha]_D$, —35°.

The filtrates from the last two filtrations still contained about half of the beta acid and practically all of the alpha acid, both, for the most part, as ortho-acetone ethers.

After recovery of the alpha isomer in the form of its methyl ester (see below) a further yield of beta acid was obtained as follows. The alcoholic filtrates from the alpha isomer were treated with a slight excess of sodium hydroxide solution and warmed until a sample gave no turbidity when diluted with water. Water and dil. hydrochloric acid were added and the product was extracted with ether. The ether extract was treated with acetone, hydrochloric acid and petroleum ether as above described, except that half quantities were used. For the hydrolysis, 200 cc. of concd. hydrochloric acid was used, 24 hours being sufficient. The subsequent purification was performed as for the first crop; yield, 11 g.; m. p., 77°; $[\alpha]_D$, —33°.

The product of the above described process is nearly pure β-dihydroxy-dihydrochaulmoogric acid, with a molecule of water of crystallization. Further purification was effected by crystallization from ethyl acetate and then from chloroform, after which the melting point, 78°, was unchanged by further crystallization. Although the solvents used contained no more than traces of water, the product (see below, hydrate crystals), dried in air at 40°, was found to retain the molecule of water of crystallization.

Anal. Subs., 1.9506 g. (hydrate crystals) powdered and dried to constant weight in a vacuum desiccator: loss, 0.1077 g. Calcd. for $C_{18}H_{34}O_4 + H_2O$: 5.42. Found: 5.52.

Subs. (anhydrous), 0.1404: CO_2, 0.3558; H_2O, 0.1394. Calcd. for $C_{18}H_{34}O_4$: C, 68.7; H, 10.9. Found: C, 69.1; H, 11.1.

Subs., 0.5083 (anhydrous): 16.17 cc. of 0.1 *N* NaOH. Calcd. for $C_{18}H_{34}O_4$: equiv. wt., 314.3. Found: 314.3.

5.00 g. (hydrate crystals) in 50 cc. of alcohol (U.S.P.) solution, using a 2dcm. tube, gave α_D, —7.22°, whence $[\alpha]_D^{30}$, —36.1° for the hydrated form, and —38.2° for the anhydrous acid.

The hydrate crystals (colorless blades or needles) were found to be readily soluble in alcohol, less so in ether, chloroform, ethyl acetate, acetone and benzene, practically insoluble in water, petroleum ether or cold benzene. Recrystallization did not usually remove the molecule of firmly retained water. Dehydration was effected, however, by boiling the xylene solution, by heating the crystals near their melting point, or by powdering and leaving two weeks in a vacuum desiccator.

The anhydrous acid was found to be somewhat more soluble than the hydrate and crystallized in much smaller blades. Its solution, when exposed to the air, absorbed moisture, and deposited crystals of the hydrate. The anhydrous acid melts at 85°.

The solubilities of both forms are so close to those of the alpha isomer that separation of the isomers by crystallization alone is unsatisfactory, but a small amount of β-dihydroxy acid, in hydrate form, can be obtained pure by long continued, fractional crystallization of the crude reaction product from chloroform.

Ortho-acetone Ether.—β-Dihydroxy-dihydrochaulmoogric acid was dissolved in acetone, and a very little hydrochloric acid was added. The ortho-acetone ether crystallized on cooling. The same product resulted when the original crude mixture of dihydroxy acids (containing traces of mineral acid) was crystallized several times from acetone, the alpha isomer remaining in solution; m. p., 60°.

Anal. Subs., 0.8134: 23.04 cc. of 0.1 *N* NaOH. Calcd. for $C_{18}H_{32}O_4.C_3H_6$: equiv. wt., 354.3. Found: 353.1.

5.00 g. in 50 cc. alcohol solution, using a 2dcm. tube, gave α_D, —2.10°, whence $[\alpha]^{30}_D$, = —10.5°.

