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

Trachelanthic and Viridifloric Acids

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α-Isopropyl-α,β-dihydroxybutyric acid (I), m.p. 119°, previously synthesized, was resolved with brucine and both optical isomers obtained. The diastereoisomer of I was synthesized by the pertungstic acid oxidation of α-isopropylcrotonic acid. This acid (II) was also resolved with brucine and both optical isomers were obtained. Trachelanthic acid, obtained by the hydrolysis of the alkaloids trachelanthine, trachelanthamine, lindelofine, lindelofamine and supinine has been shown to be paritally racemized I, and viridifloric acid, from the alkaloid viridiflorine, partially racemized II.

In a recent paper from his Laboratory,[1] the synthesis of α-isopropyl-α,β-dihydroxybutyric acid was reported. This acid was considered identical with viridifloric acid obtained by the hydrolysis of the alkaloid viridiflorine found in *Cynoglossum viridiflorum*[2] on the basis of essentially the same melting point as that reported in the literature for the natural acid. Trachelanthic acid obtained by the hydrolysis of various alkaloids from different genera of plants (Table I) was considered by previous investigators to be the diastereoisomer of viridifloric acid.

TABLE I

SOURCES OF TRACHELANTHIC ACID

Plant	Alkaloid
Trachelanthus korolkovi	Trachelanthine[3-5]
Lindelofia anchusoides	Lindelofine[6]
	Lindelofamine[6]
Heliotropium supinum	Supinine[7]

Previous attempts to synthesize trachelanthic acid from α-isopropylcrotonic acid by oxidation with organic peracids were unsuccessful.[1]

In the continuation of this program of research, new attempts were made to synthesize trachelanthic acid from α-isopropylcrotonic acid by other methods of hydroxylation. The latter acid was prepared from ethyl α-isopropyl-β-hydroxybutyrate by dehydration and hydrolysis.[1] Hydroxylation of methyl α-isopropylcrotonate with osmium tetroxide gave α-isopropyl-α,β-dihydroxybutyric acid identical with that obtained by Adams and Herz[1] by alkaline permanganate oxidation of α-isopropylcrotonic acid.

Mugdan and Young[8] have described the hydroxylation of unsaturated compounds by the use of pertungstic acid. Whereas permanganate and osmium tetroxide usually cause *cis*-hydroxylation, this reagent gave *trans*-hydroxylation products.

This method was therefore examined with the more readily available α-ethylcrotonic acid. The dihydroxy acid obtained was identical in melting point with that obtained by the permanganate oxidation of α-ethylisocrotonic acid[9] and also with that obtained by the performic acid oxidation of α-ethylcrotonic acid,[1] thus providing further proof that it is a *trans*-hydroxylating agent.

(1) R. Adams and W. Herz, THIS JOURNAL, **72**, 155 (1950).
(2) G. P. Menshikov, *J. Gen. Chem.* (*U.S.S.R.*), **18**, 1736 (1948).
(3) G. P. Menshikov and G. M. Borodina, *ibid.*, **11**, 209 (1941).
(4) G. P. Menshikov and G. M. Borodina, *ibid.*, **15**, 225 (1945).
(5) G. P. Menshikov, *ibid.*, **17**, 343 (1947).
(6) A. S. Labenskii and G. P. Menshikov, *ibid.*, **18**, 1836 (1948).
(7) G. P. Menshikov and E. L. Gurevich, *ibid.*, **19**, 1382 (1949).
(8) M. Mugdan and D. P. Young, *J. Chem. Soc.*, 2988 (1949).
(9) R. Fittig, P. Borstelmann and M. Lurie, *Ann.*, **334**, 101 (1904).

The hydroxylation of α-isopropylcrotonic acid with pertungstic acid gave a product melting at 150°. This acid gave a ferric chloride test for an α-hydroxy acid,[10] Criegee's glycol test[11] with fuchsin and on oxidation with lead tetraacetate liberated acetaldehyde, identified as the dimedone bis-adduct. There remained little doubt that this acid was the diastereoisomer of α-isopropyl-α,β-dihydroxybutyric acid, synthesized by Adams and Herz.[1] The infrared absorption curves provided further proof.

The melting point for trachelanthic acid obtained by the hydrolysis of various alkaloids with 10% aqueous ethanolic alkali varied from 93–96°. This acid was called "racemic" trachelanthic acid. In the hydrogenolysis of supinine,[7] trachelanthic acid having a melting point of 93–94° and a specific rotation of +1.3° was obtained. The authors of the latter paper noted that racemization of the optically active acid might have taken place during the hydrolysis. Furthermore, viridifloric acid obtained by the hydrolysis of viridiflorine melted at 119–123°, whereas the synthetic acid which was assumed to be identical[1] melted sharply at 119°,

In view of these facts, it was considered desirable to attempt resolution of both diastereoisomers. Both acids were resolved with brucine and both optical isomers from each racemate were obtained. The melting points and rotations are given in Table II.

