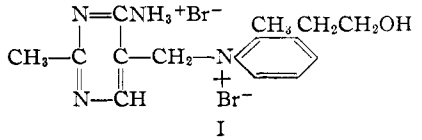
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Synthesis and Properties of Neopyrithiamine Salts[1]

BY ANDREW N. WILSON AND STANTON A. HARRIS

A synthesis of a product reported to be 1-[(4-amino - 2 - methyl) - 5 - pyrimidylmethyl] - 2-methyl-3-(β-hydroxyethyl)-pyridinium bromide hydrobromide (I), in which the pyridine ring



I

replaces the thiazole ring of thiamine, has been described by Tracy and Elderfield.[2] This substance was given the trivial name pyrithiamine by Woolley and White,[3] who found that the product prepared by the Tracy and Elderfield method was antagonistic to the action of thiamine in mice.

It has been found that the product prepared by the above method did not have the composition or the physical properties expected of a compound illustrated by formula I. We have obtained a new product whose properties and analytical data are in agreement with a compound having such a structure. We have used the name neopyrithiamine hydrobromide for this substance in order to distinguish it from pyrithiamine[3] (hydrobromide) as prepared by the previously described method.[2] The essential conditions for the preparation of neopyrithiamine hydrobromide are the use of a solvent, such as acetone or isopropyl alcohol, a low temperature, and a several-fold excess of the pyridine reactant.

The differences between the properties and analyses of pyrithiamine (hydrobromide) and neopyrithiamine hydrobromide are shown in the accompanying tables. Table I and Fig. 1 show that neopyrithiamine salts are characterized by two absorption bands in the ultraviolet, giving spectra which are similar to the spectra for thiamine salts.[4] Pyrithiamine salts show a single band spectrum which is more characteristic of the pyrimidines. Neopyrithiamine hydrobromide has acceptable analyses for a compound having the formula, $C_{14}H_{20}N_4OBr_2$, whereas pyrithiamine (hydrobromide) has low carbon and high nitrogen

TABLE I

PROPERTIES OF NEOPYRITHIAMINE AND PYRITHIAMINE

	Neopyrithiamine Hydrobromide	Pyrithiamine (Hydrobromide)
Ultraviolet Absorption Spectra		
	$\lambda_{max.}$ 235 and 273 mμ in water[a]	$\lambda_{max.}$ *ca.* 265 mμ. (broad) in water
Analyses		
(Calcd. for $C_{14}H_{20}N_4OBr_2$: C, 40.02; H, 4.80; N, 13.34)		
Sample	C H N	C H N
1	40.16 4.78 13.33	38.10 4.65 16.50
2	39.70 5.02 12.99	38.04 4.37 15.88
3	40.36 5.09 12.92	38.53 5.11 14.30
		37.24 4.35 16.49[b]
		37.54 4.45 17.77[c]
Decomposition Points		
	ca. 205–210°[cd]	chars. *ca.* 240–260°
Solubilities		
	Soluble in water and methanol; insoluble in ethanol	Soluble in water, methanol, and ethanol
Electrometric Titration Equivalent		
	Calcd. 331[a]	Calcd. 420
	Found 330[a]	Found 845 (first span)
		916 (second span)

[a] Determined on the hydrochloride. [b] The sample was dissolved in water, filtered with norit, concentrated to dryness and recrystallized from ethanol. [c] Treated similarly, but was recrystallized twice from ethanol. [d] This decomposition point varies and is not a good criterion of purity.

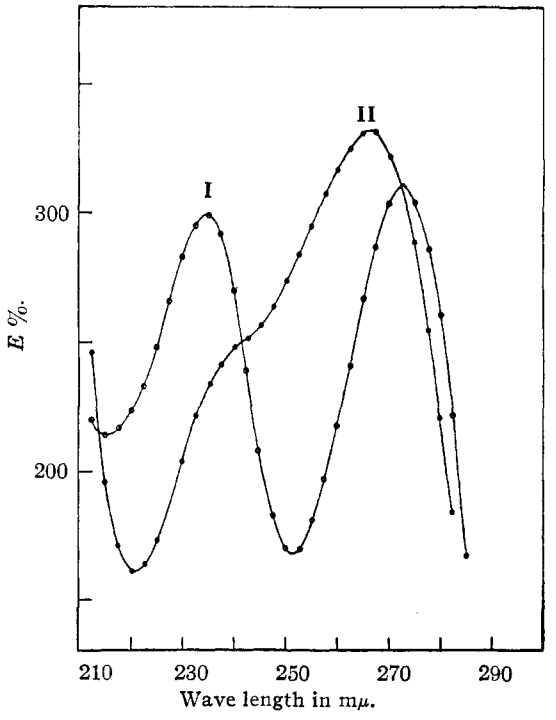


Fig. 1.—Ultraviolet absorption spectra in aqueous solution: I, neopyrithiamine hydrochloride; II, pyrithiamine hydrobromide.