This substance is very soluble in most organic solvents, including benzene. It crystallizes in colorless leaflets from cold (about 10°) acetone, alcohol or ligroin or from petroleum ether, in which it is somewhat less soluble. Its solubility in petroleum ether affords a sharp separation from most of the oxidation products of chaulmoogric acid.

The ether is quite stable toward alkali, but is hydrolyzed readily by warming with mineral acid, especially when dissolved in alcohol. One part dissolved in petroleum ether and emulsified with ten parts of concd. hydrochloric acid is hydrolyzed almost completely within 24 hours at room temperature.

Methyl Ester.—Twenty g. of pure β-dihydroxy-dihydrochaulmoogric acid was treated overnight with 100 cc. of acetone-free methyl alcohol and 5 cc. of sulfuric acid. The ester was crystallized from alcohol and ethyl acetate, in both of which it is very soluble. It separated in colorless masses of a microcrystalline appearance; m. p., 55°.

Anal. Subs., 0.5151: 7.96 cc. of 0.2 *N* KOH. Calcd. for $C_{18}H_{33}O_4.CH_3$: equiv. wt., 328. Found: 324.

2.50 g. in 25 cc. of $CHCl_3$ solution, using a 2dcm. tube gave α_D, —6.86°, whence $[\alpha]^{30}_D$ = —34.3°.

This ester is very soluble in most organic solvents and moderately soluble in petroleum ether and ligroin.

Methyl Ester Ortho-acetone Ether.—The ester just described was treated with acetone and a small amount of hydrochloric acid. The product was extracted with ether and washed with water. It was found to be very soluble in the ordinary organic solvents, but crystallized well from a small amount of cold petroleum ether; m. p., 34.5°.

Anal. Subs., 0.8060: 10.86 cc. of 0.2 *N* KOH. Calcd. for $C_{18}H_{31}O_4.CH_3.C_3H_6$: equiv. wt., 368. Found: 370.

5.00 g. in 25 cc. of $CHCl_3$ solution, using a 2dcm. tube, gave α_D, —3.47°, whence $[\alpha]^{30}_D$ = —8.7°.

α-Dihydroxy-dihydrochaulmoogric Acid.—This acid was obtained from its methyl ester and from its methyl ester ortho-acetone ether.

Of these the latter compound is the more easily separated from the corresponding beta isomer.

Ten g. of the methyl ester ortho-acetone ether was boiled for half an hour with 100 cc. of alcohol and 50 cc. of concd. hydrochloric acid. The solution was then cooled and diluted with water. The precipitated ester was saponified in alcoholic alkali. The resulting acid was precipitated in crystalline condition by the addition of dil. hydrochloric acid. Small amounts of ortho-acetone ether and resinous by-products were removed by crystallization from a mixture of benzene and ether or from chloroform.

Further crystallization from chloroform or ethyl acetate did not change the melting point, 106°. The solubilities of α-dihydroxy-dihydrochaulmoogric acid were found to be similar to those of the beta isomer. It crystallizes in blades, without water of crystallization.

Anal. Subs., 0.8147: 26.01 cc. of 0.1 *N* NaOH. Calcd. for $C_{18}H_{34}O_4$: equiv. wt., 314.3. Found: 313.2.

Subs., 0.1559: CO_2, 0.3926; H_2O, 0.1549. Calcd. for $C_{18}H_{34}O_4$: C, 68.7; H, 10.9. Found: C, 68.7; H, 11.1.

5.00 g. in 50 cc. of alcohol solution, using a 2dcm. tube, gave α_D, +0.97°, whence $[\alpha]_D^{30} = +4.9°$.

ORTHO-ACETONE ETHER.—This can be made in the manner described for the corresponding β-isomer, but was more conveniently prepared by warming the methyl ester ortho-acetone ether with alcoholic alkali. If the mixture is kept cold during the subsequent acidification very little hydrolysis of the ether linkage occurs. The product was dissolved in five parts of benzene and the solution cooled (about 10°) and filtered. The residue from evaporation of the filtrate was crystallized twice from alcohol, then showing a melting point of 64°, unchanged by further crystallization from acetone.