TABLE II

PROPERTIES OF OPTICAL ISOMERS FROM α-ISOPROPYL-α,β-DIHYDROXYBUTYRIC ACIDS

M.p. of racemate, °C.	M.p., °C.	$[\alpha]_D$ *d*	*l*
(*cis* OH's) 119	89	2.9	3.4
(*trans* OH's) 150	127.5	1.8	1.6

These results make it appear that the conclusions of Adams and Herz[1] that their *cis*-hydroxylated stereoisomer, m.p. 119°, was probably viridifloric acid[1] are erroneous. Viridifloric acid is probably the partially racemized optical isomer of the *trans*-hydroxylated racemate melting at 150°. Trachelanthic acid is probably the partially racemized optical isomer of the *cis*-hydroxylated racemate melting at 119°.

Evidence that racemization of the optically active acids probably took place during the hydrolysis of the alkaloids with 10% aqueous ethanolic alkali, as was suggested by Menshikov and Gerevich[7] was obtained in the present investigation. The pure optically active acids were treated with

(10) A. Berg, *Bull. soc. chim.*, **11**, 882 (1894).
(11) R. Criegee, *Ber.*, **64**, 260 (1931).

alkali under conditions which were only slightly more drastic than those used for the hydrolysis of the alkaloids. The melting points of the products indicated that the 89° *cis*-hydroxylated optical isomer was racemized almost completely (m.p. 117–118°) whereas the 127.5° *trans*-hydroxylated isomer was racemized to a lesser extent (m.p. 130–132°).

The melting points of mixtures of one of the optically active forms of each dihydroxy acid and its racemate were determined and plotted on temperature–composition diagrams (Figs. 1 and 2).

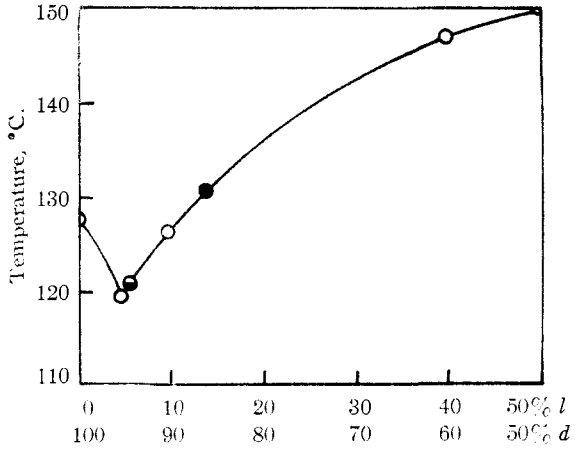

Fig. 1.—Melting point curve of *trans*-hydroxylation racemate (m.p. 150°) and its optical isomer: O, observed m.ps. of mixtures; ◒, m.ps. reported for natural acids; ●, observed m.ps. of racemized optically active acids.

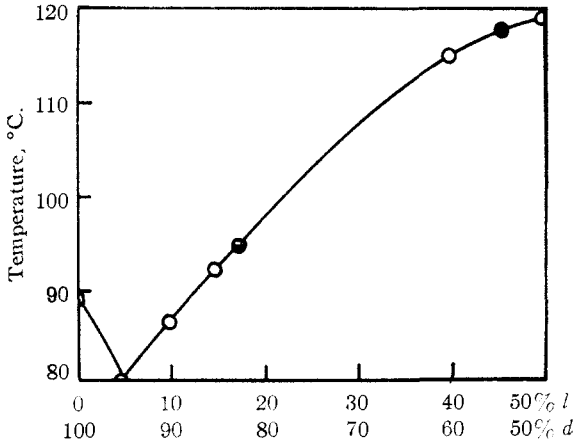

Fig. 2.—Melting point curve of *cis*-hydroxylation racemate (m.p. 119°) and its optical isomer: O, observed m.ps. of mixtures; ◒, m.ps. reported for natural acids: ●, observed m.ps. of racemized optically active acids.

From the positions on these diagrams of the melting points of the racemized acids obtained in this investigation and those reported for the natural acids, the percentage racemization of these products were calculated (Table III).

