

The hydrochloride melted at 195–196° dec. after recrystallization from absolute ethanol-diisopropyl ether.

*Anal.* Calcd. for  $C_{24}H_{31}O_4N_3 \cdot HCl$ : N, 9.10; Cl, 7.68. Found: N, 8.89; Cl, 7.46.

2-Methyl-2-piperidinomethyl-1,3-propanediol was synthesized in the following manner. A mixture of 8.5 g. of 2-methyl-2-bromomethyl-1,3-propanediol, 31.5 g. of piperidine and 50 cc. of benzene was heated at 100° in a citrate bottle for 4 days. After removal of the solvent, the residue was treated with alkali and then extracted with ether. The solvent was removed from the dried extract, and the residue

was distilled; the amine (3.6 g.), which boiled at 123–126° (2 mm.), still contained unchanged bromide.

Two grams of the impure amine was mixed with 2.6 g. of phenyl isocyanate. After the reaction had subsided, the product was dissolved in dry ether and treated with the calculated amount of ethereal hydrogen chloride. After liberation of the amine from the salt, and recrystallization from petroleum ether (90–100°), the pure bisphenylurethan melted at 148–149° dec.; mixed m.p. 148–149° dec.

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## The Isolation of $\beta$ -Hydroxy- $\beta$ -methylglutaric Acid from the Seed of Flax (*Linum usitatissimum*)<sup>1</sup>

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RECEIVED AUGUST 24, 1953

The amorphous product, extracted from fat-free linseed meal with ethanol-dioxane, yields upon treatment with sodium methoxide (a) a methyl ester, (b) a crystalline glucoside and (c) a non-crystalline glucoside. The ester is shown to be methyl  $\beta$ -hydroxy- $\beta$ -methylglutarate (I) and the crystalline acid derived from it has been synthesized from diallylmethylcarbinol by ozonolysis and subsequent oxidation.

When linseed meal previously freed from fat is extracted with a mixture of equal parts of ethanol and dioxane a 2–4% yield of an amorphous tan powder (A) is produced<sup>2</sup>; this material appears to be a complex glucoside. It is shown herein that treatment of a solution of this powder (A) in methanol-dioxane with sodium methoxide affords three compounds: a colorless liquid methyl ester (I); a colorless crystalline glucoside; and a yellow powder which appears to be the glucoside of a polyhydroxy phenol. The constitution of compound I, the colorless liquid methyl ester, forms the subject of this paper. The two glucosides will be discussed in later communications.

The experimental basis for assigning formula I to the ester isolated from flaxmeal is as follows: The elementary analysis, molecular weight and equivalent weight determinations agreed with this formulation. Conversion of the ester I into the acid II by means of alkali was shown to involve the loss of two methyl groups thus showing that II is a dicarboxylic acid. One hydroxyl group was shown to be present in I by acetylation, and its tertiary character was indicated by the method of Murahashi.<sup>3</sup> Support for the presence of one side-chain methyl group was forthcoming from the observation that one mole of acetic acid was formed upon oxidation of I with chromic acid.<sup>4</sup>

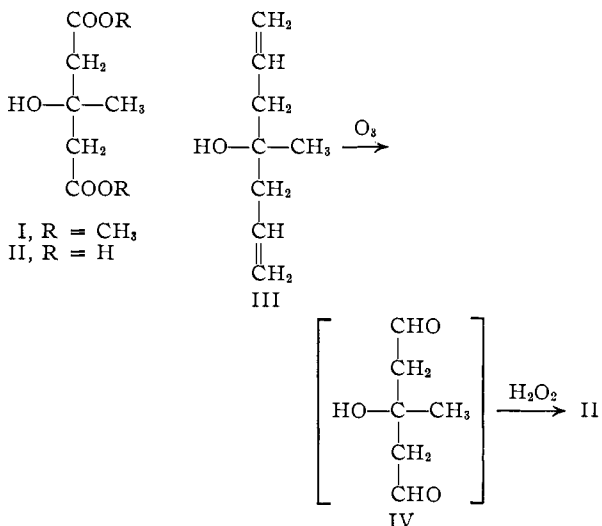
Finally,  $\beta$ -hydroxy- $\beta$ -methylglutaric acid, synthesized by the ozonization of diallylmethylcarbinol (III) followed by oxidation of the derived aldehyde IV, with hydrogen peroxide, was found to be identical with the acid II isolated from flax seed meal.

(1) Presented at the 124th National American Chemical Society Meeting, September, 1953. Paper No. 3046, Scientific Journal Series, Minnesota Agricultural Experiment Station. This work will form part of a thesis to be submitted to the graduate school of the University of Minnesota for the degree of Ph.D. Published by permission of the Director, North Dakota Agricultural Experiment Station.

