Experimental[5]

Oxidation by Linch's[1] Procedure.—This experiment was run using the procedure and quantities reported by Linch.[1] There was obtained 3.5 g. of biurea, m.p. 248° dec. The yield was 66%. Three recrystallizations from water gave a product melting at 257° dec. which did not depress the melting point of a sample of authentic biurea melting with decomposition at 257°. The two materials were also shown to be identical by X-ray diffraction diagrams.

Anal. Calcd. for $C_2H_6N_4O_2$: N, 47.47. Calcd. for $C_2H_4N_4O_2$: N, 48.27. Found: N, 47.47.

Oxidation Using Equimolecular Amounts of Bromine and Semicarbazide.—A solution of sodium hypobromite was prepared by adding 5.1 ml. (16 g., 0.1 mole) of bromine to a solution of 12 g. (0.3 mole) of sodium hydroxide in 100 ml. of water. This solution was cooled to 5° and added dropwise with stirring to a solution of 11.5 g. (0.1 mole) of semicarbazide hydrochloride in 60 ml. of water while keeping the reaction mixture at 5–15°. During the reaction there was a vigorous evolution of a neutral gas, presumably nitrogen. The reaction mixture was cooled in an ice-bath and stirred for one hour longer. Filtration and drying of the product gave 5.4 g. (91%) of biurea, m.p. 257° dec. This product did not depress the melting point of an authentic sample of biurea, m.p. 257° dec.

---

[5] Melting points are uncorrected.

THE LILLY RESEARCH LABORATORIES
ELI LILLY AND COMPANY
INDIANAPOLIS 6, INDIANA

Pantothenic Acid Salts

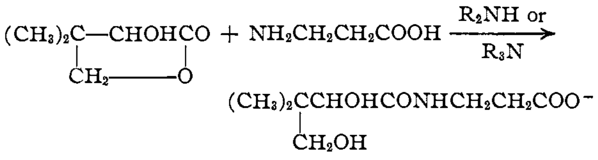
BY EVELYN H. WILSON, JOHN WEIJLARD AND MAX TISHLER

RECEIVED JUNE 3, 1954

The reaction of an alkaline or alkaline earth salt of β-alanine with d(−)α-hydroxy-β,β-dimethyl-γ-butyrolactone, d(−)-pantolactone in an anhydrous alcoholic medium is considered the method of choice for the preparation of salts of d(+)-pantothenic acid.[1]

The direct combination of this d(−)-pantolactone with β-alanine has been accomplished only by the fusion of the two components; this method usually gives d(+)-pantothenic acid in poor yields.[2]

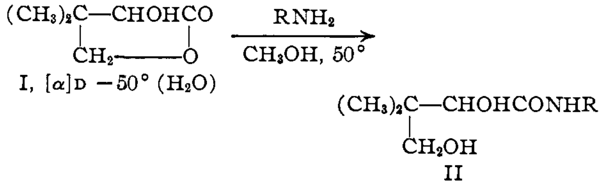
A new and practical method of synthesizing salts of pantothenic acid has been devised which does not require metal salts of β-alanine. When equimolar quantities of the pantolactone, β-alanine and a secondary or tertiary amine are heated in an anhydrous alcoholic medium, a homogeneous solution results from which calcium d(+)-pantothenate can be obtained in high yield upon the addition of calcium oxide. Sodium d(+)-pantothenate is similarly obtained, if, instead of calcium oxide, sodium ethoxide is used.



$$\underset{\mathrm{CH_2}\text{———}\mathrm{O}}{\mathrm{(CH_3)_2C\text{—}CHOHCO}} + \mathrm{NH_2CH_2CH_2COOH} \xrightarrow[\mathrm{R_3N}]{\mathrm{R_2NH\ or}} \underset{\mathrm{CH_2OH}}{\mathrm{(CH_3)_2CCHOHCONHCH_2CH_2COO^-}}$$

Some observations pertinent to an understanding of the condensation reaction were made. (1) β-Alanine does not react with the amine to a measurable extent under the conditions used for the condensation. The amino acid remains undissolved during protracted heating with the amine in alcohol and is recovered completely by filtration of such a mixture.

(2) Prolonged heating of a solution of the lactone and the amine in ethanol does not produce a change in optical rotation. Accordingly, amide or ester formation does not occur during the condensation since in all recorded cases a pantolactone derivative containing the lactone ring opened has a rotation opposite in direction from that of the parent lactone. The rotations of some amides II of pantolactone[3] illustrate this point.



$$\underset{\mathrm{CH_2}\text{———}\mathrm{O}}{\mathrm{(CH_3)_2C\text{—}CHOHCO}} \xrightarrow[\mathrm{CH_3OH,\ 50°}]{\mathrm{RNH_2}} \underset{\mathrm{CH_2OH}}{\mathrm{(CH_3)_2C\text{—}CHOHCONHR}}$$

I, $[\alpha]_D$ −50° (H_2O)

II

R- (II)	$[\alpha]_D$ (H_2O)	R- (II)	$[\alpha]_D$ (H_2O)
$-CH_2CH_2CH_2OH$	+29.7°	$-CH_2CH_2OH$	+31.5°
$-CH(CH_3)CH_2CH_2OH$	+16.1°	$-H$	+30.9°

(3) When β-alanine is added to the alcoholic solution of the amine and d(−)α-hydroxy-β,β-dimethyl-γ-butyrolactone, the β-alanine dissolves rapidly, and the levorotatory solution becomes dextrorotatory, indicating the lactone ring has opened. The combination of the lactone with β-alanine occurs prior to the addition of the inorganic salt-forming agent.

