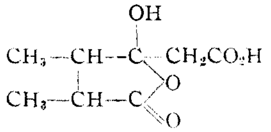
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

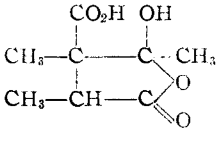
# Structure of Monocrotaline. XII. Monocrotalic Acid[1]

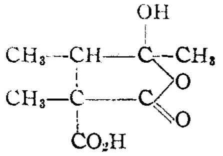
BY ROGER ADAMS* AND T. R. GOVINDACHARI

Monocrotalic acid, which is obtained by the hydrogenolysis of the alkaloid monocrotaline,[2] has been assigned[1c] the structural formula I.



I





II III

Originally, the structure of monocrotalic acid was considered to be limited to one of the three formulas I, II or III and the reasons for preferring structure I have been presented by Adams and Wilkinson.[1c] While the structural formula I satisfactorily explains the conversion of monocrotalic acid to α,β-dimethyllevulinic acid by treatment with alkali and its oxidation to α,α′-dimethylmaleic anhydride by nitric acid, it is not entirely acceptable in some other respects. Monocrotalic acid could not be made to yield an acetyl derivative or an O-methyl ether, while a hydroxylactone of formula I (or even II and III) should readily undergo both these reactions. When the lactone ring in a compound of formula I is opened up by alkali, the β-keto acid so formed should yield different hydrolytic products, depending on the concentration of the alkali. Only α,β-dimethyllevulinic acid or its precursor α,β-dimethylangelicalactone was isolated by treatment with alkali of any concentration and no α,α′-dimethylsuccinic acid was ever obtained. It was also not established whether the decarboxylation process involved in this transformation was brought about merely by the alkali or was initiated at the instant of acidification, necessary for isolating the product. Attempts to secure direct experimental evidence for structure I either through synthesis or conversion to an open chain compound which could be identified by synthesis proved unsuccessful.

The remarkable facility of reductions secured with lithium aluminum hydride suggested a new approach to a solution of this problem. The only instance on record involving the reduction of a lactone by lithium aluminum hydride is that of γ-valerolactone to pentanediol-1,4 in 85% yield.[3]

On reduction with lithium aluminum hydride, methyl monocrotalate gave an almost quantitative yield of a neutral crystalline product whose analysis corresponded to the empirical formula $C_8H_{18}O_4$. The product was easily soluble in water and ethanol, sparingly soluble in ether and almost insoluble in benzene. It did not give any reaction characteristic of a carbonyl group. The infrared spectrum did not show any absorptions in the carbonyl region, but showed an intense and broad absorption in the hydroxyl region. The product readily yielded a dibenzoate by the Schotten–Baumann procedure. The infrared spectrum of the dibenzoate showed an absorption in the hydroxyl region at 3400 cm.$^{-1}$. The dibenzoate gave a positive reaction with periodic acid reagent[4] indicating the presence of two unesterified hydroxyls in adjacent positions. The compound $C_8H_{18}O_4$ was therefore a tetrahydroxy compound, all four oxygen atoms being present as hydroxyl groups.

The compound $C_8H_{18}O_4$ consumed exactly two mole equivalents of sodium metaperiodate. The products of the reaction were formaldehyde, acetic acid and β-methyl-γ-ketobutanol. The last two products were presumably combined with each other, since only about 10% of free acid could be detected at the end of the reaction. After the complete removal of formaldehyde in the form of its dimedone derivative, the rest of the organic material was isolated by ether extraction. The oil so obtained was refluxed in dioxane solution with 2,4-dinitrophenylhydrazine and a drop of concentrated hydrochloric acid. On removing the solvent *in vacuo* approximately 0.3 mole of acetic acid was recovered from the distillate and identified through preparation of the *p*-bromophenacyl derivative. The residual material was separated into two 2,4-dinitrophenylhydrazones by chromatography. The analysis of one corresponded to that of the 2,4-dinitrophenylhydrazone of β-methyl-γ-ketobutanol acetate. The other was positively identified as the 2,4-dinitrophenylhydrazone of methyl isopropenyl ketone by comparison with an authentic specimen,[5] kindly provided by Dr. E. M. McMahon. It was also established that β-methyl-γ-ketobutanol[6] undergoes dehydration when refluxed with an ethanolic solution of 2,4-dinitrophenylhydrazine, yielding

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* Harvard University Ph.D. 1912.

[1] For previous papers, see (a) Adams, Rogers and Long, THIS JOURNAL, **61**, 2822 (1939); (b) Adams and Long, *ibid.*, **62**, 2289 (1940); (c) Adams and Wilkinson, *ibid.*, **65**, 2203 (1943).

[2] Adams and Rogers, *ibid.*, **61**, 2815 (1939).

[3] Nystrom and Brown, *ibid.*, **70**, 3738 (1948).