(2) F. C. McIntyre, private communication.

(3) S. Murahashi, *Sci. Papers Inst. Phys. Chem. (Tokyo)*, **30**, 272 (1936); *C. A.*, **31**, 3001 (1937).

(4) R. Kuhn and H. Roth, *Ber.*, **66**, 1274 (1933).



It is of some interest to note that the ethyl ester lactone of the acid I is said to be obtained by the action of ketene on acetoacetic ester<sup>5</sup> and since this work was completed a report has been given<sup>6</sup> of the synthesis of dicrotalic acid, which is also  $\beta$ -hydroxy- $\beta$ -methylglutaric acid, isolated previously from *Crotalaria dura* and *Crotalaria globifera*.<sup>7</sup> The synthetic method used by these authors, which is similar to one formerly employed,<sup>8</sup> appears to be inferior as far as yield is concerned to that reported herein.

### Experimental

**Isolation of the Complex Linseed Glucoside.**—Linseed meal freed from fat and ground in a ball mill (3 kg.) was extracted at room temperature by stirring with a mixture of equal parts of 95% ethyl alcohol and 1,4-dioxane (8 l.).

(5) U. S. Patent 2,496,791 (1950); *C. A.*, **44**, 4026 (1950).

(6) Roger Adams and B. L. Van Duuren, *THIS JOURNAL*, **75**, 2377 (1953).

(7) J. S. Mairais, *Onderspoort J. Vet. Sci. Animal Ind.*, **20**, 61 (1944).

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

After 48 hours the suspension was filtered and the extract evaporated under reduced pressure to a sirup. The residual sirup was poured into petroleum ether (10 volumes), causing the separation of a heavy brown plastic material. This was dissolved in 50% aqueous alcohol (200 ml.). The alcoholic solution was acidified to pH 3 with hydrochloric acid and poured into 2 liters of ice-water. The flocculent precipitate A which formed, coagulated and settled; it was collected and dried under reduced pressure. The dried light brown material A weighed from 140 to 280 g. depending on the source. The product A, found only in the hull of the seed and extractable only after thorough grinding of the meal, contained negligible amounts of ash, phosphorus and nitrogen and showed  $[\alpha]^{24D} -30^\circ$  in alcohol-dioxane (1:1); this is an approximate value since the solutions were colored and the optical rotation was difficult to determine accurately.

The amorphous powder A is weakly acidic; it showed a neutral equivalent of about 4,000 and a saponification equivalent of 480 (found:  $\text{OCH}_3$ , 5.2).

When a solution of the amorphous powder (0.1 g.) was heated with *N* sulfuric acid in 50% ethanol by volume (20 ml.), hydrolysis occurred and a resinous material separated. Neutralization with barium carbonate, followed by passage through a cation exchange resin (Amberlite IR 120) gave a solution containing a mixture of glucose and two organic acids. Partition chromatography using phenol-water as the irrigating solvent revealed the presence of glucose  $R_f$  0.39 (located by spraying with Tollens reagent); by spraying a similar chromatogram with brom phenol blue,  $\beta$ -hydroxy- $\beta$ -methylglutaric acid ( $R_f$  0.68) and an unknown acid ( $R_f$  0.2) were detected.

**Isolation of Methyl- $\beta$ -hydroxy- $\beta$ -methylglutarate.**—To a solution of the light brown amorphous powder A (15 g.) in 150 ml. of a 1-1 mixture of dry dioxane and dry methanol, sodium methoxide (15 ml., 2 *N*) was added, and the resulting mixture shaken occasionally for two hours and allowed to stand overnight. The solution was treated with dilute sulfuric acid equivalent to the amount of sodium methoxide and the sodium sulfate removed by centrifugation. The clear supernatant solution was poured into four volumes of dry ethyl ether, whereupon a yellow material separated. This yellow product which was soluble in water appeared to be the glucoside of a polyhydroxyphenol.

The supernatant liquid was evaporated under reduced pressure to a thick sirup. The sirup was treated with water (15 ml.) and extracted with an equal volume of the ethyl ether to remove the methyl ester I. After keeping the aqueous solution in a cold room for several days the crystalline glucoside B was filtered and recrystallized from a small amount of dry methanol to give colorless needles (0.7 g.), m.p.  $167^\circ$ ,  $[\alpha]^{25D} -73^\circ$  in methanol, *c*, 1. The constitution of this compound will form the subject of a later communication.

Distillation of the ether layer from which the crystalline glucoside B was extracted by water left methyl- $\beta$ -hydroxy- $\beta$ -methylglutarate (I) which distilled as a colorless liquid, b.p.  $119-120^\circ$  (13 mm.),  $n^{24.6D}$  1.4381, yield 1 g. Solutions of the ester in water and in chloroform were optically inactive.