Anal. Subs., 1.0142: 28.62 cc. of 0.1 *N* NaOH. Calcd. for $C_{18}H_{32}O_4.C_3H_6$: equiv. wt., 354.3. Found: 354.4.

Ten g. in 50 cc. of $CHCl_3$ solution, using a 2dcm. tube, gave α_D, +11.45°, whence $[\alpha]_D^{30} = +28.6°$.

This ether is very similar to the corresponding derivative of the β-dihydroxy- acid, but is hydrolyzed less readily. Cold concd. hydrochloric acid attacks it in petroleum ether solution only very slowly.

METHYL ESTER.—The mixed dihydroxy acids and by-products resulting from the oxidation of 1 kg. of chaulmoogric acid were crystallized from benzene. The crystals, drained but not dried, were dissolved in 1 liter of acetone-free methyl alcohol to which 20 cc. of sulfuric acid had been added, and the solution was warmed for one hour. The mixed esters were extracted with ether and washed with water and dil. potassium hydroxide solution. A small amount of acid extracted by the alkali was esterified and added again to the main portion of ester.

The washed and dried methyl ester (747 g., $[\alpha]_D$, —17.7°) was then fractionally crystallized from ethyl alcohol. At the start 2 liters of 55% alcohol was used, one fraction of crystals being obtained at room temperature and a second in the refrigerator. Further fractions were obtained after evaporation of some of the solvent. Each fraction was recrystallized several times, the first from successive portions of fresh alcohol of gradually increasing strength, and each of the others from the filtrates of the fraction above it in the series, according to the usual system for fractional crystallization. After 64 crystallizations the fractions were found to have the following weights, freezing points, and specific rotatory powers: (1) 25 g., 77.2°, +4.2°; (2) 24 g., 76.6°, +3.0°; (3) 28 g., 71.7°, —5.7°; (4) 98 g., 63°, —18°; (5) 169 g., 55°, —25°; (6) 116 g., 44°, —21°; (7) 74 g., 39°, —18°; (8) 208 g., 37°, —14°.

The freezing points were determined with thermometer bulb immersed in the ester. The specific rotatory powers were determined in alcoholic solution.

Fractions 6, 7, and 8 gave on hydrolysis β-dihydrochaulmoogric acid, nearly free from the isomeric acid, but contaminated with large amounts of non-crystalline by-products which were easily removed by crystallization from benzene and washing with ether. The intermediate fractions gave both alpha and beta isomers when subjected to the sharper processes of separation already described.

Fraction 1 had been crystallized thirteen times. During the last three crystallizations its freezing point rose only 0.5°. It was given a final crystallization from three volumes of pure methyl alcohol. Both the crystals and the evaporated filtrate showed a freezing point of 77.2°. From this fact, and because the acid obtained by hydrolysis proved identical with that resulting from entirely different methods of purification, this ester was considered to be pure, although its rotation was lower than that recorded in the literature. Its melting point, by the ordinary capillary-tube method, was 79°.

Anal. Subs., 0.5286: 8.23 cc. of 0.2 N KOH. Calcd. for $C_{18}H_{33}O_4.CH_3$: equiv. wt., 328. Found: 323.

Five g. in 25 cc. of $CHCl_3$ solution, using a 2dcm. tube, gave α_D, +1.63°, whence $[\alpha]_D^{30} = +4.1°$.

This ester is very soluble in most organic solvents, but can readily be crystallized from cold ligroin, methyl or ethyl alcohol. In the last two solvents it is less soluble than the β-methyl ester, but separation based on this fact is tedious. In contrast to the beta ester it crystallizes well, in colorless leaflets.

Methyl Ester Ortho-acetone Ether.—In the section describing the isolation of β-dihydroxy-dihydrochaulmoogric acid two filtrates were mentioned which contained the alpha isomer. These were evaporated and the combined residues warmed for one hour in a mixture of 50 cc. of methyl alcohol, 10 cc. of acetone and 2 cc. of sulfuric acid. The ester was extracted with ether, washed with water, and crystallized twice from 100 cc. of alcohol (10°); yield, 16 g.; m. p., 68°; $[\alpha]_D$, +26.5°. Further crystallization raised the melting point to 70°.