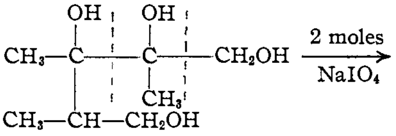
[4] Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 115.

[5] McMahon, Roper, Utermohlen, Hasek, Harris and Brant, THIS JOURNAL, **70**, 2971 (1948).

[6] Morgan, Megson and Pepper, *J. Soc. Chem. Ind.*, **57**, 885 (1938).

exclusively the 2,4-dinitrophenylhydrazone of methyl isopropenyl ketone. It is reasonable to expect that β-methyl-γ-ketobutanol acetate would similarly eliminate acetic acid yielding the 2,4-dinitrophenylhydrazone of methyl isopropenyl ketone. Actually, only the latter product was isolated when the duration of heating was extended to three hours and none of the derivative corresponding to β-methyl-γ-ketobutanol acetate was isolated.

The tetrahydroxy compound $C_8H_{18}O_4$ should therefore be formulated as 1,2,3,5-tetrahydroxy-2,3,4-trimethylpentane (IV).

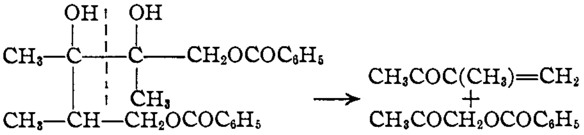


IV

HCHO + $CH_3CO_2H$ + $CH_3COCH(CH_3)CH_2OH$

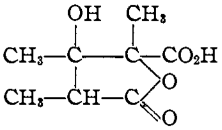
The dibenzoate of the compound $C_8H_{18}O_4$ reacted with exactly one mole of lead tetraacetate. The mixture of carbonyl compounds formed was converted to the 2,4-dinitrophenylhydrazone and separated by chromatography. The two pure products isolated were found to be identical with the 2,4-dinitrophenylhydrazones of methyl isopropenyl ketone and acetol benzoate,[7] by comparison with authentic specimens. β-Methyl-γ-ketobutanol benzoate was one of the expected products in the cleavage with lead tetraacetate, but elimination of benzoic acid has occurred in the process of formation of the 2,4-dinitrophenylhydrazone, leading to the derivative of methyl isopropenyl ketone.

These reactions can be explained only by formulating the dibenzoate as 1,5-dibenzoyloxy-2,3-dihydroxy-2,3,4-trimethylpentane (V) and confirm structure (IV) for the tetrahydroxy compound.

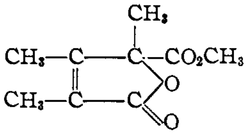


V

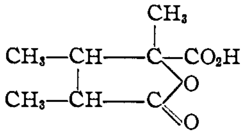
If it can be assumed that the reduction with lithium aluminum hydride does not involve any rearrangements, the only possible structure that could be deduced for monocrotalic acid would be α,β,γ-trimethyl-β-hydroxy-γ-carboxy-γ-valerolactone (VI). If monocrotalic acid is formulated as (VI), methyl anhydromonocrotalate would be



VI



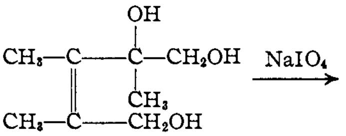
VII



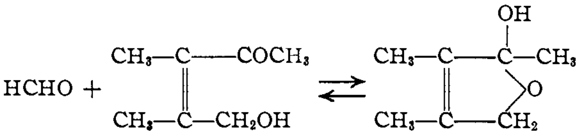
VIII

(VII) and dihydroanhydromonocrotalic acid would be (VIII). The ultraviolet absorption spectrum of methyl anhydromonocrotalate ($\lambda_{max.}$, 214 mμ, $\epsilon_{max.}$, 10,860) is consistent with the spectra of α,β-unsaturated lactones,[8] lending support to structure (VII).

On reduction with lithium aluminum hydride, methyl anhydromonocrotalate gave in excellent yield a sirupy oil, whose analysis corresponded to the empirical formula $C_8H_{16}O_3$. On treatment with *p*-nitrobenzoyl chloride in pyridine solution, the oil yielded a crystalline di-*p*-nitrobenzoate which gave a negative reaction with periodic acid reagent.[4] The oil readily decolorized neutral permanganate and bromine water and absorbed one mole of hydrogen in the presence of platinic oxide catalyst. The infrared absorption spectrum of the oil showed an intense absorption in the hydroxyl region, and no absorptions in the carbonyl or carbon–carbon double bond regions. Olefins of the type $R_2C{=}CR_2$ may not always show the C=C stretching vibration.[9] On the basis of structure VII for methyl anhydromonocrotalate, the lithium aluminum hydride reduction product may be formulated as (IX). On



