

***p*-Bromophenacyl Ester of Monocrotalic Acid.**—This was prepared by refluxing 0.68 g. of monocrotalic acid, exactly neutralized with alkali, with 1 g. of *p*-bromophenacyl bromide in 50% ethanol for five hours. The product was purified from ethanol: white crystals, m. p. 162–163° (corr.); yield, 0.47 g. (34%).

*Anal.* Calcd. for  $C_{16}H_{17}O_5Br$ : C, 49.87; H, 4.42. Found: C, 49.66; H, 4.46.

*Rotation.* 0.142 g. made up to 3.74 cc. in ethanol at 30.5°.  $\alpha_D -1.07$ ; *l*, 2;  $[\alpha]^{30.5}_D -14.1^\circ$ .

**Retronecanol,  $C_8H_{15}ON$ .**—After extraction with ether of the acid just described, the aqueous solution was clarified with norite, filtered and made strongly alkaline with sodium hydroxide. It was then extracted with five 50-cc. portions of ether. The ether extracts were dried with anhydrous sodium carbonate and the ether removed *in vacuo*. The oily basic residue quickly solidified. It was best purified by distillation, 140° (30 mm.): white crystals, m. p. 95–96°.

*Anal.* Calcd. for  $C_8H_{15}ON$ : C, 68.04; H, 10.70; N, 9.91. Found: C, 67.90; H, 10.50; N, 10.09.

*Rotation.* 1.524 g. made up to 25 cc. in ethanol at 28°.  $\alpha_D -11.0$ ; *l*, 2;  $[\alpha]^{28}_D -91.1^\circ$ .

**Retronecanol Hydrochloride.**—This product was prepared from retronecanol in the same manner as described for retronecine hydrochloride: white prisms from methanol-ether, m. p. 210° (corr.) with decomposition.

*Anal.* Calcd. for  $C_8H_{15}ON \cdot HCl$ : C, 54.03; H, 9.07. Found: C, 54.14; H, 9.14.

**Retronecanol Methiodide.**—This product was prepared by treating a dry ether solution of the base with the calculated amount of methyl iodide. It was purified from methanol-ether: white plates, m. p. 193° (corr.) with decomposition.

*Anal.* (Dried at 100°.) Calcd. for  $C_8H_{15}ON \cdot CH_3I$ : I, 44.88. Found: I, 45.22.

*Rotation.* 0.473 g. made up to 10 cc. in methanol at 27°.  $\alpha_D -5.00$ ; *l*, 2;  $[\alpha]^{27}_D -52.8$ .

**Retronecanol Picrate.**—The picrate was prepared in

aqueous solution and was purified from water: thin yellow plates, m. p. 210° (corr.).

*Anal.* Calcd. for  $C_8H_{15}ON \cdot C_6H_3O_7N_3$ : N, 15.13. Found: N, 14.93.

**Alkaline Degradation of Monocrotalic Acid to Monocrotic Acid.**—A mixture of 5 g. of monocrotalic acid and 30 cc. of 10% aqueous sodium hydroxide was heated under reflux for one hour. The solution was then acidified and extracted rapidly with ether. After drying the ether solution over anhydrous sodium sulfate, the solvent was removed and the product distilled, b. p. 145–147° (20 mm.),  $d^{26}_4$  1.072;  $n^{19}_D$  1.4480.

*Anal.* Calcd. for  $C_7H_{12}O_5$ : C, 58.31; H, 8.39. Found: C, 58.66; H, 8.39.

The acid gave a *p*-bromophenacyl ester, m. p. 78°, identical with that from monocrotic acid obtained directly from the monocrotaline.

### Summary

The alkaloid, monocrotaline, is extracted by ethanol in good yields from *Crotalaria spectabilis* or *Crotalaria retusa*. It has the formula  $C_{16}H_{23}O_8N$  and resembles the alkaloids occurring in various species of *Senecio*, *Heliotropium*, *Trichodesma* and *Erechtites*.

Monocrotaline undergoes alkaline hydrolysis to retronecine,  $C_8H_{13}O_2N$ , and an optically inactive, monobasic acid,  $C_7H_{12}O_5$ , called monocrotic acid. By hydrogenolysis monocrotaline gives retronecanol,  $C_8H_{15}ON$ , and an acid designated as monocrotalic acid,  $C_8H_{12}O_5$ .

