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Synthesis of Taurine and *N*-Methyltaurine

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A modified procedure for the synthesis of taurine was developed which utilized inexpensive and readily available materials. Ethylene chloride was sulfonated with sodium sulfite and then aminated with (*a*) anhydrous ammonia and (*b*) aqueous ammonia (27%) and ammonium carbonate. A colorimetric method for the determination of minute amounts of taurine consisted of developing a blue color from the reaction of taurine with a solution of phenol and calcium hypochlorite. *N*-Methyltaurine was synthesized by the amination of sodium 2-chloroethane-1-sulfonate with (*a*) anhydrous methylamine and (*b*) aqueous methylamine (30–40%).

TAURINE was first prepared synthetically in 1885 when James treated silver and ammonium salts of 2-chloroethane-1-sulfonic acid with an excess of ammonia (*7*). Since then it has been synthesized from 2-bromoethylamine hydrochloride and metallic sulfites (*15*), by decarboxylation of cysteic acid (*16*), addition of ammonia to vinylsulfonic acid (*5*), ammonolysis of isethionic acid (*6, 10, 13*), sulfonation of aminoalkyl sulfates with alkali sulfite (*5*), hydrolysis of sodium tauroglycocholate (*9*), and the oxidation of cystamine. It occurs naturally in marine animals and mammals and thus has been isolated from the muscles of fish, mollusks, and crustacea (*14*), as well as from the bile of oxen, sheep, dogs, and human beings (*2*).

Although the synthetic methods mentioned are very good, they require starting materials that are expensive and difficult to obtain. The present investigation, carried out during the war years, was conducted for the prime purpose of developing a method adaptable to commercial production utilizing the least costly and most readily available materials. Interest was centered upon taurine and related compounds because of their potentialities as cheap intermediates for wetting agents and detergents (*4, 8*).

N-Methyltaurine was synthesized by Dittrich in 1878 when he reacted methylamine with the silver salt of 2-chloroethane-1-sulfonic acid (*1*). A German patent claims that the sodium salt of vinylsulfonic acid can be reacted with a primary amine—for example, methylamine—to give *N*-methyltaurine (*5*).

N-Methyltaurine crystallizes as prisms (melting point 241.2° C.) and is soluble in water; it is insoluble in ethyl alcohol and ethyl ether, and does not form salts with acids or bases (*3*).

Carius tubes (200-ml. capacity) were used in bomb reactions for small samples, and a nickel-lined stationary autoclave was used for larger samples.

PREPARATION OF SODIUM 2-CHLOROETHANE-1-SULFONATE (*12*)

One hundred grams of ethylene chloride (1.0 mole) and 126 grams of anhydrous sodium sulfite (1.0 mole) were heated under reflux in a 2-liter three-necked flask equipped with a mechanical stirrer and an efficient condenser, with 530 grams of water and 400 grams of ethanol in the presence of copper turnings. (The copper turnings act not only as a catalyst but also as an aid to efficient stirring.) After refluxing for 72 hours, a Vigreux fractionating column was substituted for the condenser, and the reaction mixture was distilled. The first fraction (boiling point 72° C.) contained 8.3% water and 91.7% ethylene chloride. The second fraction (boiling point 73–95° C.) contained ethanol and water. The combined fractions were utilized in the next batch reaction.

The aqueous residue from the distillation was evaporated to dryness on a steam bath. The resultant salt cake had a mother-of-pearl luster. The impure salt was ground in a mortar, and

