Preparation and Evaluation of Thiamine N-Cyclohexylsulfamate Hydrochloride

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The presently available salts of thiamine are known to have a characteristic bitter taste. The N-cyclohexylsulfamic acid salt of thiamine hydrochloride was prepared and was found to have a taste which was greatly improved over that of the presently available salts of thiamine. After characterization, the salt was placed under short term accelerated aging conditions. The data obtained appears to indicate that the salt possesses good stability.

THE THIAMINE MOLECULE contains two basic nitrogen atoms, the quaternary nitrogen of the thiazole ring and the nitrogen of the primary amino group attached to the pyrimidine ring. Two types of thiamine salts are, therefore, possible. The first type involves only the nitrogen of the thiazole ring which is a more strongly basic center than the primary amino function (1). The second type of salt results when further salt formation occurs at the primary amino group. An example of the former would be thiamine mononitrate, whereas an example of the latter would be thiamine chloride hydrochloride.

Thiamine chloride hydrochloride and thiamine mononitrate appear to be the salts of choice in pharmaceutical dosage forms at the present time. The mononitrate is reported to be preferred in dry dosage forms because of greater stability in the dry state (1).

Various salts of thiamine have been reported. Okumura and Sakurai (2, 3), with the aid of ion exchange resins, prepared the following salts: nitrate·HNO_3; acid sulfate; iodide·HI; bromide·HBr; thiocyanate·HCNS; chloride; bromide; iodide; and thiocyanate. Water-soluble disulfonates of thiamine have also been reported by the same authors (4).

Thiamine salicylate (5) was prepared in Germany a number of years ago and was reported to be useful in the treatment of rheumatic and arthritic disease.

Several phosphoric acid derivatives of thiamine are quite well known. These include thiamine phosphoric acid ester chloride, thiamine phosphoric acid ester phosphate salt, thiamine phosphoric acid salt, thiamine triphosphoric acid ester, thiamine triphosphoric acid salt, and others (6).

Although many thiamine derivatives have been described, nothing has been reported concerning the improvement of the bitter taste which is characteristic of thiamine. The primary objective in preparing thiamine N-cyclohexylsulfamate hydrochloride was to obtain a salt of thiamine with improved taste and with stability at least as good as that of the presently available salts of thiamine.

Silver nitrate was reacted with N-cyclohexylsulfamic acid to form insoluble silver N-cyclohexylsulfamate. The silver N-cyclohexylsulfamate was reacted with thiamine chloride hydrochloride to produce thiamine N-cyclohexylsulfamate hydrochloride, leaving behind the insoluble silver chloride. The reactions are illustrated by the equations.

TABLE I.—STABILITY OF B_1 IN MULTIPLE VITAMIN SOLUTIONS UNDER VARIOUS CONDITIONS OF TEMPERATURE AND pH

Type of B_1 Salt	Conditions of Storage pH	°C.	Original Assay, mg./ml.	3 Months Assay, mg./ml.	% Loss
TM[a]	3	25	9.99	9.98	0.1
TN-C[b]	3	25	9.90	9.82	1.6
TM	4	25	9.94	9.60	3.4
TN-C	4	25	10.24	10.24	0.0
TM	5	25	9.97	9.26	7.1
TN-C	5	25	9.95	9.40	3.5
TM	3	40	9.99	9.18	8.0
TN-C	3	40	9.90	9.14	7.7
TM	4	40	9.94	7.49	24.7
TN-C	4	40	10.24	7.48	26.9
TM	5	40	9.97	6.43	35.5
TN-C	5	40	9.95	6.69	32.8
TM	3	50	9.99	8.74	12.5
TN-C	3	50	9.90	8.92	9.9
TM	4	50	9.94	5.13	48.3
TN-C	4	50	10.24	5.23	48.0
TM	5	50	9.97	3.38	66.0
TN-C	5	50	9.95	3.45	65.3

[a] Thiamine mononitrate. [b] Thiamine N-cyclohexylsulfamate hydrochloride.