IX



X XI

treatment with one mole-equivalent of sodium metaperiodate, of which the entire quantity was consumed, a heavy water-insoluble oil separated. The amount of formaldehyde in the supernatant aqueous solution was estimated as 0.44 mole, the rest of the formaldehyde having presumably reacted with the other product of the reaction. On the basis of structure (IX) for the trihydroxy compound, the two products of the reaction with sodium metaperiodate would be formaldehyde and 2,3-dimethyl-4-oxo-$\Delta^2$-pentene-1-ol (X). A molecule of structure (X) would be expected to exist entirely in the cyclic form (XI), being a

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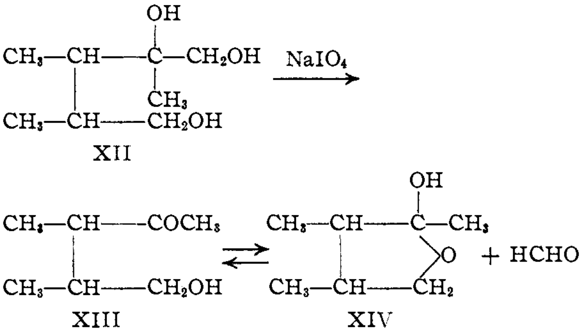
[7] Kling, *Ann. chim. phys.*, [8] **5**, 484 (1905).

[8] Haynes and Jones, *J. Chem. Soc.*, 954 (1946); Wenner and Reichstein, *Helv. Chim. Acta*, **27**, 24 (1944).

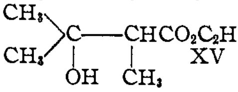
[9] Rasmussen and Brattain, *J. Chem. Phys.*, **15**, 120 (1947); "Progress in the Chemistry of Organic Natural Products," Zechmeister, Springer-Verlag, 1948, p. 350.

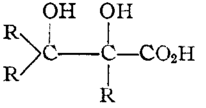
γ-hydroxy ketone.[10] It is also possible that it might undergo further transformations, leading to a completely aromatized furan derivative. Actually, the colorless oil isolated as the second product of the reaction with sodium metaperiodate, resinified on contact with dilute acid and darkened progressively on exposure to air. On treatment with *p*-nitrobenzoyl chloride in pyridine solution, a series of color changes from red to green to dark brown was noticed, resulting finally in a dark resin which could not be purified. Attempts at preparation of a 2,4-dinitrophenylhydrazone in ethanolic solution with a trace of acid also failed to lead to a pure product.

On reduction of methyl dihydroanhydromonocrotalate with lithium aluminum hydride, a heavy colorless sirup was obtained in excellent yield whose empirical formula corresponded to $C_8H_{18}O_3$. The infrared spectrum of this sirup showed an intense absorption in the hydroxyl region and no absorptions in the carbonyl region. The compound yielded a crystalline di-*p*-nitrobenzoate, which gave a negative reaction with periodic acid reagent.[4] On the basis of the new structure for dihydroanhydromonocrotalic acid (VIII), the reduction product should be formulated as XII. It reacted with sodium metaperiodate, consuming exactly one mole equivalent and liberating one mole equivalent of formaldehyde. The other product of the cleavage was a colorless volatile oil with a camphoraceous odor, presumably of structure (XIII), which would be expected to exist solely as a 2-hydroxytetrahydrofuran derivative (XIV). The simplest prototype would be γ-acetylpropyl alcohol which has been characterized both as a benzoate[11] and as an oxime.[12] The oil presumed to have the structure (XIII) (or (XIV)) could not be made to yield a 2,4-dinitrophenylhydrazone or a benzoate or a *p*-nitrobenzoate.



The fact that the lithium aluminum hydride reduction products from methyl anhydromonocrotalate and methyl dihydroanhydromonocrotalate both react with periodate, yielding formaldehyde as products of cleavage, lends strong support to the structures (VII) and (VIII) formulated for these esters and also to the structure (VI) formulated for monocrotalic acid itself. Assuming the course of the reaction with lithium aluminum hydride to be normal, none of the previously proposed structures can account for these facts. It is only by placing the carboxyl group on the carbon atom involved in lactone formation as in structures (VI), (VII) and (VIII) that the formation of formaldehyde from all three lithium aluminum hydride reduction products (IV), (IX) and (XII) by periodate cleavage could be explained. The formation of dimethylmaleic anhydride by nitric acid oxidation of monocrotalic acid is perhaps more readily explained on the basis of the new structure (VI), involving a dehydration followed by oxidation. The original structure (I) would require a dehydrogenation followed by oxidation or *vice versa.*

One objection that may be raised against structure (VI) is the stability of monocrotalic acid to boiling hydrochloric acid. This is apparently inconsistent with the presence of a tertiary hydroxyl group, which is also in the β-position to a carboxyl group. However, ethyl 3-hydroxy-2,3-dimethylbutanoate (XV)  $(CH_3)_2C(OH)—CH(CH_3)CO_2C_2H_5$ XV which has an analogous structure, is reported to be exceptionally stable and could not be dehydrated by dry hydrogen chloride.[13]

