neutralized with concentrated sodium hydroxide while cooling under running tap water. The precipitated solid was filtered and dried. It was thoroughy extracted with chloroform; the insoluble sodium acetate was removed by filtration. Evaporation of the chloroform extract yielded 2.79 g. of crude product (87%). It was dissolved in methanol, treated with Darco and evaporated with an air jet until about one-third of the solid crystallized. The crystals were removed and redissolved in methanol and the solution again partially evaporated. The operation was performed three times. The resulting solid was recrystallized twice from toluene. The yield of the *trans* isomer was 0.35 g. It melted at 225–226°.

Anal. Calcd. for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.25; H, 7.43; N, 7.07.

The combined methanol filtrates were concentrated to about one-third of their original volume and the precipitated solid removed. The filtrate was evaporated to dryness. This residue was recrystallized to constant melting point from toluene. The yield of the *cis* isomer was 0.28 g. It melted at 204–205°.

Anal. Calcd. for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.48; H, 7.65; N, 7.13.

An attempt was made to brominate the *trans* isomer with bromine in chloroform using powdered iron as catalyst. After 6 hours of refluxing, most of the compound was recovered unchanged.

The infrared spectra of the isomers in chloroform solution are very similar but not identical. Small differences were observed in the intensities of peaks and bands in the regions 840 to 1010 cm.$^{-1}$ and 1325 to 1350 cm.$^{-1}$. A shift of 3 to 4 cm.$^{-1}$ toward the higher frequencies was found for the *cis* isomer in the region 925 to 1010 cm.$^{-1}$. Spectra were also run in nitromethane solution in the region of intense absorption by chloroform. The spectrum of the *cis* isomer in nitromethane shows a band and peak at 1227 and 1210 cm.$^{-1}$ which appears only as a slight shoulder in the spectrum of the *trans* isomer.

Bis-(α,α-dimethylglutarimido)-nitromesitylene. A.—*trans*-Isomer.—To 5 ml. of 90% fuming nitric acid (sp. g. 1.5) at 0° was added 0.14 g. of *trans*-bis-(α,α-dimethylglutarimido)-mesitylene. The solution was maintained at 0° for 45 minutes, then poured onto 50 g. of cracked ice. The precipitated solid was filtered, washed with water and dried. The yield was 0.16 g. (quant.). Recrystallization from ethanol gave white shiny leaflets, m.p. 256.5–257.5°.

Anal. Calcd. for $C_{23}H_{29}N_3O_6$: C, 62.29; H, 6.59; N, 9.47. Found: C, 62.19; H, 6.41; N, 9.58.

B. *cis*-Isomer.—Treatment of 0.14 g. of *cis*-bis-(α,α-dimethylglutarimido)-mesitylene in the same manner yielded 0.14 g. (90%) of the lower-melting nitro compound, which crystallized from aqueous ethanol as colorless prisms, m.p. 234–236°.

Anal. Calcd. for $C_{23}H_{29}N_3O_6$: C, 62.29; H, 6.59; N, 9.47. Found: C, 62.58; H, 6.62; N, 9.68.

The spectra of the isomers in chloroform show much the same differences found for the unsubstituted glutarimides—small intensity variations in the regions 860 to 1010 cm.$^{-1}$ and 1300 to 1400 cm.$^{-1}$, and a 1 to 2 cm.$^{-1}$ shift toward the higher frequencies between 900 and 1000 cm.$^{-1}$ in the spectrum of the *cis* isomer.

4-Bromobutyl Thiocyanate.—To a stirred refluxing solution of 333 g. of tetramethylene bromide in 600 ml. of absolute ethanol was added over a period of 1.5 hours a solution of 82.5 g. of potassium thiocyanate in 60 ml. of water. Refluxing was continued for one additional hour, then the reaction mixture was poured into 1.5 l. of water and the oily layer decanted. The aqueous layer was extracted with ether, and the combined oil and ether extract was dried first over sodium sulfate, then over magnesium sulfate. Distillation yielded 150 g. of recovered tetramethylene bromide. The product was a colorless liquid, b.p. 97–99° (1 mm.). The yield was 81 g. (50%). A portion was redistilled for analysis, n^{20}_{D} 1.5288.

Anal. Calcd. for C_5H_8BrNS: C, 30.94; H, 4.15; N, 7.22. Found: C, 31.42; H, 4.34; N, 6.90.