Anal. Subs., 0.5786: 7.88 cc. of 0.2 N KOH. Calcd. for $C_{18}H_{31}O_4.CH_3.C_3H_6$: equiv. wt., 368. Found: 367.

Ten g. in 50 cc. of $CHCl_3$ solution, using a 2dcm. tube, gave α_D, +11.03°, whence $[\alpha]_D^{30} = +27.6°$.

This ester-ether is very similar to the ester, but is in general less soluble. It crystallizes well, usually in colorless blades; a distinct form of short, thick prisms has also been observed. It can be separated rather sharply from the corresponding β-isomer by crystallization from alcohol.

Oxidation of Chaulmoogric Acid in Acetic Acid Solution

Twenty g. of chaulmoogric acid was dissolved in 300 cc. of warm 90% acetic acid in a 600cc. beaker, which was then placed in ice water. The solution was violently agitated by a mechanical stirrer and its temperature was maintained at 20–25° during the addition of 50 g. of powdered potassium permanganate, which required about one-half hour. Five minutes after all had been added the stirring was discontinued and the solution gradually decanted into a cylinder containing 30 cc. of water through which an excess of sulfur dioxide was constantly bubbling. The sediment of excess of potassium permanganate was not transferred to the cylinder, but was washed with a little acetic acid. The precipitated manganous salts were filtered off with suction and washed with acetic acid. The filtrate was reduced, by rapid distillation, to a volume of 100 cc., bumping being minimized by pieces of porous porcelain. It was then transferred (still hot) to a separatory funnel and shaken with 100 cc. each of hydrochloric acid and benzene. The benzene layer was washed with 50 cc. of warm, dil. hydrochloric acid and then twice with 50 cc. of warm water. The aqueous layer was again extracted with 50 cc. of warm benzene, which was then washed with the same solutions as the first extract. The combined benzene extracts were evaporated until the odor of benzene had disappeared, and the residue (still containing a little acetic acid) was dissolved in 100 cc. of ether. One hundred cc. of water was added, and the whole allowed to stand at about 10° overnight. The keto-dicarboxylic acid ($C_{17}H_{30}O_5$, Formula V), prepared in essentially the same way, but isolated in a different manner, by Barrowcliff and Power, crystallized and was filtered off by suction. The yield, in several experiments, varied from 2.7 to 3.4 g. After recrystallization by dissolving in acetic acid and adding ether and water, this melted at 126°; yield, 1.8–2.5 g.; m. p. of methyl ester, 67° (B. and P. 128°, methyl ester 66°).

Several methods for the separation of the tricarboxylic acid ($C_{18}H_{32}O_6$, Formula IV) were tried, of which the following was the least unsatisfactory.

The ether filtrate from the keto-dicarboxylic acid was evaporated, and the residue (16.8 g.) dissolved in 50 cc. of warm alcohol. Four-tenths of the solution was neutralized by alcoholic potassium hydroxide solution, the remainder added, and the whole made up to 100 cc. The solution was left for 20 hours at about 10° for the monopotassium salt to precipitate. The salt was filtered off (15.1 g.) and warmed with 5 cc. of sulfuric acid and 50 cc. of methyl alcohol for one hour. The ester was extracted with ether, washed with water and then with dil. alkali. A small amount of acid extracted by the alkali was esterified and added. The combined ester (14.4 g.) was dissolved in 200 cc. of petroleum ether and the solution cleared with decolorizing carbon. The solution was evaporated to 30 cc. and cooled on ice. The solid was crystallized four more times from petroleum ether, then twice from 50 cc. of 90% methyl alcohol, and twice again from petroleum ether. Second crops from the filtrates were treated in a similar manner, seven fractions being eventually obtained, of amounts and freezing points as follows: 1, 3.2 g., 35.6°; 2, 1.85 g., 35.1°; 3, 1.15 g., 33.7°; 4, 0.5 g., 29°; 5, 0.85 g., 27°; 6, 0.45 g., 26°; 7, 2.9 g., pasty at 0°.

