κ-Cyclopentyl-undecano-amide; m. p., 114–115° (corr.). A mixed melting point with dihydrohydnocarpamide showed no depression.

Summary

1. μ-Cyclopentyl-tridecanoic acid and κ-cyclopentyl-undecanoic acid have been synthesized and shown to be identical with dihydrochaulmoogric and dihydrohydnocarpic acids, respectively.

2. The amides of these synthesized acids were prepared and shown to be identical with the amides of dihydrochaulmoogric and dihydrohydnocarpic acids.

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

THE SYNTHESIS OF HOMOLOGS OF DIHYDROCHAULMOOGRIC AND DIHYDROHYDNOCARPIC ACIDS CONTAINING A CYCLOHEXYL IN PLACE OF A CYCLOPENTYL GROUP. III

BY G. S. HIERS[1] WITH ROGER ADAMS

RECEIVED JANUARY 18, 1926 PUBLISHED APRIL 5, 1926

The investigations of Dean and Wrenshall[2] have shown that ethyl dihydrochaulmoograte can be effectively used in the treatment of leprosy. Although the number of clinical cases tested was small, the results indicated that ethyl dihydrochaulmoograte was not far behind the ethyl esters of the mixed acids of chaulmoogra oil in effectiveness. Moreover, the former has the distinct advantage of not causing local irritation upon injection. It has been shown[3] that sodium dihydrochaulmoograte and sodium dihydrohydnocarpate are bactericidal toward *lepra* bacillus when tested *in vitro*, though relatively much less effective than the corresponding unsaturated compounds.

Since the straight-chained saturated and unsaturated aliphatic acids are not effective toward *lepra* bacillus but the dihydrochaulmoogric and dihydrohydnocarpic acids are effective, it may be concluded that the ring structure is at least one of the important groupings in the molecule and that the double bond which appears in chaulmoogric and hydnocarpic acids is not absolutely necessary, but merely enhances the effectiveness.[2b] The object of this research was to build up acids homologous to dihydrochaulmoogric and dihydrohydnocarpic acids containing a cyclohexyl ring in place of the cyclopentyl ring and to determine their effectiveness toward *lepra* bacillus.

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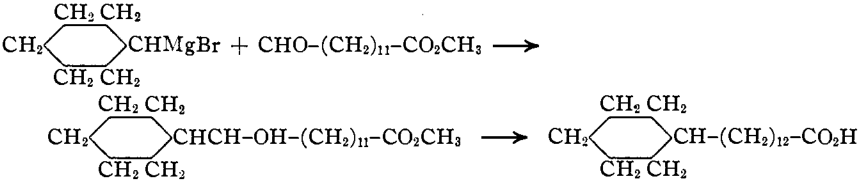
[1] This communication is an abstract of a portion of a thesis submitted by G. S. Hiers in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] (a) Dean and Wrenshall, *U. S. Pub. Health Bull.*, **141**, 7 (1924). (b) See also Schöbl, *Philippine J. Sci.*, **25**, 123, 135 (1924).

[3] Unpublished results from this Laboratory.

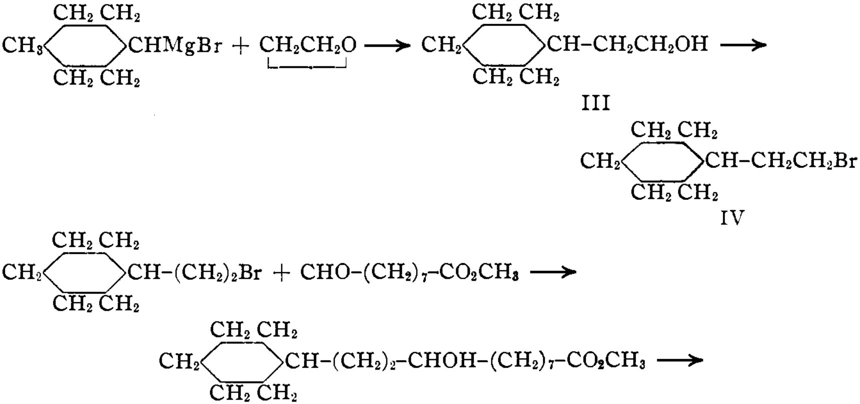
The synthesis of these homologs has been carried out in a somewhat similar manner to that for the synthesis of dihydrochaulmoogric and dihydrohydnocarpic acids[4] described in a previous paper.