No reaction occurs in the absence of the amine. The effect of the amine, however, is not catalytic, since at least equimolar amounts of the amine, lactone and β-alanine are required for complete reaction.

The efficacy of amines in this reaction does vary. Secondary amines are more effective (88% yield) than tertiary amines (46% yield), while primary amines have a negligible effect. The failure of primary amines in this reaction is probably attributable to their preferential formation of an amide (I → II) of the lactone.[3]

Notwithstanding the apparent lack of reactivity between the β-alanine and secondary and tertiary amines, it is likely that an equilibrium exists between the zwitterion I and the amine salt II, however small the concentration of the latter, which is responsible for the condensation reaction.

$$\underset{\mathrm{I}}{\mathrm{H_3\overset{+}{N}CH_2CH_2COO^-}} + \mathrm{R_3N} \rightleftarrows \underset{\mathrm{II}}{\mathrm{NH_2CH_2CH_2COO^-{\cdot}HNR_3}}$$

This system would permit β-alanine in its highly enhanced donor form II to react with the lactone producing an amine salt of pantothenic acid.

In the course of this work we have prepared the calcium chloride salt of d(+)-pantothenic acid

$$\underset{\mathrm{CH_2OH}}{\mathrm{(CH_3)_2CCHOHCONHCH_2CH_2COOCaCl}}$$

---

[1] H. C. Parke and E. J. Lawson, THIS JOURNAL, **63**, 2869 (1941); S. Funabashi and K. Michi, *Bull. Inst. Phys. Chem. Research* (Japan), **22**, 681 (1934); *C. A.*, **41**, 6199 (1947); R. J. Williams, U. S. Patent 2,414,682 (1947); *ibid.*, **41**, 3118 (1947).

[2] R. J. Williams, H. K. Mitchell, H. H. Weinstock and E. E. Snell, THIS JOURNAL, **62**, 1784 (1940); N. Okochi and T. Egawa, *J. Agr. Chem. Soc.* (Japan), **17**, 578 (1941); *C. A.*, **45**, 2037 (1951).

[3] S. A. Harris, G. A. Boyack and K. Folkers, THIS JOURNAL, **63**, 2662 (1941); H. C. Parke and E. J. Lawson, *ibid.*, 2869; O. Schnider, *Jubilee Vol.*, Emil Barell, 85 (1946).

a crystalline, non-hygroscopic compound. The salt was also obtained by the addition of an alcoholic solution of calcium chloride to a quaternary ammonium salt of $d(+)$-pantothenic acid.

Experimental

A. **Calcium $d(+)$-Pantothenate.**—A mixture of 26 g. (0.2 mole) of $d(-)\alpha$-hydroxy-β,β-dimethyl-γ-butyrolactone, 18 g. (0.2 mole) of β-alanine, 50 cc. of absolute methanol and 25 cc. (0.24 mole) of diethylamine was refluxed overnight. Absolute ethanol (100 cc.) was added to the clear solution, which was then distilled. During the distillation the volume of solution was maintained at 175 cc. by the addition of more ethanol. The distillation was continued until the distillate contained 0.2 mole of amine as indicated by titration. The solution was cooled slightly and filtered through a pad of Norit. The almost colorless filtrate was mechanically stirred while 6.2 g. (0.11 mole) of solid calcium oxide was added. Stirring at room temperature was continued until all the calcium oxide had dissolved (about five hours), and the solution was clarified by filtration through a bed of Supercel. The filtrate was seeded with calcium $d(+)$-pantothenate and mechanically stirred at room temperature for 48 hours. The white solid was then filtered, washed well with absolute alcohol and dried *in vacuo;* yield 40 g. (84%), $[\alpha]^{24}D$ +27° (water). From the filtrate an additional amount (2.3 g.) of calcium pantothenate was obtained. The total yield was 89%.

Anal. Calcd. for $C_{18}H_{32}O_{10}N_2Ca$: N, 5.88; Ca, 8.41. Found: N, 5.84; Ca, 8.22.

B. **Sodium $d(+)$-Pantothenate.**—A solution of 0.2 mole of sodium ethoxide in absolute alcohol was added to the filtrate from the Norit filtration (A). The solution was seeded with sodium $d(+)$-pantothenate and mechanically stirred for 48 hours. The solid was filtered, washed with isopropyl alcohol and dried at 60° (75% yield).