Although the actual amount of racemization obtained in the present investigation is higher than had occurred in the natural acids, the data presented in Table III indicate that the *cis*-hydroxylated acid racemizes more readily than the *trans*-hydroxylated acid.

TABLE III

PERCENTAGE RACEMIZATION OF OPTICALLY ACTIVE ACIDS

	cis-Hydroxylated racemate		*trans*-Hydroxylated racemate	
	M.p., °C.	Racemization, %	M.p., °C.	Racemization, %
Racemization of pure optically active acids	117–118	90	130–132	30
Natural acids	93–96	34	119–123	14

Experimental

All melting points are corrected.

α-Isopropylcrotonic Acid.—This acid was prepared from ethyl α-isopropylacetoacetate[12] by hydrogenation, dehydration and finally hydrolysis of the resultant ester mixture.[1] The acid was purified by steam distillation followed by recrystallization from water and gave no depression on admixture with an authentic specimen.

Methyl α-Isopropylcrotonate.—A solution of 1 g. of recrystallized α-isopropylcrotonic acid in 20 ml. of dry ether was treated with an excess of an ethereal solution of diazomethane at 0°. The solution was kept at 0° for 12 hours and the excess of diazomethane removed by bubbling air through. Removal of the solvent left a colorless liquid; 1.05 g. (94.5%). The product was purified by distillation, b.p. 137–139° (atm. press.), $n^{20}D$ 1.4369.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.60; H, 9.85. Found: C, 67.41; H, 9.90.

Osmium Tetroxide Oxidation of Methyl α-Isopropylcrotonate.—One gram of methyl α-isopropylcrotonate was added to 3.9 g. of 6.32% hydrogen peroxide dissolved in 5 ml. of *t*-butanol (free from unsaturates). The mixture was cooled to 0° and 0.6 ml. of a 0.5% solution of sublimed osmium tetroxide in *t*-butanol added. The mixture turned dark brown in color and was kept at 0° for 12 hours. After allowing to warm to room temperature overnight, the product was hydrolyzed with alkali, acidified and steam distilled. Unchanged starting material weighing 0.70 g. was obtained from the steam distillate. The residue from the steam distillation was extracted with ether in a continuous extractor for 24 hours and the extract dried with anhydrous sodium sulfate. Removal of the solvent left 0.10 g. of a crystalline residue. The product was crystallized from an ether–petroleum ether (b.p. 30–60°) mixture; m.p. 119°, 0.07 g. (28%, based on recovered starting material). The product gave no depression of melting point on admixture with an authentic specimen of α-isopropyl-α,β-dihydroxybutyric acid, m.p. 119°.

Pertungstic Acid Oxidation of α-Ethylcrotonic Acid.—To a solution of 2 g. of α-ethylcrotonic acid[13] in a mixture of 50 ml. of water and 30 ml. of acetone, 1.5 g. of 30% hydrogen peroxide containing 25 mg. of tungsten trioxide in solution was added. The mixture was allowed to react at 60° for 18 hours. Removal of the solvent under reduced pressure gave 0.6 g. (27.2%) of a colorless oil which crystallized on drying in vacuum. The substance was recrystallized from an acetone–petroleum ether (b.p. 30–60°) mixture and after two crystallizations melted at 145° (lit. m.p. 144.5–145.5°, prepared by permanganate oxidation).[9] The product gave no depression of melting point on admixture with α-ethyl-α,β-dihydroxybutyric acid prepared by the performic acid oxidation of α-ethylcrotonic acid.[1]

Pertungstic Acid Oxidation of α-Isopropylcrotonic Acid.—To a solution of 5 g. of α-isopropylcrotonic acid in a mixture of 220 ml. of water and 75 ml. of acetone, a solution of 50 mg. of tungsten trioxide in 4.5 g. of 30% hydrogen peroxide was added. The mixture was kept at 55–60° for 24 hours. Removal of the solvent left 2.77 g. (43.8%) of a colorless crystalline residue. The product was recrystallized from an ether–petroleum ether (b.p. 30–60°) mixture. After two recrystallizations the product melted sharply at 150°. The acid sublimed unchanged in melting point at 0.01 mm. and 110°.

Anal. Calcd. for $C_7H_{14}O_4$: C, 51.85; H, 8.64. Found: C, 51.88; H, 8.84.

(12) J. T. Adams, R. Levine and C. R. Hauser, *Org. Syntheses*, **27**, 35 (1947).

(13) E. Blaise and P. Bagard, *Ann. chim.*, **11**, 111 (1907).