Cyclohexylmagnesium bromide was condensed with methyl λ-aldehydododecanoate. The hydroxy ester, methyl μ-cyclohexyl-μ-hydroxy-tridecanoate I thus produced was reduced to the saturated acid μ-cyclohexyltridecanoic acid II through the corresponding bromide and olefinic acid.


I II

The yield of hydroxy ester was about 18% of the calculated amount, a much more satisfactory result than was obtained when cyclopentylmagnesium bromide was used. The by-products, which consisted of a low-boiling and a high-boiling fraction,[4] were not studied, but undoubtedly contained alcohol ester and perhaps the corresponding pinacol formed by the reduction of the aldehyde ester.

To prepare the corresponding homolog to dihydrohydnocarpic acid, cyclohexylmagnesium bromide was converted to cyclohexyl-ethanol III by the action of ethylene oxide. This in turn was converted to the bromide IV and the Grignard reagent and then condensed with methyl η-aldehydo-octanoate. The resulting hydroxy ester, methyl κ-cyclohexyl-θ-hydroxy-undecanoate V was obtained in 26% yields and was then converted by the method previously described through the bromide and olefinic acid into the saturated acid, κ-cyclohexyl-undecanoic acid VI.


III
IV
V

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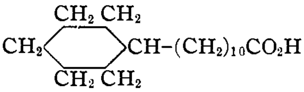
[4] Noller with Adams, This Journal, **48,** 1080 (1926).



VI

Other acids of a similar character but with side chains of various lengths are now being synthesized.

Experimental Part

β-Cyclohexyl-ethanol, $C_6H_{11}CH_2CH_2OH$.—The Grignard reagent from 24.3 g. (1 mole) of magnesium and 163 g. of cyclohexyl bromide was made in dry ether, then diluted with dry ether to a volume of about 1 liter, cooled to —5°, and to it 70 g. (1.6 moles) of condensed ethylene oxide was added during about one hour through a 5mm. tube, the end of which was 20 mm. above the surface of the liquid. After an hour of refluxing, 330 cc. of ether was distilled, 330 cc. of dry benzene added and the distillation of more solvent continued until the temperature of the distilling vapors reached 66°. The mixture was then refluxed for another hour, cooled to 40° and then decomposed with ice water and 30% sulfuric acid. The benzene layer was separated and the aqueous portion extracted twice with ether. After the liquid had been dried and the solvents removed, the product was distilled under diminished pressure. It boiled at 98–101° (10 mm.), or 86–89° (5 mm.); n_D^{25}, 1.4698; d_{25}^{25}, 0.9165; yield, 56 g., or 53%. It is obviously the same product as that obtained by Zelinsky[5] by the action of cyclohexylmethylmagnesium bromide and paraformaldehyde.

Variation in the size of the run apparently made some difference in the temperature of the rearrangement. In a run doubling the quantities mentioned above, the reaction mixture became viscous when the temperature of the vapors reached 44°; yield, 44%.

β-Cyclohexyl-ethyl Bromide, $C_6H_{11}CH_2CH_2Br$.—A mixture of 32.5 g. (0.25 mole) of β-cyclohexyl-ethanol, 29 g. of concd. sulfuric acid and 135 g. of 40% hydrobromic acid was refluxed for four hours. Upon diluting with water, the bromide separated. It was washed with several portions of cold concd. sulfuric acid and with water, dried with calcium chloride and distilled; yield, 31 g., or 65%. It boiled when pure at 70–71 (6 mm.); n_D^{25}, 1.4888; d_{25}^{25}, 1.2069.