X. **Calcium Chloride $d(+)$-Pantothenate.**—A mixture of 3.5 g. (0.04 mole) of β-alanine and 100 cc. of absolute methanol containing 0.03 mole of trimethylphenylammonium methoxide was refluxed until all the β-alanine had dissolved. The solution was cooled to room temperature and filtered. $d(-)\alpha$-Hydroxy-β,β-dimethyl-γ-butyrolactone (3.9 g., 0.03 mole) was dissolved in the filtrate, which was then kept at room temperature for 48 hours. A solution of 3.3 g. (0.03 mole) of anhydrous calcium chloride in absolute ethanol was added to the solution of the pantothenate salt. A white crystalline material began to separate almost immediately. The reaction mixture was kept three days at room temperature. The solid was then filtered and washed with absolute alcohol; yield 4.6 g. (58%), $[\alpha]^{24}D$ +25.3° (water).

Anal. Calcd. for $C_9H_{16}O_5NCaCl$: C, 36.79; H, 5.49; Cl, 12.07; Ca, 13.64. Found: C, 36.81; H, 5.63; Cl, 12.28; Ca, 13.37.

The same salt is obtained if the alcoholic solution of calcium chloride is added to the solution from the Norit filtration (procedure A).

PROCESS RESEARCH AND DEVELOPMENT DIV.
MERCK AND CO., INC.
RAHWAY, N. J.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Kinetics of Polymerization of Styrene Initiated by the System Benzoyl-Peroxide–Dimethylaniline

BY THEODORE H. MELTZER AND ARTHUR V. TOBOLSKY

RECEIVED APRIL 9, 1954

The rates of polymerization and degrees of polymerization produced in styrene by the initiator–activator system benzoyl peroxide–dimethylaniline were studied at several temperatures. At 0° the initiation of polymer chains appears to result from a bimolecular reaction between peroxide and amine. At higher temperatures the kinetics are more complex.

Introduction

For benzoyl peroxide initiated polymerization of pure styrene, the following relationship obtains[1]

$$R_p = K[\mathrm{M}][\mathrm{Bz_2O_2}]^{1/2} \qquad (1)$$

where R_p is the initial rate of polymerization in moles per liter per second, [M] and $[\mathrm{Bz_2O_2}]$ are the concentrations of monomer and benzoyl peroxide in moles per liter and K is a function of temperature alone tabulated in reference 1.

Horner and Schwenk[2] have noted that the polymerization of styrene by benzoyl peroxide is very much activated by the presence of dimethylaniline.

In this paper we show how the initial rate of polymerization of pure styrene initiated by the catalyst–activator system benzoyl peroxide–dimethylaniline depends on the concentrations $[\mathrm{Bz_2O_2}]$ and [DMA]. The experiments were carried out in pure styrene at temperatures of 0, 30, 45 and 60°. The relation between $1/\bar{P}_n$ (reciprocal number average degree of polymerization) and R_p was obtained at all four temperatures. It is important to emphasize that R_P is an *initial* rate of polymerization measured at very low conversions. At higher conversions the rate of polymerization decreases markedly.

Experimental

The experimental procedure for measuring R_p has been described previously.[3] $\bar{P}_n$ was calculated by means of the relationship[4]

$$\bar{P}_n = 1605\,[\eta]^{1.37} \qquad (2)$$

The purification of the dimethylaniline was accomplished as follows.

Eastman Kodak mono-free grade of dimethylaniline was refluxed four hours with 10% of its weight of acetic anhydride. The cooled reaction mixture was poured into an excess of 20% hydrochloric acid. After cooling this mixture was extracted with four 50-ml. portions of ether.

The aqueous layer was cautiously made alkaline to phenolphthalein with 30% NaOH solution, and the amine layer drawn off. The crude amine was dried over KOH pellets prior to fractionation through a Vigreux column. A good middle cut of colorless material was collected under nitrogen at 87° and 14 mm. pressure. It was stored in the refrigerator under nitrogen.

Results.—The results of the experimental work are tabulated in Table I. In this table are presented the values of $[\mathrm{Bz_2O_2}]$, [DMA], $[\mathrm{Bz_2O_2}]$ [DMA], R_p, $[\eta]$ and $1/\bar{P}_n$.

It was established that R_p was a function only of the product $[\mathrm{Bz_2O_2}]$ [DMA], not of the individual concentrations $[\mathrm{Bz_2O_2}]$ and [DMA]. Figure 1

---

[1] A. V. Tobolsky and B. Baysal, *J. Polymer Sci.*, **11**, 471 (1953).

[2] L. Horner, *Angew. Chem.*, **61**, 458 (1949); L. Horner and E. Schwenk, *ibid.*, **61**, 411 (1949); *Ann.*, **566**, 69 (1950).

[3] D. H. Johnson and A. V. Tobolsky, THIS JOURNAL **74**, 938 (1952).

[4] F. R. Mayo, R. A. Gregg and M. S. Matheson, *ibid.*, **73**, 1691 (1951).