

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

## The Structure of Heliotrinic Acid

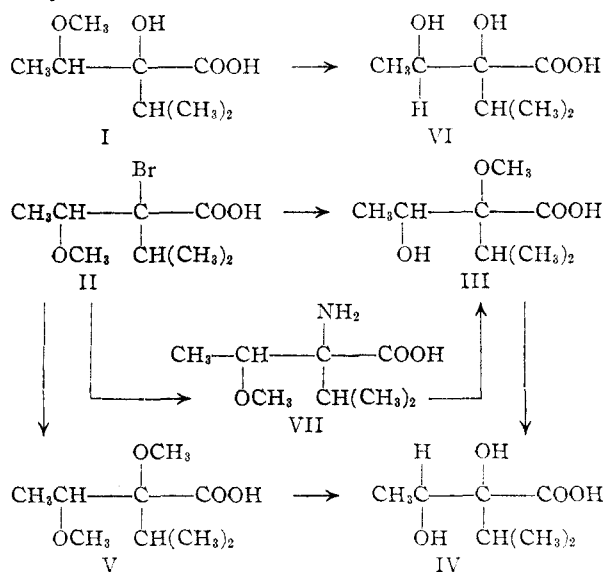
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RECEIVED APRIL 30, 1953

Further experimental evidence is provided for the proposed structure of heliotrinic acid, the acid cleavage product of the alkaloid heliotrine. Heliotrinic acid has been demethylated with hydrobromic acid to *d*- $\alpha$ -isopropyl- $\alpha,\beta$ -dihydroxybutyric acid. The latter acid is identical with trachelanthic acid, the cleavage product of various Senecio alkaloids, previously synthesized in this Laboratory. This experiment confirms the previously assigned structures of heliotrinic acid, *vis.*,  $\alpha$ -isopropyl- $\alpha$ -hydroxy- $\beta$ -methoxybutyric acid. A number of the reactions of  $\alpha$ -isopropylcrotonic acid is described. Benzyl-oxybromination of crotonic acid yielded the expected  $\alpha$ -bromo- $\beta$ -benzyloxybutyric acid.

The alkaloid heliotrine from *Heliotropium lasiocapium*<sup>1</sup> and *Heliotropium europeum*<sup>2</sup> yielded on alkaline hydrolysis a base, heliotridine, and a crystalline, optically active, monobasic acid,  $C_8H_{16}O_4$ , heliotrinic acid.

On the basis of degradation reactions, Menschikov,<sup>3</sup> suggested that heliotrinic acid is an optically active form of  $\alpha$ -isopropyl- $\alpha$ -hydroxy- $\beta$ -methoxybutyric acid (I).



In an attempt to synthesize this acid a number of reactions were carried out:  $\alpha$ -isopropylcrotonic acid, prepared as described in a previous communication from this Laboratory,<sup>4</sup> was subjected to methoxybromination by a method which had been used earlier<sup>5,6</sup> for the addition of methylhypobromite to unsaturated acids.

The resulting bromomethoxy acid (II) was obtained as a low melting crystalline solid. The bromine atom of this acid was readily replaced by hydroxyl with aqueous potassium carbonate. The resultant product, which analyzed correctly for  $C_8H_{16}O_4$ , was a liquid whereas the desired acid was a crystalline solid. On treatment with brucine a crystalline salt was obtained. Hydrolysis of the salt afforded an oil,  $[\alpha]_D -14^\circ$  (ethanol) which was

not investigated further. The optically inactive oil could be readily demethylated with 48% hydrobromic acid to  $\alpha$ -isopropyl- $\alpha,\beta$ -dihydroxybutyric acid (IV), m.p.  $150^\circ$ , previously synthesized by the *trans*-hydroxylation of  $\alpha$ -isopropylcrotonic acid.<sup>7</sup> From these results it could be concluded that the oil is either a diastereoisomer of heliotrinic acid, which is unlikely in view of its physical properties, or that during the replacement of the bromine a rearrangement takes place. Similar rearrangements are known to occur in the presence of neighboring methoxyl groups.<sup>8</sup> The oil would then be  $\alpha$ -isopropyl- $\alpha$ -methoxy- $\beta$ -hydroxybutyric acid (III). The absence of a hydroxyl group  $\alpha$  to the carboxyl was indicated by failure of the oil to undergo oxidation with lead dioxide in phosphoric acid. This reaction was used by Menschikov in the degradation of heliotrinic acid to a ketone.<sup>3</sup>

The same oil was obtained by treating the bromomethoxy acid with moist silver oxide in acetone, and also by conversion of the bromomethoxy acid to *d*- $\alpha$ -isopropyl- $\alpha$ -amino- $\beta$ -methoxybutyric acid (VII) followed by treatment with nitrous acid.