(1) This paper was presented before the Division of Biological Chemistry at the American Chemical Society Meeting in Washington, D. C., on August 31, 1948.

(2) Tracy and Elderfield, *J. Org. Chem.*, **6**, 54 (1941).

(3) Woolley and White, *J. Biol. Chem.*, **149**, 285 (1943).

(4) Cline, Williams and Finkelstein, THIS JOURNAL, **59**, 1052 (1937).

values. Furthermore, the nitrogen values on different samples of the latter substance are inconsistent, varying over a range of several per cent., indicating that the preparations are not homogeneous. The melting points and solubilities of these two products are further indications of their different natures.

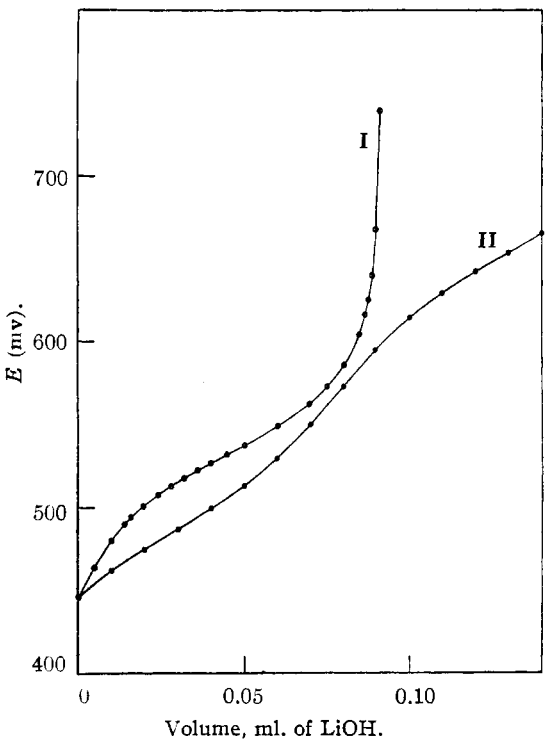


Fig. 2.—Electrometric titration: I, neopyrithiamine hydrochloride (34.02 mg. in 3 ml. of water plus one drop of *n*-octanol; titrated with 1.13 *N* lithium hydroxide); *p*H $^1/_2$ 4.86; II, pyrithiamine hydrobromide (6.756 mg. in 3 ml. of water; titrated with 0.1038 *N* lithium hydroxide); *p*H $^1/_2$ (1st span) 4.25.

Neopyrithiamine hydrobromide has been converted into the picrate, which in turn has been converted into the hydrochloride. The analytical values for these additional derivatives are in agreement with the theoretical values for neopyrithiamine picrate, $C_{26}H_{24}N_{10}O_{15}$, and neopyrithiamine hydrochloride, $C_{14}H_{20}N_4OCl_2$, respectively. The electrometric titration equivalent for neopyrithiamine hydrochloride (Table I and Fig. 2), is in close agreement with the theoretical value, while for pyrithiamine (hydrobromide) there is a wide discrepancy between the experimental and the theoretical values.

Table II shows a comparison of the infrared absorption spectral data of the two products. Here again, the differences are quite apparent.

The structure of pyrithiamine (hydrobromide) has not been fully elucidated. It has been split by the sodium bisulfite method into the pyrimidine-sulfuric acid[5] and the original 2-methyl-3-(β-hydroxyethyl)-pyridine. Similarly, it has been cleaved in a borate-buffered solution at *p*H 7 and separated by extraction with chloroform into the original pyridine compound and what appears to be the starting pyrimidine. These experiments have shown that the pyridine moiety was present in this product. As mentioned above, different samples have given widely varying nitrogen analyses. In addition, attempted purification by recrystallization has yielded products having progressively higher nitrogen values. These observations and the electrometric titration data lead to the conclusion that pyrithiamine (hydrobromide) is a mixture of compounds having the pyridine and pyrimidine moieties present in ratios of 1:2, 1:3, 1:4, etc. The nature of combination is not apparent.

