2-Hydroxy-4-methyl-8-(γ-N-diethylaminopropyl)-aminoquinoline.—Four grams of 2-methoxy-4-methyl-8-aminoquinoline, 11 g. of the hydrobromide of γ-N-diethylaminopropyl bromide and 4 g. of sodium acetate in 50 cc. of absolute ethanol was refluxed for twelve hours. The product was cleaved and isolated as was the ethyl derivative to give 2.5 g. (41% yield) of white tetragonal needles, m. p. 115°.

Anal. Calcd. for $C_{17}H_{25}ON_3$: N, 14.63. Found: N, 14.57, 14.57.

2-Methoxy-4-methyl-8-(4-quinolylmethyleneamino)-quinoline.—One gram of the hydrate of quinoline-4-aldehyde and 1.05 g. of 2-methoxy-4-methyl-8-aminoquinoline in 25 cc. of absolute ethanol were refluxed for twelve hours. The product was precipitated by dilution with water and recrystallized from ethanol to give 1.4 g. (70% yield) of the anil, m. p. 144°.

Anal. Calcd. for $C_{21}H_{17}ON_3$: N, 12.83. Found: N, 12.50, 12.40.

Acknowledgment.—The authors are indebted to Messrs. Robert Coles and C. M. Hollenbeck for much of the analytical work.

Summary

1. Nitration of 2-chloro-4-methylquinoline gave largely 2-chloro-4-methyl-8-nitroquinoline and a small amount of the isomeric 6-nitro derivative.

2. 2-Methoxy-4-methyl-8-aminoquinoline was most conveniently prepared by catalytic reduction of 2-chloro-4-methyl-8-nitroquinoline followed by treatment with sodium methylate. While investigating other means for obtaining this compound, several new quinoline compounds were prepared.

3. 2-Methoxy-4-methyl-8-aminoquinoline was condensed with quinoline-4-aldehyde to give an anil. The same amine was condensed with β-N-diethylaminoethyl and γ-N-diethylaminopropyl bromide hydrobromides followed by cleavage of the methoxy group to give 2-hydroxy-4-methyl-8-(dialkylaminoalkyl)-aminoquinolines.

LINCOLN, NEBRASKA RECEIVED JULY 28, 1941

[CONTRIBUTION FROM THE RESEARCH AND BIOLOGICAL LABORATORIES OF PARKE, DAVIS AND COMPANY]

The Preparation and Properties of Sodium *d*-Pantothenate

BY HERVEY C. PARKE AND ELMER J. LAWSON

Since the announcement by Williams and Major[1] of the structure and synthesis of pantothenic acid, the synthetic vitamin has been available chiefly in the form of the calcium salt. We have found that the sodium salt possesses certain advantages, including ease of preparation and manipulation, which indicate it to be the most suitable form of *d*-pantothenic acid for use as a primary vitamin standard. A similar conclusion has been reached by Gätzi-Fichter, Reich and Reichstein,[2] although the data which they have furnished do not seem completely adequate to characterize the material for such a standard.

Sodium *d*-pantothenate is crystallized readily from absolute ethanol or isopropanol, and may thus be obtained in a high state of purity as fluffy needles which are considerably less hygroscopic than either the microcrystalline calcium salt or the amorphous sodium salt. Samples of the salt were subjected to a crystallographic study under the polarizing microscope through the kindness of Dr. Chester B. Slawson of the University of Michigan. He states: "The hair-like crystals show parallel extinction and are probably orthorhombic. The plane of the optic axes is parallel to the elongation with the obtuse bisectrix perpendicular to the elongation. The index of refraction parallel to the elongation is 1.486 ± 0.001 and perpendicular to the elongation 1.464 ± 0.003."

Sodium pantothenate has been prepared by a variety of methods, of which perhaps the simplest is the fusion of α-hydroxy-β,β-dimethyl-γ-butyrolactone with the sodium salt of β-alanine.[3]

We have found that sodium pantothenate can also be prepared by (1) the fusion of α,γ-dihydroxy-β,β-dimethylbutyramide with the sodium salt of β-alanine, (2) by the fusion of sodium α,γ-dihydroxy-β,β-dimethylbutyrate with β-alanine, and (3) by refluxing a solution of α-hydroxy-β,β-dimethyl-γ-butyrolactone and the sodium salt of β-alanine in ethanol or isopropanol. The second method is particularly interesting and, as far as we are aware, has no parallel in the literature.