TABLE II.—STABILITY OF THIAMINE N-CYCLOHEXYLSULFAMATE HCl IN MULTIPLE VITAMIN TABLETS

Condition, °C.	Original, mg./Tablet	One Month, mg./Tablet	Three Months, mg./Tablet	% Loss
25	10.1	10.0	10.0	1
40	10.1	9.5	9.8	3
50	10.1	9.1	9.2	9

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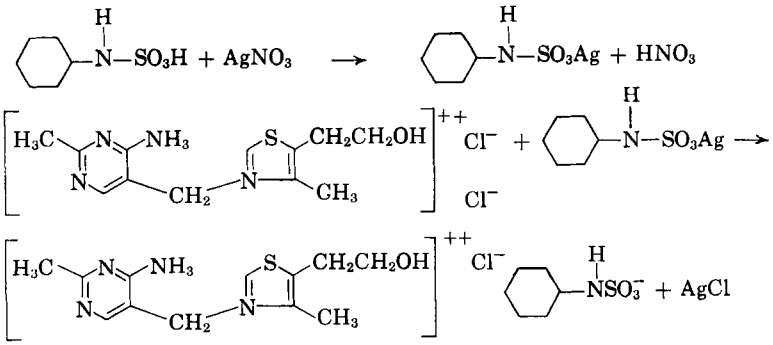

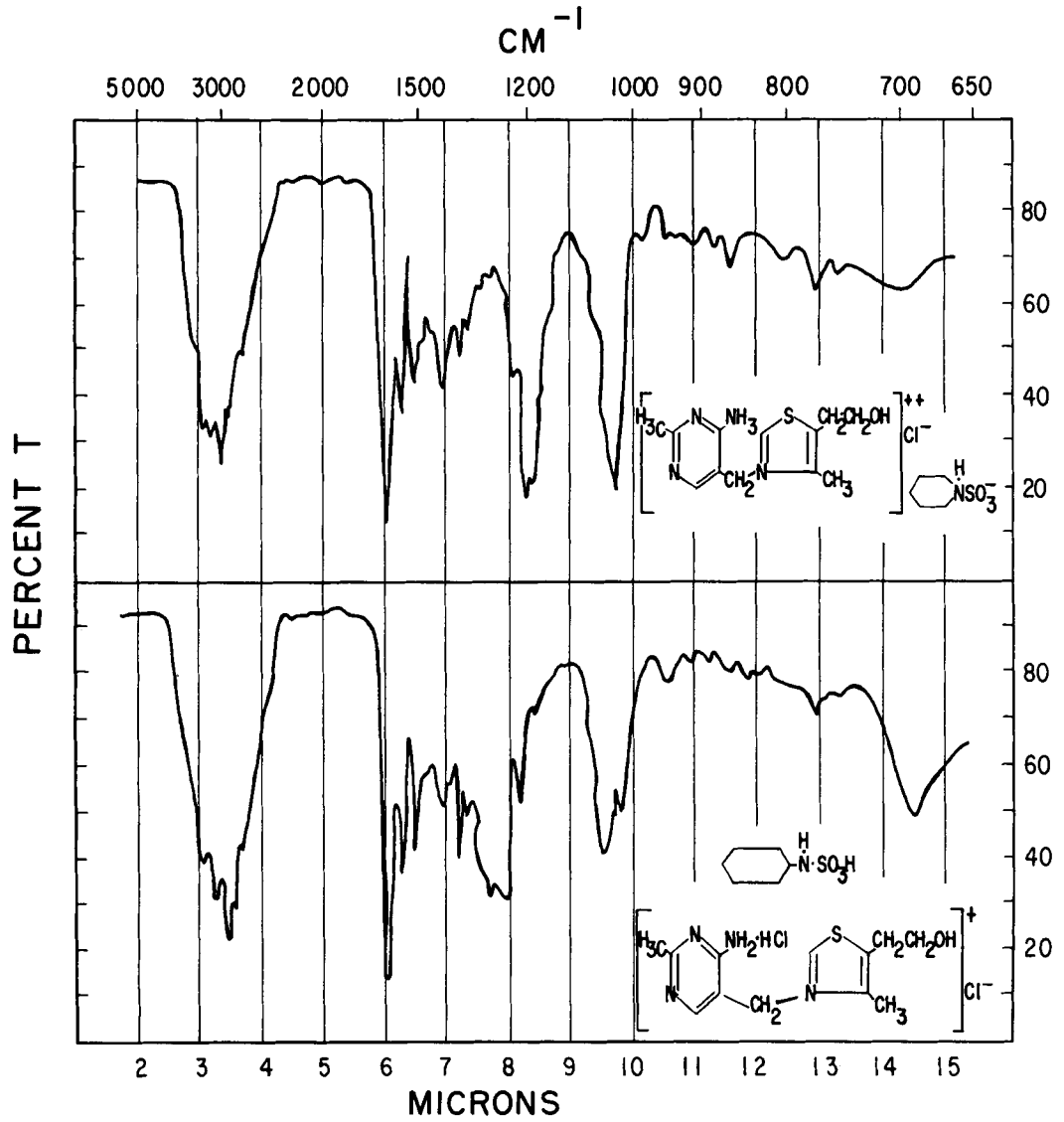

Fig. 1.—Infrared spectra. Above: thiamine N-cyclohexylsulfamate hydrochloride; below: equimolar mixture of thiamine hydrochloride and N-cyclohexylsulfamic acid.