It has been shown that monocrotalic acid is optically active, monobasic, and upon treatment with alkali gives the optically inactive acid, monocrotic acid,  $C_7H_{12}O_5$ , obtained by alkaline hydrolysis of the alkaloid.

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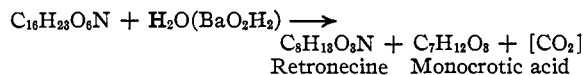
RECEIVED JULY 20, 1939

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

## Structure of Monocrotaline. II. Monocrotic Acid Obtained by Alkaline Hydrolysis of the Alkaloid<sup>1</sup>

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By alkaline hydrolysis of monocrotaline, the alkaloid present in the seed of the *Crotalaria spectabilis* and *Crotalaria retusa*, there were obtained retronecine and an acid,  $C_7H_{12}O_5$ , called monocrotic acid.



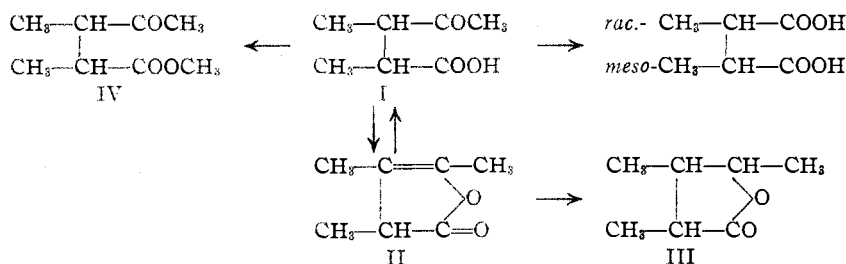
(1) For previous paper see, Adams and Rogers, THIS JOURNAL, 61, 2815 (1939).

(2) An abstract of a portion of a thesis submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

The same acid resulted when monocrotalic acid,  $C_8H_{12}O_5$ , obtained by hydrogenolysis of monocrotaline, was treated with aqueous alkali.

Monocrotic acid is optically inactive. It is monobasic and forms a monomethyl ester with diazomethane. The character of the third oxygen was determined by condensation of the methyl ester with dinitrophenylhydrazine. A hydrazone was formed in 85% yield and, since the ester shows no reducing action with Tollens' reagent or Feh-

ling's solution, the presence of a ketone group was assumed. The action of iodine and alkali on the acid gave iodoform, thus indicating a  $\text{CH}_3\text{CO}$ -group. Oxidation with sodium hypobromite resulted in a mixture of two products which proved to be *meso* and racemic  $\alpha,\alpha'$ -dimethylsuccinic acids, identified by comparison with authentic samples. Certain derivatives also were compared and shown to be identical. On the basis of these data the structural formula of monocrotic acid may be postulated as  $\alpha,\beta$ -dimethyllevulinic acid (I).



Monocrotic acid (I) on heating at atmospheric pressure loses water to give a neutral substance,  $\text{C}_7\text{H}_{10}\text{O}_2$ , which is reconverted to the acid by hydrolysis. Undoubtedly this is a lactone (II), and its formation may be explained by the loss of water between the enol form of the ketone group and the carboxyl, a reaction characteristic of  $\gamma$ -ketonic acids. Moreover, the lactone (II) was shown to be unsaturated by catalytic reduction to the saturated lactone (III). The lactone (II) also gave a positive test with Legal's reagent and Tollens' reagent, which is characteristic of  $\beta,\gamma$ -unsaturated  $\gamma$ -lactones.<sup>3</sup>

The formation of approximately an equal mixture of *meso* and racemic  $\alpha,\alpha'$ -dimethylsuccinic acids by hypobromite oxidation may be due to rearrangements taking place during the reaction, or it may be due to the fact that diastereoisomers exist in the monocrotic acid which cannot be separated by distillation. The former possibility is favored, since methyl monocrotate gives an 85% yield of pure dinitrophenylhydrazone. The clarification of this point must await synthesis.