Although  $\alpha$ -isopropyl- $\alpha$ -bromo- $\beta$ -hydroxybutyric acid could be prepared very readily, this acid could not be converted to the corresponding epoxy acid, even after boiling for 24 hours with ethanolic potash. Only starting material could be isolated. The corresponding  $\alpha$ -isopropyl- $\alpha$ -bromo- $\beta$ -methoxybutyric acid, however, on treatment with methanolic potash gave  $\alpha$ -isopropyl- $\alpha,\beta$ -dimethoxybutyric acid (V), an oil isolated as its *p*-bromophenacyl ester. This dimethoxy acid on demethylation with 48% hydrobromic acid gave the *trans*  $\alpha$ -isopropyl- $\alpha,\beta$ -dihydroxybutyric acid, m.p.  $150^\circ$ , referred to above.

A small amount of natural heliotrinic acid was kindly sent us by Dr. C. C. J. Culvenor of Melbourne University, Australia. It was, therefore, decided to determine first the configuration of natural heliotrinic acid since this would be of importance in synthesizing the acid.

A small amount of the natural acid was demethylated by treatment with 48% hydrobromic acid. The resultant product gave no depression of melting point on admixture with *d*- $\alpha$ -isopropyl- $\alpha,\beta$ -dihydroxybutyric acid (VI), m.p.  $89^\circ$ , *i.e.*, trachelanthic acid, obtained by *cis*-hydroxylation of  $\alpha$ -isopropylcrotonic acid.<sup>7</sup> A mixture of this acid and the corresponding *l*-acid in approximately equal amounts melted at  $115$ – $118^\circ$ . The reported melting point of the *dl*-acid is  $119^\circ$ .<sup>7</sup>

- (1) G. P. Menschikov, *Ber.*, **65**, 974 (1932).
- (2) E. M. Trautner and E. O. Neufeld, *Austr. J. Sci.*, **11**, 211 (1949).
- (3) G. P. Menschikov, *J. Gen. Chem.*, U.S.S.R., **9**, 1851 (1939).
- (4) R. Adams and W. Herz, *THIS JOURNAL*, **72**, 155 (1950). See also L. J. Dry and F. L. Warren, *J. Chem. Soc.*, 3445 (1952).
- (5) J. B. Conant and E. L. Jackson, *THIS JOURNAL*, **46**, 1727 (1920).
- (6) H. D. West, G. S. Krummel and H. E. Carter, *J. Biol. Chem.*, **122**, 605 (1938).

- (7) R. Adams and B. L. Van Duuren, *THIS JOURNAL*, **74**, 5249 (1952).
- (8) S. Winstein and L. L. Ingraham, *ibid.*, **74**, 1160 (1952).

This experiment provided not only confirmatory proof to the structure assigned to heliotrinic acid by Menschikov,<sup>3</sup> but also showed that heliotrinic acid has the *cis*-configuration corresponding to trachelanthic acid. It follows that the attempts at synthesizing this acid by methods described above would always yield the wrong diastereoisomer.

During this investigation  $\alpha$ -bromo- $\beta$ -benzyloxybutyric acid was prepared from crotonic acid in benzyl alcohol solution and bromine at 0–5°. As far as is known this type of reaction has not been carried out before in benzyl alcohol, although it is known that benzyl alcohol does form a hypobromite.<sup>9</sup>

**Acknowledgments.**—We are indebted to Mr. J. Nemeth, Mrs. Esther Fett and Mrs. Lucy Chang for the microanalyses.

### Experimental

All melting points are corrected.