(1) Williams and Major, *Science*, **91**, 246 (1940).

(2) Gätzi-Fichter, Reich and Reichstein, *Helv. Chim. Acta*, **24**, 185 (1941).

(3) Williams, Mitchell, Weinstock and Snell, THIS JOURNAL, **62**, 1784 (1940).

In order to determine the configuration of the biologically active form of pantothenic acid, we studied the conversion of α-hydroxy-β,β-dimethyl-γ-butyrolactone into α,γ-dihydroxy-β,β-dimethylbutyramide. The amide is prepared readily by allowing a solution of the lactone in liquid ammonia to stand for several hours. Application of this method to the (−) lactone yielded a strongly dextrorotatory amide; $[\alpha]^{25}D$ +52°. Hence, in accordance with Hudson's amide rules,[4] (−)-α-hydroxy-β,β-dimethyl-γ-butyrolactone very likely has the *d* configuration. The same conclusion, based on the rotation of the phenylhydrazide, has been reached by Grüssner, Gätzi-Fichter and Reichstein.[5] The racemic and the two active forms of the amide have been reported by Reichstein and Grüssner.[6] However, we are unable to confirm their value (124–124.5°) for the melting point of the amide from the (−) lactone. Our (+) amide, prepared according to their method as well as according to our own, was crystallized from several solvents, until the melting point (93–94°) and optical rotation remained constant. We are inclined to believe the Swiss workers had the racemic amide, rather than an allotropic form of the (+) amide. Unfortunately, they gave no values for the optical rotation of their preparation; so the nature of their product can only be surmised. It is significant, however, that their corresponding amide from the (+) lactone was without substantial rotatory power.

Experimental Part

Racemic Barium α,γ-Dihydroxy-β,β-dimethylbutyrate Monohydrate.—Racemic α-hydroxy-β,β-dimethyl-γ-butyrolactone[7] was refluxed with a solution of barium hydroxide, the excess barium ion removed with carbon dioxide, and the solution concentrated, whereupon crystalline racemic barium α,γ-dihydroxy-β,β-dimethylbutyrate separated as the monohydrate. Samples dried overnight at 100° (0.01 mm.) lost 4.27, 4.01% in weight. Calcd. for the monohydrate, 4.01%. *Anal.* (dry basis). Calcd. for $Ba(C_6H_{11}O_4)_2$: Ba, 31.82. Found: Ba, 32.15, 31.91.

Barium (+)-α,γ-dihydroxy-β,β-dimethylbutyrate was prepared from the *l*-lactone by the same method as used for the racemic salt. The material was purified by recrystallization from water–acetone; m. p. 213–215°; $[\alpha]^{34}D$ +7.4° (*C* = 5% in water); both of these values are somewhat higher than those described by Reichstein and co-workers.[5]

Anal. Calcd. for $Ba(C_6H_{11}O_4)_2$: Ba, 31.82. Found: Ba, 31.73, 31.67.

Racemic sodium α,γ-dihydroxy-β,β-dimethylbutyrate was obtained by mixing hot aqueous solutions of equimolar amounts of racemic barium α,γ-dihydroxy-β,β-dimethylbutyrate monohydrate and sodium sulfate, removing the barium sulfate by filtration, evaporating the filtrate to dryness and crystallizing the residue from acetone–methanol.

Anal. Calcd. for $C_6H_{11}O_4Na$: Na, 13.52. Found: Na, 14.02, 14.10.

Sodium (+)-α,γ-dihydroxy-β,β-dimethylbutyrate was prepared from the corresponding barium salt by double decomposition with sodium sulfate in a manner similar to that used for the racemic salt above. The product, after removal of the water, was taken up in methanol and precipitated by the addition of a large excess of acetone. The material separated first as an oil, but crystallized rapidly upon standing and was very hygroscopic; m. p. 166–171°; $[\alpha]^{29}D$ 8.4° (*C* = 4% in water).