TABLE II

INFRARED ABSORPTION SPECTRA,[a] λ in μ

Neopyrithiamine Hydrobromide Columns 1 & 3 Pyrithiamine Hydrobromide Columns 2 & 4			
14.12 S[b]		9.06 M	8.87 VW
13.80 S		8.64 M	8.61 M
13.32 W	13.29 W[b]	8.22 M	8.20 S
12.86 M		8.12 W	
12.39 S	12.45 W	7.96 M	
12.15 VW		7.76 W	7.79 M
11.84 M	11.67 M (broad)	6.69 S	7.11 S
11.45 W		6.55 S	6.51 M
10.55 M	10.54 S	6.47 S	
10.36 VW		6.19 S	
10.11 M	9.96 M	5.98 S	6.04 S
9.66 M		3.05 S	3.05 M
9.56 S	9.57 S		

[a] The spectrum was taken on a solid mull in petrolatum using a Perkin-Elmer 12A Recording Spectrometer. [b] Letters represent the relative absorption intensities of the maxima: S = strong, M = medium, W = weak, VW = very weak.

It has been found by Dr. Gladys A. Emerson and Misses Dorothea Casey and Elizabeth Wurtz of the Merck Institute for Therapeutic Research that neopyrithiamine hydrobromide is at least four times as active as an inhibitor of thiamine hydrochloride as is pyrithiamine (hydrobromide). The index of inhibition is *ca.* 10:1. The details of this work, including the description of other physiological changes in the rats, will be published elsewhere.

Experimental

Preparation of Neopyrithiamine Hydrobromide in Isopropyl Alcohol.—Six hundred milligrams of 2-methyl-3-(β-hydroxyethyl)-pyridine was dissolved in 3-4 ml. of isopropyl alcohol. Two hundred and forty milligrams of 2-methyl-5-bromomethyl-6-aminopyrimidine dihydrobromide was added, and the mixture was shaken until solution was obtained. The resulting solution was filtered and was allowed to stand overnight at room temperature, during which time the product separated from solution. It was centrifuged, washed with fresh isopropyl alcohol, with petroleum ether and dried. The yield of neopyri-

(5) Williams, Waterman, Keresztesy and Buchman, THIS JOURNAL, **57**, 536 (1935).

thiamine hydrobromide was 200 mg. (73% based on pyrimidine); m. p. 205–210° (dec.); $\lambda_{max.}$ in water 238 and 270 mμ.

Anal. Calcd. for $C_{14}H_{20}N_4OBr_2$: C, 40.02; H, 4.80; N, 13.34. Found: C, 39.70; H, 5.02; N, 12.99.

Preparation of Neopyrithiamine Hydrobromide in Acetone.—Six hundred milligrams of 2-methyl-3-(β-hydroxyethyl)-pyridine was dissolved in 10 ml. of acetone, and to this solution was added 240 mg. of 2-methyl-5-bromomethyl-6-aminopyrimidine dihydrobromide. The mixture was shaken until most of the pyrimidine had dissolved. In a few minutes a gummy precipitate had formed. The supernatant liquor was decanted from the gum and was allowed to stand overnight at room temperature. The product separated from solution as a solid. It was centrifuged, washed with fresh portions of acetone and with petroleum ether, and dried. The yield of neopyrithiamine hydrobromide was 150 mg. (55% based on pyrimidine); m. p., 218–220° (dec.); $\lambda_{max.}$ in water, 238 and 271 mμ.

Anal. Calcd. for $C_{14}H_{20}N_4OBr_2$: C, 40.02; H, 4.80; N, 13.34. Found: C, 40.36; H, 5.09; N, 12.92.

Preparation of Neopyrithiamine Picrate.—One hundred milligrams of neopyrithiamine hydrobromide was dissolved in 20 ml. of water and added to a solution of 200 mg. of picric acid in 50 ml. of water. The solution was filtered from a small amount of gummy precipitate and was allowed to stand overnight in the refrigerator where the product separated in a crystalline condition. The product was filtered, washed with water and dried. The yield of neopyrithiamine picrate was 70 mg. (40%); m. p. 186–188°.

