[CONTRIBUTION FROM THE CHEMICAL SECTION, CULION LEPER COLONY, PHILIPPINE HEALTH SERVICE][1]

SYNTHESIS OF COMPOUNDS SIMILAR TO CHAULMOOGRIC ACID. I

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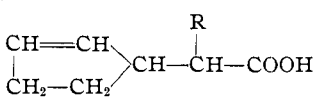
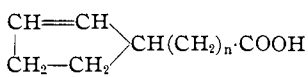
Bacteriological tests[2] have shown that the remarkable activity of the Δ^2-cyclopentenyl group in chaulmoogric acid against the bacillus of tuberculosis *in vitro* is readily reduced or destroyed by certain changes in this group involving the double bond. One change has been found (addition of two hydroxyl groups) which does not markedly reduce the activity, but on the whole the indications are in favor of allowing the double bond to remain unchanged, in seeking to improve the chaulmoogric acid molecule for medicinal purposes. On the other hand, the superiority of hydnocarpic acid over chaulmoogric acid, as indicated by bacteriological tests, renders desirable the preparation and testing of Δ^2-cyclopentene fatty acids of lower molecular weight.

Of these acids one, Δ^2-cyclopentene-acetic acid, was synthesized by J. F. Eykman[3] by the malonic ester process, for the purpose of refractometric study. In the present investigation the introduction of *two* radicals into malonic ester has been applied to the preparation of various Δ^2-cyclopentene fatty acids, including bis-Δ^2-cyclopentene-acetic acid. From the nature of the synthesis, the products have the general formula I, in which the cyclopentenyl group is in the alpha position. The synthesis of the ω-substituted series (II), which includes chaulmoogric acid, has been found more difficult, but an aceto-acetic ester synthesis through the keto acids is now giving us encouraging results, which will be reported in a later paper.



I



II

Eykman condensed sodio-malonic ester in alcoholic solution with chlorocyclopentene. The latter substance, obtained directly from the

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[2] These were made by Dr. Otto Schöbl of the Bureau of Science, Manila, and are to be reported in the *Philippine Journal of Science*. For descriptions of the compounds tested see Perkins, THIS JOURNAL, **48**, 1714 (1926), and the literature cited therein.

[3] Eykman, *Chem. Weekblad*, **6**, 702 (1909); see Eijman, *Chem. Zentr.*, **80** [II], 2147 (1909). A paper [Noller with Adams, THIS JOURNAL, **48**, 2444 (1926)] has come to our attention since our work was completed in which the condensation was performed at a low temperature, excellent yields being obtained.

coal-tar crude, cyclopentadiene, and hydrogen chloride, is an excellent starting material for the synthesis of Δ^2-cyclopentenyl compounds. Its extraordinary reactivity renders unusual precautions necessary in its preparation and handling, but by certain simple modifications of the older methods[4] we have been able to prepare it conveniently and keep it for some time.

We found that in alcoholic solution a considerable portion of the chloride reacted with the sodium ethylate present rather than with the sodiomalonic ester. Therefore, toluene was chosen as a solvent, and powdered sodium was used instead of sodium ethylate. Fair yields of various disubstituted malonic esters were thus obtained.

These disubstituted malonic esters were readily saponified by alcoholic potassium hydroxide to the monopotassium salts, but complete saponification was much more difficult. Heating with concentrated alkali for a relatively short time at a high temperature produced the best results. Small amounts of amyl alcohol, water or glycerol were used as solvents.

The disubstituted malonic acids were found to crystallize well, and to be quite stable when pure, although some samples, allowed to remain in impure condition, gradually became converted into viscous liquids. When heated above their melting points they evolved carbon dioxide and gave α-Δ^2-cyclopentene fatty acids (I). Preliminary reports of the bacteriological tests[2] indicate that some members of this series will be found suitable for clinical tests in cases of leprosy.

Experimental Part

Dicyclopentadiene.—A low-boiling fraction of crude benzol forerunnings,[5] which had aged more than a month, was distilled in 10-liter portions through a fractionating column. When the distillation slackened (at about 55°) steam was passed into the liquid. The portion distilling with steam at 95–98° was separated and dried; yield, 20% by volume.

This crude dicyclopentadiene was a semi-solid at 20°. Repeated melting, freezing and draining gave crystals melting as high as 32.7°, but for the purpose of preparing cyclopentadiene no advantage was found to result from this purification.

Δ^2-Chlorocyclopentene.—Crude dicyclopentadiene was boiled with iron turnings in a flask fitted with a fractionating column and a glass-worm condenser cooled with ice water. A thermometer in the top of the column registered 40–42°. To avoid repolymerization[6] as well as loss of the cyclopentadiene, it was received in an approximately equal amount of weighed toluene, kept at about 0°. Usually an amount of

[4] Kraemer and Spilker, *Ber.*, **29**, 552 (1896). Noeldechen, *Ber.*, **33**, 3348 (1900).

