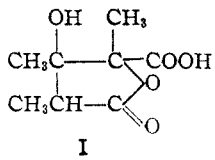
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Total Structure of Monocrotaline. XIII. Synthesis of Dihydroanhydromonocrotalic Acid

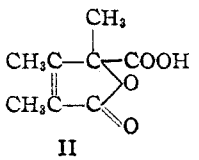
BY ROGER ADAMS AND F. B. HAUSERMAN[1]

The hydrolysis of the methyl ester of dihydroanhydromonocrotalic acid has been restudied. It has been demonstrated that by hydrolysis, either with basic or acidic reagents, two optically active stereoisomers are formed. The pure stereoisomers are converted into an equilibrium mixture, with either hot acid or base. It has been deduced that epimerization is occurring on the carbon atom alpha to the lactone grouping either by acid-catalyzed enolization or base-catalyzed ionization. The postulation of epimerization of the carbon atom alpha to the lactone, and not of the one alpha to the carboxyl, has been strongly supported by a study of optically active γ-carboxy-γ-valerolactone, synthesized by addition of hydrogen cyanide to levulinic acid followed by hydrolysis and resolution with quinine. This product is not racemized by boiling with acid or base which indicates that the carbon alpha to the carboxyl is stable under these conditions. By addition of hydrogen cyanide to α,β-dimethyllevulinic acid, followed by hydrolysis of the cyano lactone, first to the amide and then to the acid, an oily product is formed. From this, a pure brucine salt was readily obtained which on decomposition gave an acid identical in melting point and infrared spectrum and exactly opposite in rotation to one of the stereoisomers of dihydroanhydromonocrotalic acid. The structure of dihydroanhydromonocrotalic acid is thus proven and hence that of monocrotalic acid and of the alkaloid monocrotaline.

In a recent paper,[2] the structures of monocrotalic acid, anhydromonocrotalic acid and dihydroanhydromonocrotalic acid were established as I, II and III, respectively, by reducing their methyl esters



I



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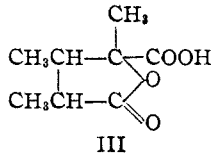


III

with lithium aluminum hydride, followed by oxidative degradation of the products. They are all optically active. The hydrolysis of the methyl ester of dihydroanhydromonocrotalic acid (III) has been previously studied and three isomeric acids with different melting points and rotations were reported as formed in this reaction. Hydrolysis with hydrochloric acid gave one isomer,[3] with sodium hydroxide a second,[4] and treatment of the ester with potassium cyanide at high temperature followed by boiling with hydrochloric acid, a third.[5] These hydrolysis experiments have now been repeated. The products from the hydrochloric acid hydrolysis and from the potassium cyanide treatment were again obtained. These acids require several recrystallizations before a constant melting point and rotation are attained. Especially careful purification revealed that they had slightly different constants from those originally reported. The new values are m.p. 132.4–134.4°, $[\alpha]_D$ +5.60° by acid hydrolysis; m.p. 117.6–119.5°, $[\alpha]_D$ −60.00° by potassium cyanide treatment. Repeated recrystallization of the product from sodium hydroxide saponification of the ester established that it was not a pure entity but a mixture of the two isomeric acids just described.

The pure +5.60° and −60.00° stereoisomers of dihydroanhydromonocrotalic acid were treated with acidic and basic reagents in an attempt to explain how they were formed from the pure ester by acid and basic hydrolysis and to determine if they were interconvertible. It was found that by either procedure an interconversion occurs and that an equilibrium is reached which contains predominately the −60.00° isomer, if the reactions are continued the proper length of time (several hours to several days). The rotation at equilibrium was −56.00° (±1.00°). Dilute acids and alkalies at room temperature have no effect; the high temperature (200°) treatment with potassium cyanide followed by boiling concentrated hydrochloric acid or dilute hydrochloric acid at room temperature results in achieving an equilibrium rapidly; the same point is reached much more slowly by the action of concentrated hydrochloric acid. These experiments indicate the probability that the methyl dihydroanhydromonocrotalate has the same configuration as the +5.60° stereoisomeric acid. This equilibrium may best be explained by a mechanism involving epimerization of the carbon alpha to the lactone by acid-catalyzed enolization and base-catalyzed ionization,[6] formulated in equations A and B, respectively. In equation B it is necessary to assume that ionization in the presence of base occurs prior to any possible opening of the lactone ring. This might be anticipated in view of the unusual stability of lactones of this type. If the difference between the stereoisomers involved a change in the configuration of the groups on the α-carbon to the carboxyl, epimerization of the α-carbon by both acid and alkali would be difficult to explain. If the hydrolysis resulted in the α-carbon atom forming an intermediate carbonium ion, possible rearrangement of groups could be envisioned. However, such hydrolysis would predicate alkyl–oxygen cleavage in hydrolysis between the α-carbon to the carboxyl and the alcohol oxygen of the lactone, a very unlikely possibility.[7]

(1) An abstract of a thesis submitted by F. B. Hauserman to the Graduate College of the University of Illinois, 1951, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Standard Oil Company of California Fellow, 1949–1950; and Allied Chemical and Dye Corporation Fellow, 1950–1951.

(2) R. Adams and T. R. Govindachari, THIS JOURNAL, **72**, 158 (1950).