Anal. Calcd. for $C_{26}H_{24}N_{10}O_{15}$: C, 43.58; H, 3.38; N, 19.55. Found: C, 43.52; H, 3.28; N, 19.61.

Preparation of Neopyrithiamine Hydrochloride.—Eight hundred and forty milligrams of neopyrithimine hydrobromide was converted into the picrate as described above. The melting point of a dried sample was 183–184°. The main crop was suspended in water, was acidified with dilute hydrochloric acid, and was extracted with nitrobenzene to remove the liberated picric acid. The aqueous solution was extracted further with ether, and then concentrated to a small volume under reduced pressure and at a low temperature. On addition of isopropyl alcohol to the residue, the product crystallized slowly. It was filtered, washed with isopropyl alcohol, washed with ether and dried. The yield of neopyrithiamine hydrochlorid was 260 mg. (40% from the bromide); m. p. 234-236° (dec.); $\lambda_{max.}$ in water 235 and 273 mμ.

Anal. Calcd. for $C_{14}H_{20}N_4OCl_2$: C, 50.76; H, 6.09; N, 16.92. Found: C, 50.69; H, 6.08; N, 16.76.

Stability of Neopyrithiamine Salts in Solution.—The ultraviolet absorption spectrum of a freshly prepared methanolic solution of neopyrithiamine hydrobromide changed when the solution was allowed to stand for several days at room temperature. The 235 mμ band shifted to 240 mμ and had a lower intensity, while the 273 mμ band shifted to 267 mμ and was of greater intensity. At the same time the minimum point of the curve at 252 mμ changed to 250 mμ and was of much greater intensity. In short, the two bands seemed to coalesce and to resemble that of pyrithiamine (hydrobromide).

The decomposition was only slight in aqueous solution at room temperature. When the temperature was increased, however, the decomposition was much more rapid. In neutral or alkaline solutions, the decomposition was rapid even at room temperature. Under these conditions the 235 mμ band completely disappeared.

Both neopyrithiamine hydrobromide and neopyrithiamine hydrochloride can lose hydrogen bromide or hydrogen chloride when heated under reduced pressure. The loss was greater with longer heating and with higher temperatures. Conversely, some samples crystallized from solution with varying amounts of hydrogen bromide or hydrogen chloride.

Acknowledgments.—The authors wish to express their appreciation and thanks to Dr. Nelson R. Trenner and Dr. Charles Rosenblum for their helpful suggestions on this problem, and for determining and interpreting the physical measurements reported in this paper. The authors also wish to thank Mr. R. N. Boos and his associates for the microanalyses.

Summary

The previously reported method of preparation of 1-[(4-amino-2-methyl)-5-pyrimidylmethyl]-2-methyl-3-(β-hydroxyethyl)-pyridinium bromide hydrobromide was found to yield a substance that was not analytically in agreement with the desired product. This product has been prepared now, and its analytical and physical properties are described. It has been named neopyrithiamine hydrobromide. Neopyrithiamine hydrobromide has been converted first into the picrate and then into the hydrochloride.

RAHWAY, N. J. RECEIVED FEBRUARY 10, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Schmidt Reaction. I. Conditions and Reaction Mechanism with Primary, Secondary and Tertiary Aliphatic Acids

BY CONRAD SCHUERCH, JR.,[1,2] AND ERNEST H. HUNTRESS

Although carboxylic acids react with sulfuric and hydrazoic acids to give primary amines, a recent review[3] indicates only meager information on the behavior of the lower primary, secondary and tertiary representatives, and that for the last group high yields of amine have been obtained only with acids containing a cyclopentyl radical adjacent to the carboxyl. The influence of reaction conditions upon yield of amine has been inadequately characterized, and whether yields less than theoretical were due to incomplete reaction or to diversion into side reactions has rarely been established. The present study adds to our knowledge of acetic, isobutyric and tri-

(1) This paper is constructed from part of a dissertation submitted by Conrad Schuerch, Jr., to the Faculty of the Massachusetts Institute of Technology in June, 1947, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. It was presented before the Division of Organic Chemistry at the 112th meeting of the A. C. S. in New York on September 18, 1947.

(2) Present address: Division of Cellulose and Industrial Chemistry, McGill University, Montreal 2, Canada.

(3) Wolff, "The Schmidt Reaction, Organic Reactions," Vol. 3, John Wiley and Sons, New York, N. Y., 1946, pp. 307–336.