### Experimental

**Methyl Monocrotate.**—Pure monocrotic acid<sup>1</sup> was treated in ether solution with excess diazomethane, b. p. 94–96° (18 mm.);  $n_D^{25}$  1.4273;  $d_4^{25}$  0.9968; yield 90%.

*Anal.* Calcd. for  $\text{C}_8\text{H}_{14}\text{O}_3$ : C, 60.75; H, 8.93. Found: C, 60.63; H, 8.77.

Esterification of monocrotic acid with methanol and sulfuric acid gave the same product in somewhat lower yields.

**Methyl Monocrotate 2,4-Dinitrophenylhydrazone.**—A mixture of 2 cc. of methyl monocrotate and 2.64 g. of 2,4-dinitrophenylhydrazine in 100 cc. of methanol was heated to boiling, 1 cc. of concentrated hydrochloric acid was added and the solution, after five minutes of refluxing, was allowed to cool. The orange crystals which separated were pure and the melting point did not change by recrystallization; m. p. 95–96°; yield, 3.63 g. (85%).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{18}\text{O}_6\text{N}_4$ : C, 49.70; H, 5.36. Found: C, 49.42; H, 5.31.

### Iodoform Reaction and Hypobromite Oxidation of Monocrotic Acid

**Meso and Racemic  $\alpha,\alpha'$ -Dimethylsuccinic Acids.**—From 1 g. of monocrotic acid dissolved in 13 cc. of 10% aqueous sodium hydroxide and treated with 35 cc. of a solution containing 10 g. of iodine and 20 g. of potassium iodide per 80 cc. of water, 0.157 g. of iodoform was isolated, m. p. 119°.

A solution of 5 g. of monocrotic acid in 30 cc. of water was made slightly alkaline with potassium hydroxide and cooled to 0°. A potassium hypobromite solution prepared by dissolving 18 g. of potassium hydroxide and 10 g. of bromine in 225 cc. of water was then added dropwise. The reaction mixture was stirred vigorously and maintained at 0° during the addition. After one and one-half hours at 0°, the solution was allowed to warm to room temperature, then concentrated to half its volume, acidified and extracted with ether. Upon evaporation of the ether, 4.6 g. of a yellow oily solid was obtained. This was dissolved in boiling water, treated with norite, then concentrated to 20 cc. and cooled. This caused 1.75 g. of an acid to separate which, after further purification from water, formed white crystals, m. p., 203–204° (the exact value depending upon the rate of heating). This compound gave no depression in a mixed melting point determination with authentic *meso*- $\alpha,\alpha'$ -dimethylsuccinic acid.

*Anal.* Calcd. for  $\text{C}_8\text{H}_{10}\text{O}_4$ : C, 49.31; H, 6.90. Found: C, 49.33; H, 6.81.

The mother liquors from the isolation of the *meso*  $\alpha,\alpha'$ -dimethylsuccinic acid gave on concentration to 5 cc. 1.29 g. of acid which, on purification by crystallization from benzene, melted at 121–122.5°. This compound gave no depression in a mixed melting point determination with racemic  $\alpha,\alpha'$ -dimethylsuccinic acid.

*Anal.* Calcd. for  $\text{C}_8\text{H}_{10}\text{O}_4$ : C, 49.30; H, 6.90. Found: C, 49.50; H, 7.03.

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

These two products were converted to their half anilides by the method of Auwers<sup>4</sup> and compared with synthetic half anilides of *meso* and racemic  $\alpha, \alpha'$ -dimethylsuccinic acids. From 203° melting acid was obtained a half anilide, m. p. 169–170°, and from the 121° melting acid, a half anilide, m. p. 135–136°.

*Anal.* (Half-anilide, m. p. 169–170°.) Calcd. for  $C_{12}H_{16}O_3N$ : C, 65.15; H, 6.84; N, 6.34. Found: C, 65.14; H, 7.09. (Half anilide, m. p. 135–136°.) Found: N, 6.29.

***p*-Bromophenacyl Ester of Acid, M. P. 203°.**—This was made by the usual procedure. It was purified from ethanol and gave white needles, m. p. 155–156°. The *p*-bromophenacyl ester of authentic *meso*- $\alpha, \alpha'$ -dimethylsuccinic acid gave the same product.