**$\alpha$ -Isopropyl- $\alpha$ -bromo- $\beta$ -methoxybutyric Acid.**—A suspension of 3.9 g. of finely powdered silver nitrate in 30 ml. of absolute methanol was cooled to 5°, stirred, and 2.5 g. of  $\alpha$ -isopropylcrotonic acid<sup>4</sup> in 30 ml. of absolute methanol and 3.6 g. of bromine added simultaneously from two separatory funnels at such a rate that the temperature remained between 0 and 5°. The addition required 25 minutes. The mixture was stirred for one hour after the addition was complete and was allowed to heat to room temperature overnight. The excess bromine was then removed by adding 20 ml. of water and passing a rapid current of air through the solution. Silver bromide was filtered off and washed with methanol. The filtrate was taken to a small volume under reduced pressure. A water-insoluble oil separated. The oil was extracted with ether, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. A light-yellow oil, 4.40 g. (94.4%), was obtained. The product was purified by vacuum distillation, b.p. 100–105° (0.3 mm.). The viscous distillate (4.0 g.) crystallized after standing at room temperature for one week and was recrystallized from petroleum ether (b.p. 30–60°) at –20°; m.p. 55°.

*Anal.* Calcd. for  $C_8H_{15}O_3Br$ : C, 40.16; H, 6.25. Found: C, 40.38; H, 6.18.

**Hydrolysis of  $\alpha$ -Isopropyl- $\alpha$ -bromo- $\beta$ -methoxybutyric Acid.**—A solution of 2.5 g. of potassium carbonate in 25 ml. of water was added to 1.0 g. of the bromomethoxy acid and the solution heated at 100° for 6 hours. The resultant solution was acidified and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residual oil, 0.45 g. (61.5%), was distilled *in vacuo*. The distillate was a colorless viscous liquid.

*Anal.* Calcd. for  $C_8H_{16}O_4$ : C, 54.54; H, 9.09. Found: C, 54.75; H, 9.10.

**Brucine Salt of  $\alpha$ -Isopropyl- $\alpha$ -methoxy- $\beta$ -hydroxybutyric Acid.**—To a solution of 0.42 g. of the liquid just described, in 10 ml. of acetone, a solution of 0.90 g. of brucine in 50 ml. of acetone was added. The mixture was boiled down to 25 ml. and ether added until the solution was just turbid. On standing a crystalline salt separated; m.p. 119–125°; 0.36 g. (27.2%). After five recrystallizations from acetone the melting point remained constant; m.p. 145–148°, yield 0.14 g. (10.6%).

*Anal.* Calcd. for  $C_{31}H_{48}O_8N_2$ : N, 4.91. Found: N, 4.81.

**Rotation.**—0.0118 g. made up to 1.60 ml. in chloroform at 28° gave  $\alpha_D - 0.182^\circ$ ;  $[\alpha]_D^{25} - 24.9^\circ (\pm 1.0^\circ)$ .

**$\alpha$ -Isopropyl- $\alpha$ -amino- $\beta$ -methoxybutyric Acid.**—Ten grams of  $\alpha$ -isopropyl- $\alpha$ -bromo- $\beta$ -methoxybutyric acid was dissolved in 75 ml. of 28% aqueous ammonia and heated for three hours at 100° in a sealed tube. The resultant solution was taken to dryness under reduced pressure. This process was repeated three times. The residue was dried

at 100° under reduced pressure, extracted with absolute ethanol and filtered. Removal of the solvent left a white crystalline solid, 4.0 g. (54.8%), m.p. 250°. The product was purified by sublimation at 255°.

*Anal.* Calcd. for  $C_8H_{17}O_3N$ : C, 54.85; H, 9.71. Found: C, 54.51; H, 9.99.

**Reaction of  $\alpha$ -Isopropyl- $\alpha$ -amino- $\beta$ -methoxybutyric Acid with Nitrous Acid.**—A solution of 1.0 g. of the amino acid just described was treated with an equivalent amount of hydrochloric acid in 20 ml. of water, 0.87 g. of silver nitrite added and the mixture stirred at 40° for 48 hours. The solution was then filtered, acidified and extracted with chloroform. The oily residue, 0.20 g. (20%), was converted to a brucine salt, m.p. 145–147°, identical with that described above. The two salts gave no depression of melting point on admixture.