4-Chlorobutyl Thiocyanate.—To a stirred refluxing solution of 282 g. of tetramethylene chloride in 500 ml. of absolute ethanol was added over a period of 3 hours 108 g. of potassium thiocyanate in 50 ml. of water. Refluxing was continued for 30 minutes longer. The isolation procedure described for 4-bromobutyl thiocyanate was used. Distillation at the water-pump yielded 142 g. of tetramethylene chloride. The product was obtained as a colorless liquid, b.p. 88.5–90.5° (1.5 mm.). The yield was 72 g. (44%). A portion was redistilled for analysis, n^{20}_{D} 1.5023.

Anal. Calcd. for C_5H_8ClNS: C, 40.13; H, 5.39. Found: C, 40.43; H, 5.48.

Attempts to prepare 4-bromobutanesulfonyl chloride and 4-chlorobutanesulfonyl chloride were unsuccessful. No distillable product was obtained by oxidation of the thiocyanates with chlorine in water at 5–10° or with chlorine in acetic acid solution containing the theoretical amount of water at 25–35°. In some cases no attempt was made to distil the product, but a dried chloroform extract of the oxidation mixture was allowed to react with diaminomesitylene. Only intractable orange oils and tars were isolated which failed to yield a solid product when subjected to ring closure conditions (refluxing aqueous sodium hydroxide).

URBANA, ILLINOIS

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

Dicrotaline. The Structure and Synthesis of Dicrotalic Acid

BY ROGER ADAMS AND BENJAMIN L. VAN DUUREN

RECEIVED JANUARY 23, 1953

Dicrotalic acid, obtained by the hydrolysis of the alkaloid dicrotaline, from *Crotalaria dura* (Wood and Evans) and *Crotalaria globifera* (E. Mey) has been shown by degradation studies to be β-methyl-β-hydroxyglutaric acid. The latter acid was synthesized and proved to be identical with the natural acid. The structure of dicrotaline is therefore completely elucidated.

Dicrotaline, $C_{14}H_{19}O_5N$, first isolated by Marais[1] yielded on hydrolysis a base, retronecine, which constitutes the basic portion of many Senecio alkaloids,[2] and a new dibasic acid, $C_6H_{10}O_5$, for which the name dicrotalic acid was suggested. A sample of this acid was kindly supplied us by Dr. J. S. C. Marais of the Department of Agriculture of the Union of South Africa which permitted the determination of its structure in this Laboratory.

The infrared absorption spectrum of dicrotalic acid showed an alcoholic hydroxyl band at 3215 cm.$^{-1}$, a bonded OH band at 2660 cm.$^{-1}$, and a carbonyl band at 1710 cm.$^{-1}$ (shoulder at 1695 cm.$^{-1}$). The acid could not be oxidized with lead dioxide in phosphoric acid and did not give a coloration with ferric chloride[3] from which it seemed improbable that the hydroxyl was in an α-position

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[1] J. S. C. Marais, *Onderstepoort J. Vet. Sci. Animal Ind.*, **20**, 61 (1944).

[2] N. J. Leonard, "The Alkaloids" (Editors R. H. F. Manske and H. L. Holmes), Vol. I, Academic Press, Inc., New York, N. Y., 1950, p. 108.

[3] A. Berg, *Bull. soc. chim.*, **11**, 882 (1894).

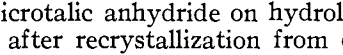
to a carboxyl group. Furthermore, the acid did not show a tendency to lactonize so characteristic of γ-hydroxy acids; this suggested that the hydroxyl group was most probably in the β-position to both carboxyl groups.

Dicrotalic acid could be readily acetylated with acetic anhydride in presence of acetyl chloride. The product from this reaction had the composition of the acetyl derivative of dicrotalic anhydride. The infrared absorption spectrum showed two anhydride bands, one at 1800 cm.$^{-1}$ and a second at 1750 cm.$^{-1}$, and an ester carbonyl band at 1725 cm.$^{-1}$. This substance readily lost a molecule of acetic acid on heating at 100° for 12 hours. The product, m.p. 85°, showed in the infrared spectrum a C=C band at 1665 cm.$^{-1}$ and anhydride bands at 1780 cm.$^{-1}$ (shoulder at 1800 cm.$^{-1}$) and 1735 cm.$^{-1}$ (shoulder at 1725 cm.$^{-1}$). There was no indication of the presence of a terminal double bond. In maleic anhydride the anhydride bands are at 1858 and 1780 cm.$^{-1}$ and the C=C band at 1596 cm.$^{-1}$. The differences in the regions of the anhydride and C=C bands in maleic anhydride and anhydrodicrotalic anhydride suggest that the latter compound is a six-membered anhydride and that the C=C is in conjugation with only one carbonyl. Anhydrodicrotalic anhydride could therefore be either α- or β-methylglutaconic anhydride. Both these anhydrides melt at 85°.