Anal. Subs., 0.1280: 13.27 cc. of 0.05018 *N* $AgNO_3$. Calcd. for $C_8H_{15}Br$: Br, 41.83. Found: 41.58.

κ-Cyclohexyl-θ-hydroxy-undecanoic Acid.—The Grignard reagent was made from 9.72 g. of magnesium, 76.4 g. of β-cyclohexyl-ethyl bromide and 300 cc. of dry ether. A solution of 55.8 g. of methyl η-aldehydo-octanoate[4] in 300 cc. of dry ether was cooled to —5° and then during mechanical stirring the Grignard solution was added through a separatory funnel over a period of 45 minutes. Stirring was continued for an hour and the product allowed to remain for two hours. The ether was decanted from the solid residue and the latter decomposed with 600 cc. of a 20% ammonium chloride solution. After standing for some time and warming on a steam cone, the decomposition was completed with a little hydrochloric acid. After several extractions with ether, the ether extracts were washed with dil. hydrochloric acid and then dried over magnesium sulfate. The product, methyl-κ-cyclohexyl-θ-hydroxy-undecanoate V was fractionally distilled, yielding 23 g. (26%) of a product boiling at 192–198° (4 mm.). It solidified on cooling and a small portion purified from low-boiling petroleum ether melted at 35–36°.

This ester was saponified by refluxing for two hours with an excess of an aqueous alcoholic potassium hydroxide solution. Dilution with water and acidification with

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[5] Zelinsky, *Ber.*, **41,** 2628 (1908).

hydrochloric acid yielded the hydroxy acid. When purified from acetone it formed white crystals melting at 76–77°.

Anal. Subs., 0.1274 g.: 4.83 cc. of 0.0930 *N* NaOH. Subs., 0.1151 g.: CO_2, 0.3011; H_2O, 0.1148. Calcd. for $C_{17}H_{32}O_3$: C, 71.76; H, 11.35; mol. wt., 284.2. Found: C, 71.33; N, 11.19; mol. wt., 283.6.

κ-Cyclohexyl-undecanoic Acid, VI.—A mixture of methyl κ-cyclohexyl-θ-hydroxy-undecanoate with twice the calculated quantity of phosphorus tribromide was allowed to stand at room temperature for an hour, then heated for several hours on a steam-bath. The reaction mixture was cooled, added to water, then extracted with ether. After the ether extract had been washed with dil. sodium carbonate and dried, the solvent was distilled and an oily bromide resulted.

The crude bromide was dissolved in alcohol and refluxed with strong alcoholic potassium hydroxide solution for several hours. Part of the alcohol was then distilled, and water was added, then dil. hydrochloric acid. An oil formed and was separated and the aqueous portions were extracted thrice with ether. When this was dried with magnesium sulfate and the solvent evaporated, a reddish oil consisting of olefinic acids resulted.

This unsaturated product was dissolved in alcohol, treated with platinum oxide (0.2 g. of platinum oxide for 10 g. of unsaturated acid) and reduced with hydrogen under 2 to 3 atmospheres pressure.[6] The reduction went very rapidly (one to two minutes) and the platinum black was then filtered off. Part of the alcohol was distilled, water added and the resulting mixture extracted several times with ether. From the dried ether solution was obtained a white solid, the κ-cyclohexyl-undecanoic acid. After several crystallizations from 70% alcohol the κ-cyclohexyl-undecanoic acid was pure and formed white crystals melting at 58–59°.

Anal. Subs., 0.1309: 5.27 cc. of 0.0930 *N* NaOH. Subs., 0.1131: CO_2, 0.3144; H_2O, 0.1203. Calcd. for $C_{17}H_{32}O_2$: mol. wt., 268.2; C, 76.02; H, 12.02. Found: mol. wt., 267.1; C, 75.82; H, 11.90.

μ-Cyclohexyl-μ-hydroxy-tridecanoic Acid.—Following the procedure given in the preparation of methyl κ-cyclohexyl-θ-hydroxy-undecanoate, 72.6 g. of methyl λ-aldehydo-dodecanoate[4] in 400 cc. of dry ether was allowed to react with the calculated amount of cyclohexylmagnesium bromide. The crude product after three fractional distillations yielded 13.5 g. of methyl μ-cyclohexyl-μ-hydroxy-tridecanoate I boiling at 212–217° (4 mm.). It did not solidify on cooling in an ice-bath.