Anal. Calcd. for $C_6H_{11}O_4Na$: Na, 13.52. Found: Na, 13.39, 13.42.

It was found that if the sodium (+)-α,γ-dihydroxy-β,β-dimethylbutyrate were allowed to crystallize slowly by addition of a very slight excess of acetone to the methanol solution, the salt had an entirely different crystalline form, m. p. 99–101°, and was non-hygroscopic. It gave the same specific rotation as the higher melting form and was assumed to be an allotropic modification. Both forms were definitely crystalline when viewed in a polarizing microscope.

Anal. Calcd. for $C_6H_{11}O_4Na$: Na, 13.52. Found: Na, 13.45, 13.33.

Racemic α,γ-Dihydroxy-β,β-dimethylbutyramide.—To 400 cc. of liquid ammonia in a 2-l. Erlenmeyer flask was added 75 g. of racemic α-hydroxy-β,β-dimethyl-γ-butyrolactone. The resulting solution was left unstoppered overnight, allowing the ammonia to evaporate slowly. The residual crystalline solid was triturated with petroleum ether, collected and re-crystallized from acetone. The product, m. p. 127°, was racemic α,γ-dihydroxy-β,β-dimethylbutyramide; yield 60 g. or 71%.

Anal. Calcd. for $C_6H_{13}O_3N$: C, 48.96; H, 8.91; N, 9.52. Found: C, 49.40, 49.38; H, 9.19, 9.00; N, 9.43, 9.51.

(+)-α,γ-Dihydroxy-β,β-dimethylbutyramide.—A.—This was prepared from the (−) lactone by the same method used for the racemic amide described above. It was found necessary, however, to employ a dewar flask in order to allow the lactone and the ammonia to remain in contact sufficiently long to ensure complete reaction. The residue, crude (+) α,γ-dihydroxy-β,β-dimethylbutyramide, was purified by recrystallization from acetone: m. p. 92–94°; $[\alpha]^{34}D$ +30.8° (*C* = 3% in water); $[\alpha]^{34}D$ +52° (*C* = 2% in methanol).

B.—A solution at 3 g. of (−)-α-hydroxy-β,β-dimethyl-γ-butyrolactone in 25 cc. of methanol was saturated with ammonia and allowed to stand overnight at room temperature. The methanol was then removed under reduced pressure and the (+)-α,γ-dihydroxy-β,β-dimethylbutyr-

(4) Armstrong and Armstrong, "The Carbohydrates," Longmans, Green and Co., New York, N. Y., 1934, p. 43.

(5) Grüssner, Gätzi-Fichter and Reichstein, *Helv. Chim. Acta*, **23**, 1276 (1940).

(6) Reichstein and Grüssner, *ibid.*, **23**, 650 (1940).

(7) Stiller, Harris, Finkelstein, Keresztesy and Folkers, THIS JOURNAL, **62**, 1785 (1940).

amide purified by recrystallization from acetone; m. p. 93–94°, $[\alpha]^{25}D$ +52° (C = 1% in methanol).

Anal. Calcd. for $C_6H_{13}O_3N$: C, 48.96; H, 8.91; N, 9.52. Found: C, 49.08, 49.16; H, 8.57, 8.59; N, 9.73, 9.65.

Further repeated recrystallizations from acetone or from methanol–ether did not affect either the melting point or the specific rotation.

Racemic Sodium Pantothenate.—**A.**—A mixture of 1.70 g. of racemic sodium α,γ-dihydroxy-β,β-dimethylbutyrate and 0.89 g. of β-alanine[8] was heated to 175°, at which point fusion took place. The fused mass was maintained at 150° for an hour and allowed to cool in a desiccator. The glassy product was assayed by the bacterial growth method; the activity corresponded to a 91% yield of racemic sodium pantothenate.

B.—A mixture of 0.970 g. of the dry sodium salt[3] of β-alanine and 1.28 g. of α,γ-dihydroxy-β,β-dimethylbutyramide was heated with frequent stirring at 100°. The mixture melted and foamed with liberation of ammonia. After three hours, the mixture was cooled and a sample assayed by the bacterial growth method. The result showed a 70% yield of racemic sodium pantothenate.

