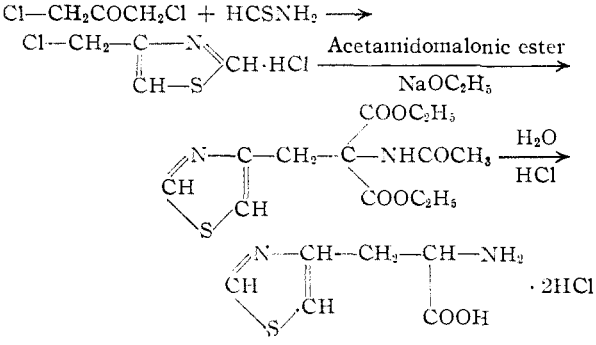
zole hydrochloride. Although our program has not yet been completed, the recent appearance of an article by Jones, Kornfeld and McLaughlin[2] describing the use of a solution containing 4-chloromethylthiazole (not isolated and purified) by what appears to us a less convenient process than ours moves us to a preliminary report on a part of our work. We are therefore submitting a description of a simple procedure for the preparation of crystalline 4-chloromethylthiazole hydrochloride and an illustration of its use in making β-(4-thiazolyl)-alanine dihydrochloride through the intermediate ethyl α-acetamido-α-carbethoxy-β-(4-thiazolyl)-propionate. (This intermediate was prepared also by Jones, Kornfeld and McLaughlin.[2])



Experimental

4-Chloromethylthiazole Hydrochloride.—Crude thioformamide[3] (15 g.) in 250 cc. of acetone was added with stirring to a solution of 25.4 g. of *sym*-dichloroacetone in 100 cc. of acetone. There was no apparent reaction but, by the next day, crystals appeared in the flask. These crystals, and those that formed on standing for five days, were filtered off and, when dry, weighed 21 g. Repeated recrystallization from a mixture of ethyl acetate and absolute methanol gave a pure product that melted with evolution of gas and sublimed rapidly at 166–167°. However, purification by recrystallization was impractical because of large attendant loss of material and it was found to be much more satisfactory to purify the product first by sublimation and then recrystallization from a 60–40 anhydrous ethyl acetate–methyl alcohol mixture. In this way a yield of 48% based upon the dichloroacetone used was obtained. In a run that stood for three days, a yield of 24% was obtained; standing, however, for ten days did not increase the yield above 48%.

Anal.[4] Calcd. for $C_4H_5Cl_2NS$: Cl, 41.7; N, 8.2. Found: Cl, 41.84; N, 8.11.

Ethyl α-Acetamido-α-carbethoxy-β-(4-thiazolyl)-propionate.—To a solution of 2.3 g. of freshly cut sodium in 200 cc. of absolute ethanol was added 21.7 g. (0.1 mole) of ethyl acetamidomalonate. When the solution became clear, it was cooled and 8.5 g. (0.05 mole) of 4-chloromethylthiazole hydrochloride was added rapidly with stirring. A precipitate of sodium chloride formed at once but the mixture was permitted to stand at room temperature for two hours before filtering through a layer of charcoal. The pale yellow oil that remained after evaporation was dissolved in hot water. Part of the water needed for solution was evaporated before chilling in ice. The crystals that separated were recrystallized from water; yield 9 g. or 53% based upon the 4-chloromethylthiazole used. After two recrystallizations the m.p. was 104–105°.

Anal. Calcd. for $C_{13}H_{18}O_5N_2S$: N, 8.92. Found: N, 8.72, 8.84.

β-(4-Thiazolyl)-alanine Dihydrochloride.—Six and five-tenths grams of the above ester was added to 100 cc. of concentrated hydrochloric acid and the mixture was then refluxed for five hours. Upon concentration under reduced pressure, a pale yellow solid remained that was recrystallized from a mixture of dilute hydrochloric acid and acetone; yield 1.5 g. that decomposed at 222–226°.

Anal. Calcd. for $C_6H_{10}Cl_2O_2N_2S$: Cl, 28.98; N, 11.43. Found: Cl, 29.24; N, 11.39.

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(2) R. G. Jones, E. C. Kornfeld and K. C. McLaughlin, THIS JOURNAL, **72**, 4526 (1950).

(3) R. Willstätter and T. Wirth, *Ber.*, **42**, 1911 (1909).

(4) Analysis by Carl Tiedcke, 366 Fifth Avenue, New York, N. Y.

An Improved Preparation of 2,6,8-Trichloropurine[1]

BY JOHN DAVOLL[2] AND BERTRAM A. LOWY

2,6,8-Trichloropurine is a valuable intermediate for the preparation of a number of purine derivatives. The present communication describes a convenient synthesis of this compound by direct chlorination of uric acid with phosphoryl chloride in the presence of dimethylaniline.

Unlike previously described syntheses of trichloropurine from uric acid,[3] this method does not involve the isolation of 2,6-dichloro-8-hydroxypurine as an intermediate, or the use of phosphoryl chloride in sealed vessels at high temperatures. The yield from uric acid (16–25%) compares favorably with those obtained by the older procedures.

Experimental

Uric acid (40 g.) was suspended in 200 ml. of redistilled phosphoryl chloride and treated with 91 ml. (3 moles per mole of uric acid) of dimethylaniline, which had been dried over potassium hydroxide. The mixture was boiled gently under reflux with exclusion of moisture for 20 hours. The dark solution was then evaporated under reduced pressure to about half-volume and, with stirring, poured slowly on to 1000 g. of crushed ice. After one hour the mixture was filtered and the solid washed by decantation with three 250-ml. portions of ether, each of which was then used to extract the aqueous filtrate. The combined ether extract was evaporated to dryness and the solid residue extracted with 120 ml. of boiling 3 *N* aqueous ammonia. On cooling, the filtrate deposited the ammonium salt of 2,6,8-trichloropurine as a mass of fine needles; yield 9–14 g. (16–25%). A solution of the ammonium salt in 75 parts of boiling water was acidified with dilute sulfuric acid, treated with a little Norit, and filtered hot. On cooling, trichloropurine pentahydrate separated in fine needles, and was dried at 110° to give anhydrous 2,6,8-trichloropurine, m.p. 185° (dec.).

Anal. Calcd. for $C_5HN_4Cl_3$: Cl, 47.6. Found: Cl, 47.9.

(1) The authors wish to acknowledge the support of the National Cancer Institute of the United States Public Health Service and the James Foundation of New York, Inc.

(2) Postdoctorate Research Fellow of the National Cancer Institute, United States Public Health Service.

(3) E. Fischer and L. Ach, *Ber.*, **30**, 2208 (1897); E. Fischer, *ibid.*, **30**, 2220 (1897); Boehringer and Sons, German Patents 94076, 94286, 96363; J. Davoll, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 833 (1946).

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Some Acylamino Acid Esters and Amides[1,2]

BY SIDNEY W. FOX AND HARRY WAX

In the course of enzymic experiments with a number of acylamino acids,[3] esters or amides of a num-

(1) Journal Paper No. J-1859 of the Iowa Agricultural Experiment Station, Project 1111. This project is supported in large part by the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) From the Ph.D. thesis of Harry Wax, Iowa State College, 1949.

(3) S. W. Fox and H. Wax, THIS JOURNAL, **72**, 5087 (1950).