The only pertinent objection to the formulation of monocrotalic acid as (VI) is that it does not furnish any obvious explanation for the formation of α,β-dimethyllevulinic acid by alkali treatment and acidification. It has to be assumed that when the lactone ring is opened up, decarboxylation occurs as the first step involving the tertiary carboxyl group. This is a reaction of which there is no prototype. Following this must be the elimination of water to form an enol or free radical, which rearranges to α,β-dimethyllevulinic acid. An analogy to support this latter reaction is the ease with which 2,3-dihydroxy-3-methylbutane rearranges to methyl isopropyl ketone merely by heating under pressure in aqueous solution[14] or by warming with dilute hydrochloric acid.[15] The loss of carbon dioxide upon alkali treatment of monocrotalic acid and acidification may be characteristic of the system  $R_2C(OH)—C(OH)(R)—CO_2H$ and an examination of model compounds of this type is now under way.

The decomposition of monocrotalic acid to dimethyllevulinic acid may then be formulated as

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[10] Owen, "Ann. Repts. Progress Chem. (Chem. Soc. London)," **42**, 161 (1945).

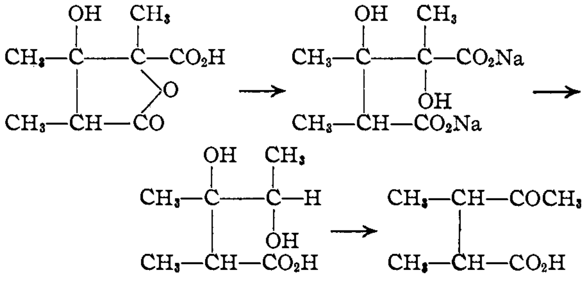
[11] Lipp, *Ber.*, **22**, 1196 (1889).

[12] Marshall and Perkin, *J. Chem. Soc.*, **59**, 853 (1891).

[13] Huston and Goerner, THIS JOURNAL, **68**, 2504 (1946).

[14] Eltekow, *J. Russ. Phys.-Chem. Soc.*, **10**, 217 (1878).

[15] Eltekow, *ibid.*, **14**, 355 (1882); *Ber.*, **16**, 396 (1883); Bauer, *Ann.*, **115**, 90 (1860).



We are grateful to Mrs. J. L. Johnson and Miss Elizabeth Peterson for determination and interpretation of infrared spectra and to Dr. E. M. McMahon for supply of an authentic specimen of the 2,4-dinitrophenylhydrazone of methyl isopropenyl ketone.

## Experimental

**Reduction of Methyl Monocrotalate with Lithium Aluminum Hydride; 1,2,3,5-Tetrahydroxy-2,3,4-trimethylpentane (IV).**—In a three-necked flask fitted with stirrer, condenser and dropping funnel, was placed 250 ml. of absolute ether to which 8 g. of coarsely powdered lithium aluminum hydride was added in one portion. After stirring for five minutes, a solution of 10 g. of methyl monocrotalate in 300 ml. of absolute ether was added dropwise at such a rate that a vigorous rate of reflux was maintained. The stirring was continued for a further two hours. The flask was then cooled in ice and 30 ml. of water was added cautiously, followed by 600 ml. of 10% sulfuric acid which was needed to dissolve all the precipitate formed.

The aqueous layer was separated and the ether layer was washed with three 50-ml. portions of water. The combined aqueous solution was cooled and neutralized with 50% aqueous sodium hydroxide so that the *p*H of the solution was between 6.5-7. The precipitated alumina was filtered off and the residue repeatedly washed with water. The filtrate was concentrated *in vacuo* (water pump) until the solution became turbid with separation of an oily layer. The turbid concentrated solution was continuously extracted with ether for forty-eight hours. The ether extract was dried over anhydrous sodium sulfate. After filtration, the ether was distilled off and the residual sirup on drying *in vacuo* in a desiccator was transformed to a colorless crystalline solid. The yield of this crude material was 8.1 g. (92%). It was recrystallized by dissolving in the minimum volume of hot dioxane and diluting with about ten volumes of benzene. Colorless crystals separated, m. p. 103° (cor.).

*Rotation.* 0.0515 g. made up to 1 ml. with absolute ethanol at 25° gave $\alpha_D$ + 0.48°; *l*, 1; $[\alpha]^{25}_D + 9.32°$.

*Anal.* Calcd. for $C_8H_{18}O_4$: C, 53.91; H, 10.18. Found: C, 54.08; H, 10.30.

**Dibenzoate of IV ($C_8H_{18}O_4$); 1,5-Dibenzoyloxy-2,3-dihydroxy-2,3,4-trimethylpentane (V).**—This was prepared by the Schotten-Baumann procedure from compound (IV) and purified by recrystallization from a benzene-petroleum ether (b. p. 60-110°) mixture. The product melted at 107° (cor.).

