no mixture melting point depression with an authentic sample prepared by platinum catalyzed hydrogenation.[5] Both samples rapidly decolorized potassium permanganate solution. No evidence of the formation of a stereoisomer was observed.

The identification of II was complicated by the fact that a mixture melting point with IV (of m. p. 111–112°) showed no depression. The acetyl derivative and the methyl ether likewise, though melting differently and characteristically, gave no mixture melting point depressions with the corresponding derivatives of IV. These derivatives gave mixture melting point depressions with the parent compounds (II and IV). A qualitative graduated mole-fraction study of mixture melting points of II and IV indicated no compound formation, and isomorphism is therefore presumed. The evidence of non-identity of II and IV consists in the differences in melting points of the two compounds and of their derivatives, the resistance of IV but not II to attack by permanganate, and by differences in ultraviolet absorption spectra.

1,2-Dimesitylpropanol-1 (IV) was made by lithium aluminum hydride reduction of III by the procedure used in the reduction of I (yield 80%). After several crystallizations from absolute ethanol it melted at 111–112°. Careful examination of the residue failed to reveal the diastereoisomer. The compound failed to decolorize permanganate.

Anal. Calcd. for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 85.05; H, 9.80.

Platinum and hydrogen in absolute ethanol medium was without effect on III (18 hr. at room temperature, atmospheric pressure).

The **acetyl derivative** was made by refluxing a solution of 1 g. of IV in 150 ml. of acetic anhydride for four hours. Hydrolysis of the reaction mixture gave 0.76 g. of product which after three crystallizations from isoöctane melted at 112.5–113°. It gave a 10° mixture melting point depression with starting material (IV) of m. p. 111–112°.

Anal. Calcd. for $C_{25}H_{30}O_2$: C, 81.62; H, 8.94. Found: C, 81.46; H, 8.99.

The **methyl ether** of IV was made by refluxing a solution of 1 g. of IV in 50 ml. of methanol containing 2 ml. of saturated ethereal hydrogen chloride for 18 hr. Concentration of the solution, treatment with 10% sodium carbonate, and extraction with ether, drying and evaporating, gave 0.75 g. It crystallized as cubes from isooctane; m. p. 155.5–156°.

Anal. Calcd. for $C_{22}H_{30}O$: C, 85.10; H, 9.74. Found: C, 84.75; H, 9.56.

Curve in Fig. 1	Maxima $\epsilon \times 10^{-3}$	Maxima mμ	Minima $\epsilon \times 10^{-3}$	Minima mμ	$\epsilon \times 10^{-3}$ at 220 mμ
A	0.72	259	0.27	240	
	.89	265	.68	260	2.2
	.79	272	.59	270	
B	.16	268	.07	245	5.8
C	.45	270	.17	248	
	.38	275	.37	273	17.7
D	.50	269	.16	249	
	.40	275	.38	274	21.7
E	.51	270	.22	247	
	.43	275	.41	274	23.0
F	.56	310	.38	290	19.7
G	.40	312	.31	295	16.5
H	1.55	259	1.15	244	25.5
I[a]	...	...	..	...	20.2
J	..	...	..	...	25.5

[a] *Cf.* Rodebush and Feldman, THIS JOURNAL, **68**, 896 (1946).

1,2-Dimesitylethanol[6] was obtained from desoxymesitoin in quantitative yield by the above method of reduction with lithium aluminum hydride; m. p. 128.5–129.5°.

The **ultraviolet absorptions** were determined in 0.001 *M* isoöctane solution using a Beckman quartz DU spectrophotometer. None of the curves show maxima other than indicated and they cross the vertical 220 mμ axis at the points listed in the last column of the table of data.

Summary

1,2-Dimesitylpropenone is reduced 1,4 to the metastable enol by lithium aluminum hydride. 1,2-Dimesitylpropanol has been made for comparison with the enol.

(6) Fuson, Denton and Best, *J. Org. Chem.*, **8**, 67 (1943).