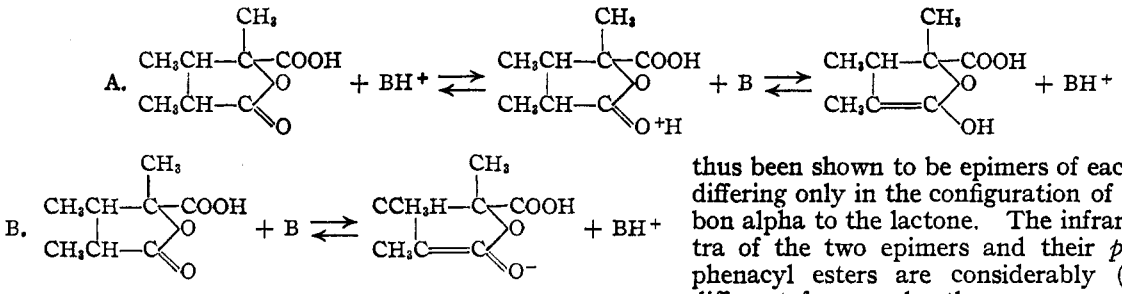
(3) R. Adams, E. F. Rogers and R. S. Long, *ibid.*, **61**, 2822 (1939).

(4) R. S. Long, Thesis, Doctor of Philosophy, University of Illinois, 1940, p. 50.

(5) R. Adams and J. M. Wilkinson, THIS JOURNAL, **65**, 2203 (1943).

(6) G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 255.

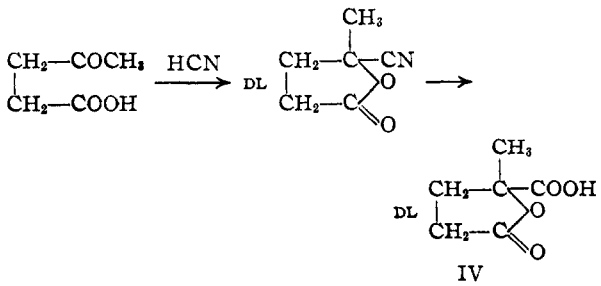
(7) F. A. Long and L. Friedman, THIS JOURNAL, **72**, 3692 (1950).



Strong evidence that merely the α-carbon to the lactone is involved resulted from a study of the action of acidic and basic reagents on optically active γ-carboxy-γ-valerolactone (IV). This compound differs from dihydroanhydromonocrotalic acid (III) only by the absence of methyl substituents on each of the methylene groups and, therefore, contains only one asymmetric carbon. The optically active acid was recovered completely unchanged in rotation when refluxed with concentrated hydrochloric acid for five hours or 10% aqueous sodium hydroxide for 11 hours. If the carbon alpha to the carboxyl group in the dihydroanhydromonocrotalic acid is involved in the interconversion of its stereoisomers when each is treated with acid or base, then racemization of the optically active γ-carboxy-γ-valerolactone (IV) would be expected to occur by similar treatment.

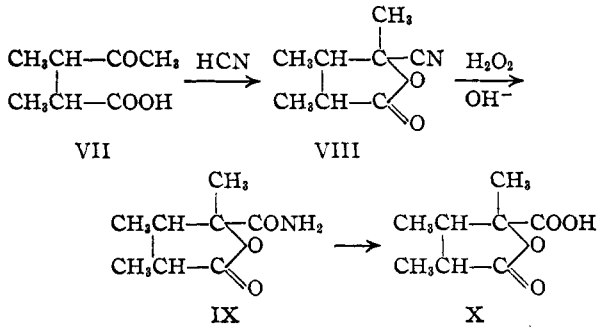
The treatment of γ-carboxy-γ-valerolactone (IV) with potassium cyanide at high temperature followed by acid did not result in simple hydrolysis. Moreover, neither α-cyano-α-methylglutaric acid nor α-methylglutaric acid could be isolated which might have formed if the reaction proceeded according to that described for γ-valerolactone or its γ-methyl-δ-carbethoxy derivative with the same reagent.[8,9] The difference in reactivity of γ-carboxy-γ-valerolactone (IV) and dihydroanhydromonocrotalic acid (III) with potassium cyanide can be explained by the presence of the additional methyl groups in the latter compound. These groups increase the stability of the lactone ring and may act as a shield to the hydroxyl group in a way to inhibit attack by the potassium cyanide.

γ-Carboxy-γ-valerolactone (IV) was prepared by the addition of hydrogen cyanide to levulinic acid followed by acid hydrolysis of the cyanolactone. The DL-acid was resolved by means of quinine and a pure enantiomorph with $[\alpha]_D$ +15.39° was obtained.



The +5.60° and the −60.00° rotating stereoisomers of dihydroanhydromonocrotalic acid have thus been shown to be epimers of each other, differing only in the configuration of the carbon alpha to the lactone. The infrared spectra of the two epimers and their *p*-bromophenacyl esters are considerably (Fig. 1) different from each other.

The synthesis of dihydroanhydromonocrotalic acid has now been successfully achieved. α,β-Dimethyllevulinic acid (VII) was prepared by the introduction of a methyl group and an α-propionic ester residue into ethyl acetoacetate followed by saponification and decarboxylation. The addition



of hydrogen cyanide to VII yielded the cyano lactone VIII. Although VIII boiled over a narrow range, it probably consisted of a mixture of stereoisomers. Acid hydrolysis of the nitrile (VIII) gave an oily acid (X) which could not be crystallized. This oil was probably a mixture of racemates as deduced from the study of acidic and basic reagents on the stereoisomers of dihydroanhydromonocrotalic acid (III). However, a pure *p*-bromophenacyl ester was prepared from the oil and its infrared spectrum was almost identical to that of the *p*-bromophenacyl ester of the −60.00° form of dihydroanhydromonocrotalic acid as shown in Fig. 1, curve 3. Partial hydrolysis of the cyano lactone (VIII) with alkaline hydrogen peroxide gave a solid amide. This amide varied in purity dependent on the conditions used in the preparation. With less than one mole equivalent of hydrogen peroxide a more nearly pure amide resulted than with excess over one mole; this may indicate selective reaction with one of the stereoisomers. The purity of the amide, however, is unimportant since it has been established that on hydrolysis of the amide to the acid, epimerization will occur on the α-carbon to the lactone and thus a mixture of acids will always result. The oily acid from the acid hydrolysis of impure amides (melting between 95 and 128°) was resolved with brucine. The brucine salt which separated was readily purified. Upon decomposition, a solid acid resulted, m.p. 117.6–119.3°, $[\alpha]_D$ +60.00°, identical in infrared spectrum to the −60.00° stereoisomer of dihydroanhydromonocrotalic acid shown in Fig. 1, curve 2. The synthetic acid is thus the mirror image of the product from the natural source. The *p*-bromophenacyl esters of the synthetic acid and that de-

(8) W. Wislicenus, *Ann.*, **238**, 101 (1886).
(9) L. Ruzicka, *Ber.*, **50**, 1362 (1917).