The ester thus obtained was refluxed for two hours with aqueous alcoholic potassium hydroxide and then part of the alcohol was distilled. The resulting liquid was added to water, the solution acidified with hydrochloric acid and the solid organic acid separated. After several crystallizations from acetone it gave white crystals; m. p., 72–73°.

Anal. Subs., 0.1427: 4.94 cc. of 0.0930 *N* NaOH. Subs., 0.1038: CO_2, 0.2760; H_2O, 0.1092. Calcd. for $C_{19}H_{36}O_3$: C, 73.01; H, 11.62; mol. wt., 312.3. Found: C, 72.51; H, 11.99; mol. wt., 310.6.

μ-Cyclohexyl-tridecanoic Acid, II.—This acid was made from methyl μ-cyclohexyl-μ-hydroxy-tridecanoate in a similar manner to the preparation of κ-cyclohexyl-undecanoic acid from methyl κ-cyclohexyl-θ-hydroxy-undecanoate. The μ-cyclohexyl-tridecanoic acid was purified from 80% alcohol and formed white crystals; m. p., 63–64°.

Anal. Subs., 0.1507, 0.1117: 5.44 cc. of 0.0930 *N* NaOH; CO_2, 0.3157; H_2O,

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[6] Kern and Shriner with **Adams**, THIS JOURNAL, **47**, 1147 (1925).

0.1223. Calcd. for $C_{19}H_{36}O_2$: mol. wt., 296.3; C, 76.95; H, 12.24. Found: mol. wt., 297.9; C, 77.08; H, 12.25.

Summary

The syntheses of κ-cyclohexyl-undecanoic acid and μ-cyclohexyl-tridecanoic acid have been completed. These acids are homologs of dihydrochaulmoogric and dihydrohydnocarpic acids in which the cyclohexyl group has replaced the cyclopentyl group.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

THE PREPARATION OF ORTHO-PHTHALALDEHYDIC ACID

BY REYNOLD C. FUSON[1]

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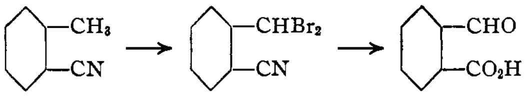
In connection with the preparation of certain substituted phenylparaconic acids used in a study of the structure of naphthalene[2] it was necessary to prepare considerable quantities of *o*-phthalaldehydic acid. Although several methods for the preparation of this compound are given in the literature none of them proved to be entirely satisfactory for its preparation in the desired quantity. It was, therefore, decided to study the various methods and to try to develop a procedure which would give satisfactory and consistent results. This paper is a report of the results of this study and comprises not only improved directions for the preparation of *o*-phthalaldehydic acid but also certain theoretical points of interest in connection with the preparation.

In the first method to be tried *o*-tolunitrile was the starting material. This was converted into the *o*-cyanobenzal bromide (I) by bromination and from the latter compound *o*-phthalaldehydic acid (II) was formed by hydrolysis. The synthesis is represented by the following scheme.



I II

The method proved to be unsatisfactory because of the great difficulty encountered in introducing the second bromine atom into *o*-tolunitrile. The yields were small and the preparation of *o*-phthalaldehydic acid in this way was abandoned.

Gilliard, Monnet and Cartier[3] prepared the compound from phthalonic acid obtained by oxidation of naphthalene with potassium permanganate. The directions for this procedure, which are to be found only in the patent

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[1] National Research Fellow in Chemistry.

[2] Fuson, THIS JOURNAL, **46,** 2784 (1924); **47,** 516 (1925).

[3] Gilliard, Monnet and Cartier, Ger. pat. 97,241 (1897). See also Friedländer, "Fortschritte der Teerfarbenfabrikation," **5,** 139 (1897–1900).