*Anal.* Calcd. for $C_{22}H_{26}O_6$: C, 68.36; H, 6.78. Found: C, 68.86; 68.81; H, 6.94; 6.97.

**Di-*p*-nitrobenzoate of IV ($C_8H_{18}O_4$); 1,5-Di-*p*-nitrobenzoyloxy-2,3-dihydroxy-2,3,4-trimethylpentane.**—This was prepared by the action of *p*-nitrobenzoyl chloride on a pyridine solution of IV. The sticky material initially obtained by following the usual procedure of isolation was transformed to a crystalline solid by treatment with dilute ethanol and was purified by two crystallizations, first from dilute ethanol and the second from benzene. It formed pale yellow crystals, m. p. 115-116° (cor.).

*Anal.* Calcd. for $C_{22}H_{24}O_{10}N_2$: C, 55.46; H, 5.07; N, 5.88. Found: C, 55.75; H, 5.26; N, 5.93.

**Action of Sodium Metaperiodate on IV ($C_8H_{18}O_4$).**—One gram of the tetrahydroxy compound was accurately weighed in a 100-ml. volumetric flask, dissolved in 10 ml. of water and 58 ml. of 0.196 *M* solution of sodium metaperiodate was run in from a buret. The solution was then made up to 100 ml. and vigorously shaken. The solution warmed up noticeably, and was left at room temperature for fifteen hours.

Five ml. of the solution was then withdrawn and the excess periodate was estimated by the standard procedure: 56.6 ml. consumed; theory for two moles, 57.4 ml.

Two ml. of the solution was titrated against standard sodium hydroxide solution with phenolphthalein as indicator. Assuming that all the free acid present was acetic acid and allowing for the alkali required for bringing the excess periodate present to neutral end-point, the amount of free acetic acid found in the total solution was found to be 30 mg. If all the acetic acid liberated were in the free state, 330 mg. should have been present.

Two ml. of the solution was shaken with 15 ml. of a saturated aqueous solution of dimedone. After fifteen hours, the dimedone derivative of formaldehyde (m. p. 188-189°) was filtered off and dried to constant weight *in vacuo*. It amounted to 33 mg. which was equivalent to 168.8 mg. of formaldehyde in the total solution; theory for one mole equivalent, 168.6 mg.

Eighty-eight ml. of the solution was evaporated to dryness *in vacuo* at 30-35°, using two receivers, the first cooled in a freezing mixture and the second in an acetone-carbon dioxide mixture. More water was added and the evaporation process was repeated to ensure as complete a removal of formaldehyde as possible. The white residue still had a persistent odor of formaldehyde. It was thoroughly extracted with ether (200 ml.). The ether extract on removal of ether left only a trace of material.

The combined aqueous distillates from both the receivers was added to a warm solution of 1.5 g. of dimedone in 150 ml. of water, vigorously shaken and left overnight. The dimedone derivative of formaldehyde was filtered off (1.219 g.) and the filtrate was made basic to phenolphthalein end-point, saturated with sodium sulfate and continuously extracted with ether for twenty-four hours. The ether extract was dried over anhydrous sodium sulfate, filtered and the ether removed by distillation. The residual oil was dissolved in 20 ml. of dioxane, 0.9 g. of 2,4-dinitrophenylhydrazine and a drop of concentrated hydrochloric acid were added and the solution refluxed for thirty minutes.

The dioxane was then removed *in vacuo* collecting the distillate in a cooled receiver. The distillate was treated with 20 ml. of water and titrated to phenolphthalein end-point with 0.05 *N* sodium hydroxide, of which 32 ml. was required. The solvent was then removed and the residue was taken up in 3 ml. of water and 10 ml. of ethanol, 400 mg. of *p*-bromophenacyl bromide was added and the mixture refluxed for two hours. The solution was filtered hot and concentrated to 5 ml. and water was added to incipient turbidity. The crystals that separated (235 mg.) melted at 85°, identical with the *p*-bromophenacyl ester of acetic acid. More derivative was recovered from the filtrate.

The yellow residue of dinitrophenylhydrazones after removal of dioxane was dissolved in 50 ml. of dry benzene and passed through an alumina column (100 g.). The column was washed by benzene. The first zone which was bright orange yellow passed into the filtrate completely with about 500 ml. of benzene. On concentrating this effluent portion to 20 ml. scarlet crystals separated. The yield was 0.67 g. of product, m. p. 190-191° (cor.). A melting point of the mixture of this product with an authentic specimen of the dinitrophenylhydrazone of methyl isopropenyl ketone was 190-191°.

*Anal.* Calcd. for $C_{11}H_{12}O_4N_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 50.31; H, 4.57; N, 20.81.