Anhydrodicrotalic anhydride on hydrolysis with alkali gave, after recrystallization from ether, an acid, m.p. 149–150°. The reported melting points for *cis*-β-methylglutaconic acid and *trans*-α-methylglutaconic acid vary between 145–150° for both acids.

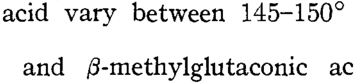
Both α- and β-methylglutaconic acids were prepared by previously described methods. On admixture of *cis*-β-methylglutaconic acid with anhydrodicrotalic acid, no depression of melting point was obtained. A mixture of *trans*-α-methylglutaconic acid and anhydrodicrotalic acid gave a 20° depression of melting point. Also, β-methylglutaconic anhydride and anhydrodicrotalic anhydride gave no depression of melting point on admixture and their infrared absorption curves were identical.

From these experiments it was concluded that dicrotalic acid is β-methyl-β-hydroxyglutaric acid (I). The isomeric β-methyl-α-hydroxyglutaric acid (II) is a known acid[4] and can be isolated only as its corresponding lactone.



$$\mathrm{HOOC{-}CH_2{-}\underset{OH}{\overset{CH_3}{C}}{-}CH_2{-}COOH}$$

I



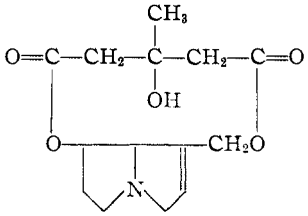
$$\mathrm{HOOC{-}\overset{OH}{C}H{-}\overset{CH_3}{C}H{-}CH_2{-}COOH}$$

II

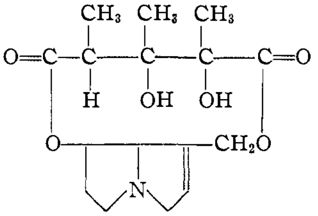
β-Methyl-β-hydroxyglutaric acid has been described as an *oily* acid obtained by the potassium permanganate oxidation of methyldiallylcarbinol.[5] Nieuwland and Daly[6] synthesized diethyl β-methyl-β-hydroxyglutarate in 27% yield from ethyl acetoacetate and ethyl chloroacetate by the Reformatsky reaction but did not report its properties and did not hydrolyze it to the corresponding acid.

Diethyl β-methyl-β-hydroxyglutarate was synthesized in this investigation by the method of Nieuwland and Daly in somewhat lower yield than they reported. On hydrolysis it yielded β-methylhydroxyglutaric acid, m.p. 109°. The melting point of this acid was not depressed on admixture with dicrotalic acid and it had an identical infrared absorption spectrum.

The alkaloid dicrotaline can now be represented by the bridged-ring diester structure III characteristic of the Senecio alkaloids.



III



IV

Dicrotaline is therefore very similar in structure to monocrotaline (IV) the only other alkaloid of the Senecio group from the plant family Leguminosae, genus Crotolaria, of which the structure has been elucidated.

Acknowledgment.—The authors are indebted to Dr. J. S. C. Marais for the dicrotalic acid, Miss Helen Miklas for the infrared spectra, Mr. J. Nemeth, Mrs. K. Pih and Mrs. Esther Fett for the microanalyses.

Experimental

All melting points are corrected.

Rotation. Dicrotalic Acid.—Dicrotalic acid, obtained by direct extraction of the plant material,[1] m.p. 108–109°, was purified by three recrystallizations from ether–petroleum ether (b.p. 30–60°), m.p. 109°. It showed no optical activity.

Alkaloid Salts of Dicrotalic Acid.—Only a single salt was apparently formed with either strychnine or brucine.

Monostrychnine Salt.—A solution of 0.10 g. of natural dicrotalic acid in 10 ml. of acetone was added to a solution of 0.21 g. of strychnine in 10 ml. of acetone and the mixture evaporated to 15 ml. On standing white needle-clusters separated which were purified by recrystallization from acetone, m.p. 162–164°. Rotation: 0.0342 g. made up to 1.59 ml. at 28° with chloroform gave α_D −0.290°, l 1, $[\alpha]^{28}_D$ −12.71° (±0.5°).

