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[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES DIVISION OF MERCK & CO., INC.]

## Synthesis of DL-3,5-Dihydroxy-3-methylpentanoic Acid (Mevalonic Acid)

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The racemate of a new acetate-replacing factor, DL-3,5-dihydroxy-3-methylpentanoic acid (VII), has been synthesized. The Reformatsky reaction between 4-acetoxy-2-butanone and ethyl bromoacetate gave ethyl 5-acetoxy-3-hydroxy-3-methylpentanoate (IV), which was hydrolyzed by alkali to 3,5-dihydroxy-3-methylpentanoic acid (VII).

A new acetate-replacing factor has been obtained<sup>1</sup> from dried distillers' solubles and has been shown<sup>2</sup> to be 3,5-dihydroxy-3-methylpentanoic acid (XI). The racemate was synthesized<sup>2</sup> from

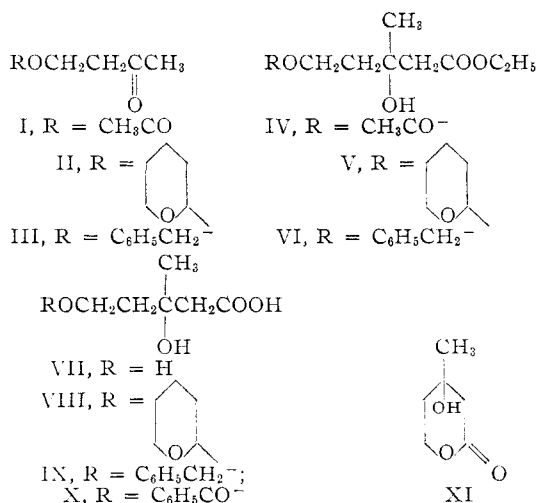
hydroxyester were extremely low with both the 4-acetoxy derivative I and the 4-(2-tetrahydropyran-5-yl) derivative II.

The hydroxyesters (IV, V, VI) were hydrolyzed with alkali to the corresponding free acids (VII, VIII, IX), which were isolated as oils and purified by conversion to N,N'-dibenzylethylenediammonium salts. Ethyl 5-acetoxy-3-hydroxy-3-methylpentanoate (IV) was hydrolyzed to the corresponding dihydroxyacid VII, which was isolated as an equilibrium mixture of the hydroxyacid and its  $\delta$ -lactone. The pure lactone XI was isolated from the equilibrium mixture by a short-path distillation. The distilled lactone was crystallized from acetone-ether to yield DL- $\beta$ -methyl- $\beta$ -hydroxy- $\delta$ -valerolactone (XI), m.p. 27-28°. The acid-lactone mixture was converted by an excess of N,N'-dibenzylethylenediamine in semi-aqueous media into N,N'-dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate).

Both the lactone XI and the salt of VII are fully active in the *Lactobacillus acidophilus* ATCC 4963 assay.<sup>3</sup>

Ethyl 3-hydroxy-3-methyl-5-(2-tetrahydropyran-5-yl)pentanoate (V) and ethyl 5-benzoyloxy-3-hydroxy-3-methylpentanoate (VI) were hydrolyzed with alkali to the corresponding hydroxyacids (VIII and IX), which formed crystalline N,N'-dibenzylethylenediammonium salts. The acetal derivative, N,N'-dibenzylethylenediammonium-bis-[3-hydroxy-3-methyl-5-(2-tetrahydropyran-5-yl)pentanoate], had 65% of the calculated activity in the L-4963 assay. This derivative is the only one of this series which showed activity in the L-4963 assay. The acetal VIII was converted to the dihydroxyacid VII by acid hydrolysis.

Benzoylation of the 5-hydroxyl group in 3,5-dihydroxy-3-methylpentanoic acid was accomplished in low yield with benzoyl chloride in aqueous alkali. The product, 5-benzoyloxy-3-hydroxy-3-methylpentanoate (X), was isolated as an oil and characterized as the N,N'-dibenzylethylenediammonium salt. This derivative was inactive in the L-4963 assay; alkaline hydrolysis regenerated full activity. Using other acylating reagents, little or none of the 5-acylated products could be isolated. These results indicate that self-acylation to the



diethyl 3-hydroxy-3-methylglutarate. This paper describes a new synthesis of DL-3,5-dihydroxy-3-methylpentanoic acid and several of its 5-O-derivatives. In addition, the N,N'-dibenzylethylenediammonium salts of the parent acid and its corresponding 5-O-derivatives are described.