On continuing the washing with benzene, after an interval in which no material passed into the filtrate, another zone moved into the filtrate and was collected separately. The deep yellow solution was concentrated to 2 ml. and treated with petroleum ether (b. p. 60–110°) when a dark red oil was thrown down, which solidified on rubbing to form a yellow powder. The yield was 0.12 g. of the 2,4-dinitrophenylhydrazone of β-methyl-γ-ketobutanol acetate. The material was purified by two crystallizations from ethanol, m. p. 78° (cor.).

*Anal.* Calcd. for $C_{13}H_{16}O_6N_4$: C, 48.15; H, 4.97; N, 17.28. Found: C, 48.18; H, 5.21; N, 17.41.

**Preparation of the 2,4-Dinitrophenylhydrazone of Methyl Isopropenyl Ketone from β-Methyl-γ-ketobutanol.**—A solution of 200 mg. of β-methyl-γ-ketobutanol[6] in 60 ml. of methanol was heated for a few minutes with 400 mg. of 2,4-dinitrophenylhydrazine, two drops of concentrated hydrochloric acid was added and the solution was refluxed for three hours. The orange yellow solution was concentrated to 15 ml. and three successive fractions of crystalline material totaling 320 mg. were collected, by further concentration and cooling. All the three fractions, after one recrystallization from ethanol, melted at 190–191° and admixture with an authentic specimen of the 2,4-dinitrophenylhydrazone[5] of methyl isopropenyl ketone did not depress the melting point. It was also noticed that the melting point of this dinitrophenylhydrazone varied over a range of 3–4° depending on the rate of heating. When plunged into a pre-heated bath at 180° it melted at 191–192° (cor.). When heated from about 100° at a slow rate, the crystals melted at 188–189° (cor.).

*Anal.* Calcd. for $C_{11}H_{12}O_4N_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 50.30; H, 4.78; N, 20.64.

**Action of Lead Tetraacetate on the Dibenzoate (V) of Compound IV, $C_8H_{18}O_4$.**—A solution of 0.5 g. of the dibenzoate in 25 ml. of dry benzene was treated with shaking with 0.57 g. (1 mole) of pure lead tetraacetate in two portions within five minutes. The lead tetraacetate was immediately taken up (negative test with moistened starch-potassium iodide paper). An additional 0.05 g. of the lead tetraacetate was added and an excess of this reagent persisted even after shaking for two hours. The excess was destroyed by the dropwise addition of ethylene glycol.

The solution was filtered and the residue was washed repeatedly with benzene. The clear benzene solution was distilled *in vacuo* at 35° and the residual mobile colorless oil was dried to constant weight in a vacuum desiccator at room temperature. The yield was 0.4 g.

The oil was dissolved in 5 ml. of pure dioxane and treated with a solution of 0.45 g. of 2,4-dinitrophenylhydrazine in 20 ml. of pure dioxane. One drop of concentrated hydrochloric acid was added and the solution was refluxed for two hours. The dioxane was then completely removed *in vacuo* and the residue taken up in 100 ml. of dry benzene. The benzene solution was passed through a column of alumina (100 g.) and washed continuously with dry benzene. A yellowish brown zone moved rapidly into the filtrate (500 ml.). This was collected separately and concentrated to 10 ml. The scarlet crystals that separated on cooling (0.185 g.) melted at 190° (cor.). One recrystallization from benzene gave crystals, m. p. 190–191° (cor.). The melting point of a mixture with an authentic sample of the derivative of methyl isopropenyl ketone was not depressed. On continuing the washing of the column with benzene, no more material passed into the filtrate. The column was then developed by 100 ml. of benzene containing 10% chloroform, and then by a 50-50 mixture of benzene and chloroform. A deep yellowish-brown zone moved into the filtrate and was collected separately (1500 ml.). The material recovered from this filtrate by evaporation was purified by another passage through alumina, rejecting the forerun and collecting the major zone separately. The filtrate from this chromatogram was concentrated to 10 ml. when yellow crystals (0.075 g.), m. p. 184–186° (cor.) separated. Another crystallization from benzene did not change the melting point. The melting point of a mixture with an authentic specimen of the 2,4-dinitrophenylhydrazone of acetol benzoate was not depressed.

*Anal.* Calcd. for $C_{16}H_{14}O_6N_4$: C, 53.62; H, 3.94; N, 15.63. Found: C, 53.62; H, 4.20; N, 15.47.

On continuing the elution of the column, after removal of the last zone, with chloroform as solvent, a rose-colored zone moved into the filtrate. The material from this zone was purified by another passage through alumina and yielded pink crystals, m. p. 300°. The quantity was insufficient to permit further characterization.