Anal. Calcd. for $C_{27}H_{32}O_7N_2$: C, 65.32; H, 6.45; N, 5.64. Found: C, 65.42; H, 6.49; N, 5.60.

(2) **Monobrucine Salt.**—A solution of 0.32 g. of dicrotalic acid in 20 ml. of acetone was added to a solution of 0.77 g. of brucine in 50 ml. of acetone and the mixture boiled down to 20 ml. On standing white prisms separated, m.p. 197–198° (dec.). The salt was purified by recrystallization

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[4] C. K. Ingold, *J. Chem. Soc.*, **121**, 2676 (1922).

[5] B. Sorokin, *J. prakt. Chem.*, **23**, 276 (1880).

[6] J. A. Nieuwland and S. F. Daly, THIS JOURNAL, **53**, 1842 (1931).

from acetone; m.p. 198° (dec.). Rotation: 0.0175 g. made up to 1.59 ml. with chloroform at 28° gave α_D −0.130°, *l* 1, $[\alpha]^{28}_D$ −11.81° (±0.5°).

Anal. Calcd. for $C_{29}H_{36}O_9N_2$: C, 62.59; H, 6.47; N, 5.03. Found: C, 62.67; H, 6.67; N, 5.07.

Acetyldicrotalic Anhydride.—A solution of 0.50 g. of dicrotalic acid in 10 ml. of benzene and 5 ml. of acetic anhydride was boiled under reflux for 2 hours in the presence of a few drops of acetyl chloride. The excess solvent and reagent was removed under reduced pressure. On addition of ether to the residual oil, a colorless crystalline solid separated; 0.35 g. The substance was recrystallized from ether; transparent prisms, m.p. 85°.

Anal. Calcd. for $C_8H_{10}O_5$: C, 51.61; H, 5.37. Found: C, 51.85; H, 5.58.

Anhydrodicrotalic Anhydride.—Acetyldicrotalic anhydride, 0.25 g., was heated at 100° for 12 hours. The resultant oil crystallized as fine needles on standing in a vacuum desiccator. The product was purified by crystallization from ether; m.p. 85°.

Anal. Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.76. Found: C, 56.88; H, 4.99.

Anhydrodicrotalic Acid.—Anhydrodicrotalic anhydride, 0.10 g., was treated with a slight excess of 10% aqueous sodium hydroxide on a steam-cone for 0.5 hours. The solution was acidified and extracted with ether (6 × 10 ml.). The ether solution was dried over anhydrous sodium sulfate. Removal of the solvent left a crystalline solid; 0.06 g. (60%). The product was recrystallized from ether; m.p. 149–150°.

Anal. Calcd. for $C_6H_8O_4$: C, 50.00; H, 5.55. Found: C, 50.17; H, 5.78.

trans-α-**Methylglutaconic Acid.**—Diethyl malonate and chloroform were condensed in presence of sodium ethoxide using the procedure of Conrad and Guthzeit.[7] The yellow sodium salt was treated with methyl iodide in ethanol by the method of Thole and Thorpe.[8] Diethyl α-methyl-α,γ-dicarbethoxyglutaconate was obtained in 70% yield, b.p. 205–206.5° (15 mm.) (reported b.p. 211° (21 mm.)).[8] This ester gave on alkaline hydrolysis and recrystallization from ether *trans*-α-methylglutaconic acid, m.p. 145–146° (reported m.p. 145–146°).[8]

Anal. Calcd. for $C_8H_8O_4$: C, 50.00; H, 5.55. Found: C, 50.21; H, 5.50.

cis-β-**Methylglutaconic Acid.**—Ethyl isodehydroacetate[9] was hydrolyzed with 10% aqueous alkali and pure *cis*-β-methylglutaconic acid, m.p. 149–150°, obtained by repeated crystallization from ether (reported m.p. 147°).[9] This acid gave no depression of melting point on admixture with anhydrodicrotalic acid.

β-**Methylglutaconic Anhydride.**—The anhydride was prepared from a mixture of *cis*- and *trans*-β-methylglutaconic acids by boiling with acetyl chloride. The product was recrystallized from ether, m.p. 85° (reported m.p. 86°).[10] This substance gave no depression of melting point on admixture with anhydrodicrotalic anhydride.

