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

The Structure of Monocrotaline. III. Monocrotalic Acid[1]

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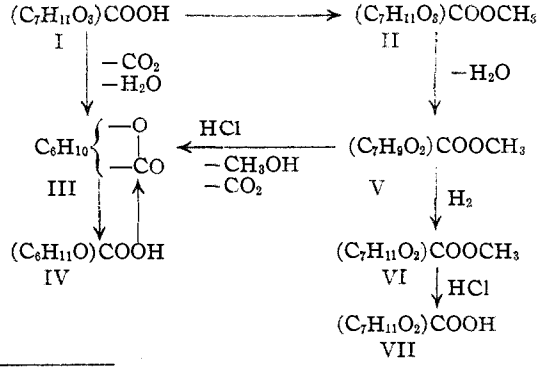
On catalytic hydrogenation of monocrotaline, two moles of hydrogen are absorbed with formation of an alkanolamine, retronecanol, and an optically active acid, $C_8H_{12}O_5$, called monocrotalic acid.[3]

$$C_{16}H_{23}O_6N + 2H_2 \longrightarrow \underset{\text{Retronecanol}}{C_8H_{15}ON} + \underset{\text{Monocrotalic acid}}{C_8H_{12}O_5}$$

Monocrotalic acid (I) contains one carboxyl group. On back titration of the acid from excess alkali, the presence of a lactone group is indicated. The acid gives a crystalline monomethyl ester (II) with diazomethane which shows one active hydrogen by a Zerewitinoff determination. Esterification of the acid with methanol and sulfuric acid was unsuccessful and only a very poor yield of ester was obtained with methanol saturated with hydrogen chloride.

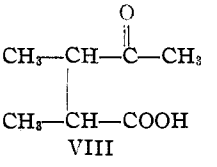
The acid decomposes on heating past its melting point to give an optically inactive neutral compound, $C_7H_{10}O_2$ (III or IX), which is identical with α,β,γ-trimethylangelicalactone obtained by dehydration of monocrotic acid, $C_7H_{12}O_3$ (IV or VIII).

The same lactone can be obtained by a two-step procedure which clarifies the reaction. Methyl monocrotalate (II) on heating *in vacuo* loses water to give an unsaturated ester $(C_7H_9O_2)$-$COOCH_3$ (V), together with a small amount of lactone (III). This ester reduces acid permanganate and can be hydrogenated under high pressure to a dihydro ester (VI) which in turn may be hydrolyzed to a crystalline lactonic acid, $(C_7H_{11}O_2)COOH$ (VII). The unsaturated ester (V) on hydrolysis with concentrated hydrochloric acid, yields the same lactone, $C_7H_{10}O_2$ (III), which is obtained by thermal decomposition of monocrotalic acid. It is obvious then that upon heating monocrotalic acid two reactions occur, dehydration and decarboxylation. These reactions just discussed are shown in tabular form.

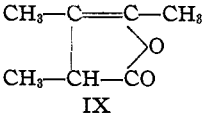


The above observations show that monocrotalic acid contains a lactone group which, while stable to heat and strong acid, cleaves readily with alkali to give an unstable, easily decarboxylated acid which could not be isolated. The ease of dehydration of monocrotalic acid and especially of its methyl ester is best explained by the presence of a tertiary hydroxyl group.

It has been demonstrated[1] that the acid obtained by alkaline hydrolysis of monocrotalic acid is α,β-dimethyllevulinic acid (VIII).



VIII



IX

Since IV has the structural formula VIII, it follows that the corresponding lactone (III) must be α,β,γ-trimethylangelicalactone (IX) which was obtained by the dry distillation of monocrotalic acid (I). Three structures of monocrotalic acid (I) may be considered, XI, XII and XIII.

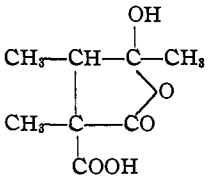
Structures XIV, XV and XVI would then represent, respectively, the anhydromonocrotalate (V). All three of these structures have as a common feature the grouping which explains the smooth formation of a keto acid on breaking the lactone ring. The structures differ in the position given the free carboxyl group.

Structure XIII appears unlikely due to the fact that monocrotalic acid is esterified with acid and methanol only with great difficulty. This is indicative of a tertiary carboxyl. Structure XIII should not decarboxylate as readily on heating as was actually observed. Moreover, methyl anhydromonocrotalate does not give a Legal test al-

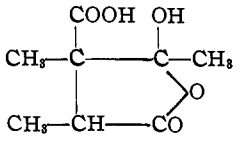
(1) For previous paper see Adams, Rogers and Sprules, THIS JOURNAL, **61**, 2819 (1939).

(2) An abstract of a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in chemistry.