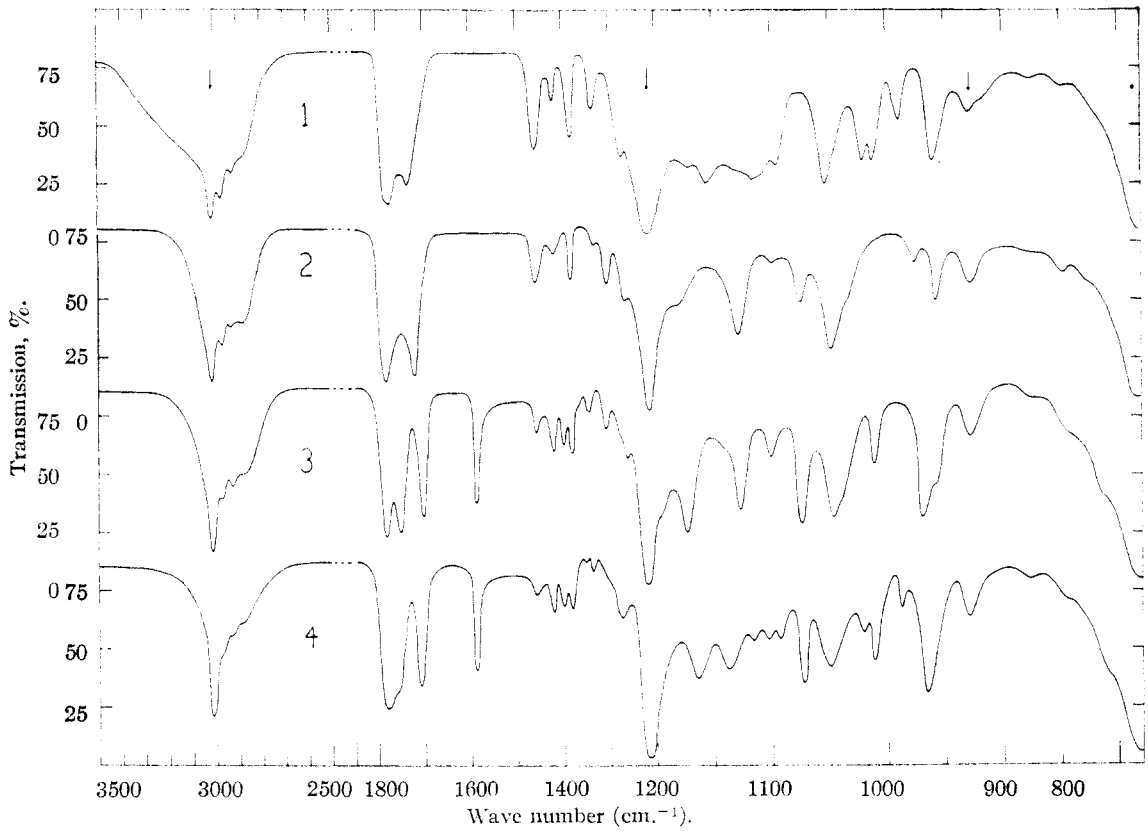
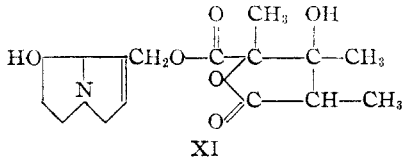


Fig. 1.—(1) stereoisomer, +5.60°, of dihydroanhydromonocrotalic acid; (2) stereoisomer, −60.00°, of dihydroanhydromonocrotalic acid; (3) *p*-bromophenacyl ester of stereoisomer, −60.00°, of dihydroanhydromonocrotalic acid; (4) *p*-bromophenacyl ester of stereoisomer, +5.60°, of dihydroanhydromonocrotalic acid. All spectra were taken in chloroform solution. Arrows indicate chloroform absorption bands.

rived from the monocrotalic acid had identical infrared spectra (Fig. 1, curve 3), melting points and exactly opposite rotations. The structure of dihydroanhydromonocrotalic acid is, therefore, unequivocally confirmed as III and monocrotalic acid must have structure I.

With this information and a knowledge of the structure of retronecine,[10] the constitution of the alkaloid monocrotaline must be XI.



XI

The authors are indebted to Miss Elizabeth Petersen for determining, plotting and interpreting the infrared spectra and to Miss Emily Davis, Mrs. Jean Fortney and Mrs. Katherine D. Pih for microanalytical work.

Experimental

Hydrogenolysis of Monocrotaline: Monocrotalic Acid.—The procedure previously used[11] was slightly modified. A solution of 216 g. of monocrotaline in a mixture of 800 ml. of ethanol and 200 ml. of glacial acetic acid was hydrogenated in a 2.5-liter bomb at an initial pressure of 500 p.s.i. with 0.7 g. of platinum oxide catalyst. The theoretical amount of hydrogen was absorbed after 2.5 hours. The viscous residue, after evaporation of the solvent *in vacuo*, was dissolved in 700 ml. of *N* hydrochloric acid and the solution continuously extracted with ether for 8 days. The ether solution was evaporated *in vacuo*, yielding a solid residue containing acetic acid. The acetic acid was removed by drying over potassium hydroxide in a vacuum desiccator. The crude product (115.8 g., 92.5%) was purified by recrystallization from a mixture of benzene and ethanol (7:1); white plates, m.p. 180.5–182.0° (cor.); yield 99.2 g. (79.4%).