**Acetol Benzoate.**—This has been prepared previously[7] but the details are meager. An improved procedure is as follows. A mixture of 15 g. of dry potassium benzoate (dried to constant weight at 110°) and 9 g. of chloroacetone was heated for four hours in an oil-bath at 160°. After cooling, the residue in the flask was thoroughly stirred with 300 ml. of ether, filtered and the residue washed repeatedly with ether. The combined ether filtrate was dried over anhydrous sodium sulfate, filtered and the ether removed by distillation. The residue was distilled *in vacuo.* The product boiled at 140–141°(10 mm.) or 98–99°(0.5 mm.); $n^{20}D$ 1.5223. The yield was 13.5 g. (81%) of a colorless limpid oil.

*Anal.* Calcd. for $C_{10}H_{10}O_3$: C, 67.39; H, 5.66. Found: C, 67.11; H, 5.92.

The 2,4-dinitrophenylhydrazone of the above compound was prepared by the usual procedure and purified by crystallization from benzene; yellow crystals, m. p. 184–186° (cor.).

*Anal.* Calcd. for $C_{16}H_{14}O_6N_4$: C, 53.62; H, 3.94; N, 15.63. Found: C, 53.80; H, 3.95; N, 15.35.

**Reduction of Methyl Anhydromonocrotalate with Lithium Aluminum Hydride.**—The procedure was the same as that previously described for methyl monocrotalate. The product was a thin colorless sirup, the yield being 1.5 g. from 2 g. of the ester (86%). On distillation *in vacuo,* it passed over at 120–122° (0.4 mm.).

*Rotation.* 0.2045 made up to 1 ml. with absolute ethanol at 27.5° gave $\alpha_D$ +0.87°; *l*, 1; $[\alpha]^{27.5}D$ +4.25°.

*Anal.* Calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.75; H, 10.13.

**Di-*p*-nitrobenzoate of the above Product.**—This was prepared in pyridine solution and isolated as usual. The product was first recrystallized from dilute ethanol and then from benzene until a constant melting point was obtained. It formed colorless crystals, m. p. 144–145° (cor.).

*Anal.* Calcd. for $C_{22}H_{22}O_9N_2$: C, 57.62; H, 4.84; N, 6.12. Found: C, 57.15; H, 5.10; N, 6.25.

**Catalytic Reduction of the Lithium Aluminum Hydride Reduction Product of Methyl Anhydromonocrotalate.**—A solution of 204 mg. of the lithium aluminum hydride reduction product in 10 ml. of ethanol was added to a suspension of 25 mg. of platinic oxide catalyst, which had been previously shaken with hydrogen to constant absorption. The reduction was carried out at atmospheric pressure and one mole of hydrogen was absorbed. After filtration of the catalyst and removal of solvent, 210 mg. of a colorless oil was obtained. This was converted to the *p*-nitrobenzoate by the usual procedure. In spite of repeated crystallization from dilute ethanol or benzene-petroleum ether (b. p. 60–110°) mixture, the product melted over a range from 125–145°. The first crop obtained by crystallization from absolute ethanol melted fairly sharply at 149–151°. This was analyzed. Presumably, a mixture of diastereoisomers is involved, but no attempt was made to isolate both forms.

*Anal.* Calcd. for $C_{22}H_{24}O_9N_2$: C, 57.38; H, 5.25; N, 6.09. Found: C, 57.15; H, 5.48; N, 6.25.

**Action of Sodium Metaperiodate on the Lithium Aluminum Reduction Product from Methyl Anhydromonocrotalate.**—A solution of 313 mg. of the freshly distilled sirup in 5 ml. of water was treated with 10 ml. of 0.196 *M* sodium metaperiodate solution and made up to 25 ml. with water. The solution became milky instantaneously, with separation of a heavy oil. At the end of twenty-four hours no free periodate was detectable. One ml. of the supernatant aqueous layer was withdrawn and shaken with 15 ml. of a saturated solution of dimedone and left for twenty-four hours. The formaldehyde dimedone derivative was filtered and dried to constant weight (10 mg.). This was equivalent to 26 mg. of formaldehyde in the total solution. The total formaldehyde, if one mole had been split off, should be 59 mg.

The rest of the solution was extracted with ether and the ether extract was dried over anhydrous sodium sulfate. On filtration and removal of the ether, 200 mg. of a colorless oil was obtained. This darkened progressively on keeping. Attempts to characterize the oil, by preparation of crystalline derivatives, were unsuccessful.

**Reduction of Methyl Dihydroanhydromonocrotalate with Lithium Aluminum Hydride.**—By following the procedure previously described for methyl monocrotalate, 3.2 g. of the ester gave 2.6 g. (93%) of the reduction product as an extremely viscous colorless sirup. A small portion of the product was distilled at 0.05 mm.

*Rotation.* 0.1259 g. made up to 1 ml. with absolute ethanol at 32° gave $\alpha_D$ +0.44°; $l$, 1; $[\alpha]^{32}D$ +3.49°.