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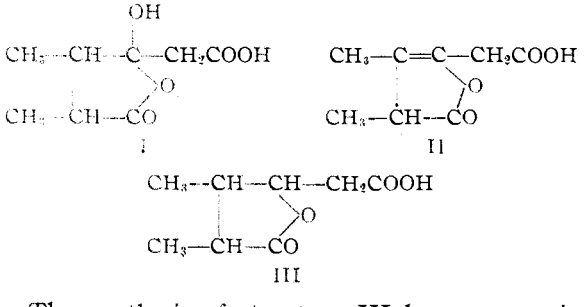
[CONTRIBUTION NO. 74 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

An Isomer of Dihydroanhydromonocrotalic Acid

BY GEORGE P. MUELLER

A new formulation of the structure of monocrotalic acid was recently proposed by Adams and Govindachari[1] and the evidence so far presented in its favor seems very promising. Leading references and discussions of the structure of this acid may be found also in reviews of the subject.[2,3] Of the various formulas considered earlier, structure I was the favored representation of monocrotalic acid. Accordingly, the derivatives, anhydromonocrotalic acid and dihydroanhydromonocrotalic acid, were given the related formulas II and III, with placement of the double bond in the former being uncertain.



The synthesis of structure III by an unequivocal route was undertaken with the hope that isolation and resolution of the proper diastereoisomer could be accomplished to provide a compound identical with the optically active dihydroanhydromonocrotalic acid obtained from

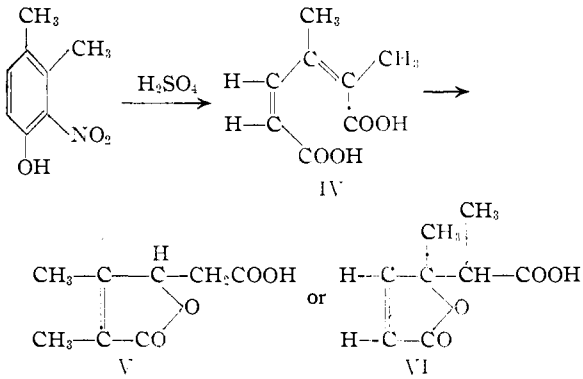
(1) Adams and Govindachari, THIS JOURNAL, **72**, 158 (1950).

(2) Wicks, Ph.D. Dissertation, University of Illinois, 1944.

(3) Leonard, "Senecio Alkaloids" in "The Alkaloids, Chemistry and Physiology," edited by Manske and Holmes, Academic Press, Inc., New York N. Y., 1950, p. 138.

the alkaloid. Such evidence together with that already obtained from degradative studies would confirm I as the structure of monocrotalic acid.

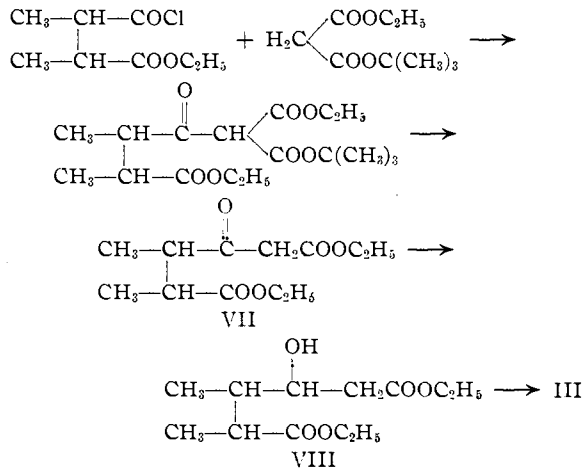
Previous attempts to synthesize dihydroanhydromonocrotalic acid are few. Adams and Wilkinson tried to do so by synthesizing and cyclizing α,β-dimethylmuconic acid to the olefinic acid V; however, they were unable to prepare the muconic acid. The late review[3] directs attention to the work of Wicks[2] who sought to form and cyclize the dimethylmuconic acid *in situ* by the ring cleavage of 2-nitro-3,4-xylenol; this reaction was expected to proceed according to the scheme for the cleavage of 2-nitro-*p*-cresol.[4]