Diethyl β-**Methyl**-β-**hydroxyglutarate.**—A mixture of 170 g. of ethyl acetoacetate and 220 g. of ethyl bromoacetate in 800 ml. of benzene was added to 70 g. of zinc at such a rate that the benzene refluxed gently. The mixture was stirred during the addition. After addition was complete the mixture was refluxed for 2 hours, acidified with cold 10% sulfuric acid and the benzene layer separated. The aqueous solution was extracted with benzene (2 × 100 ml.) and the combined benzene extract washed first with aqueous sodium bicarbonate and then with water. The extract was dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure. Distillation of the product yielded 30 g. (13.7%) of a colorless liquid, b.p. 143.5° (16 mm.). The product was redistilled without change in boiling point; n^{20}_D 1.4348.

Anal. Calcd. for $C_{10}H_{18}O_5$: C, 55.04; H, 8.25. Found: C, 54.80; H, 7.94.

β-**Methyl**-β-**hydroxyglutaric Acid.**—Hydrolysis with 10% aqueous alkali of the ester described above yielded an acid which was extracted with ether from the acidified aqueous solution. It was purified by recrystallization from ether-petroleum ether (b.p. 30–60°); colorless flakes, m.p. 109°. This acid gave no depression of melting point on admixture with dicrotalic acid.

Anal. Calcd. for $C_6H_{10}O_5$: C, 44.44; H, 6.17. Found: C, 44.70: H, 6.22.

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(7) M. Conrad and M. Guthzeit, *Ann.*, **222**, 249 (1884).

(8) F. B. Thole and J. C. Thorpe, *J. Chem. Soc.*, **99**, 2187 (1911).

(9) F. Feist, *Ann.*, **345**, 60 (1906).

(10) H. Rogerson and J. F. Thorpe, *J. Chem. Soc.*, **87**, 1685 (1905).

URBANA, ILLINOIS

[CONTRIBUTION NO. 1705 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

On the Stereochemistry of Azines: Cinnamalazine and Phenylpentadienalazine*

BY JOHANNES DALE† AND L. ZECHMEISTER

RECEIVED NOVEMBER 3, 1952

Either of the azines mentioned can be partially converted by thermic or photochemical treatments and by iodine catalysis into two *cis* forms. Interconversions of the respective stereoisomers cause typical shifts in the spectral curves. On the basis of the respective thermo- and photostabilities and of spectroscopic phenomena, including the *cis*-peak effect, and behavior toward iodine, tentative configurations are proposed for the new *cis*-azines.

In the last few years some studies have been carried out in this Laboratory on the *cis-trans* isomerization of aliphatic conjugated carbon–carbon double bond systems such as carotenoid pigments, phytofluene and diphenylpolyenes.[1] In the present paper we wish to report on an extension of this work to symmetrical azines containing the =N—N= group located in the center of the chromophore, according to the general formula, $C_6H_5\cdot(CH{=}CH)_n\cdot CH{=}N{-}N{=}CH\cdot(CH{=}CH)_n\cdot C_6H_5$. The calculated number of stereoisomers is 10 for cinnamalazine ($n = 1$) and 36 for phenylpentadienalazine ($n = 2$) which figures may have to be reduced by the probable effect of steric hindrance.[2]

As in corresponding carbon–carbon sets, a pure sample of ordinary (all-*trans*) azine forms a single zone on the chromatographic column, but a partial *trans* → *cis* rearrangement becomes manifest by the appearance of more complex chromatograms. It was advantageous, and in many instances indeed necessary, to inspect such chromatograms in ultra-

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* Presented at the Meeting of the American Chemical Society, March 19, 1953, in Los Angeles, Calif.

† Norwegian Defence Research Establishment, Lilleström, Norway.

(1) L. Zechmeister, *Chem. Revs.*, **34**, 267 (1944); L. Zechmeister and A. Sandoval, THIS JOURNAL, **68**, 197 (1946); F. J. Petracek and L. Zechmeister, *ibid.*, **74**, 184 (1952); A. Sandoval and L. Zechmeister, *ibid.*, **69**, 553 (1947); J. H. Pinckard, B. Wille and L. Zechmeister, *ibid.*, **70**, 1938 (1948).

(2) L. Zechmeister and A. L. LeRosen, *ibid.*, **64**, 2755 (1942).