**Dimethylation of  $\alpha$ -Isopropyl- $\alpha$ -methoxy- $\beta$ -hydroxybutyric Acid.**—A solution of 0.20 g. of the oily acid in 5 ml. of 48% hydrobromic acid was heated at 100° for 2 hours. The excess reagent was removed under reduced pressure and the crystalline residue recrystallized from ether, m.p. 150°. This product gave no depression of melting point on admixture with an authentic specimen of  $\alpha$ -isopropyl- $\alpha$ , $\beta$ -dihydroxybutyric acid (*trans*-hydroxylated, m.p. 150°).<sup>7</sup>

**$\alpha$ -Isopropyl- $\alpha$ -bromo- $\beta$ -hydroxybutyric Acid.**—A suspension of 5.0 g. of  $\alpha$ -isopropylcrotonic acid in 200 ml. of water was cooled to 5° and 6.5 g. of bromine vapor passed through the stirred suspension by means of an air jet. The addition of bromine was conducted at such a rate that the solution was never more than pale yellow in color. When no more decolorization of bromine occurred and all the unsaturated acid originally in suspension had disappeared, the solution was stirred for an additional 30 minutes with a slight excess of bromine. The excess bromine was then removed by bubbling air through. A small amount of the water-insoluble oily dibromo acid was removed by extraction with petroleum ether. The aqueous solution was then extracted with ether, the ether extract dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. A colorless oil was obtained; 7.8 g. (90.0%). The oil was purified by vacuum distillation, b.p. 100–105° (0.75 mm.). On standing in a vacuum desiccator the oil solidified as large transparent prisms, m.p. 85°. The substance was purified by sublimation at 60° and 0.01 mm.

*Anal.* Calcd. for  $C_7H_{13}BrO_3$ : C, 37.33; H, 5.77. Found: C, 37.36; H, 5.88.

***p*-Bromophenacyl  $\alpha$ -Isopropyl- $\alpha$ , $\beta$ -dimethoxybutyrate.**—A solution of 0.40 g. of  $\alpha$ -isopropyl- $\alpha$ -bromo- $\beta$ -methoxybutyric acid in 10 ml. of a 20% methanolic potassium hydroxide solution was boiled under reflux for one hour. Potassium bromide was precipitated. The precipitate was filtered off, the filtrate taken to a small volume under reduced pressure, acidified and extracted with ether. Removal of the solvent left a yellow oil, 0.35 g. (80%). Equivalent amounts of the oily acid, as its sodium salt, and *p*-bromophenacyl bromide in ethanol-water were boiled under reflux for three hours. On cooling a crystalline solid separated. The product was purified by crystallization from ethanol-water; needles, m.p. 89°.

*Anal.* Calcd. for  $C_{17}H_{25}BrO_5$ : C, 52.71; H, 5.94. Found: C, 52.69; H, 5.93.

**Demethylation of Heliotrinic Acid.**—A solution of 10 mg. of heliotrinic acid in 1 ml. of 48% hydrobromic acid was heated at 100° for 2 hours. The excess reagent was removed under reduced pressure and the residue sublimed at 78° and 0.1 mm. A colorless crystalline sublimate was obtained; m.p. 89–90°. A melting point determination with a mixture of the starting material gave a 33° depression (m.p. of heliotrinic acid, 93–95°). On admixture with *d*- $\alpha$ , $\beta$ -dihydroxy- $\alpha$ -isopropylbutyric acid (*cis*-hydroxylated, m.p. 89°)<sup>7</sup> there was no depression of melting point. On admixture with an approximately equal amount of the *l*-acid,<sup>7</sup> the melting point was raised to 115–118° (m.p. of the *dl*-acid, 119°).<sup>7</sup>

**$\alpha$ -Bromo- $\beta$ -benzyloxybutyric Acid.**—A solution of 5 g. of crotonic acid in 100 ml. of benzyl alcohol was added to a solution of 10 g. of silver nitrate in 100 ml. of benzyl alcohol at 0–5° simultaneously with the addition of 9.5 g. of bromine. Silver bromide rapidly separated from the stirred mixture. After the addition was complete, the mixture was stirred for one hour more at 0–5°, filtered and the excess benzyl alcohol

(9) M. C. Taylor, R. B. McCullin and C. A. Gammal, *ibid.*, **47**, 395 (1925).