*Anal.* Calcd. for  $C_{22}H_{20}O_3Br_2$ : C, 48.93; H, 3.73. Found: C, 48.78; H, 3.66.

**Anhydride of Acid, M. P. 121°.**—This was prepared according to the procedure of Bone and Sprankling.<sup>5</sup> It was purified by crystallization from dry ether, m. p. 88°. It proved to be racemic  $\alpha, \alpha'$ -dimethylsuccinic anhydride.

*Anal.* Calcd. for  $C_8H_8O_3$ : C, 56.25; H, 6.25. Found: C, 55.58; H, 6.39.

**Dehydration of Monocrotic Acid to a Lactone;  $\alpha, \beta, \gamma$ -Trimethylangelicalactone.**—In a distillation apparatus 5 g. of monocrotic acid was heated to 240–250° at atmospheric pressure. At this temperature a colorless neutral liquid distilled. The product was taken up in ether, the ether solution washed with aqueous sodium bicarbonate and dried. The product boiled at 121° (20 mm.);  $n_D^{20}$  1.4665;  $n_D^{25}$  1.4640;  $d_4^{20}$  1.024.

*Anal.* Calcd. for  $C_7H_{10}O_2$ : C, 66.66; H, 7.94;  $M_D$  33.95. Found: C, 66.09; H, 7.90;  $M_D$  33.55.

This compound decolorizes permanganate, gives a positive test with Tollens' reagent and with sodium nitroprusside (Legal's test). These latter two tests were performed according to the procedure recommended by Jacobs and Hoffman.

A solution of 5 g. of the lactone in 20 cc. of 10% ethanolic potassium hydroxide was refluxed for one hour. It was

then neutralized with hydrochloric acid to litmus and the ethanol evaporated *in vacuo*. The residue was taken up in water, ether was added and hydrochloric acid also. Continuous extraction took up the acid: colorless liquid, 145–147° (20 mm.), which was identical with the acid from which the lactone was formed.

*Anal.* Calcd. for  $C_7H_{12}O_3$ : C, 58.31; H, 8.79. Found: C, 58.40; H, 8.40.

**Hydrogenation of Lactone:  $\alpha, \beta$ -Dimethyl- $\gamma$ -valerolactone.**—A solution of 10 g. of the lactone just described in 100 cc. of ether was hydrogenated under 2000-lb. (133 atm.) pressure at 120° in the presence of 2 g. of Raney nickel. Reduction was complete in three hours; yield, 9.8 g. The product boiled at 106–107° (20 mm.);  $n_D^{15}$  1.4382;  $n_D^{20}$  1.4348;  $d_4^{20}$  0.987.

*Anal.* Calcd. for  $C_7H_{12}O_2$ : C, 65.62; H, 9.44;  $M_D$  34.02. Found: C, 65.28; H, 9.62;  $M_D$  33.84.

The same product resulted when methyl monocrotate was hydrogenated under similar conditions except that reduction was carried on for seven hours.

*Anal.* Found: C, 65.18; H, 9.39.

### Summary

Monocrotic acid,  $C_7H_{12}O_3$ , was obtained from the alkaloid monocrotaline by alkaline hydrolysis or by the action of alkali on monocrotalic acid.

It is optically inactive, monobasic and forms a monomethyl ester by the action of diazomethane. The methyl ester gives a dinitrophenylhydrazone indicating the presence of a ketone group. The acid is oxidized by sodium hypobromite to *meso* and racemic  $\alpha, \alpha'$ -dimethylsuccinic acid.

Monocrotic acid dehydrates on heating to a neutral lactone which can be hydrolyzed to the acid. The lactone gives the color reactions characteristic for  $\beta, \gamma$ -unsaturated lactones.

It is concluded, therefore, that monocrotic acid is  $\alpha, \beta$ -dimethyllevulinic acid.

URBANA, ILLINOIS

RECEIVED AUGUST 14, 1939

(4) Auwers, Oswald and Thorpe, *Ann.*, **285**, 226 (1895).

(5) Bone and Sprankling, *J. Chem. Soc.*, **75**, 861 (1899).