Rotation.—0.5000 g. made up to 20 ml. with water at 27° gave α_D −0.24°; *l*, 2; $[\alpha]^{27}D$ −4.80° (±0.20°).

Methyl Monocrotalate.—When monocrotalic acid was esterified with diazomethane,[3] it was found that a solid product was obtained more readily if the reaction mixture was filtered before evaporation of the solvent.[12] The yield of crude product was 103 g. (97.5%). The ester was used in the next step after one recrystallization from ether.

Methyl Anhydromonocrotalate.—The procedure used was developed by Eilar.[12] In a 200-ml. flask equipped with a Claisen head and a water-cooled adapter, a mixture of 95.5 g. of methyl monocrotalate and 7.5 g. of sirupy phosphoric acid was heated at 150–168° (bath temperature) and at a pressure of 0.7–1.5 mm. The product distilled at a rate of one drop every 10 seconds. The yield of crude ester was 82.6 g. (95%). Fractionation of this distillate gave 69.5 g. (80.2%) of methyl anhydromonocrotalate, b.p. 82–83° (0.5 mm.). This product had a higher rotation than any previously prepared.

Rotation.—(Pure liquid at 27°) α_D +37.44°; *l*, 1; $[\alpha]^{27}D$ +33.13°.

Methyl Dihydroanhydromonocrotalate.—A total of 68 g. of methyl anhydromonocrotalate was hydrogenated in two batches. A solution of 34 g. of anhydro ester in 170 ml. of dry ether was refluxed for 1 hour over Raney nickel. After filtering, the ether solution was hydrogenated at 2500 p.s.i. and 125° using Raney nickel as the catalyst.

(10) R. Adams and N. J. Leonard, THIS JOURNAL, **66**, 257 (1944).
(11) R. Adams and E. F. Rogers, *ibid.*, **61**, 2819 (1939).
(12) K. R. Eilar, Research Report, Department of Chemistry, University of Illinois, 1950.

After 3 hours no more hydrogen was absorbed with the reduction only 90% complete. The catalyst was removed by filtration and the filtrates from two batches were combined and the ether removed by distillation. Fractionation of the residue yielded 59.7 g. of material which still contained some of the unreduced ester. This crude product was rehydrogenated in four batches using a more dilute ether solution. A solution of 15 g. of ester in 155 ml. of dry ether was hydrogenated at 1450 p.s.i. and 125° for 3.5 hours. The residue obtained from four batches, after removal of the ether, was carefully fractionated yielding 44.4 g. (63.2%) of pure methyl dihydroanhydromonocrotalate; b.p. 73–74° (0.24 mm.), 92–93° (0.77 mm.); $n^{20}D$ 1.4526; d^{29}_4 1.099.

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.06; H, 7.53. Found: C, 58.30; H, 7.30.

Rotation.—(Pure liquid at 29°) αD +1.70°; *l*, 1; $[\alpha]^{29}D$ +1.55°.

A further 5.8 g. (8.3%) of product was recovered from the fractionation column.

Acid Hydrolysis of Methyl Dihydroanhydromonocrotalate: Stereoisomer, +5.60°, of Dihydroanhydromonocrotalic Acid.—The hydrolysis was carried out according to the procedure previously described[3] and from 12.7 g. of ester, 5.95 g. (50.8%) of crude acid resulted. The acid, which melted at 121–126° (cor.) after one recrystallization, required twelve more recrystallizations from benzene before a product with constant melting point and rotation was obtained; white plates, m.p. 132.4–134.4° (cor.); yield 2.3 g. (19.5%).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.79; H, 7.26.

Rotation.—0.5000 g. made up to 20 ml. with absolute ethanol at 29° gave αD +0.28°; *l*, 2; $[\alpha]^{29}D$ +5.60° (±0.20°).

The infrared spectrum of the acid (Fig. 1, curve 1) shows a lactone absorption band at 1774 cm.$^{-1}$ and a carboxyl absorption band at 1736 cm.$^{-1}$.

The *p*-Bromophenacyl Dihydroanhydromonocrotalate (+5.60°).—From 0.2 g. of the +5.60° isomer and an equivalent amount of *p*-bromophenacyl bromide, the ester was formed according to the standard procedure. Purified from 80% ethanol it formed white needles, m.p. 141.7–143.2° (cor.); yield 0.27 g. (63%).

Anal. Calcd. for $C_{16}H_{17}O_5Br$: C, 52.03; H, 4.61. Found: C, 52.01; H, 4.55.

Rotation.—0.2000 g. made up to 20 ml. with C.P. acetone at 28° gave αD −0.09°; *l*, 2; $[\alpha]^{28}D$ −4.50° (±0.50°).

The infrared spectrum of the ester is shown in Fig. 1, curve 4.

Brucine Salt of Dihydroanhydromonocrotalic Acid, +5.60°.—The brucine salt of the +5.60° isomer was prepared by dissolving 0.120 g. of the acid and an equivalent amount of brucine in 50 ml. of ethyl acetate. The solution was filtered hot and the filtrate concentrated to 12 ml. Upon the addition of 6 ml. of petroleum ether (b.p. 30–60°) and 12 ml. of cyclohexane, 0.36 g. (80.8%) of solid separated. The salt was purified by a similar procedure; white needles, m.p. 156.2–158.7° (cor.) (dec.); yield 0.21 g. (47%).