The product obtained, m. p. 168–169°, was assumed, therefore, to be V and indeed showed the correct analysis for this structure. It is unfortunate in this regard that the reviewer states[5] that the acid was "slightly contaminated" since the analysis is good and the compound was in fact examined quantitatively for nitrogen, which was absent. Subsequent treatment with diazomethane and hydrogenation of the unsaturated methyl ester gave a liquid whose boiling point at 1 mm. and refractive index were in fair agreement with those of methyl dihydroanhydromonocrotalate. Both the saturated and unsaturated esters, however, contained about 1% nitrogen. Wicks assumed that this nitrogen was carried through from the xylenol cleavage, although he did not actually prove the presence of that element in his unsaturated acid prior to esterification. This point is important as will be seen, because there is a tendency to attribute the difficulty of purifying the acid to a nitrogen-containing impurity when in fact diazomethane may be responsible for the latter, the "contaminated" acid actually consisting of isomers.

It is also possible that the compound prepared by ring cleavage of 2-nitro-3,4-xylenol was the acid VI since it is theoretically possible for α,β-dimethylmuconic acid (IV) to lactonize in two directions. Not knowing of the prior work, we attempted to prepare V by this same method[6] and obtained likewise a small quantity of an acid, m. p. 178–181°, which was not further characterized but may be identical with that of Wicks. In addition there was isolated an acid, m. p. 103.5–105°, which crystallized well from benzene and gave the correct analysis for either V or VI. Although this is tenuous evidence for the presence of both V and VI in the reaction products, it does cast doubt on this reaction as an unequivocal synthesis of V.

The sequence of reactions used in the present synthesis of III involved acylation of ethyl *t*-butylmalonate and acid decomposition of the product to give VII. The latter was enolic but was hydrogenated to the non-enolic VIII which on acid hydrolysis produced III. This *dl*-acid crystallized after a long period of standing and melted only after extensive purification at 132.5–133.5°. While this value corresponds well



with the melting point, 131–132°, of dihydroanhydromonocrotalic acid,[7] a mixture of the two materials melted over the range 98–118°. Also the *p*-bromophenacyl ester of the *dl*-acid melted 20° lower and the specific rotation of the resolved, but non-crystalline acid was about nine times that of the natural derivative.[8]

It was evident by the oily nature of the hydrolysate from ethyl α,β-dimethyl-γ-hydroxy-δ-carbethoxyvalerate (VIII) that a mixture of diastereoisomers was present. Although four diastereoisomers are possible for III, this number would be halved had the acid chloride prepared from *dl*-dimethylsuccinic anhydride retained its configuration during condensation. The compound mentioned above was the only pure diastereoisomer obtained and its configuration is not known. Resolution of this *dl*-acid was successful only in yielding rotation values for the strychnine salts, the ammonium salts, and the *d*- and *l*-acids as liberated by acidification. In no case among several trials was a crystalline, optically-active acid isolated; for some reason

(4) Pauly, Gilmour and Will, *Ann.*, **403**, 119 (1914).
(5) Leonard, ref. 3, p. 144.
(6) Mueller and Pelton, THIS JOURNAL, **71**, 1504 (1949), and unpublished work.
(7) Adams, Rogers and Long, *ibid.*, **61**, 2822 (1939).
(8) Adams and Long, *ibid.*, **62**, 2289 (1940).

only optically-active oils were recovered which sometimes yielded small amounts of the crystalline *dl*-acid.

Ethyl α,β-dimethyl-δ-carbethoxylevulinate (VII) had been prepared and hydrolyzed earlier.[4] For example, acylation of the sodio derivative of ethyl acetate using α-methyl-β-carbethoxybutyryl chloride and triphenylmethylsodium yielded an ester having properties identical with the ester reported in this paper. Acid hydrolysis of the product yielded α,β-dimethyllevulinic acid instead of structure I. This result was not unexpected in view of the experience with isomers of the keto ester.[9] Similar acylations of malonic ester and acetoacetic ester under the usual conditions for such condensations led variously to materials having incorrect analytical values and also to mixtures of O- and C-acylated products in the latter instance.