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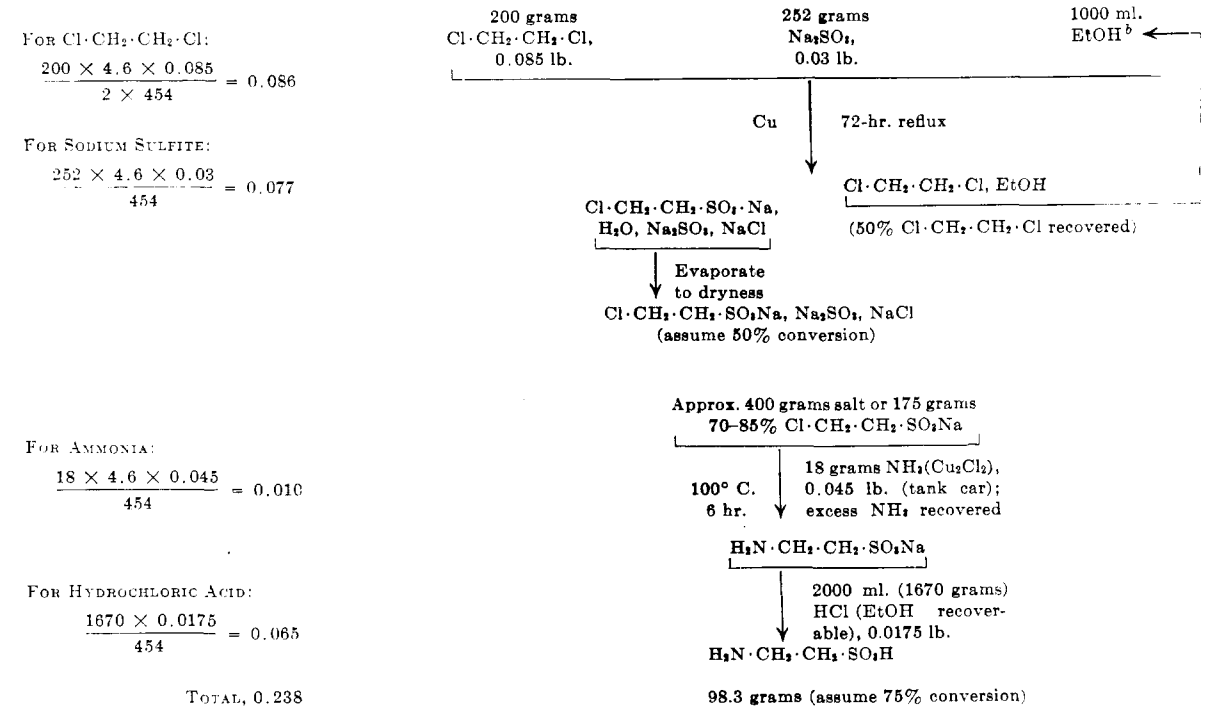
Figure 1. Materials Cost[a] and Flow Sheet for Taurine Production



[a] Price on basis of 1 pound of taurine; 454/98.3 = 4.6 factor.
[b] Cost of alcohol is not included because it is recoverable.

the powder was extracted with hot 95% ethanol in a Soxhlet extractor. White platelets were filtered and dried. The product weighed 130 grams; this indicated a 78% conversion of the ethylene chloride. Sulfur analysis of $Cl \cdot C_2H_4SO_3Na$: experimental, 19.08%; calculated, 19.10%.

PREPARATION OF TAURINE

Ethanolamine Process. One hundred twenty-two grams of ethanolamine (2.0 moles) were cooled in an ice bath and carefully neutralized with concentrated hydrochloric acid. After complete neutralization a slight excess of hydrochloric acid was added, and the solution was evaporated to a viscous liquid which crystallized when allowed to cool. Ninety-six grams of the ethanolamine hydrochloride (1.0 mole) were suspended in 200 ml. of chloroform and placed in a 500-ml. three-necked flask equipped with a mechanical stirrer, condenser, and dropping funnel. One hundred fifty-eight grams of thionyl chloride (33% excess) in 100 ml. of chloroform were added dropwise. The suspended ethanolamine hydrochloride seemed to disappear with the voluminous evolution of hydrogen chloride. After evolution of the hydrogen chloride had ceased, the chloroform was removed under diminished pressure. The crystalline product (m.p. 140° C., conversion 80%) was extracted with amyl alcohol.

Fifty grams of the 2-chloroethylamine hydrochloride (0.43 mole), dissolved in 200 ml. of water, were added to 91 grams of sodium bisulfite (0.86 mole) and heated strongly under reflux for approximately 6 hours. The solution was evaporated under diminished pressure until a white crystalline residue was obtained. This residue was thoroughly mixed with 250 ml. of concentrated hydrochloric acid. The precipitated salts were filtered and washed several times with small portions of concentrated hydrochloric acid. The filtrate was concentrated to 200 ml., and 150 ml. of 95% ethanol were added to the hot solution. Twenty-eight grams (51% of a white needlelike product, taurine) were obtained upon cooling the solution.