EXPERIMENTAL

Preparation.—A solution consisting of 5 Gm. of silver nitrate in 3 ml. of water was added, with stirring, to a solution consisting of 5.25 Gm. of N-cyclohexylsulfamic acid in 50 ml. of water. The silver N-cyclohexylsulfamate which precipitated was collected on a filter, washed with water, and dried in an oven at 50°.

A 5-Gm. portion of thiamine chloride hydrochloride was dissolved in 10 ml. of water and to this was added 5 Gm. of the silver N-cyclohexylsulfamate. The suspension was stirred at 50° for 30 minutes and was then cooled and filtered. The filtrate was evaporated to dryness under reduced pressure. The solid residue was dissolved in warm methanol; and after cooling, ether was added to the solution to precipitate the final product as a white granular substance having a sweet taste and being freely soluble in water. The salt turned pink at 160° and decomposed between 185 and 190°.

Infrared Spectra.—A potassium bromide pellet was made containing an equimolar mixture of thiamine chloride hydrochloride and N-cyclohexylsulfamic acid. An equivalent concentration of the thiamine N-cyclohexylsulfamate hydrochloride was also incorporated into a potassium bromide pellet and the infrared spectra of both were obtained. The spectra, as shown in Fig. 1, are considerably different. Certain absorption peaks appeared in the spectrum of the compound that were absent in the spectrum of the mixture. These peaks can be observed at 805, 875, 1040, 1170–1220, and 1280–1320 cm.$^{-1}$. Likewise, certain absorption peaks appeared in the spectrum of the mixture that were absent in the spectrum of the compound. These peaks can be observed at 695, 833, 945, and 1065 cm.$^{-1}$.

Anal.—Calcd. for $C_{18}H_{30}ClN_5O_4S_2$: N (total), 14.60; N (basic), 5.83; HCl, 7.60; mol. wt., 480.05. Found: N (total, Kjeldahl), 14.58; N (basic), 6.09; HCl, 7.74.

Stability Studies.—An accelerated aging program was designed and carried out to determine the stability of the compound when combined in multiple vitamin preparations.

Solution Stability.—Three solutions of the following content were prepared

Substance	mg./ml.
Thiamine N-cyclohexylsulfamate HCl	10
Riboflavin-5-phosphate sodium	2
Nicotinamide	50
Panthenol (*dl*)	10
Pyridoxine HCl	5
Ascorbic acid	25
Chlorobutanol	0.6
Water *q.s.*	

Three solutions were prepared identical to that above except that thiamine mononitrate was substituted for the thiamine N-cyclohexylsulfamate hydrochloride in the same concentration.

One solution of each type was adjusted to pH 5 using sodium hydroxide, one solution of each type was adjusted to pH 4 using hydrochloric acid, and one solution of each type was adjusted to pH 3 using hydrochloric acid. Each of the final solutions was assayed for thiamine content and each was subdivided into three portions. The solutions were placed in amber glass bottles and a portion of each solution was stored at each of the following temperatures: 25, 40, and 50°. The solutions were assayed for thiamine content at the end of 3 months. The thiochrome method of assay was used in all assays and the assay results are shown in Table I.

Tablet Stability.—The thiamine N-cyclohexylsulfamate hydrochloride was incorporated into multiple vitamin tablets containing the following vitamins

Vitamins	Amount
Thiamine N-cyclohexylsulfamate HCl	10.0 mg.
Niacinamide	20.0 mg.
Riboflavin	2.5 mg.
Pyridoxine HCl	1.0 mg.
Sodium ascorbate	62.0 mg.
Vitamin B_{12}	1.0 mcg.
Vitamin A	5000.0 units
Vitamin D	500.0 units
Excipients *q.s.*	

The tablets were stored in tightly closed bottles for a period of three months at 25, 40, and 50°. The thiochrome method of assay was performed for thiamine content at zero, 1 month, and 3 month time intervals. The results are shown in Table II.

SUMMARY AND CONCLUSIONS

1. The N-cyclohexylsulfamic acid salt of thiamine was prepared and characterized.

2. The salt was found to have a pleasant taste which was judged to be superior to that of thiamine hydrochloride or thiamine mononitrate.

3. When combined with other vitamins in typical multiple vitamin preparations and subjected to accelerated aging, the salt has demonstrated a stability that compares favorably with that of thiamine mononitrate. It also appears that the optimum pH for the salt in aqueous solution is 3 or below.

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