Sodium *d*-Pantothenate.—**A.**—A solution of 55.5 g. of the sodium salt of alanine and 65 g. of (−)-α-hydroxy-β,β-dimethyl-γ-butyrolactone in 350 cc. of isopropyl alcohol was refluxed for three hours, diluted with an additional 350 cc. of isopropyl alcohol and cooled. The crystalline sodium *d*-pantothenate, which separated slowly, was collected and recrystallized from isopropyl alcohol; $[\alpha]^{25}D$ 27.04° (C = 5%, in water, l = 2 dm.); yield 110 g. or 91%.

(8) Clarke and Behr, "Organic Syntheses," Vol. 16, John Wiley & Sons, Inc., New York, N. Y., p. 1.

It separates in clustered aggregates of parallel fibers. In crude samples, the fibers may be cemented together by an isotropic impurity into flat bundles. The pure salt loses its crystalline character rather sharply at 122–124° and becomes an isotropic glass which decreases in viscosity as the temperature is raised.

Anal. Calcd. for $C_9H_{16}O_5NNa$: N, 5.81; Na, 9.54. Found: N, 5.82, 5.73; Na, 9.32, 9.37.

Absolute ethyl alcohol may be substituted throughout the procedure outlined above but the greater solubility of sodium *d*-pantothenate in ethyl alcohol necessitates reducing the volume to one half, which is disadvantageous in the manipulation of the bulky product.

B.—A mixture of 3.4 g. of sodium (+)-α,γ-dihydroxy-β,β-dimethylbutyrate and 1.78 g. of β-alanine was fused at 180° for fifteen minutes, then cooled quickly. An estimate based upon specific rotation and bacterial growth assay indicated a yield of 61% of sodium *d*-pantothenate. Prolonged heating caused considerable racemization.

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Summary

Sodium *d*-pantothenate has been obtained in a pure, crystalline form which offers advantages as a standard for this vitamin.

DETROIT, MICH. RECEIVED JULY 5, 1941

[CONTRIBUTION FROM THE WOOD CONVERSION LABORATORY OF THE UNIVERSITY OF IDAHO]

The Constitution of Arabo-galactan. I. The Components and Position of Linkage*

BY E. V. WHITE

The water-soluble gum of the western larch has been isolated in 12–18% yield[1] by water extraction of larch sawdust. Schorger and Smith[1] named the substance "e galactan" since they were unable to identify any monosaccharide other than galactose in the products of acid hydrolysis although they observed that furfural was obtained upon distillation by the Tollens method. Later investigators[2–5] have shown that the furfural originates from a pentose constituent and have identified *d*-galactose and *l*-arabinose as the products of hydrolysis. The two monosaccharides were found in six to one molecular ratio, and larch gum, re-named "arabo-galactan," was assumed tentatively to be a homogeneous polysaccharide with the empirical formula $[(C_5H_8O_4)(C_6H_{10}O_5)_6]_n$. In later investigations the individuality of the arabo-galactan complex has been questioned and Huseman,[6] from viscosity studies, reported the degree of polymerization of the gum as being between 180 and 280 units. Similarly, Peterson and co-workers[7] fractionated arabo-galactan derivatives and concluded since their preparations were non-homogeneous that in all probability the original arabo-galactan

* Presented before the Division of Cellulose Chemistry at the Detroit Meeting of the American Chemical Society, Sept. 8–13, 1940.

(1) Schorger and Smith, *Ind. Eng. Chem.*, **8**, 494 (1916).
(2) Wise and Peterson, *ibid.*, **22**, 362 (1930).
(3) Wise, Hamer and Peterson, *ibid.*, **25**, 184 (1933).
(4) Peterson, Maugham and Wise, *Cellulose Chem.*, **15**, 109 (1934).
(5) Wise and Unkauf, *ibid.*, **14**, 20 (1933).
(6) Huseman, *J. prakt. Chem.*, **155**, 13 (1940).
(7) Peterson, Barry, Unkauf and Wise, THIS JOURNAL, **62**, 2361 (1940).