Sodium sulfite was substituted for sodium bisulfite, and 20 grams (40%) of taurine (2-aminoethane-1-sulfonic acid) were obtained.

Ammonolysis with Anhydrous Ammonia. Ten grams of sodium 2-chloroethane-1-sulfonate (0.06 mole) and 20 grams of anhydrous ammonia (1.8 moles) were sealed in a Carius tube (200-ml. capacity) and subjected to a temperature no higher than 50° C. for four days. The tube was carefully opened and the excess ammonia permitted to escape. The solid residue was treated with approximately 100 ml. of concentrated hydrochloric acid. The insoluble salts were filtered, and the filtrate was evaporated to one third its original volume. Four volumes of 95% ethanol were added, and the solution was set aside to crystallize. Small needlelike crystals of taurine weighing 3.47 grams (47%) were obtained. The product was further purified by dissolving in five times its weight of hot water and then crystallized by the addition of four volumes of 95% ethanol.

Time of contact and temperature appeared to be important factors in determining the conditions for optimum yields. Table I shows some effects of changes in time and temperature.

The general procedure for the preparation of taurine using a 500-ml. nickel-lined stationary autoclave is as follows:

Twenty-five grams of sodium 2-chloroethane-1-sulfonate were added to 100 ml. of anhydrous ammonia in the presence of 0.015 mole of a catalyst. The nickel-lined autoclave was sealed and heated to 100° C. After the desired time of reaction had elapsed, the autoclave was cooled and a needle valve was carefully opened to permit escape of excess ammonia. The residue was taken up in 300 ml. of concentrated hydrochloric acid. The insoluble salts were filtered, and the filtrate was concentrated to one third the original volume. The hot solution was quickly poured into 300 ml. of 95% ethanol and set aside to cool. The crystalline product was filtered and recrystallized from water-alcohol (1:4) mixture. Recovery of the recrystallizing liquor increased the yields of taurine.

Table I. Effects of Temperature and Reaction Time on Yield of Taurine

Expt.	$Cl \cdot C_2H_4SO_3Na$, Grams	NH_3, Grams	Time, Hr.	Temp., °C.	Taurine Yield, Grams	Taurine Yield, %[a]
45	10	20	96	25–50	3.47	47
46	10	20	120	25	5.7	77
48	10	27	96	25	3.5	47
47	50[b]	228	6	− 33	1.0	3
49	50[c]	182	1	50	13.0	35

[a] Pure.
[b] Reaction performed at atmospheric pressure.
[c] Reaction performed in an autoclave.

TABLE II. EFFECTS OF CATALYSTS ON YIELD OF TAURINE

Expt.	Time, Hr.	Catalyst	Catalyst, Grams	Yield[a], %
58	2	.....	...	57
59	2	NaI	2.0	46
60	2	Cu_2Cl_2	2.8	75
61	2	NH_4I	1.6	50
62	2	Cu_2Cl_2-NH_4I	2.8–1.6	50
63	6	.....	...	54
64	10	Cu_2Cl_2	2.8	75
65	6	Cu_2Cl_2	2.8	62
66	6	NaI	2.0	65
74	5	Cu_2Cl_2	5.0	90

[a] Kjeldahl nitrogen analysis of taurine: experimental, 10.8%; calculated, 11.4%.

TABLE III. AMMONOLYSIS OF CRUDE SODIUM 2-CHLOROETHANE-1-SULFONATE[a] WITH ANHYDROUS AMMONIA

Expt.	NH_3, Grams	Cu_2Cl_2, Grams	Taurine, Grams	Crude Yield, %
79	204	5.0	50	95
80	163	...	40	80
81	163	5.0	51	95

[a] Using 100 grams of $Cl.C_2H_4.SO_3Na$.