[5] This material is apparently not a commercial product in the United States or Germany. We were unable to obtain any until the United States Steel Corporation generously prepared and donated an ample supply for the investigation. The fraction furnished was essentially a mixture of hydrocarbons containing five carbon atoms in the molecule, and was evidently cut at 35–50° or closer.

[6] In five and one-half hours, 8% is polymerized at 20° [Stobbe and Reuss, *Ann.*, **391**, 151 (1912)].

dimer was taken considerably larger than the amount of distillate desired, and the residue reserved for the next distillation. The proportion of finally undistillable residue was very small.

The toluene solution of cyclopentadiene, still cooled with salt and ice, was treated with dry hydrogen chloride gas. Absorption was rapid and the liquid remained nearly colorless until the weight showed an absorption of one molecular equivalent. If the passage of gas is continued beyond this point, further absorption occurs slowly, resulting in a strongly-fuming, dark purple product, changing to brown in the presence of moisture. For the purposes of this investigation a slight excess of cyclopentadiene was harmless, but an excess of acid was avoided.

The nearly colorless toluene solution of chlorocyclopentene was either used immediately or diluted with petroleum ether. A 2 *M* solution in the latter solvent may be kept several weeks in a desiccator charged with solid caustic alkali. It was found inadvisable to isolate the pure chloride on account of its extreme susceptibility to the action of the atmosphere.

Samples of the toluene solution distilled with negligible residue even at atmospheric pressure, the temperature rising to about 125°. Difficulty in vacuum distillation previously reported[4] was probably due to the addition of too much hydrochloric acid.

Δ^2-Cyclopentene-malonic Acid.—Twenty-three g. of sodium was melted in 100 cc. of toluene and powdered by violent shaking. One hundred and sixty g. of ethyl malonate (b. p., 90–100°, at 20 mm.) in 500 cc. of toluene was slowly added, with agitation. The mixture was allowed to stand about an hour and then a solution was added which contained, according to calculation, slightly more than one mole of chlorocyclopentene. A drop of the mixture was added to a few drops of alcohol containing phenolphthalein. Chlorocyclopentene is so active that in alcoholic solution it rapidly neutralizes alkali. Therefore, if the color produced did not rapidly disappear, more chloride solution was added to the reaction mixture until a slight excess was found to be present. The mixture was then warmed for a few hours, until a sample no longer colored phenolphthalein test paper.

The product was washed with water, the toluene distilled off and the residue fractionated at 20 mm. One hundred and twenty-eight g. distilled between 145° and 148°. Eykman[3] records 141°, at 16 mm., for the pure ester.

No difficulty was encountered in preparing the malonic and acetic acids from this ester as described by Eykman. The malonic acid is very soluble in water but easily extracted from it by ether. It crystallizes well from benzene containing a little ether. Tested by the Hanus method it showed an iodine number of 147; calculated, 149.

Disubstituted Malonic Esters and Acids.—The following general method was found satisfactory for the preparation of the disubstituted esters mentioned in this paper.

Ethyl malonate in toluene was treated with sodium and chlorocyclopentene as described in the preceding section. Without isolation of the product the reaction mixture was treated with a second equivalent of powdered sodium. The solution was warmed, with occasional shaking, for one or two hours, until the sodium was practically all dissolved. A slight excess of the second halide was then added and the mixture was kept at about 90° until no longer alkaline to phenolphthalein. The sodium halide was removed by washing with water, and the toluene by distillation to a temperature of about 170° (thermometer in liquid). The residue was either purified by fractionation in a vacuum or hydrolyzed to the disubstituted malonic acid, which was purified by crystallization. Water was found to be a good solvent for this crystallization, since it did not dissolve the tarry impurities, and it retained any accompanying monosubstituted malonic acids.

The solubility of the malonic acids in water was found to decrease in general with increase of molecular weight. Cyclopentene-malonic acid is very soluble in water; its ethyl derivative requires about 10 parts of boiling water for solution, and its butyl derivative about 50 parts. The solubility in benzene increases with the molecular weight, cyclopentene-malonic acid being practically insoluble and its butyl derivative readily soluble in hot benzene; bis-cyclopentene-malonic acid, however, is only slightly soluble in hot benzene.

The melting temperature of these acids is dependent upon the rate of heating, due to the accompanying decomposition. The data reported were obtained by heating at a rate of about 6° per minute.

In the titration of the malonic acids, phenolphthalein did not give a sharp endpoint. Thymolphthalein was found satisfactory.