Titration of the lactonic acid, besides confirming its structure, showed clearly that the molecule was constrained to assume the cyclic form. Referring to Fig. 1 it is seen that the opening of the lactone in excess alkali (a) was a slow reaction, not complete in twenty-two hours, but that during back titration the *p*H began an upward drift just before the equivalence point for one carboxyl group was reached. When approaching (b) the drift was so rapid that the points became scattered. After passing (d) all appreciable drift had ceased. This behavior means that the sodium salt of the dicarboxylic acid corresponding to the ester VIII, when half neutralized, had such a strong tendency to undergo lactonization that the hydrogen ion was lost to form water at a rate comparable to the titration. This effect is well known, some lactones yielding stable acyclic structures which may even require strong acid for lactonization, while more highly substituted lactones as in the present case are extremely stable.

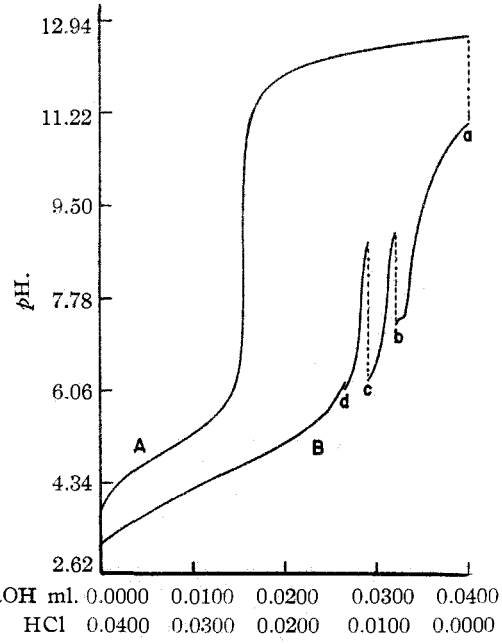


Fig. 1.—Titration curve of α,β-dimethyl-γ-hydroxy-δ-carboxyvaleric acid lactone representing on curve A the titration with sodium hydroxide, 53 experimental readings, and on curve B the back-titration with hydrochloric acid, 97 points. The broken line at (a) shows the drift toward lower *p*H values, from A to B, during twenty-two hours. At (b), (c) and (d) the drift is toward higher *p*H values over periods of one hour, nineteen hours and one hour, respectively.

(9) Adams and Mueller, unpublished work.

Experimental

α-Methyl-β-carbethoxybutyryl Chloride.—Ethyl hydrogen *dl*-α,β-dimethylsuccinate,[10] 43.6 g. (0.25 mole), was treated with 36.0 g. (0.30 mole) of purified thionyl chloride, first at 40° for three hours and then at 60° for a like period. The excess reagent was removed at 55° *in vacuo* followed by successive addition and distillation *in vacuo* of two 10-ml. portions of benzene. The yield was 47.7 g. (99%) of a product which was free of inorganic halides and acids which were always present when phosphorus halides were used. The undistilled acid chloride was quite suitable for acylation.

Ethyl α,β-Dimethyl-δ-carbethoxylevulinate.—According to the procedure of Breslow, Baumgarten and Hauser[11] a 500-ml. flask was fitted for stirring, reflux and addition, dried thoroughly and charged with 14.0 g. (0.12 mole) of freshly prepared magnesium ethoxide and 75 ml. of sodium-distilled ether. Ethyl *t*-butyl malonate, 23.0 g. (0.12 mole), was added, followed by 25 ml. of ether. The mixture was warmed for fifteen minutes, cooled, and treated slowly with 25.8 g. (0.134 mole) of α-methyl-β-carbethoxybutyryl chloride in 25 ml. of ether. After being warmed for twenty minutes, the mixture was cooled, diluted with water, and acidified to *p*H 6 with 1% sulfuric acid. The ester was collected in ether as usual and completely dried by refluxing with benzene under a Stark and Dean trap. After elimination of carbon dioxide and isobutylene by refluxing in 50 ml. of benzene and 0.5 g. of *p*-toluenesulfonic acid, the solution was rinsed with aqueous sodium bicarbonate, water, dried and distilled. The main fraction, b. p. 120–128° (2.5 mm.), 18.2 g., was redistilled and the correct keto ester collected, b. p. 132–134° (4.7 mm.), $n^{25}D$ 1.4421, d^{20}_4 1.0689.