Alkaline Permanganate Oxidation of α-Isopropylcrotonic Acid.—The method of Adams and Herz[1] was modified as follows: A solution of 8 g. of α-isopropylcrotonic acid in 650 ml. of water containing 3 g. of sodium hydroxide was saturated with sodium chloride and cooled in an ice-salt-bath to −7°. To this was added with stirring 480 ml. of a 2% aqueous solution of potassium permanganate at such a rate that the temperature remained between −5 and −7°. The addition required 6 hours. The solution was filtered from the manganese dioxide and the oxide washed with boiling water. The wash liquor was added to the main filtrate and concentrated under reduced pressure to 200 ml. The solution was then acidified and steam distilled. Unchanged starting material, weighing 2.5 g., was recovered from the steam distillate. The aqueous residue from the steam distillation was treated with 20 g. of calcium carbonate on a steam-bath for 1 hour. After cooling, the precipitate was filtered off, washed and the filtrate taken to a small volume under reduced pressure. The residue was acidified with hydrochloric acid and extracted with ether (30 × 15 ml.). The ether extract was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. An oily residue remained. The product, weighing 3.50 g. (50%, reported yield[1] 22.2%), crystallized on scratching. The acid was purified by crystallization from a chloroform–petroleum ether (b.p. 30–60°) mixture; m.p. 119°. The yield was 2.70 g.

Resolution of *cis*-Hydroxylated α-Isopropyl-α,β-dihydroxybutyric Acid (M.p. 119°) with Brucine.—A solution of 0.80 g. of the racemate and 2.30 g. of brucine in 50 ml. of ethanol was heated to boiling and filtered. On cooling a solid separated; white prisms, m.p. 214–218°, yield 1.55 g. (50%). After three recrystallizations from absolute ethanol a salt of constant melting point and rotation was obtained; m.p. 217–220°, yield 0.91 g. (29.3%).

Rotation.—Less soluble salt: 0.0400 g. made up to 5 ml. with chloroform at 26° gave α_D −0.17° *l* 1, $[\alpha]^{26}_D$ −21.1° (±1.0°).

Anal. Calcd. for $C_{30}H_{40}N_2O_8$: N, 5.03. Found: N, 5.00.

The combined mother liquors from the crystallization of the less soluble salt were evaporated under an air jet to 40 ml. On standing, 1.00 g. (32.2%) of a mixture of needles and prisms separated from the filtrate on standing; m.p. 182.5–187.5°. The yield was 0.54 g. (17.4%). The melting point and rotation remained unchanged on recrystallization.

Rotation.—More soluble salt: 0.0500 g. made up to 5 ml. with chloroform at 26° gave α_D −0.250° *l* 1, $[\alpha]^{25}_D$ −25.0° (±1.0°).

Anal. Calcd. for $C_{30}H_{40}N_2O_8$: N, 5.03. Found: N, 5.08.

***d*- and *l*-*cis*-Hydroxylated α-Isopropyl-α,β-dihydroxybutyric Acid (from 119° Racemate). *d*-Acid.**—Acidification of 0.80 g. of the less soluble brucine salt with 10 ml. of 10% sulfuric acid was followed by extracting continuously with ether for 24 hours. The extract was dried over anhydrous sodium sulfate. Filtration and removal of the solvent left an oil which on drying in vacuum crystallized. The acid was recrystallized from ether–petroleum ether (b.p. 30–60°); white needles, m.p. 89°, yield 0.15 g. (75%). Recrystallization from carbon tetrachloride did not alter the melting point.

Rotation. *d*-**Acid.**—0.0500 g. made up to 2 ml. with water at 25° gave α_D +0.072° *l* 1, $[\alpha]^{25}_D$ +2.9° (±0.5°).

Anal. Calcd. for $C_7H_{14}O_4$: C, 51.83; H, 8.70. Found: C, 51.54; H, 8.68.

l-**Acid.**—The *l*-acid was obtained from the more soluble brucine salt in the same manner. This acid was recrystallized from carbon tetrachloride; colorless needles, m.p. 89°. The yield was 80%.

Rotation. *l*-**Acid:** 0.0500 g. made up to 2 ml. with water at 25° gave α_D −0.085° *l* 1, $[\alpha]^{25}_D$ −3.4° (±0.5°).

***p*-Bromophenacyl Ester of the *d*-Rotatory Acid.**—The ester, prepared by the standard procedure, was crystallized from ethanol–water; colorless needles, m.p. 99–99.5°.

Rotation.—0.0500 g. made up to 3 ml. with chloroform–ether at 27° gave α_D +0.065° *l* 1, $[\alpha]^{27}_D$ +3.9° (±0.5°).