Rotation.—0.1000 g. made up to 20 ml. with absolute ethanol at 30° gave αD −0.09°; *l*, 2; $[\alpha]^{30}D$ −9.00° (±1.00°).

Further attempts at recrystallization failed. An oil was obtained which could not be crystallized.

Treatment of Methyl Dihydroanhydromonocrotalate with Potassium Cyanide: Stereoisomer, −60.00°, of Dihydroanhydromonocrotalic Acid.—A mixture of 5.0 g. of methyl dihydroanhydromonocrotalate and 2.5 g. of potassium cyanide was heated for 9 hours at 205–212° (bath temperature) and the procedure previously described[5] was followed. After the treatment with hydrochloric acid and extraction with ether, the yellow oil obtained was crystallized from 300 ml. of carbon tetrachloride. The yield of solid was 3.58 g. (77.5%). One recrystallization from the same solvent yielded 3.21 g. (69.5%) of acid melting at 71–91.8°. About 25 recrystallizations from carbon tetrachloride were required for complete purification; white plates, m.p. 117.6–119.5° (cor.); yield 0.35 g. (7.6%).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.55; H, 6.89.

Rotation.—0.2000 g. made up to 20 ml. with absolute ethanol gave αD −1.20°; *l*, 2; $[\alpha]^{17}D$ −60.00° (±0.50°).

The infrared spectrum of this isomer of dihydroanhydromonocrotalic acid (Fig. 1, curve 2) shows the lactone absorption band at 1782 cm.$^{-1}$ and the carboxyl absorption band at 1720 cm.$^{-1}$.

The *p*-Bromophenacyl Dihydroanhydromonocrotalate (−60.00°).—The product, obtained by the standard procedure from equivalent amounts of the acid and *p*-bromophenacyl bromide, was purified from ethanol. It formed white crystals, m.p. 106.7–107.8° (cor.); yield 0.14 g. (32.7%).

Anal. Calcd. for $C_{16}H_{17}O_5Br$: C, 52.03; H, 4.61. Found: C, 52.32; H, 4.72.

Rotation.—0.1000 g. made up to 20 ml. with C.P. acetone at 24° gave αD −0.20°; *l*, 2; $[\alpha]^{24}D$ −20.00° (±1.00°).

The infrared spectrum of the ester is shown in Fig. 1, curve 3.

Brucine Salt of Dihydroanhydromonocrotalic Acid (60−.00°).—A mixture of 0.068 g. of acid and an equivalent amount of brucine dissolved in 44 ml. of benzene and 2 ml. of absolute ethanol was filtered hot and the filtrate concentrated to 8 ml. On cooling, no crystallization occurred. Evaporation of the solution to dryness yielded a solid melting at 90–128°. All attempts to recrystallize this product were unsuccessful.

Alkaline Saponification of Methyl Dihydroanhydromonocrotalate. A Mixture of the Stereoisomers of Dihydroanhydromonocrotalic Acid.—A mixture of 8.6 g. of methyl dihydroanhydromonocrotalate and 31.5 g. of 20% sodium hydroxide was refluxed for 13 hours.[4] The alkaline solution was extracted twice with ether to remove any unsaponified ester. After acidification to congo red with concentrated hydrochloric acid, the solution was continuously extracted with ether for 48 hours. After removal of the solvent, the residual oil was crystallized from carbon tetrachloride. The yield of crude product was 6.31 g. (80%). After one recrystallization from the same solvent, the acid melted at 84.5–95° and had $[\alpha]^{25}D$ −19.20° in absolute ethanol. After a second recrystallization from 1650 ml. of carbon tetrachloride and 16 recrystallizations from benzene, a pure isomer resulted; white plates, m.p. 132.6–134.6° (cor.); yield 0.61 g. (7.7%).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.82; H, 7.26.

Rotation.—0.5000 g. made up to 20 ml. with absolute ethanol at 28° gave αD +0.27°; *l*, 2; $[\alpha]^{28}D$ +5.40° (±0.20°).

The infrared spectrum of this product was identical to the spectrum of the acid hydrolysis product shown in Fig. 1, curve 1. Furthermore, the melting point of a mixture of this acid and that obtained by acid hydrolysis of the ester was 132.6–134.6° (cor.).

From an earlier run, the filtrates from eight recrystallizations using carbon tetrachloride were combined and evaporated to a mixture of solid and oil. Two recrystallizations of this crude product from carbon tetrachloride yielded 1.8 g. of acid melting at 60–90° and having $[\alpha]^{24}D$ −39.80° in absolute ethanol. The acid was partially purified by seven more recrystallizations from the same solvent; white crystals, m.p. 90.8–97° (cor.): yield 1.15 g.

Rotation.—0.5000 g. made up to 20 ml. with absolute ethanol at 25° gave αD −2.30°; *l*, 2; $[\alpha]^{25}D$ −46.00° (±0.20°).

It is obvious that by further purification, the −60.00° stereoisomer could have been obtained pure.

Treatment of Stereoisomers of Dihydroanhydromonocrotalic Acid with Acidic and Basic Reagents

(a) Treatment of +5.60° Stereoisomer with Potassium Cyanide.—A mixture of 1.0 g. of the +5.60° isomer and 1.08 g. of potassium cyanide was heated at 206–211° (bath temperature) for 9 hours. The dark reaction mixture was refluxed with 6 ml. of concentrated hydrochloric acid for 5 hours. After diluting with 35 ml. of water, the acid solution was continuously extracted with ether for 24 hours. The oil obtained on evaporation of the ether solution was crystallized from carbon tetrachloride; white crystals, $[\alpha]^{26}D$ −54.66° (±0.33°). The crude product was purified by 16 recrystallizations from carbon tetrachloride; white plates, m.p. 117.8–119.3° (cor.); yield 0.32 g. (32%).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.93; H, 7.03.