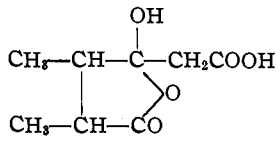
(3) Adams and Rogers, THIS JOURNAL, **61**, 2815 (1939).



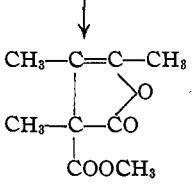
XI



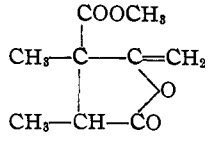
XII



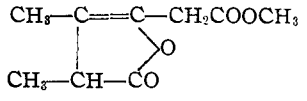
XIII



XIV



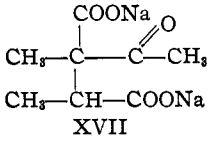
XV



XVI

though the unsaturated ester (XVI) derived from an acid of structure XIII should do so, since this test is specific for β,γ-unsaturated γ-lactones containing a free hydrogen in the α-position.[4] On the basis of this evidence, structure XIII may be excluded.

The degradation of monocrotalic acid (I) with alkali goes smoothly and quantitatively to monocrotic acid (VIII).[3] This reaction proceeds equally well whether dilute or concentrated alkali is used. Unquestionably the first step in the degradation is the formation of the salt of the tautomeric keto acid. Thus, XII would be converted to XVII, which is a β-ketonic acid. A difference

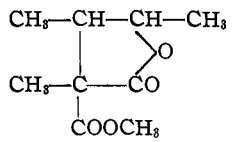


XVII

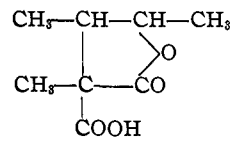
in the decarboxylation products should result whether diluted or concentrated alkali is used, for the former should give a ketone splitting to a levulinic acid derivative, whereas the latter should give at least partially an acid splitting with formation of a α,α'-dimethylsuccinic acid. None of the latter product could be isolated.

Methyl anhydromonocrotalate can be reduced catalytically only under high pressure. This fact is better reconciled with a substituted angelicalactone of formula XIV rather than XV. It is concluded, therefore, that formula XI represents the most likely structure for monocrotalic acid, namely, α-carboxy-α,β-dimethyl-γ-hydroxy-γ-valerolactone. It explains also the presence of one active hydrogen in methyl monocrotalate.

On this basis, the other degradation products would have the structures: hydrogenated methyl anhydromonocrotalate (XVIII) and its acid hydrolysis product (XIX).



XVIII



XIX

Monocrotalic acid and all of its derivatives in which the carboxyl group is intact are optically active, whereas the lactone obtained from monocrotalic acid or its derivatives is inactive due probably to its ease of enolization.

Experimental

Methyl Monocrotalate.—To a suspension of 5 g. of monocrotalic acid[3] in 30 cc. of chloroform was added slowly with stirring an ether solution of diazomethane until a slight excess was present as evidenced by a yellow color in the solution. The temperature was not allowed to rise above 10°. Evaporation of the ether and chloroform under diminished pressure left an oil which crystallized rapidly. The product was purified by recrystallization from ether: white crystals, m. p. 79–80° (corr.); yield, 5.17 g. (97%).

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.47; H, 6.93. Found: C, 53.87; H, 7.09.

Rotation. 0.502 g. made up to 10 cc. at 30° in absolute ethanol. α_D −1.63; l, 2; $[\alpha]^{30}D$ −16.24°.

A Zerewitinoff determination showed 1.18 active hydrogens.

Heat Decomposition of Monocrotalic Acid: α,β,γ-Trimethylangelicalactone.—In a small modified Claisen distilling flask immersed in a Woods' metal bath was placed 15 g. of pure monocrotalic acid. Heat was applied and, at a bath temperature of 200°, the evolution of carbon dioxide and water was apparent. When this had ceased the bath was cooled and the resldue distilled: colorless liquid, b. p. 82–83° (1 mm.); d^{29}_4 1.024; $n^{20}D$ 1.4664; yield, 8.6 g. (86%).

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.67; H, 7.94. Found: C, 66.45; H, 8.04.

(4) Jacobs and Hoffman, *J. Biol. Chem.*, **61**, 333 (1925).

Methyl Anhydromonocrotalate.—In a small modified Claisen distilling flask 15 g. of methyl monocrotalate was heated at 200–210° until the evolution of water was complete. Fractionation of the residue gave 4.5 g. of material, b. p. 100–115° (3 mm.), and 7.5 g. of pure methyl anhydromonocrotalate, b. p. 115–116° (3 mm.); $n^{20}D$ 1.4700; d^{32}_4 1.131.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.70; H, 6.52. Found: C, 58.83; H, 6.82.