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.20; H, 8.35.

The yield from each of two preparations was 25%. The product gave a cherry red color in alcoholic ferric chloride.

Ethyl α,β-Dimethyl-γ-hydroxy-δ-carbethoxyvalerate.—The keto ester, 6.9 g., in 35 ml. of alcohol was hydrogenated over Raney nickel at 100° and 1450 p. s. i. Distillation yielded 4.2 g. of product, b. p. 142–143° (5.0 mm.), $n^{25}D$ 1.4487, d^{20}_4 1.0755.

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.89; H, 8.27.

This product gave a negative enolic test with ferric chloride, whereas the products obtained from a similar attempt at 25° and from hydrogenation over platinum oxide at 60 p. s. i. at 25° gave positive enolic reactions.

α,β-Dimethyl-γ-hydroxy-δ-carboxyvaleric Acid Lactone.—The hydroxy ester, 2.7 g., was refluxed for five hours with 10 ml. of concentrated hydrochloric acid. Following evaporation at room temperature, the residual oil was dried *in vacuo* over potassium hydroxide. This product would not crystallize immediately but was per-

(10) Adams and Wilkinson, *loc. cit.*; *cf.* Conn, Kistiakowsky, Roberts and Smith, THIS JOURNAL, **64**, 1747 (1942).

(11) Breslow, Baumgarten and Hauser, *ibid.*, **66**, 1286 (1944).

mitted to stand. After two years it had set to a mass of oily crystals. The solid was collected and recrystallized from benzene to give a mixture, m. p. 121–135°.[12] Fractional crystallization of the 1.2 g. of crude material gave a pure product crystallizing as fern leaves, m. p. 132.5–133.5°. This was the lactonic acid.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 6.98; neut. equiv., 172. Found: C, 56.03, 55.91; H, 6.82, 6.85; neut. equiv., 179.

The micro-titration[13] was carried out at 25.0 ± 0.1° with the hydrogen electrode–calomel electrode system calibrated in millivolts against buffer solutions from the U. S. Bureau of Standards. The *p*H–millivolt curve was a straight line within 0.01 unit of *p*H. Using 2.80 mg. of α,β-dimethyl-γ-hydroxy-δ-carboxyvaleric acid lactone dissolved in 2 ml. of water and 2 ml. of 95% ethyl alcohol, the titration was made with 1.010 *N* sodium hydroxide and the back-titration with 1.018 *N* hydrochloric acid from a microburet calibrated in 0.0001-ml. divisions. From the data so obtained were derived the neutral equivalent, the value of 5.00 for pK' and evidence for the lactonic structure.

By the usual procedure 14 mg. of the acid yielded the *p*-bromophenacyl ester, m. p. 122.2–124.0°, which crystallized readily from aqueous ethanol.

Anal. Calcd. for $C_{16}H_{17}O_5Br$: C, 52.03; H, 4.61. Found: C, 51.90; H, 4.35.

Resolution of α,β-Dimethyl-γ-hydroxy-δ-carboxyvaleric Acid Lactone.—In a typical resolution 0.1072 g. (6.23×10^{-4} mole) of the acid was dissolved in 0.5 ml. of boiling water and 0.2081 g. (6.23×10^{-4} mole) of purified strychnine added. After centrifuging, the clear, hot solution was pipetted into a clean tube and permitted to cool slowly. Large, clear crystals of the strychnine salt separated and these were recrystallized from hot water until a constant rotation was achieved; $[\alpha]^{30}D$ −32.1° (α, −0.316°; 49.2 mg. in 5.00 ml. of aqueous solution). The salt crystals evidently lost water of hydration, for they became white and opaque upon drying at 60° over phosphoric anhydride; m. p. 98–260°. Such anhydrous crystals were difficult to get completely into solution again, there always being a trace of the alkaloid present as insoluble material.

