zole hydrochloride. Although our program has not yet been completed, the recent appearance of an article by Jones, Kornfeld and McLaughlin² 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 4chloromethylthiazole hydrochloride and an illustration of its use in making β -(4-thiazoly1)-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)

 $C1-CH_2COCH_2C1 + HCSNH_2 \longrightarrow$

Cl-CH2-C-N CH-HCl-Acetamidomalonic ester NaOC₂H₅ COOC₂H₅ CH2 NHCOCH, ÈOOC₂H₅ Ċн /N-CH---CH2- $-CH--NH_2$ · 2HC1 CH ĊΗ COOH

Experimental

4-Chloromethylthiazole Hydrochloride.-Crude thioformamide³ (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 retory to purify the product first by submation and then re-crystallization from a 60-40 anhydrous ethyl acetate-niethyl 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 C₄H_bCl₂NS: 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 be-fore 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 $104-105^{\circ}$.

Anal. Caled. for $C_{13}H_{13}O_{\delta}N_{2}S$: N, 8.92. Found: N, 8.72, 8.84.

 β -(4-Thiazolyl)-alanine Dihydrochloride.—Six and fivetenths grams of the above ester was added to 100 cc. of concentrated hydrochloric acid and the mixture was then

(2) R. G. Jopes, E. C. Kornfeld and K. C. McLanchlin, This JOURNAL, 72, 4526 (1950).

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

(1) Analysis by Carl Tiedeke, 366 Fifth Avenue, New York, N. Y.

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. Caled. for C6H10Cl2O2N2S: Cl, 28.98; N, 11.43. Found: Cl, 29.24; N, 11.39.

DEPARTMENT OF CHEMISTRY

COLLEGE OF LIBERAL ARTS AND SCIENCES

TEMPLE UNIVERSITY PHILADELPHIA 22, PENNA. **Received January 10, 1951**

An Improved Preparation of 2,6,8-Trichloropurine¹

BY JOHN DAVOLL² 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 250ml. 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. Caled. for C₅HN₄Cl₃: 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)

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH **Received February 2, 1951** NEW YORK, N. Y.

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 acvlamino acids,3 esters or amides of a num-

(1) Journal Paper No. J-1859 of the Iowa Agricultural Experiment Station, Project 1113. 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)

ber of the acids were prepared. The esters were prepared by modification of a method previously described,⁴ and the amides were, in general, made from the corresponding esters by reaction with alcoholic ammonia.

Experimental

Benzoyl-DL-valine Ethyl Ester (I).—A solution of 7.25 g. (0.04 mole) of DL-valine ethyl ester hydrochloride in 19 ml. of water was stirred with 90 ml. of 2 N sodium carbonate (0.09 mole) and 200 ml. of chloroform. The mixture was cooled in an ice-bath and a solution of 6.5 g. of benzoyl chloride (0.046 mole, 15% excess) in dry chloroform was added with stirring over a 30-minute period. The ice-bath was removed and the stirring continued for an additional 30 minutes. The chloroform layer was separated and the aqueous layer was extracted twice with chloroform (25 ml.) and twice with ether (25 ml.). All extracts were combined and dried over sodium sulfate. After evaporation of the solvent a yellow sirup was obtained. This was dissolved in 25 ml. of benzene and treated with 275 ml. of hexane. A seed, obtained by pre-treating a small quantity of benzene solution, was introduced and the mixture set aside to crystallize in the cold. Filtration gave 8.2 g. (82%) of I; m.p. $65-68^\circ$.

Anal. Calcd. for $C_{14}H_{19}O_3N$: N, 5.62. Found: N, 5.42.

Carbobenzoxy-DL-valine Ethyl Ester (II).—Treatment of 5.5 g. (0.03 mole) of DL-valine ethyl ester hydrochloride with a 15% excess of carbobenzoxy chloride,⁵ as described for the benzoyl derivative, yielded an oil which was soluble in benzene-hexane and crystallized on long standing at -12° . Recrystallization from benzene-hexane gave 2.7 g. (32%) of II; m.p. 32-33°.

Anal. Calcd. for $C_{15}H_{21}O_4N$: N, 5.02. Found: N, 5.04. Carbobenzoxy-DL-leucine Ethyl Ester (III).—This derivative was prepared by treating 5.9 g. (0.03 mole) of DL-leucine ethyl ester hydrochloride with 5.9 g. (0.034 mole) of carbobenzoxy chloride by the same general procedure. The residue obtained after evaporation of the extraction solvent was crystallized from benzene—hexane. The solid was filtered off in the cold; a second crop was obtained from the filtrate; yield 6.9 g. (78%); m.p. 18.5–19°.

Anal. Calcd. for $C_{16}H_{23}O_4N$: N, 4.78. Found: N, 4.79. Carboallyloxy-DL-valine Ethyl Ester (IV).—Treatment of 5.4 g. (0.03 mole) of DL-valine ethyl ester hydrochloride with 4.2 g. (0.034 mole) of allylchloroformate,⁶ according to the general acylating procedure, yielded an oil which showed no tendency to crystallize from benzene-hexane at -12° . Removal of the solvents yielded solid after chilling at -12° . This was washed with cold hexane. The total yield was 2.5 g. (36%); m.p. 9–11°.

Anal. Calcd. for $C_{11}H_{19}O_4N$: N, 6.11. Found: N, 5.94.

