New Compounds

2-(Purin-6-yl)-2-thiopseudourea Hydrochloride

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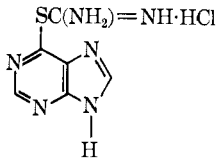
The reaction of 6-chloropurine with thiourea in refluxing ethanol has been reported to give 6-mercaptopurine monohydrate and 2,2-diamino-2H-thiazolo[3,4,5-*q*,*h*]purine.[2,3] Although 2-(purin-6-yl)-2-thiopseudourea hydrochloride (I) was postulated to be an intermediate in this reaction, this compound was not isolated and characterized. We have found that I can be prepared in 97% yield by allowing 6-chloropurine to react with thiourea in refluxing acetonitrile.



I

Experimental Section[4]

2-(Purin-6-yl)-2-thiopseudourea Hydrochloride (I).—A mixture of 6-chloropurine (0.47 g, 0.003 mole), thiourea (0.23 g, 0.003 mole), and acetonitrile (6 ml) was refluxed for 1 hr after which time the mixture was cooled with an ice–water bath. The resulting yellow precipitate was collected on a filter, washed with cold acetonitrile, and dried to give 0.67 g (97% yield) of I as a water-soluble yellow powder: mp 243° dec; infrared, ν_{max}^{KBr} 2941, 1656, 1590, 1565, 1408 sh, 1389, 1321, 1269, 1236, 1155, 1101, 994, 924, 848, 792, 694, and 638 cm^{-1}; far-infrared, ν_{max}^{KBr} 640, 616, 527, 484, and 454 cm^{-1}; ultraviolet, λ_{max}^{EtOH} 212 mμ (ϵ 14,100), 282 (10,400), and 330 (3000).

Anal. Calcd for $C_6H_7ClN_6S$: C, 31.24; H, 3.06; N, 36.43. Found: C, 31.42; H, 3.20; N, 36.00.

Conversion of I to 6-Mercaptopurine Monohydrate. A.—A solution of I (0.35 g, 0.0015 mole) in ethanol (5 ml) was refluxed for 1 hr. The yellow solid which precipitated after the solution had cooled was collected on a filter and dried to give 0.21 g (81% yield) of crude 6-mercaptopurine monohydrate, mp 269° dec. A single recrystallization from H_2O raised the melting point to 295–300° dec (lit.[2] mp 313–315° dec), no depression on admixture with an authentic sample, infrared spectrum essentially identical with that of an authentic sample.

B.—A solution of I (0.50 g, 0.0022 mole) in H_2O (6 ml) was titrated with 2 *N* NaOH to the phenolphthalein end point. The yellow solid which precipitated was collected on a filter and dried to give 0.27 g (73% yield) of 6-mercaptopurine monohydrate, mp 312° dec, no depression on admixture with an authentic sample.

(1) To whom inquiries should be directed.

(2) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

(3) C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **31**, 1417 (1966).

(4) Melting points were determined with a Mel-Temp capillary melting point apparatus and are uncorrected. The elemental analysis was performed by Dr. G. Weiler and Dr. F. Strauss, Microanalytical Laboratory, Oxford, England. The infrared data were obtained with a Beckman IR 8 infrared spectrophotometer. The far-infrared data were obtained with a Perkin-Elmer Model 21 double-beam infrared spectrophotometer which was fitted with a CsBr prism and purged with nitrogen. The ultraviolet data were obtained with a Bausch and Lomb Spectronic 505 spectrophotometer.

Eugenolglycolic Acid Derivatives

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The bactericidal quality of eugenol and the exhibition by eugenolglycolic acid amides of hypnotic, sedative, anticonvulsive, and anesthetic activities[2] prompted us to use eugenolglycolic acid as the starting material for the synthesis of compounds of possible pharmacological interest, including amides, thioureas, hydrazides, hydrazones, and a thiosemicarbazide. Conventional methods of preparation have been used. Some of the compounds prepared are described in the experimental section and others are listed in Tables I–III.

Experimental Section[3]

Eugenolglycolic acid was prepared by us from eugenol and chloroacetic acid in the presence of alkali and was crystallized from benzene; mp 103° (lit.[4] mp 81, 75, 100°).

Preparation of Amides. A.—A cold solution of 2.22 g of eugenolglycolic acid in benzene was treated with 0.75 ml of $SOCl_2$. The solution was allowed to warm up gradually and, after the brisk evolution of HCl had subsided, it was refluxed for 1 hr. Excess $SOCl_2$ and benzene were then removed under reduced pressure, leaving behind a pale brown, pungent-smelling oil.

B.—The acid chloride was added dropwise to a solution of 0.01 mole of the amine in benzene containing 1 ml of pyridine to give the amide.

Preparation of Thioureas. A.—Eugenolglycolic acid chloride was added dropwise to a stirred solution of 0.38 g of ammonium thiocyanate in 4.0 ml of dry acetone. After the addition was complete, the mixture was refluxed for 15 min and then filtered to remove the NH_4Cl.

B.—To the filtrate, now containing eugenolglycolic acid isothiocyanate, was added dropwise a solution of 0.01 mole of the amine in acetone. The mixture was refluxed gently for 1 hr. On cooling, crystals of the thiourea separated out.

C.—Eugenolglycolic acid thiourea was prepared by refluxing 22.2 g of eugenolglycolic acid and 7.6 g of thiourea in toluene for 15 hr. The toluene was then removed under reduced pressure, leaving behind a residue which was recrystallized three times from ethanol to give white needles (see Table II).

Preparation of Hydrazides. A.—The primary hydrazide was prepared by converting the acid chloride to the ethyl ester and subsequently treating the ester with 80% hydrazine hydrate in the usual manner; white fluffy needles, mp 69° (10% EtOH), yield 87.6%.

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.01; H, 6.83; N, 11.85. Found: C, 61.22; H, 6.90; N, 11.67.

B.—The *sym*-diacyl hydrazide was prepared by adding the acid chloride dropwise to 80% hydrazine hydrate and then refluxing for 0.5 hr; white needles, mp 124° (95% alcohol), yield 86.18%.

Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.27; H, 6.34; N, 6.29.

Hydrazo Hydrazones.—Molar proportions of the primary hydrazide and the carbonyl compound were refluxed in ethanol for 3 hr. Either crystals of the hydrazones separated on cooling the reaction mixture or the reaction mixture was worked up by customary procedures to yield the hydrazones.

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(2) J. E. Thuillier, F. Litvan, and W. Stoll, U. S. Patent 2,911,440 (1959); *Chem. Abstr.*, **54**, 4498*b* (1960).

(3) Melting points were observed in capillary tubes and are corrected.

(4) M. Saarbach, *J. Prakt. Chem.*, **21**, 158 (1880); C. Gassmann and E. Krafft, *Ber.*, **28**, 1870 (1895); R. Clauser, *Chem. Zentr.*, **72**, 1049 (1901).