The synthesis was accomplished by a Reformatsky reaction between a 4-O-substituted 4-hydroxy-2-butanone and ethyl bromoacetate to give a hydroxyester, which was hydrolyzed to the corresponding hydroxyacid. Three O-substituted 4-hydroxy-2-butanones were investigated in this reaction. In refluxing ether solution, the best yield (51%) was obtained with 4-acetoxy-2-butanone (I). With the acetal, 4-(2-tetrahydropyran-5-yl)-2-butanone (II), the yields were about 20%, while with the ether, 4-benzoyloxy-2-butanone (III), the yields were even lower. When the condensation was carried out in refluxing benzene, the yields of

(1) L. D. Wright, E. L. Cresson, H. R. Skeggs, G. D. E. MacRae, C. H. Hoffman, D. E. Wolf and K. Folkers, *THIS JOURNAL*, **78**, 5273 (1956).

(2) D. E. Wolf, C. H. Hoffman, P. E. Aldrich, L. D. Wright and K. Folkers, *ibid.*, **78**, 4499 (1956); D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright and K. Folkers, *ibid.*, **79**, 1486 (1957).

(3) H. R. Skeggs, L. D. Wright, E. L. Cresson, G. D. E. MacRae, C. H. Hoffman, D. E. Wolf and K. Folkers, *J. Bact.*, **72**, 519 (1956).

lactone was the preferred reaction under the acylating conditions.

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### Experimental

**4-Acetoxy-2-butanone.**—To a mixture of 200 ml. of acetic anhydride and one drop of concentrated sulfuric acid was added 100 g. of 4-hydroxy-2-butanone<sup>4</sup> during a period of one hour. The temperature of the reaction mixture was maintained at 50° by occasional cooling. The reaction mixture was fractionated under reduced pressure and the fraction boiling at 92–95° (25 mm.) was collected yielding 119 g. (80%) of 4-acetoxy-2-butanone,  $n_D^{25}$  1.4148.

*Anal.* Calcd. for  $C_6H_{10}O_3$  (130.14): C, 55.37; H, 7.75. Found: C, 55.51; H, 7.79.

**4-(2-Tetrahydropyranloxy)-2-butanone.**—Equimolar quantities (0.59 mole) of 4-hydroxy-2-butanone (51.5 g.) and dihydropyran (48.7 g.) were mixed and 4 drops of concentrated hydrochloric acid was added. The mixture was cooled to keep the temperature below 45° and then was allowed to stand overnight at room temperature.

The reaction mixture was dissolved in 500 ml. of ether and the solution was washed with dilute aqueous sodium bicarbonate and then with water. The ether solution was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* yielding 78 g. (78%) of product,  $n_D^{25}$  1.4492.

The product was distilled *in vacuo* yielding 57 g. of 4-(2-tetrahydropyranloxy)-2-butanone, b.p. 60–63° (100  $\mu$ ),  $n_D^{25}$  1.4488.

*Anal.* Calcd. for  $C_9H_{16}O_3$  (172.22): C, 62.77; H, 9.37. Found: C, 62.85; H, 8.99.

**4-Benzyloxy-2-butanone.**—A solution of 90 g. (0.5 mole) of 4-benzyloxy-2-butanone<sup>5</sup> in 200 ml. of acetic acid was cooled to 10–15°. A solution of 33.3 g. (0.33 mole) of chromium trioxide in 30 ml. of water and 180 ml. of acetic acid was added to the stirred reaction mixture over a period of 2 hours. The reaction mixture was diluted with 1 liter of water and extracted with 3 portions of chloroform. The combined chloroform extracts were washed with water, sodium bicarbonate solution and water. The residue (77 g.) obtained after removal of the chloroform was distilled at reduced pressure yielding 54 g. (60%) of 4-benzyloxy-2-butanone, b.p. 88–91° (0.5 mm.),  $n_D^{25}$  1.5040.

*Anal.* Calcd. for  $C_{11}H_{14}O_2$  (178.22): C, 74.13; H, 7.92. Found: C, 74.51; H, 8.19.

**Ethyl 5-Acetoxy-3-hydroxy-3-methylpentanoate.**—A mixture of 124 g. (0.96 mole) of 4-acetoxy-2-butanone and 166 g. (1.0 mole) of ethyl bromoacetate in 450 ml. of dry ether was added slowly to 120 g. (1.84 moles) of clean, dry, granular zinc. The reaction began immediately and the addition of reagents was regulated so that a gentle refluxing of ether was maintained. The time required for the addition was about 1 hour. The mixture was stirred gently and warmed an additional 2 hours.

