

faculty of obtaining pure samples of the synthetic intermediate N-propargyl-2-pyrrolidone. We now report an improved synthesis of this intermediate which enables oxotremorine to be obtained in an over-all yield of 46% based on the starting material 2-pyrrolidone.

Experimental

N-Propargyl-2-pyrrolidone.—A solution of 28 g. of A.R. KOH in 100 ml. of dry methanol was added to 45 g. of 2-pyrrolidone. The solvent was slowly removed under reduced pressure from the stirred solution at an internal temperature not exceeding 25°. When solid began to separate, 200 ml. of toluene was added and toluene was then continuously added during the course of all subsequent distillations. When 500 ml. of toluene had distilled, the pressure was allowed to rise and distillation was continued at an internal temperature of 90°. Finally 700 ml. of toluene was collected at atmospheric pressure. The suspension was cooled and treated at 40° with 60 g. of propargyl bromide over a period of 1 hr. The reaction mixture was then heated to 67° for 30 min., cooled, and filtered. The toluene was removed under reduced pressure, and the product was distilled. It had b.p. 77° (0.05 mm.), n_D^{25} 1.4970, yield 40 g. (61%).

1-(2-Oxopyrrolidino)-4-pyrrolidino-2-butyne, Oxotremorine.—A solution of 30 g. of N-propargyl-2-pyrrolidone, 9.2 g. of paraformaldehyde, and 23 ml. of pyrrolidine in 60 ml. of dioxane was heated at 100° for 12 hr. in an atmosphere of nitrogen. The solvent was removed under reduced pressure, and the residue was dissolved in 60 ml. of 5 N HCl. After three extractions with ether, the aqueous solution was made alkaline with 33% aqueous NaOH and extracted with chloroform. Distillation of the chloroform extracts yielded a fraction having b.p. 124° (0.1 mm.), n_D^{25} 1.5156, yield 38 g. (76%).

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80. Found: C, 69.89; H, 8.59.

Perchloric Acid in the Preparation of 2',3'-Isopropylidene 6-Thioinosine

JOHN A. ZDERIC, JOHN G. MOFFATT,

Syntex Institute for Molecular Biology, Palo Alto, California

DON KAU, KOERT GERZON,¹

The Lilly Research Laboratories, Indianapolis 6, Indiana

AND WILLIAM E. FITZGIBBON

Southern Research Institute, Birmingham, Alabama

Received September 25, 1964

The preparation of the title compound reported in the literature²⁻⁴ can be greatly improved by using perchloric acid⁵ as a catalyst for the condensation of 6-thioinosine and acetone. Adequate amounts of this isopropylidene intermediate, required for chemotherapeutic work,⁶ can be prepared readily following the procedure described in the Experimental section.

Experimental

The extent of formation of the isopropylidene derivatives was estimated by paper chromatography of an aliquot of the reaction mixture on Schleicher and Schuell No. 589 paper (orange ribbon) by the descending method. The solvent system used

(1) To whom request for reprints should be directed. Initial experiments performed at the Syntex Institute, Palo Alto, Calif.

(2) A. Hampton and M. H. Maguire, *J. Am. Chem. Soc.*, **83**, 150 (1961).

(3) A. Hampton, *ibid.*, **83**, 3641 (1961).

(4) P. R. Taylor and R. H. Hall, *J. Org. Chem.*, **29**, 1079 (1964).

(5) J. A. Zderic, H. Carpio, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 446 (1960).

(6) J. A. Montgomery, G. J. Dixon, E. A. Dulmage, H. J. Thomas, R. W. Brockman, and H. E. Skipper, *Nature*, **199**, 769 (1963).

throughout consisted of the standard isopropyl alcohol-water-ammonia mixture (70:20:10). For each isolated product, the R_f value was compared with an authentic sample of the same material prepared by previously reported procedures.