Anal. Calcd. for $C_{15}H_{19}BrO_5$: C, 50.14; H, 5.29. Found: C, 50.26; H, 5.53.

Resolution of *trans*-Hydroxylated α-Isopropyl-α,β-dihydroxybutyric Acid (M.p. 150°) with Brucine.—A solution of 0.8 g. of the racemate and 2.30 g. of brucine in 40 ml. of ethanol was boiled under reflux for 10 minutes and filtered. On cooling a white crystalline solid separated; needles, m.p. 182–185°. The yield was 1.31 g. (41.9%). After two recrystallizations from ethanol a salt of constant rotation was obtained; m.p. 183–186°, yield 1.0 g. (32.2%).

Rotation.–Less soluble salt: 0.0500 g. made up to 5 ml. with chloroform at 26° gave α_D −0.221° *l* 1, $[\alpha]^{26}_D$ −22.1° (±1.0°).

Anal. Calcd. for $C_{30}H_{40}N_2O_8$: N, 5.03. Found: N, 5.15.

The mother liquors from the crystallization of the crude less-soluble salt were evaporated under an air jet to 25 ml. On standing 0.9 g. (29.0%) of a white solid separated, m.p. 186–188°. This product was recrystallized several times to constant rotation and melting point; white needles, m.p. 187–189°. The yield was 0.55 g. (17.9%).

Rotation.—More soluble salt: 0.0500 g. made up to 5 ml. with chloroform at 29° gave α_D 0.233 *l* 1, $[\alpha]^{29}_D$ −23.3° (±1.0°).

Anal. Calcd. for $C_{30}H_{40}N_2O_8$: N, 5.03. Found: N, 5.01.

Evaporation of the mother liquors to dryness left 0.8 g. of a white solid of indefinite melting point.

***d*- and *l*-*trans*-Hydroxylated α-Isopropyl-α,β-dihydroxybutyric Acids (from 150° Acid). *d*-Acid.**—This acid was obtained by hydrolysis of the less-soluble salt and extraction with ether as described above. The acid was recrystallized from ether–petroleum ether (b.p. 30–60°); white needles, m.p. 127.5°. The yield was 79%. Recrystallization from the same solvent mixture or from carbon tetrachloride did not alter the melting point.

Rotation. *d*-**Acid.**—0.0500 g. made up to 2 ml. with water at 26° gave α_D +0.045° *l* 1, $[\alpha]^{26}_D$ +1.8° (±0.5°).

Anal. Calcd. for $C_7H_{14}O_4$: C, 51.83; H, 8.70. Found: C, 51.61; H, 8.65.

l-**Acid.**—The *l*-acid was obtained from the more soluble brucine salt in the manner described above. The acid was recrystallized from carbon tetrachloride; m.p. 127.5°, yield 72%.

Rotation. *l*-**Acid.**—0.0500 g. made up to 2 ml. with water at 26° gave α_D −0.040° *l* 1, $[\alpha]^{26}_D$ −1.6° (±0.5°).

***p*-Bromophenacyl Ester of the *d*-Rotatory Acid.**—The ester, prepared by the standard procedure was crystallized from ethanol–water; colorless needles, m.p. 110–111°.

Rotation.—0.0500 g. made up to 5 ml. with chloroform at 29° gave α_D +0.030°, $[\alpha]^{29}_D$ +3.0° (±0.5°).

Anal. Calcd. for $C_{15}H_{19}BrO_5$: C, 50.14; H, 5.29. Found: C, 50.06; H, 5.33.

Melting Points of Mixtures of Optical Isomers and Their Racemates.—A solution of 0.100 g. of each racemate and of one optical isomer of each racemate in 10 ml. of chloroform–ether mixture (1:1) were prepared. Appropriate mixtures were made up, evaporated to dryness and the melting points of the residues determined. The melting points of all the mixtures were over a range of 2 to 3°. The results were plotted on temperature–composition diagrams (Figs. 1 and 2).

Racemization of Optically Active Acids.—A solution of 50 mg. of the *d*-isomer (m.p. 127.5°) of the higher melting racemate in 3 ml. of 10% aqueous ethanolic (1:1) sodium hydroxide was boiled under reflux for 90 minutes. The solution was carefully neutralized with dilute hydrochloric acid until just acid to litmus, evaporated to dryness under reduced pressure and the residue extracted with ether. Removal of the solvent left a crystalline residue, 47 mg., which was recrystallized once from carbon tetrachloride; m.p. 130–132°. The *d*-isomer (m.p. 89°) of the lower melting racemate, treated in exactly the same manner gave a product melting at 117–118°.

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