The solution was decanted onto an excess of crushed ice, and the mixture was acidified to congo red with concentrated hydrochloric acid. The layers were separated; and the ether phase was washed with sodium bicarbonate solution, then with saturated ammonium sulfate solution, and was dried over sodium sulfate. The aqueous mother liquor and washes were combined, reacidified to congo red and were extracted twice with chloroform. The chloroform extracts were washed with sodium bicarbonate solution and were dried over sodium sulfate. The chloroform and ether extracts were combined and concentrated. The residue was fractionated under reduced pressure and the fraction boiling at 86–87° (0.2 mm.) was collected. The yield of ethyl 5-acetoxy-2-hydroxy-3-methylpentanoate was 106 g. (51%),  $n_D^{25}$  1.4458;  $d_4^{25}$  1.090,  $M_D^{25}$  53.34 (calcd. 53.22).

*Anal.* Calcd. for  $C_{10}H_{18}O_5$  (218.24): C, 55.03; H, 8.31; sapn. equiv., 109. Found: C, 55.32; H, 8.03; sapn. equiv., 114.

**Ethyl 3-Hydroxy-3-methyl-5-(2-tetrahydropyranloxy)-pentanoate.**—An equimolar mixture (0.32 mole) of 4-(2-

tetrahydropyranloxy)-2-butanone (55 g.) and ethyl bromoacetate (54 g.) in 200 ml. of ether was added slowly to a stirred mixture of 21 g. of granular zinc in 30 ml. of anhydrous ether. The rate of addition was such that the ether refluxed gently. After all the reactants had been added the mixture was warmed for 3 hours.

The reaction mixture was poured into 200 ml. of cold 2 *N* sulfuric acid. The ether phase was separated and the aqueous phase was extracted with three 150-ml. portions of chloroform. The chloroform and the ether extracts were washed with 10% aqueous sodium bicarbonate, saturated aqueous ammonium sulfate and dried over anhydrous magnesium sulfate. The combined organic phases were concentrated *in vacuo*.

The residue (55.3 g.) was distilled *in vacuo*. After two distillations 28 g. of ethyl 3-hydroxy-3-methyl-5-(2-tetrahydropyranloxy)-pentanoate, b.p. 96–98° (100  $\mu$ ),  $n_D^{25}$  1.4562;  $d_4^{25}$  1.054,  $M_D^{25}$  67.13 (calcd. 66.50), was obtained.

*Anal.* Calcd. for  $C_{13}H_{24}O_5$  (260.32): C, 59.98; H, 9.29. Found: C, 59.29; H, 8.78; sapn. equiv., 255.

***N,N'*-Dibenzylethylenediammonium Bis-(3,5-dihydroxy-3-methylpentanoate).**—Ethyl 5-acetoxy-3-hydroxy-3-methylpentanoate (47.5 g.) was dissolved in 100 ml. of ethanol and 50 ml. of water was added. The solution was warmed to ca. 60° and 6 *N* sodium hydroxide was added slowly to the stirred solution keeping the pH just at the turning point of phenolphthalein indicator. A total of two equivalents of alkali was added. The solution was cooled to room temperature and two equivalents of 6 *N* hydrochloric acid was added. The aqueous solution was concentrated *in vacuo* and the final traces of water were removed *in vacuo*. The residue was extracted with two 200-ml. portions of chloroform and the insoluble salts were removed by filtration. The combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* yielding a 28.7-g. residue.

The residue was dissolved in 100 ml. of water and a solution of 26 g. of *N,N'*-dibenzylethylenediamine in 100 ml. of methanol was added; the solution was kept at room temperature about 18 hours. The mixture was concentrated *in vacuo* to remove most of the methanol and the aqueous solution was extracted with 50 ml. of chloroform. The aqueous phase was concentrated *in vacuo* yielding 40 g. of salt.

The salt was dissolved in 125 ml. of hot methanol and 1 liter of ether was added to the warm solution. The product crystallized yielding 22 g. (38%) of *N,N'*-dibenzylethylenediammonium bis-(3,5-dihydroxy-3-methylpentanoate), m.p. 124–125°.

*Anal.* Calcd. for  $C_{28}H_{44}N_2O_8$  (536.65): C, 62.64; H, 8.26; N, 5.22. Found: C, 62.77; H, 8.24; N, 5.10.

The mother liquors and the chloroform wash of the aqueous solution were combined and concentrated *in vacuo* yielding a 32-g. residue. The residue was taken up in 100 ml. of water and a solution of 25 g. of *N,N'*-dibenzylethylenediamine in 100 ml. of methanol was added. After standing overnight, the reaction mixture was worked up in the manner described above yielding 9.5 g. (16%) of *N,N'*-dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate), m.p. 125–126°.