*Anal.* Calcd. for  $\text{C}_8\text{H}_{14}\text{O}_5$ : C, 50.52; H, 7.41; MeO, 32.6; OH, 8.95; side-chain methyl, 7.9; equiv. wt., 95; mol. wt., 190. Found: C, 50.73; H, 7.36; MeO, 33.1; OH (by acetylation), 8.76; side-chain methyl (by chromic acid oxidation), 7.0; equiv. wt. (by sapon.), 95; mol. wt. (Rast), 198.

The hydroxyl value was obtained in the following manner: the ester I (6.21 mg.) was heated for three hours at  $100^\circ$  with acetic anhydride (8.39 mg.) and sodium acetate (20 mg.) in

a sealed capillary tube. The tube was then broken under water and the excess acetic anhydride determined by titration with sodium hydroxide. The amount of acetic anhydride consumed corresponded to the presence of one hydroxyl group.

The procedure of Murahashi<sup>3</sup> indicated that the hydroxyl group was tertiary in nature. No reaction occurred when the ester was heated with phenylacetic acid.

**$\beta$ -Hydroxy- $\beta$ -methylglutaric Acid (II).**—When a solution of the methyl ester I (0.3 g.), obtained above, in 2 *N* hydrochloric acid (100 ml.) was boiled under reflux for 2 hours, hydrolysis occurred. Removal of the solvent *in vacuo* yielded  $\beta$ -hydroxy- $\beta$ -methylglutaric acid (II) as colorless crystals, m.p.  $108^\circ$  (after recrystallization from acetone). A solution of this acid in water (*c*, 4) was optically inactive. It showed  $R_f$  0.68 when examined by paper partition chromatography using phenol saturated with water as the irrigating solvent.

*Anal.* Calcd. for  $\text{C}_8\text{H}_{10}\text{O}_5$ : C, 44.44; H, 6.21; equiv. wt., 81. Found: C, 44.3; H, 6.3; equiv. wt. (by titration), 82.

**Ozonolysis of Diallylmethylcarbinol and Isolation of  $\beta$ -Hydroxy- $\beta$ -methylglutaric Acid (II).**—A solution of diallylmethylcarbinol (prepared from allylmagnesium bromide and ethyl acetate, b.p.  $153^\circ$  (737 mm.), b.p.  $56-57^\circ$  (14 mm.)) (6.3 g.) in ethyl acetate (150 ml.) was treated with ozone in the usual way (for generator see Henne and Perilstein<sup>9</sup>) until the reaction was complete. (Chloroform and acetic acid were less satisfactory as solvents.) Glacial acetic acid (100 ml.) was then added and the solution evaporated *in vacuo* to 25 ml. A second portion (100 ml.) of glacial acetic acid was added and evaporated as before. The residue consisting of the dialdehyde IV was dissolved in glacial acetic acid (50 ml.) and the solution added dropwise with stirring to a mixture of 30% hydrogen peroxide (25 ml.), sulfuric acid (1.1 ml.) and water (50 ml.). When the addition was complete the solution was refluxed for 2 hours.<sup>10</sup>

The sulfuric acid was neutralized with an equivalent amount of barium carbonate and the mixture evaporated to dryness *in vacuo*. Extraction of the residue with acetone followed by removal of the solvent furnished  $\beta$ -hydroxy- $\beta$ -methylglutaric acid (yield 6.5 g. or 81%), m.p.  $108^\circ$  alone or in admixture with the dicarboxylic acid obtained from flax meal.

*Anal.* Calcd. for  $\text{C}_8\text{H}_{10}\text{O}_5$ : C, 44.44; H, 6.21; equiv. wt., 81. Found: C, 44.39; H, 6.23; equiv. wt., 81.

It is to be noted that Sorokin<sup>11</sup> oxidized diallylmethylcarbinol with alkaline permanganate but obtained a sirupy product.

Conversion of the methyl ester of the synthetic acid (0.2 g.) into the bis-*p*-toluidide by the Grignard reaction<sup>12</sup> gave a product (0.14 g.), m.p.  $144-145^\circ$ . The natural methyl ester gave an identical product.

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{24}\text{O}_5\text{N}_2$ : N, 8.23. Found: N, 8.2.

The bis-anilide, prepared from the natural and synthetic methyl ester in the same manner had m.p. and mixed m.p.  $132^\circ$ .

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{20}\text{O}_5\text{N}_2$ : N, 8.97. Found: N, 9.1.

#### FARGO, NORTH DAKOTA

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(12) C. F. Koelsch and D. Tannenbaum, *THIS JOURNAL*, **55**, 3049 (1933).