Ethyl Δ^2-Cyclopentene-malonic Acid.—The condensation of ethyl bromide (40 g.) with sodio-cyclopentene-malonic ester (0.25 mole) required 24 hours' warming. The resulting ester, without fractionation, was mixed with an equal weight (47 g.) of potassium hydroxide dissolved in methanol. The solvent was distilled off until the mixture became pasty. The residue was moistened with amyl alcohol and heated in an oven for two hours at 130°, to complete the second step of saponification. The product was dissolved in water, acidified with hydrochloric acid, and extracted with ether.

The ether extract was thoroughly extracted with several portions (total about 2 liters) of boiling water, and the filtered, aqueous solution concentrated to about 200 cc. The ethyl cyclopentene-malonic acid separated on cooling, and was recrystallized from water; yield, 15 g. After recrystallization from benzene containing a little ether, the product showed a melting point of 156° (with ebullition), unchanged by further crystallization from water.

Anal. Subs., 0.1292: 12.95 cc. of 0.1 *N* NaOH. Calcd. for $C_{10}H_{14}O_4$: equiv. wt., 99.1. Found: 99.8.

***n*-Propyl Δ^2-Cyclopentene-malonic Acid.**—The condensation of *n*-propyl bromide (40 g.) with sodio-cyclopentene-malonic ester required 24 hours. The hydrolysis was effected as described for the ethyl compound, and the resulting crude acid extracted with 4 liters of boiling water. The concentrated aqueous solution deposited crystals which were recrystallized from benzene; yield, 14 g.; m. p., 153°, with ebullition.

Anal. Subs., 0.1514: 14.37 cc. of 0.1 *N* NaOH. Calcd. for $C_{11}H_{16}O_4$: equiv. wt., 106.1. Found: 105.4.

***iso*Propyl Δ^2-Cyclopentene-malonic Acid.**—The condensation of *iso*propyl bromide (40 g.) with sodio-cyclopentene-malonic ester (0.25 mole) required five days' continuous warming. The product was hydrolyzed as described for the corresponding ethyl compound. After purification by crystallizing twice from water and then from benzene with a little ether, the acid (only 4 g.) melted at 178°, with ebullition.

Anal. Subs., (I) 0.1638, (II) 0.1350: (I) 14.7 cc., (II) 12.13 cc. of 0.1 *N* NaOH. Calcd. for $C_{11}H_{16}O_4$: equiv. wt., 106.1. Found: (I) 111.4, (II) 111.3.

Allyl Δ^2-Cyclopentene-malonic Acid.—The condensation of allyl bromide (40 g.) with sodio-cyclopentene-malonic ester (0.25 mole) required 24 hours. The hydrolysis and crystallization from water were performed as described for the ethyl compound; yield, 17 g. After further purification by crystallization from water and benzene, the product melted at 146°, with ebullition.

Anal. Subs., 0.1118: 10.4 cc. of 0.1 *N* NaOH. Calcd. for $C_{11}H_{14}O_4$: equiv. wt., 105.1. Found: 107.5.

***n*-Butyl Δ^2-Cyclopentene-malonic Acid.**—The condensation of butyl bromide (40 g.) with sodio-cyclopentene-malonic ester (0.25 mole) required two days. The

ester was hydrolyzed as described for the ethyl derivative, and the product extracted with 3 liters of boiling water in several portions; yield, 20 g. Purified by recrystallization from benzene, the acid melted at 134°, with ebullition.

Anal. Subs., 0.1138: 10.15 cc. of 0.1 *N* NaOH. Calcd. for $C_{12}H_{18}O_4$: equiv. wt., 113.1. Found: 112.1.

bis-Δ^2-Cyclopentene-malonic Acid.—A second equivalent of chlorocyclopentene condensed readily with sodio-cyclopentene-malonic ester, the reaction requiring only a few hours. The resulting ester distilled at 185–186°, at 20 mm.; yield by fractionation, about 50%.

For preparation of the malonic acid, fractionation of the ester was found unnecessary. One-eighth mole of the crude ester was heated with 30 g. of potassium hydroxide in 90 cc. of methanol, the solvent being gradually distilled until the mixture was pasty. Sixty cc. of glycerol was then added, and the temperature raised to 140°. The mixture was kept at 140–145° for half an hour, with frequent stirring. The mass was dissolved in 600 cc. of water and the solution clarified with fuller's earth. The clear, alkaline solution was acidified with hydrochloric acid and extracted with ether.

The ether extract was evaporated to small bulk, and 100 cc. of warm benzene and 50 cc. of water stirred in. After complete evaporation of the ether, the solution was cooled and filtered; yield, 7 g. The bis-cyclopentene-malonic acid, recrystallized from benzene containing a little ether, melted at 184°, with ebullition.