Fractions 1 to 6 evidently consisted essentially of a single ester, in various degrees of purity. Working in a similar manner with larger quantities a sample of freezing point, 38.0°, was obtained (m. p. by capillary-tube method, 39.5°). This was found to be identical with the methyl ester (m. p. given as 38.5°) of Barrowcliff and Power's tricarboxylic acid, a sample of which was isolated in the manner described by them.

Fraction 7 showed characteristics similar to those of the non-crystalline by-products encountered in the first stage of the oxidation, and evidently was produced from them, since the crystalline products of the first stage give nearly pure tricarboxylic acid (see below).

Oxidation of the Dihydroxy-dihydrochaulmoogric Acids in Acetic Acid Solution

Twenty-two and four-tenths g. of β-dihydroxy-dihydrochaulmoogric acid was oxidized with 42.5 g. of permanganate in exactly the same manner as that described in the preceding section. The ether solution, prepared as before, gave no trace of keto-dicarboxylic acid even after seeding and long standing on ice.

The product was esterified without purification through the potassium salt or in any other way beyond the usual washing of the ester with water and alkali. The crude ester showed a freezing point of 34.9°. After a single crystallization from 100 cc. of petroleum ether the product (17.7 g.) had a freezing point of 36.5°, 0.9° higher than the tediously purified product, 3.2 g., of the preceding section.

α-Dihydroxy-dihydrochaulmoogric acid was oxidized in the same way with the same results. No trace of keto-dicarboxylic acid could be found, and the crude methyl ester had a freezing point of 35.1°, rising to 36.2° on a single crystallization.

The mixed dihydroxy acids obtained by purifying the original reaction product with benzene and ether (as described in the first section of the experimental part) were oxidized in the same way. No keto-dicarboxylic acid was found, and the crude methyl ester had a freezing point of 33°.

The fractions of by-products of the first-stage oxidation soluble in benzene and soluble in benzene-ether were separately oxidized. Very little permanganate was consumed, and no keto-dicarboxylic acid was found. The methyl esters were pasty at 10°.

The small portion of first-stage by-products soluble in petroleum ether reduced permanaganate in acetic acid solution, and gave a little keto-dicarboxylic acid. This was accounted for, however, by its estimated content of unchanged chaulmoogric acid.

Summary

1. In the course of research aiming to improve the *matériel* for the treatment of leprosy the first-stage products of the oxidation of chaulmoogric acid by permanganate in alkaline solution have been studied.

2. α-Dihydroxy-dihydrochaulmoogric acid ($[\alpha]_D^{30} = +4.9°$; m. p., 106°) has been obtained in condition believed to be purer than that of samples previously described by other investigators.

3. The β-dihydroxy-dihydrochaulmoogric acid previously described has been found to be a mixture containing the alpha isomer as well as another ($[\alpha]_D^{30} = -38.2°$; m. p., 85°) to which the designation of β-dihydroxy-dihydrochaulmoogric acid is here applied.

4. These two acids are stereo-isomers, both giving the same tricarboxylic acid on oxidation. They are presumably ω-2,3-dihydroxycyclopentane-tridecylic acid. In each stereo-isomer the hydroxyl groups have a *cis* relation to each other.

5. Ortho-acetone ethers of the dihydroxy acids have been prepared, and the properties of these have been found useful in the separation of the isomers.

6. n-Pentadecane-γ-keto-α,α'-dicarboxylic acid, a product of the oxidation of chaulmoogric acid in acetic acid solution, was not produced when the dihydroxy acids were oxidized in the same manner.

7. No first-stage oxidation product leading to the keto-dicarboxylic acid was isolated, and the origin of the latter remains an interesting question.

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