*Anal.* Calcd. for $C_8H_{18}O_3$: C, 59.24; H, 11.19. Found: C, 59.10; H, 11.15.

**Di-*p*-nitrobenzoate of the Above Compound.**—This was prepared by the usual procedure and purified by three recrystallizations from benzene. It formed colorless crystals, m. p. 174° (cor.).

*Anal.* Calcd. for $C_{22}H_{24}O_9N_2$: C, 57.38; H, 5.25; N, 6.09. Found: C, 57.67; H, 5.36; N, 5.96.

**Action of Sodium Metaperiodate on the Lithium Aluminum Hydride Reduction Product from Methyl Dihydroanhydromonocrotalate.**—A solution of 506 mg. of the sirup in 5 ml. of water was treated with 14.2 ml. of 0.196 *M* sodium metaperiodate solution and made up to 25 ml. with water. The mixture was shaken vigorously and left for twenty-four hours.

One ml. of the solution was then withdrawn and the excess periodate was estimated by the standard procedure. The amount of periodate consumed was 13.95 ml. (approximately one mole).

One ml. of the solution was employed for estimating the formaldehyde content of the solution. The total formaldehyde in solution was found to be 78 mg. and on the basis of the periodate consumed 82 mg. should be present.

The rest of the solution was added to 0.9 g. of dimedone in 50 ml. of hot water, shaken vigorously and left for twenty-four hours. The yield of dimedone derivative was 736 mg., m. p. 188–189°.

The filtrate was basified with sodium hydroxide solution to phenolphthalein end-point, saturated with sodium sulfate and repeatedly extracted with ether. The ether extract was dried over anhydrous sodium sulfate. After filtration, most of the ether was distilled off. The final portions of the ether were removed by slow evaporation at room temperature. The residue was a colorless oil with a pronounced camphoraceous odor. Attempts to characterize it through preparation of a crystalline derivative were unsuccessfull.

## Summary

A study of the reduction of methyl monocrotalate, methyl anhydromonocrotalate and methyl dihydroanhydromonocrotalate with lithium aluminum hydride and the behavior of the reduction products toward sodium metaperiodate, suggests a new structural formula for monocrotalic acid.

Methyl monocrotalate yielded a tetrahydroxy compound, $C_8H_{18}O_4$, whose structure was proved to be 1,2,3,5-tetrahydroxy-2,3,4-trimethylpentane by its cleavage with two moles of sodium metaperiodate to a mixture of formaldehyde, acetic acid and $\beta$-methyl-$\gamma$-ketobutanol.

The dibenzoate of the tetrahydroxy compound reacted with one mole of lead tetraacetate to yield a mixture of carbonyl compounds which were converted to the 2,4-dinitrophenylhydrazones and separated by chromatography. The derivatives were identified as those of methyl isopropenyl ketone (formed by the elimination of benzoic acid from $\beta$-methyl-$\gamma$-ketobutanol benzoate) and of acetol benzoate, by comparison with authentic specimens, confirming the structure proposed for the tetrahydroxy compound. Monocrotalic acid is therefore deduced to be $\alpha,\beta,\gamma$-trimethyl-$\beta$-hydroxy-$\gamma$-carboxy-$\gamma$-valerolactone.

Reduction of methyl anhydromonocrotalate and methyl dihydroanhydromonocrotalate gave the trihydroxy compounds $C_8H_{16}O_3$ and $C_8H_{18}O_3$, respectively, both of which reacted with sodium metaperiodate yielding formaldehyde as products of cleavage. Although the other fragments obtained in the cleavage process could not be properly characterized, these observations lend additional support to the newly proposed structural formula for monocrotalic acid.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

# Cryoscopic Studies in Methanesulfonic Acid[1]

BY RAYMOND A. CRAIG,[2] A. B. GARRETT AND MELVIN S. NEWMAN*

Cryoscopic investigation of the behavior of oxygenated organic compounds in sulfuric acid has provided useful information.[3,4] In some respects, however, this information is limited because the high acidity of the solvent leads to a leveling effect. Thus compounds differing in intrinsic basicity, such as ether, acetic acid, benzoic acid and methyl benzoate, all yield *i*-factors of two.[3,4]

In order to find out more about the relative basicities of such compounds and many others by cryoscopic measurements, a solvent of lower acid strength is required. A number of such acids have been studied, *e. g.*, acetic,[5] formic,[5] cinnamic,[6]

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[1] The material herein presented is taken from the Ph.D. thesis of R. A. C. presented to the Ohio State University. March, 1948.

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[3] See Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 45–48, 53–56 and 277–285.

[4] Newman, Craig and Garrett, THIS JOURNAL, **71**, 869 (1949).

[5] Raoult, *Ann. chim. phys.*, [6] **2**, 66 (1884).

[6] Falciola, *Gazz. chim. ital.*, **52**, I 175 (1922).