Carbobenzoxyglycinamide (V).—Carbobenzoxyglycyl chloride was synthesized according to the method of Bergmann and Zervas. Addition of the acid chloride, obtained from 4.2 g. (0.02 mole) of carbobenzoxyglycine, to 50 ml. of anhydrous ether previously saturated with ammonia, gave a white precipitate. Ammonia was passed through the mixture for 15 minutes. After cooling overnight, the solid was filtered off. This material was extracted with 40 ml. of boiling ethyl acetate and the residue remaining after the extraction was extracted continuously for 7 hours with ethyl acetate, in a Butt extractor. The ethyl acetate extracts were combined, heated to boiling and filtered hot. The filtrate was evaporated until, upon cooling, crystallization occurred. An additional crop was obtained by adding hexane to the filtrate. The combined yield was 2.4 g. (58%); m.p. 133-136°.

Anal. Calcd. for $C_{10}H_{12}O_3N_2$: N, 13.4. Found: N, 13.3.

A second preparation of V was obtained by treating 1.8 g. (0.0075 mole) of carbobenzoxyglycine ethyl ester, in 20 ml.

(4) S. W. Fox, THIS JOURNAL, 68, 194 (1946).

(5) M. Bergmann and L. Zervas, Ber., 65, 1192 (1932).

(6) A generous sample of this compound was furnished by the Columbia Chemical Division, Pittsburgh Plate Glass Co., Pittsburgh, Pa. It was redistilled and stored at -12° .

of absolute alcohol, with a stream of ammonia for 45 minutes. After 4 days at room temperature, crystals appeared. The alcohol was removed under reduced pressure and the solid residue was recrystallized from 15 ml. of boiling water. Filtration gave 1.1 g. (71%) of V, m.p. 136-137.5°. A mixed m.p., run with the above preparation, gave 135-136.5°.

Carboallyloxyglycinamide (VI).—Carboallyloxyglycine ethyl ester was prepared by treating 5.6 g. (0.04 mole) of glycine ethyl ester hydrochloride with 5.6 g. (0.046 mole) of allylchloroformate in 25 ml. of carbon tetrachloride. The general procedure described for benzoyl-DL-valine ethyl ester was used. An oil (7.3 g.) was obtained. The oil dissolved in 50 ml. of absolute alcohol, and dry

The oil dissolved in 50 ml. of absolute alcohol, and dry ammonia gas was passed into the solution for 15 minutes. The flask was stoppered and after 6 weeks (this period was unnecessarily long) at room temperature the alcohol was distilled off under reduced pressure. The solid residue was dissolved in a small quantity of ethyl acetate, and on the addition of hexane, the material crystallized. The yield of VI was 5.5 g. (87%) based on the 0.04 mole of glycine ethyl ester hydrochloride used in the preparation of the intermediate acylamino acid ester; m.p. 107-107.5°.

Anal. Calcd. for $C_6H_{10}O_3N_2$: N, 17.7. Found: N, 17.2.

Carboallyloxy-DL-**leucina**mide (VII).—Attempts to prepare the corresponding ester from 5.9 g. (0.03 mole) of DLleucine ethyl ester hydrochloride, according to the general acvlating procedure, yielded an oil (7.1 g.).

The oil was dissolved in 50 ml. of absolute alcohol and treated with gaseous ammonia as described above. The sirupy residue which remained after evaporation of the alcohol was dissolved in 25 ml. of hot ethyl acetate. One hundred ml. of hexane was added and after 4 hours at -12° , crystallization commenced. After filtering, washing with hexane, and drying, 1.5 g. (23%) of VII, m.p. 83-85°, was obtained.

Anal. Calcd. for $C_{10}H_{18}O_3N_2$: N, 13.1. Found: N, 13.1. Acknowledgment.—The aid of Mr. Armand McMillan in carrying out micro-Kjeldahl analyses is appreciated.

CHEMICAL LABORATORY

IOWA STATE COLLEGE Ames, IOWA

RECEIVED NOVEMBER 28, 1950

The Preparation of Nitrosyl Fluoride and Nitryl Fluoride¹

BY ALBERT V. FALOON AND WILLIAM B. KENNA

The compounds nitrosyl fluoride and nitryl fluoride have been prepared by Ruff, Menzel and Neumann.² The method consisted of the vaporphase fluorination of nitric oxide and nitrogen dioxide with the reaction products being trapped in a quartz vessel. Since these fluorides attack quartz, silicon tetrafluoride and nitrogen sesquioxide were obtained as impurities.

This investigation has shown that a vaporliquid fluorination carried out in a Fluorothene³ reaction vessel proceeds very smoothly and without the formation of the above impurities. The fluorinations were carried out at temperatures just above the melting points of the respective oxides.

Experimental

The apparatus used in this investigation is shown in Fig. 1. The reaction vessel (\mathbf{R}) was constructed from a block

(3) Chlorotrifluoroethylene plastic polymer produced by Carbide and Carbon Chemicals Division, Union Carbide and Carbon Corporation.

⁽¹⁾ This document is based on work performed for the Atomic Energy Commission by Carbide and Carbon Chemicals Division, Union Carbide and Carbon Corporation, at Oak Ridge, Tennessee.

⁽²⁾ Otto Ruff, W. Menzel and W. Neumann, Z. anorg. allgem. Chem., 208, 293 (1932).