Rotation.—0.2000 g. made up to 20 ml. with absolute ethanol at 29° gave α_D −1.20°; *l*, 2; $[\alpha]^{29}D$ −60.00° (±0.50°).

The infrared spectrum of this acid was identical to that of the −60.00° isomer of dihydroanhydromonocrotalic acid (Fig. 1, curve 2) obtained from the reaction of the methyl ester with potassium cyanide.

(b) Treatment of +5.60° Stereoisomer with Potassium Cyanide.—This was the same as (a), except that the reaction mixture was acidified with 6% hydrochloric acid at room temperature. The product had an $[\alpha]^{28}D$ −56.00° (±1.00°).

(c) Treatment of −60.00° Stereoisomer with Potassium Cyanide.—The crude oil obtained by treating the −60.00° isomer as in (b) was crystallized from carbon tetrachloride; $[\alpha]^{24}D$ −54.37° (±1.94°).

(d) Treatment of +5.60° Stereoisomer with Concentrated Hydrochloric Acid.—A solution of 0.50 g. of the +5.60° isomer in 5 g. of concentrated hydrochloric acid was refluxed for 5 hours. The acid solution was diluted with 37 ml. of water and continuously extracted with ether for 18 hours. The ether was removed and the solid residue recrystallized from benzene; $[\alpha]^{25}D$ −5.66° (±0.33°).

(e) Treatment of +5.60° Stereoisomer with Concentrated Hydrochloric Acid.—The procedure was the same as (d) except the hydrochloric acid treatment was carried out for 5 days. The crude solid was recrystallized from carbon tetrachloride; $[\alpha]^{28}D$ −56.31° (±0.53°).

(f) Treatment of −60.00° Stereoisomer with Concentrated Hydrochloric Acid.—The treatment was identical to (d). The crude solid, however, was recrystallized from carbon tetrachloride; $[\alpha]^{24}D$ −58.15° (±1.26°).

(g) Treatment of +5.60° Stereoisomer with 10% Sodium Hydroxide.—A solution of 0.10 g. of the +5.60° isomer in 10% sodium hydroxide was refluxed for 11 hours. After acidification with 40 ml. of 10% hydrochloric acid, the reaction mixture was ether extracted. The solid residue obtained on removal of the ether was recrystallized from carbon tetrachloride; $[\alpha]^{23}D$ −34.27° (±1.56°).

(h) Treatment of +5.60° and −60.00° Stereoisomers with Dilute Acid and Base.—Both stereoisomers were recovered unchanged when dissolved in 4.5% hydrochloric acid at room temperature for an hour. The −60.00° isomer was also unaffected by 1% sodium hydroxide at room temperature.

DL-γ-Cyano-γ-valerolactone.—The procedure used by Blaise[13] was followed with slight modification. A cold solution of 100 g. of levulinic acid (b.p. 86–87°, 0.35 mm.) in 100 ml. of water was added with stirring to a cold solution of 68.3 g. of potassium cyanide in 84 ml. of water over a period of 30 minutes. The reaction mixture was stirred at 0° for 24 hours, during which time it became very dark in color. The solution was acidified by the slow addition of 201 g. of concentrated hydrochloric acid and then stirred at 0° for another 24 hours. After heating at 100° for 10 minutes, the solution was diluted with 253 ml. of water and continuously extracted with ether for 70 hours. After washing with 5% sodium bicarbonate solution and water and then drying, the ether was removed and the residue distilled under reduced pressure; b.p. 89–90° (1.40 mm.); yield 60 g. (55.8%). The liquid partially solidified on standing at 28°.[14]

DL-γ-Carboxy-γ-valerolactone.—A mixture of 50 g. of DL-γ-cyano-γ-valerolactone and 1100 g. of 20.8% hydrochloric acid was refluxed for 21 hours. The acid solution was diluted with 1500 ml. of water and continuously extracted with ether for 52 hours. After removal of the ether, the viscous, light brown residue was dried in a vacuum desiccator for 2 hours. The product weighed 54.1 g. (94%). From 30 g. of this solid, after recrystallization from a mixture of carbon tetrachloride and benzene, 22.6 g. of pure white needles resulted, melting the same as previously reported,[15] 72.3–73.5° (cor.).

Resolution of DL-γ-Carboxy-γ-valerolactone.—A solution of 13.5 g. of the DL-acid and 30 g. of anhydrous quinine in 1000 ml. of hot absolute ethanol was heated to boiling and filtered. The straw-colored filtrate was cooled at 0° for 20 hours. The white crystals which separated were isolated by filtration; m.p. 198–200° (cor.) (dec.); yield 16.2 g. (37.2%). A small sample was recrystallized from ethanol for analysis; m.p. 199.5–201.3° (cor.) (dec.).

Anal. Calcd. for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.89. Found: C, 66.85; H, 7.12.

Rotation.—0.1049 g. made up to 20 ml. with ethanol at 28° gave α_D −1.41°; *l*, 2; $[\alpha]^{28}D$ −134.41° (±0.95°).

The straw-colored solution obtained on dissolving 16 g. of the quinine salt in 250 g. of 10% hydrochloric acid was continuously extracted with ether for 34 hours. After removing the ether, the residual oil crystallized from a 1:1 mixture of benzene and carbon tetrachloride, yielding 3.86 g. (78.4%) of product. The pure enantiomorph was obtained on recrystallization from the same solvents; white crystals, m.p. 87.8–89.8° (cor.); yield 3.38 g. (69%).

Anal. Calcd. for $C_6H_8O_4$: C, 50.00; H, 5.60. Found: C, 50.20; H, 5.83.

Rotation.—0.5003 g. made up to 20 ml. with water at 28° gave α_D +0.77°; *l*, 2; $[\alpha]^{28}D$ +15.39° (±0.20°). 0.5088 g. made up to 20 ml. with absolute ethanol at 26° gave α_D −0.05°; *l*, 2; $[\alpha]^{26}D$ −0.99° (±0.20°).