**$\beta$ -Hydroxy- $\beta$ -methyl- $\delta$ -valerolactone.**—*N,N'*-Dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate) (44.4 g., 0.08 mole), was dissolved in ca. 100 ml. of water and 170 ml. of 1 *N* sodium hydroxide was added. The *N,N'*-dibenzylethylenediamine was removed by ether extraction. The aqueous solution of sodium salt was passed through a column of Amberlite resin, IR 120 (H<sup>+</sup>), and the eluate was lyophilized. The residue was taken up in chloroform and the solution was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* yielding 20.3 g. of oil.

A sample of the oil was evaporatively distilled at ca. 90° (0.3 mm.)<sup>6</sup> to yield the pure lactone,  $\beta$ -hydroxy- $\beta$ -methyl- $\delta$ -valerolactone,  $\lambda_{max}^{CHCl_3}$  2.95 and 5.79  $\mu$ .

*Anal.* Calcd. for  $C_8H_{10}O_3$  (130.14): C, 55.37; H, 7.75. Found: C, 55.44; H, 7.56.

A portion of the distilled lactone (0.84 g.) was dissolved in a small amount of acetone, and ether was added to the point of incipient cloudiness. When the solution was cooled in a Dry Ice-acetone-bath, the lactone crystallized. The

(4) T. White and R. N. Haward, *J. Chem. Soc.*, 25 (1943).

(5) G. G. Mayer and H. Sobotka, *THIS JOURNAL*, 71, 2588 (1949).

(6) Higher temperatures cause loss of biological activity.

product was collected by filtration and washed with ether yielding 0.73 g. of  $\beta$ -hydroxy- $\beta$ -methyl- $\delta$ -valerolactone, m.p. 26–28°. Recrystallization of the product gave material melting at 27–28°. The product is hygroscopic.

*Anal.* Calcd. for  $C_{12}H_{16}O_2$  (180.14): C, 55.37; H, 7.75. Found: C, 55.94; H, 7.75; sapn. equiv., 131.

**N,N'-Dibenzylethylenediammonium-bis-(3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate).**—Ethyl 3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate (6.1 g.) was dissolved in 30 ml. of ethanol and 10 ml. of 3 *N* sodium hydroxide was added. The mixture was warmed on a steam-cone for 30 minutes.

The mixture was cooled, acidified to pH 4 and extracted with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* yielding 2.7 g. of oil.

The oil was dissolved in *ca.* 100 ml. of ether and 2.7 g. of N,N'-dibenzylethylenediamine in 20 ml. of ether was added. The salt precipitated and was collected by filtration yielding 3.3 g. of N,N'-dibenzylethylenediammonium-bis-(3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate), m.p. 137–139°.

*Anal.* Calcd. for  $C_{33}H_{50}N_2O_{10}$  (704.88): C, 64.74; H, 8.58; N, 3.98. Found: C, 64.69; H, 8.29; N, 4.46, 4.71.

**N,N'-Dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate)** from N,N'-Dibenzylethylenediammonium-bis-(3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate).—N,N'-Dibenzylethylenediammonium-bis-(3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate) (3.3 g.) was suspended in 10 ml. of water and 12 ml. of 1 *N* hydrochloric acid was added and warmed on the steam-cone for 10 minutes. The mixture was cooled and 10.8 ml. of 1 *N* sodium hydroxide was added. The mixture was filtered and the filtrate was lyophilized.

The residue was leached with 25 ml. of hot methanol. The methanol solution was cooled and diluted with ether yielding 450 mg. of N,N'-dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate), m.p. 122–123°. A mixture of this sample with an authentic specimen of the salt melted at 122–123°.

**N,N'-Dibenzylethylenediammonium-bis-(5-benzyloxy-3-hydroxy-3-methylpentanoate).**—A mixture of 40 g. (0.23 mole) of 4-benzyloxy-2-butanone and 37.5 g. (0.23 mole) of ethyl bromoacetate in 100 ml. of ether was added dropwise to 20 g. (0.32 mole) of clean, dry granular zinc. The reaction mixture was stirred at the reflux temperature for about two hours and was then added to a mixture of ice and 30 ml. of concentrated hydrochloric acid. The ether layer was separated and the aqueous phase was extracted with ether. The combined ether layers were washed with saturated sodium chloride solution, sodium bicarbonate solution and, again, with sodium chloride solution. The ether layer was concentrated yielding 40 g. of residual oil. A 30-g. portion of the product was distilled *in vacuo* to give *ca.* 15 g. of material boiling at <70° (0.4 mm.). The residue (14.7 g.) from this distillation was hydrolyzed on the steam-

cone with 22 ml. of 1 *N* sodium hydroxide and 50 ml. of methanol. The solution was diluted with 50 ml. of water and concentrated at reduced pressure to a volume of *ca.* 50 ml. The solution was extracted with ether and the ether phase was discarded. The aqueous phase was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was washed with saturated sodium chloride solution, dried and concentrated, yielding 2.2 g. of 5-benzyloxy-3-hydroxy-3-methylpentanoic acid.