To obtain the rotation of the ammonium salt, the solution from the preceding measurement was concentrated, treated with 0.7 ml. of 0.14 *N* ammonia, cooled for an hour and filtered with washing of the strychnine residue. Evaporation of the solution left 18.35 mg. of the 18.58 mg. theoretically present; $[\alpha]^{30}D$ −48.4° (α, −0.75°; 18.35 mg. in 1.20 ml. of aqueous solution).

The ammonium salt solution was acidified with 1.0 ml. of 0.26 *N* hydrochloric acid, the solution evaporated and the residue dried to give 19.22 mg. of the mixture of *l*-α,β-dimethyl-γ-hydroxy-δ-carboxyvaleric acid lactone with ammonium chloride. This residue was repeatedly digested with absolute alcohol, which solution was made up to volume for rotation and, by calculation, contained 14.7 mg. of the acid; $[\alpha]^{30}D$ −33.5° (α, −0.41°; 14.7 mg. in 1.2 ml. absolute alcoholic solution).

Here as in many succeeding attempts to isolate pure *d*- or *l*-acid, *e. g.* where evaporation of the residue and repeated extraction with hot benzene gave an oil, $[\alpha]^{30}D$ −35.3° (α, −0.68°; 35.8 mg. in 2.00 ml. absolute alcohol solution), only the *dl*-acid could be crystallized in small amounts. The mother liquors always showed strong rotations, + or −, according to the enantiomorph being handled, and the crystalline material, at first melting over a considerable range, finally melted at 134°, did not depress the melting point of the starting material, and showed $[\alpha]^{30}D$ 0.00°.

For isolation of the *d*-acid the original mother liquors, after removal of the crystalline *l*-salt, were concentrated and dried; $[\alpha]^{25}D$ −11.28° (α, −0.40°; 177.3 mg. in 5.00 ml. aqueous solution). This figure averaged with the above yields −21.7° for the *dl*-salt. The strychnine was removed as before, following the addition of a measured quantity of ammonia. Dilute hydrochloric acid was then added, the solution evaporated and the amount of lactonic acid calculated from the residue. Benzene extraction and evaporation left an oil; $[\alpha]^{30}D$ + 22.2° (α, +0.67°; 60.3 mg. (calcd.) in 2.00 ml. absolute alcoholic solution). Again crystallization of the residual oil gave impure, slightly dextrorotatory crystals which were optically inactive when pure.

In an experiment designed to check the recovery of the *dl*-acid, the solution containing equimolar amounts of acid and strychnine showed $[\alpha]^{26}D$ −23.7° (α, −0.24°; 50.6 mg. in 5.0 ml. aqueous solution). Here, extraction of the *dl*-acid from the dry ammonium chloride was successful, yielding the pure *dl*-acid quantitatively.

Acknowledgment.—The author wishes to thank Dr. Roger Adams for generously supplying derivatives of monocrotalic acid.

Summary

One of the structures proposed for dihydroanhydromonocrotalic acid, α,β-dimethyl-γ-hydroxy-δ-carboxyvaleric acid lactone, has been synthesized by hydrolyzing the ethyl ester of the corresponding dicarboxylic acid. The synthesis of the latter is described. Proof of the structure and approximate optical rotatory values are offered. The lactone is not identical with the natural derivative.

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(12) All melting points were observed at fifty magnifications on the Kofler hot stage and are corrected.

(13) This titration was carried out by Dr. Martin Kuna and Mr. E. F. Phares of the Biology Division, Oak Ridge National Laboratories, for whose assistance the author extends thanks.