
COMMUNICATIONS TO THE EDITOR

PREPARATION OF PYRROLIDINES

Sir:

Löffler and Freytag [*Ber.*, **42**, 3427 (1909)] prepared 1-methylpyrrolidine by heating N-bromo-N-methyl-*n*-butylamine with concentrated sulfuric acid for three hours on the water-bath and finally for thirty minutes at 135°. Other substituted pyrrolidines [Löffler, *ibid.*, **43**, 2035 (1910)] were prepared by this method from bromoamines having a methyl group on the third carbon from the nitrogen atom. However, when N-bromo-N-methyl-*n*-amylamine was heated with concentrated sulfuric acid, neither methylpiperidine nor 1,2-dimethylpyrrolidine was formed.

Britton [U. S. Patent 1,607,605, Nov. 23, 1926; *C. A.*, **21**, 249 (1927)] prepared pyrrolidines by heating with concentrated sulfuric acid or other concentrated mineral acid N-halogen derivatives of secondary aliphatic amines containing a methyl group three carbons removed from the nitrogen atom. The preparation of 1-*n*-butylpyrrolidine and 1-isoamyl-3-methylpyrrolidine by heating the corresponding bromoamines with concentrated sulfuric acid is described.

Recently Löffler's method has been used by Menshikov [*Ber.*, **69**, 1802 (1936)] to synthesize a new bicyclic system consisting of two condensed pyrrolidine rings having a nitrogen and carbon in common. From 2-isobutylpyrrolidine he prepared the N-bromine derivative and heated it with concentrated sulfuric acid. A tertiary base $C_8H_{16}N$ which he called 2-methylpyrrolizidine was isolated. The yield in the form of the picrate was 34.1% of the theoretical amount. However, when he tried the same experiment with 2-*n*-butylpyrrolidine complete resinification of the starting material resulted.

We have found that N-chloroamines are better than N-bromoamines for the preparation of pyrrolidines, that a mixture of sulfuric acid and water is a better reagent than concentrated acid for effecting ring closures of this type, and that in general temperatures considerably below those used by previous workers are preferable. From di-*n*-butylamine, for example, using the N-chlorine derivative and a mixture of sulfuric acid and

water, a 75% yield of 1-butylpyrrolidine, determined as the picrate, was formed.

Furthermore, by using a mixture of water and sulfuric acid and proper temperature control good yields of substituted pyrrolidines can also be obtained from N-halogen derivatives of amines other than those having a methyl group on the third carbon from the nitrogen atom. For example, 1,2-dimethylpyrrolidine was prepared in 73% yield from methyl-*n*-amylamine by heating the N-chlorine derivative with a mixture of sulfuric acid and water at 90° for thirty minutes. In this case eight parts of concentrated acid to three parts of water by volume was used.

The relative amounts of water and acid as well as the temperature required to produce the best yields have been found to vary with the different amines. The chloroamines and bromoamines were prepared by modifications of methods previously described [Coleman, *THIS JOURNAL*, **55**, 3001 (1933)]. Other solvents than ether may be used or the solvent omitted.

Work in this field is being continued.

CHEMICAL LABORATORY
STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA

GEORGE H. COLEMAN
GILBERT E. GOHEEN

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SYNTHESIS OF CO-CARBOXYLASE (VITAMIN B₁ PYROPHOSPHATE) FROM VITAMIN B₁

Sir:

Recently Stern and Hofer described the phosphorylation of vitamin B₁ by POCl₃. Their finding, while very interesting, results only in the phosphorylation of a minute amount of the vitamin [*Science*, **85**, 483 (1937)]. I have shown that vitamin B₁ may be phosphorylated by enzyme action [*Science*, **86**, 180 (1937); *Enzymologia*, **2**, 171 (1937)]. The isolation of the pure co-enzyme, however, owing to the presence of proteins and products of autolysis is not practical.

The following synthesis which is rapid and convenient yields fifty times more co-carboxylase than the phosphorus oxychloride method: 200 mg. sodium pyrophosphate is placed in a Pyrex test-tube and heated until all of the water of crystallization is removed. 0.5 cc. of orthophosphoric