2',3'-O-Isopropylidene 6-Thioinosine. A. Small Scale.—To 100 ml. of acetone (dried with $MgSO_4$), 0.35 ml. of 2,2-dimethoxypropane was added, followed by 0.45 ml. of 70% aqueous perchloric acid. After 5 min. 244 mg. (1 mmole) of 6-thioinosine was added rapidly, and the reaction flask was stoppered and swirled for approximately 5 min. until the solids had dissolved. After 10 min. the solution was neutralized with 0.35 ml. of pyridine and concentrated under diminished pressure to approximately 20 ml. A 10% Na_2CO_3 solution (5 ml.) was added and the remaining acetone was removed. The aqueous solution was extracted twice with 5-ml. portions of dichloromethane and acidified with glacial acetic acid (about 0.7 ml.) to pH 6. After 2 hr. at 4°, the crystalline product was filtered off, washed with water, and dried *in vacuo* at room temperature. The material obtained showed a single spot on paper chromatography (R_f 0.72) and weighed 230 mg. (yield, 80%). Calculated on the basis of the ultraviolet absorption, the aqueous filtrate contained another 30 mg. of product, but no starting material (single spot).

B. "Large" Scale.—To avoid foaming, it was necessary to replace the Na_2CO_3 with an NH_4OH solution. To 2400 ml. of dry acetone was added 65 ml. of 2,2-dimethoxypropane followed by 87.2 ml. of 70% perchloric acid solution. After 5 min., 47.3 g. (0.166 mole) of 6-thioinosine was added quickly with continuous stirring. After 20 min., the clear, yellow reaction mixture was quenched by the addition of 194 ml. of pyridine which had been dried with calcium hydride. A white precipitate formed immediately. Water (920 ml.) was added, followed by 65 ml. of 15 N NH_4OH solution, and the suspension was concentrated under reduced pressure until all of the acetone had been removed. Another 65-ml. portion of 15 N NH_4OH was added, and the clear solution obtained was extracted with two 325-ml. portions of dichloromethane. The aqueous layer was filtered, chilled, and acidified to pH 6 with glacial acetic acid. After standing for 18 hr. at 4°, the white crystalline solid was collected by filtration, washed with water, and dried *in vacuo* at 78°. The product weighed 46.5 g. 86%; m.p. 238–240° dec.; λ_{max} ($\epsilon \times 10^3$): pH 1, 322 (24.0); pH 7, 318 (22.7); pH 13, 310 (23.4). The material showed a single spot on paper chromatography (R_f 0.72).

Synthesis of Some Amino Acid Thiol Esters^{1a}

ROBERT A. RAY AND ROBERT B. JOHNSTON^{1b}

Department of Chemistry, University of Nebraska, Lincoln, Nebraska

Received October 20, 1964

In connection with a study of certain aspects of the mechanism of action of sulfhydryl enzymes, several amino acid thiol esters have been prepared in this laboratory. These compounds are of particular interest since amino acid thiol esters serve as important model compounds for the study of amino acid-sulfhydryl enzyme interaction. Certain of the N-acyl compounds have been shown to be active substrates for proteolytic enzymes.^{2,3}

The syntheses of amino acid thiol esters which have been reported have been for the most part restricted to N-acylamino acid thiol esters. Thiol esters of hippuric acid have been reported by Jeger, *et al.*,⁴ by Johnston,² and by Schwyzer and Hürlimann.⁵ A number of amino acid thioesters of thiophenol and cysteamine have been prepared by Wieland.⁶ Thiol ester

(1) (a) This work has been supported in part by Research Grant HE 2970 from the National Heart Institute of the Public Health Service. (b) To whom inquiries should be sent.

(2) R. B. Johnston, *J. Biol. Chem.*, **221**, 1037 (1950).

(3) Th. Wieland and G. Pfeleiderer, *Advan. Enzymol.*, **19**, 235 (1957).

(4) O. Jeger, J. Norymberski, S. Szpilfogel, and V. Prelog *Helv. Chim. Acta*, **29**, 684 (1946).

(5) R. Schwyzer and Ch. Hürlimann, *ibid.*, **37**, 155 (1954).

(6) (a) T. Wieland and E. Bokelmann, *Ann.* **576**, 20 (1952); (b) T. Wieland, E. Bokelmann, L. Bauer, H. U. Lang, and H. Lau, *ibid.*, **583**, 129 (1953).