Tested by the Hanus iodine-absorption method, bis-cyclopentene-malonic acid showed two active double bonds; calcd.: I no., 215. Found: 211, 203.

Anal. Subs., 0.1608: 13.4 cc. of 0.1 *N* NaOH. Calcd. for $C_{13}H_{16}O_4$: equiv. wt., 118.1. Found: 120.0.

Elimination of Carbon Dioxide from the Malonic Acids.—A few grams of each of the malonic acids described above was heated somewhat above their melting points until gas ceased to be evolved. The products were distilled at 20 mm. The boiling ranges and titration values are given in Table I.

The resulting disubstituted acetic acids are nearly colorless liquids showing solubilities similar to those of ordinary fatty acids of the same molecular weights. They are less stable than the crystallized malonic acids, and we found no effective method for purifying them, in the quantities at hand. Samples allowed to stand showed, on titration, increases in the equivalent weights of several units per month.

TABLE I

DISTILLATION AND TITRATION OF THE DISUBSTITUTED ACETIC ACIDS

Acid	Boiling range, °C.	Equivalent wt. Calcd.	Found
α-Δ^2-Cyclopentene-butyric	145–150	154	152
α-Δ^2-Cyclopentene-*n*-valeric	150–160	168	171
α-Δ^2-Cyclopentene-*iso*valeric	158–161	168	180
α-Δ^2-Cyclopentene-allylacetic	158–160	166	173
α-Δ^2-Cyclopentene-caproic	167–169	182	184
bis-Δ^2-Cyclopentene-acetic	185–187	192	194

Summary

The ethyl, *n*-propyl, *iso*propyl, allyl, *n*-butyl and Δ^2-cyclopentenyl groups, respectively, were introduced into Δ^2-cyclopentene-malonic ester.

The resulting esters gave on hydrolysis fairly stable, crystalline, disubstituted malonic acids.

The malonic acids, heated above their melting points, yielded α-Δ^2-cyclopentene fatty acids, which are closely related to chaulmoogric acid and are, therefore, important in the study of the treatment of leprosy.

CULION, PHILIPPINE ISLANDS

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

THE SYNTHESIS OF 9-, 10-, 11-, 12- AND 13-HYDROXYSTEARIC ACIDS

BY C. G. TOMECKO[1] WITH ROGER ADAMS

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The hydroxy derivatives of the higher fatty acids are of interest from many standpoints. Such compounds have been found in the waxes of certain conifers such as *Juniperus sabina, Juniperus communis, Picea excelsa, Pinus silvestris, Thuja occidentalis.*[2] They have been found in carnauba wax,[3] in certain resins long used medicinally as purgatives,[4] in cochineal,[5] in wool fat,[6] in brain tissue[7] and humus.[8] More recently they have been discovered in adipocere[9] and East Indian wax.[10] It is obvious that the hydroxy acids form an important class of naturally occurring compounds, concerning which very little is known.

Hydroxy acids are also formed readily by the addition of sulfuric acid to olefinic acids and subsequent hydrolysis of the products. When it is considered that several of the most important fatty acids are olefinic acids, such as oleic, erucic, linoleic, etc., it lends interest to the hydroxy derivatives formed from them. Although the hydroxy acids from the olefinic acids have been extensively studied by many investigators, the discrepancy in the results is surprising. This is the first of a series of researches to determine the structure of many of these hydroxy acids through synthesis by a method which can leave no doubt as to their constitution and purity.

This communication describes the preparation of 9-, 10-, 11-, 12- and

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

[2] (a) Kawalier, *J. prakt. Chem.*, **60,** 321 (1853); **64,** 16 (1855). (b) Boudier, *Compt. rend.*, **147,** 1313 (1908).

[3] Stürcke, *Ann.*, **223,** 313 (1884).

[4] (a) Kromer, *J. prakt. Chem.*, [2] **57,** 450 (1898). (b) Taverne, *Rec. trav. chim.*, **13,** 207 (1894). (c) Power and Rogerson, THIS JOURNAL, **32,** 105 (1910); *J. Chem. Soc.*, **101,** 16 (1912).

[5] Liebermann and Bergami, *Ber.*, **20,** 964 (1887).

[6] Darmstaedter and Lifschütz, *Ber.*, **29,** 2893 (1896).

[7] Thierfelder, *Z. physiol. Chem.*, **43,** 26 (1904–1905).

[8] Schreiner and Shorey, THIS JOURNAL, **32,** 1675 (1910).

[9] Ruttan and Marshall, *J. Biol. Chem.*, **29,** 323 (1917).

[10] Lipp and Kovács, *J. prakt. Chem.*, [2] **99,** 247 (1919).