A 1.93-g. portion of the acid was dissolved in 5 ml. of methanol and treated with 0.97 g. of N,N'-dibenzylethylenediamine. When *ca.* 75 ml. of ether was added, 1.5 g. of the salt, m.p. 123–127°, crystallized. A 400-mg. portion of the salt was recrystallized from chloroform-ether, chloroform-petroleum ether and finally from methanol-ether yielding 200 mg. of N,N'-dibenzylethylenediammonium-bis-(5-benzyloxy-3-hydroxy-3-methylpentanoate), m.p. 131–133°.

*Anal.* Calcd. for  $C_{42}H_{56}N_2O_8$  (716.89): C, 70.36; H, 7.87; N, 3.91. Found: C, 70.40; H, 7.60; N, 4.14.

**5-Benzyloxy-3-hydroxy-3-methylpentanoic Acid.**—Four hundred and eighty milligrams of N,N'-dibenzylethylenediammonium-bis-(5-benzyloxy-3-hydroxy-3-methylpentanoate) was suspended in 25 ml. of water and acidified with 2.5 *N* hydrochloric acid. The free acid was extracted into ether and then extracted into aqueous potassium bicarbonate. The bicarbonate solution was acidified and the product was extracted into ether. The ether extract was washed with water, dried and concentrated yielding 169 mg. of 5-benzyloxy-3-hydroxy-3-methylpentanoic acid,  $n_D^{20}$  1.5130, neut. equiv. 243 (calcd. 238).

**N,N'-Dibenzylethylenediammonium-bis-(5-benzyloxy-3-hydroxy-3-methylpentanoate).**—Ten grams of N,N'-dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate) was dissolved in 37 ml. of 1 *N* sodium hydroxide. The solution was extracted with ether and the ether extract was washed with 15 ml. of water. The combined aqueous phases were stirred and cooled while 6 g. of benzoyl chloride was added dropwise. Sodium hydroxide (1 *N*) was added dropwise during the addition of benzoyl chloride to keep the pH at *ca.* 9. After being stirred for one hour, the reaction mixture was washed with chloroform. The aqueous phase was acidified to pH 3 with hydrochloric acid and extracted with two 75-ml. portions of chloroform. The combined chloroform extracts were washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*.

The residue was leached with hot petroleum ether and then dissolved in 8 ml. of methanol. N,N'-Dibenzylethylenediamine (2.16 g.) was added, and the solution was diluted with *ca.* 80 ml. of ether. Two grams of N,N'-dibenzylethylenediammonium-bis-(5-benzyloxy-3-hydroxy-3-methylpentanoate), m.p. 142–143°, crystallized from the solution.

*Anal.* Calcd. for  $C_{42}H_{52}N_2O_{10}$  (744.86): C, 67.70; H, 7.04; N, 3.76. Found: C, 68.42, 68.31; H, 6.76, 6.93; N, 3.71.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

## Light-catalyzed Organic Reactions. VI.<sup>1</sup> The Isomerization of Some Dienones<sup>2,3</sup>

By G. BÜCHI AND N. C. YANG

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The isomerization of four dienones has been studied.  $\beta$ -Ionone yielded pyran X and spiroketone IX containing a cyclopropane ring. Irradiation of both pseudoionone and 6-methyl-3,5-heptadiene-2-one led to polymers. *trans-trans*-Crotonylideneacetone was converted to the  $\Delta^{3,4}$ -*cis* isomer. The changes observed are compared with the isomerization of tachysterol (III) and possible interpretations of the results are discussed.

The conversion of ergosterol (I) to vitamin D<sub>2</sub> (IV) is unquestionably one of the most fascinating

(1) Part V, *THIS JOURNAL*, **78**, 876 (1956).

(2) Part of a program of research supported by a grant from the Godfrey L. Cabot Fund, Publication No. 63, M. I. T. Solar Energy Conversion Project.

photochemical reactions known. The brilliant researches of Windaus and his School have led to the isolation and structure elucidation of lumisterol

(3) A preliminary account of this work was reported in *Chemistry & Industry*, 357 (1955).