Rotation. (Pure liquid at 30°) αD +58.22; *l*, 2; $[\alpha]^{30}D$ +25.74.

A second fractionation of the low boiling portion gave 1.8 g. of low boiling material and 1.7 g. of pure methyl anhydromonocrotalate. Further purification of the low boiling material from this distillation gave 0.5 g. of pure α,β,γ-trimethylangelicalactone identical with that obtained directly from monocrotalic acid, b. p. 92° (3 mm.); $n^{20}D$ 1.4658.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.67; H, 7.94. Found: C, 66.10; H, 8.02.

Hydrogenation of Methyl Anhydromonocrotalate and α,β,γ-Trimethylangelicalactone: α-Carbomethoxy-α,β-dimethyl-γ-valerolactone and α,β-Dimethyl-γ-valerolactone.—Unfractionated methyl anhydromonocrotalate (9 g.) containing α,β,γ-trimethylangelicalactone was dissolved in 70 cc. of ether and hydrogenated at 2200 pounds (167 atm.) and 125° using Raney nickel as the catalyst. The theoretical amount of hydrogen was absorbed and the residue, after removal of the ether, was carefully fractionated; yield, 0.8 g. of α,β-dimethyl-γ-valerolactone, b. p. 67–69° (2 mm.); $n^{20}D$ 1.4382; d^{29}_4 0.987, and 6.0 g. of hydrogenated methyl anhydromonocrotalate, b. p. 115–117° (1 mm.); $n^{20}D$ 1.4510; d^{28}_4 0.996.

Anal. (α,β-Dimethyl-γ-valerolactone.) Calcd. for $C_7H_{12}O_2$: C, 65.63; H, 9.38. Found: C, 65.43; H, 9.57. (Hydrogenated methyl anhydromonocrotalate.) Calcd. for $C_9H_{14}O_4$: C, 58.06; H, 7.53. Found: C, 58.09; H, 7.70.

Rotation. (Pure liquid at 29°) αD +11.15; *l*, 2; $[\alpha]^{29}D$ +5.60.

When pure methyl anhydromonocrotalate was hydrogenated under similar conditions, a pure reduced product was obtained with constants identical with those just described.

Hydrolysis of Dihydromethyl Anhydromonocrotalate: α-Carboxy-α,β-dimethyl-γ-valerolactone.—A mixture of 4.6 g. of dihydromethyl anhydromonocrotalate and 20 cc. of concentrated hydrochloric acid was refluxed for five hours. Evaporation of the water under reduced pressure left 2.7 g. (63%) of crude acid which after purification by recrystallization from benzene gave 2.5 g. of pure acid: white crystals, m. p. 131–132° (corr.).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 6.98. Found: C, 55.57; H, 6.98.

Rotation. 0.303 g. made up to 10 cc. of absolute ethanol at 30°. αD +0.23; *l*, 2; $[\alpha]^{30}D$ +3.80°.

The *p*-bromophenacyl ester was prepared from 0.1 g. of the acid and an equivalent amount of *p*-bromophenacyl bromide according to the standard procedure. Purified from ethanol it formed white crystals, m. p. 142–143° (corr.); yield, 0.12 g. (57%).

Anal. Calcd. for $C_{16}H_{17}O_5Br$: C, 52.03; H, 4.61. Found: C, 52.33; H, 4.91.

Rotation. 0.2315 g. made up to 5 cc. in acetone at 29°. αD −0.36; *l*, 2; $[\alpha]^{29}D$ −3.89°.

Hydrolysis of Methyl Anhydromonocrotalate: α,β,γ-Trimethylangelicalactone.—A solution of 6 g. of methyl anhydromonocrotalate in 10 cc. of concentrated hydrochloric acid was refluxed for eight hours. The oil which separated was extracted with ether and the ether solution was dried over anhydrous sodium sulfate. The product was pure, inactive α,β,γ-trimethylangelicalactone, b. p. 90–92° (3 mm.); $n^{20}D$ 1.4659 identical with that obtained directly from monocrotalic acid by heat decomposition.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.67; H, 7.94. Found: C, 65.97; H, 8.23.

Summary

Monocrotalic acid, obtained by hydrogenolysis of monocrotaline, has been shown to be monobasic with the carboxy group tertiary, and to contain a lactone grouping. It decomposes when heated to lose water and carbon dioxide with formation of α,β,γ-trimethylangelicalactone. It was possible to form this same lactone by heat decomposition of methyl monocrotalate and hydrolysis of the resulting methyl anhydromonocrotalate.

The discussion of the possible structure for monocrotalic acid is given with the conclusion that it is optically active α-carboxy-α,β-dimethyl-γ-hydroxy-γ-valerolactone.

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