Treatment of Optically Active γ-Carboxy-γ-valerolactone with Acidic and Basic Reagents (a) Treatment with Concentrated Hydrochloric Acid.—A solution of 0.50 g. of the +15.39° isomer of γ-carboxy-γ-valerolactone in 5 g. of concentrated hydrochloric acid was refluxed for 5 hours. About 95% of the lactonic acid was recovered, unchanged in melting point and specific rotation.

(b) Treatment with 10% Sodium Hydroxide.—A solution of 0.5 g. of the +15.39° isomer in 5 ml. of 10% sodium hydroxide was refluxed for 11 hours. About 93% of the lactonic acid was recovered, unchanged in melting point and specific rotation.

(c) Treatment with Potassium Cyanide.—When the reaction product obtained by heating the +15.39° isomer of γ-carboxy-γ-valerolactone with excess potassium cyanide at 210–215° was refluxed with 10% sodium hydroxide, ammonia was evolved. Hydrolysis of the reaction product with concentrated hydrochloric acid resulted in decarboxylation as shown by the vigorous evolution of carbon dioxide. No α-methylglutaric acid could be isolated.

α,β-Dimethyllevulinic Acid.—The procedure given by Adams and Long[16] was followed in the preparation of ethyl β-carbethoxy-α,β-dimethyllevulinate from ethyl β-carbethoxy-α-methyllevulinate.[17] The product was a colorless liquid, b.p. 105–106° (1.8 mm.); $n^{20}D$ 1.4461; yield 171.4 g. (55%).

Hydrolysis, with accompanying decarboxylation, gave α,β-dimethyllevulinic acid as a colorless oil; b.p. 113–115° (2.1 mm.); $n^{20}D$ 1.4465; yield 78 g. (77.2%).

Anal. Calcd. for $C_7H_{12}O_3$: neut. equiv., 144. Found: neut. equiv., 142.

α,β-Dimethyl-γ-cyano-γ-valerolactone.—A cold solution of 37.75 g. of α,β-dimethyllevulinic acid in 25 ml. of water was added, with stirring, to a cold solution of 20.8 g. of potassium cyanide in 31 ml. of water over a period of 15 minutes. The procedure followed was identical with that used for synthesis of γ-cyano-γ-valerolactone. The product was a colorless oil; b.p. 67–69° (0.30 mm.); $n^{21.5}D$ 1.4450; yield 17.2 g. (42.8%).

Anal. Calcd. for $C_8H_{11}O_2N$: C, 62.73; H, 7.24; N, 9.15. Found: C, 62.48; H, 7.40; N, 8.94.

A further 3.5 g. (8.8%) of product boiling at the same temperature was obtained, but it had a slightly higher refractive index, $n^{21.8}D$ 1.4461.

α,β-Dimethyl-γ-carboxy-γ-valerolactone (Dihydroanhydromonocrotalic Acid).—A mixture of 2.0 g. of the cyano lactone and 40.6 g. of 18.5% hydrochloric acid was refluxed for 26 hours. The acid solution was partially evaporated and then extracted 3 times with benzene and twice with ether. The combined extracts were evaporated and the oil was distilled *in vacuo* to remove the color. The oil did not solidify.

From 0.7 g. of the oil and an equivalent amount of *p*-bromophenacyl bromide the ester was prepared according to the standard procedure. It was purified by recrystallization from ethanol; white crystals, m.p. 136.1–137.5° (cor.).

(13) E. E. Blaise, *Bull. soc. chim.*, **23**, 918 (1900); see also J. Block, K. Kreckeler and B. Tollens, *Ann.*, **238**, 287 (1887).

(14) M. A. J. Ultee, *Rec. trav. chim.*, **28**, 1 (1909).

(15) W. Baker, *Proc. Leeds Phil. and Lit. Soc., Sci. Sect.*, **2**, 115 (1930).

(16) R. Adams and R. S. Long, THIS JOURNAL, **62**, 2819 (1939).

(17) C. Bischoff, *Ann.*, **206**, 320 (1881).

Anal. Calcd. for $C_{16}H_{17}O_5Br$: C, 52.03; H, 4.61. Found: C, 51.80; H, 4.88.

The infrared spectrum of the ester was almost identical to the spectrum of the *p*-bromophenacyl ester of the −60.00° isomer of dihydroanhydromonocrotalic acid shown in Fig. 1, curve 3. The only difference was that in the former ester the absorption bands at 1346 and 1173 cm.$^{-1}$ were weaker.

Amide of α,β-Dimethyl-γ-carboxy-γ-valerolactone (Amide of Dihydroanhydromonocrotalic Acid).—A modification of the procedure of McMaster and Noller[18,19] was used. A mixture of 10 g. of α,β-dimethyl-γ-cyano-γ-valerolactone and 130 ml. of 1% hydrogen peroxide (58% of the theoretical amount) was dissolved in 100 ml. of ethanol and made alkaline to phenolphthalein with 2.64 ml. of 6 *N* sodium hydroxide. The solution was stirred at 35–40°, without external heating, for 1 hour and then heated at 45–55° for 5 hours. A total of 12.5 ml. of 6 *N* sodium hydroxide was added in small portions during this period to maintain the solution alkaline to phenolphthalein. The cooled solution was acidified to *p*H 6.5 with 5% sulfuric acid and extracted seven times with chloroform. Evaporation of the chloroform extract yielded 2 g. (17.8%) of solid amide melting at 126–129° (cor.). The product was purified by dissolving in 325 ml. of a 2:1 mixture of ether and petroleum ether (b.p. 30–60°) and refluxing for 27 hours. After filtering hot, the solution was cooled to −10°. A yield of 0.67 g. of white crystals resulted which after one recrystallization from benzene melted at 137.1–139.3° (cor.); yield 0.59 g. (5.3%).

Anal. Calcd. for $C_8H_{13}O_3N$: C, 56.12; H, 7.65; N, 8.18. Found: C, 56.25; H, 7.79; N, 8.17.

In six other runs, it was found that the yield and the purity of the amide varied with the amount and concentration of the hydrogen peroxide used and with the alkalinity of the solution. A 10% yield of crude amide (m.p. 101.5–129°) was obtained when the amide was prepared as described above, except a 250% excess of 6% hydrogen peroxide solution was used. When a 100% excess of 4% hydrogen peroxide solution was used and sufficient 6 *N* sodium hydroxide added initially to maintain the solution alkaline to litmus throughout the heating period, a 23% yield of amide melting at 112.5–124° was obtained. However, the yield of crude amide, m.p. 91.5–113°, was increased to 49% if the solution was kept barely alkaline to litmus by the dropwise addition of 6 *N* sodium hydroxide during the heating period.

The infrared spectrum of the amide melting at 137.1–139.3° was taken and the spectra of lower melting amides, which had analyses corresponding to a pure amide, were compared with it. The spectrum of an amide melting at 133.6–136.1° was identical. The infrared spectrum of an amide melting at 127–129.3° differed only by having extra absorption bands at 1329, 1704 and 1043 cm.$^{-1}$. An amide melting at 120–124° had these same extra bands, only stronger, and there was another absorption band at 1154 cm.$^{-1}$. The infrared spectrum of an amide melting at 95–112° had extra absorption bands throughout the spectrum, in addition to the four listed which had started to shift. It is apparent that the lower melting amides contained a second racemate.

Hydrolysis of a Mixture of Racemates of the Amide of α,β-Dimethyl-γ-carboxy-γ-valerolactone. α,β-Dimethyl-γ-carboxy-γ-valerolactone (Dihydroanhydromonocrotalic Acid).—A mixture of 2.8 g. of various preparations of amide melting between 95 and 128° was dissolved in 60 ml. of 21% hydrochloric acid and refluxed for 12 hours. The acid solution was diluted with 200 ml. of water and continuously extracted with ether for 51 hours. Evaporation of the ether extract yielded *ca.* 3 g. of oil. This crude α,β-dimethyl-γ-carboxy-γ-valerolactone, which contained some solvent, was resolved directly.

Resolution of Crude α,β-Dimethyl-γ-carboxy-γ-valerolactone.—A solution of the 3 g. of crude acid just described in 46 ml. of benzene was added to a solution of 7.35 g. of brucine in 148 ml. of benzene and 6 ml. of absolute ethanol. The mixture was heated to boiling, filtered and evaporated to 150 ml. A solid separated on cooling which was isolated by filtration (Fraction 1); m.p. 234–244° (dec.); yield 1.13 g. (11.2%). The filtrate was further evaporated to 40 ml. and cooled. Another 0.41 g. (4.1%) of solid separated (Fraction 2); m.p. 230–240° (dec.). No more solid salt could be obtained by further evaporation of the filtrate and cooling.

Fraction 1 was recrystallized from benzene; white crystals, m.p. 248–251° (cor.) (dec.); yield 0.53 g. (5.3%).

Rotation.—0.1000 g. made up to 20 ml. with ethanol gave α_D +0.05°; *l*, 2; $[\alpha]^{16}D$ +5.00° (±1.00°).

Fraction 2 was added to the filtrate from the recrystallization of Fraction 1, the solution evaporated to 40 ml. and cooled. The solid which separated out formed white crystals, m.p. 245–247° (cor.) (dec.); yield 0.44 g. (4.4%) and was obviously essentially pure salt.

Anal. Calcd. for $C_{31}H_{38}N_2O_4$: C, 65.71; H, 6.76. Found: C, 66.00; H, 7.00.

Rotation.—0.1000 g. made up to 20 ml. with ethanol gave α_D +0.07°; *l*, 2; $[\alpha]^{17}D$ +7.00° (±1.00°).

Decomposition of the Brucine Salt. Stereoisomer, +60.00°, of α,β-Dimethyl-γ-carboxy-γ-valerolactone (Dihydroanhydromonocrotalic Acid).—A solution of 0.93 g. of recrystallized Fractions 1 and 2 in 66 g. of 11% hydrochloric acid was continuously extracted with ether for 38 hours. The ether was removed and the solid residue recrystallized from carbon tetrachloride; yield 0.25 g. (100%). After crystallization from the same solvent, white plates resulted, m.p. 117.6–119.3°.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.65; H, 7.22.

Rotation.—0.2000 g. made up to 20 ml. with absolute ethanol gave α_D +1.20°; *l*, 2; $[\alpha]^{17}D$ +60.00° (±0.50°).

The infrared spectrum of this acid was identical to that of the −60.00° isomer of dihydroanhydromonocrotalic acid shown in Fig. 1, curve 2.

***p*-Bromophenacyl Ester.**—The ester was prepared from 0.2 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. 107–108° (cor.); yield 0.14 g. (32.7%).

Anal. Calcd. for $C_{16}H_{17}O_5Br$: C, 52.03; H, 4.61. Found: C, 52.29; H, 4.87.

Rotation.—0.1000 g. made up to 20 ml. with C.P. acetone at 23° gave α_D +0.20°; *l*, 2; $[\alpha]^{23}D$ +20.00° (±1.00°).

The infrared spectrum of the ester was identical to the spectrum of the *p*-bromophenacyl ester of the −60.00° isomer of dihydroanhydromonocrotalic acid shown in Fig. 1, curve 3.

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(19) Br. Radziazewski, *Ber.*, **18**, 355 (1885).