Table II records the times of reaction, catalysts, and yields for a series of experiments. The sample of sodium 2-chloroethane-1-sulfonate, the volume of ammonia, and the temperature were kept constant—that is, 25 grams, 100 ml., and 100° C.

The results of a series of experiments in which the crude sodium 2-chloroethane-1-sulfonate was ammonolyzed with anhydrous ammonia are indicated in Table III.

The nitrogen analysis of the crude taurine was 13.4%. It was assumed that the crude product contained both taurine and ammonium chloride, since ammonia was detected when an aqueous solution was warmed with dilute alkali. Calculations indicated that the product contained 86% taurine. Figure 1 presents the flow sheet and material cost per pound of taurine.

AMMONOLYSIS WITH AMMONIUM CARBONATE AND AQUEOUS AMMONIA (27%). Fifty grams of crude sodium 2-chloroethane-1-sulfonate were added to 100 ml. of aqueous ammonia (27%) and 80 grams of ammonium carbonate in a nickel-lined 500-ml. stationary autoclave and heated at 120° C. for 6 hours. The ammoniacal solution was removed and the autoclave flushed with 100 ml. of water. The total volume (approximately 300 ml.) was heated on a hot plate to remove the ammonia. When the solution was evaporated to one third its original volume, two volumes of concentrated hydrochloric acid were added. This solution was concentrated to half its volume and was filtered to remove any precipitated salts. Two volumes of 95% ethanol were added to the filtrate, and the solution was cooled in an ice bath. The isolated product weighed 29 grams (an estimated yield of 90% crude taurine). Duplication of the experiment yielded a product weighing 30 grams (91%).

A series of experiments were carried out utilizing cuprous chloride as a catalyst. Table IV lists the results for batch reactions consisting of 50 grams of crude sodium 2-chloroethane-1-sulfonate, 80 grams of ammonium carbonate in 100 ml. of ammonia (27%), and 2.0 grams of cuprous chloride.

COLORIMETRIC DETERMINATION OF TAURINE

The colorimetric method of estimating the amount of taurine was developed for the purpose of a quick, fairly accurate determination of minute amounts in solution that is relatively free from other nitrogen containing compounds. The method is based upon the blue color that develops when a mixture of phenol and hypochlorite solutions is added to taurine and warmed gently. (The structure of the molecule which imparts the blue color is not definitely known.) The color deepens provided it is not arrested by cooling.

A Sheard-Cenco-Sanford photelometer was used to obtain the per cent transmittancy of colored solutions which depended upon the concentration of the taurine. The correct filter was required, however, in order that the transmittancy of the developed solution would coincide or nearly coincide with the transmittancy of a filter.

The curves in Figure 2 were obtained on an automatic recording Hardy spectrophotometer (General Electric Company). The curves *A*, *B*, *C*, and *D* are the spectrophotometric curves obtained using cells that were 0.5, 1.0, 2.0, and 5.0 cm. in width. Curve *E* is the spectrophotometric curve for a red filter. The valleys and peaks coincide rather well; this indicates that the transmittancy of the developed solutions of taurine and the red filter are nearly equivalent. The transmittancy appears to bear an almost linear relation to the change in concentration.

APPARATUS AND PROCEDURE

An automatic recording Hardy spectrophotometer was used to obtain a desirable filter that may be used in the Cenco-Sheard-Sanford photelometer. This instrument is used to obtain the per cent transmittancy for the calibration curve.

Calcium hypochlorite, 1% phenol solution, and distilled water were used for the color development.

The following general procedure was applied: A solution was made containing 0.200 gram of taurine in 100 ml. of solution. Pipetted samples of 1, 2.5, 5, 10, and 20 ml. were placed in a 25-

TABLE IV. AMMONOLYSIS OF SODIUM 2-CHLOROETHANE-1-SULFONATE WITH AMMONIUM CARBONATE

Expt.	Temp., °C.	Time, Hr.	Taurine, Grams	Yield, %
84	120	2	30	90
99	140	2	28	88
96	120	2	19	60
97	120	2	30	90
98	140[a]	8	30	90
99	125[a]	6.5	30	50

[a] Pressures for temperatures 125° and 140° C. are 138 and 174 pounds, respectively.

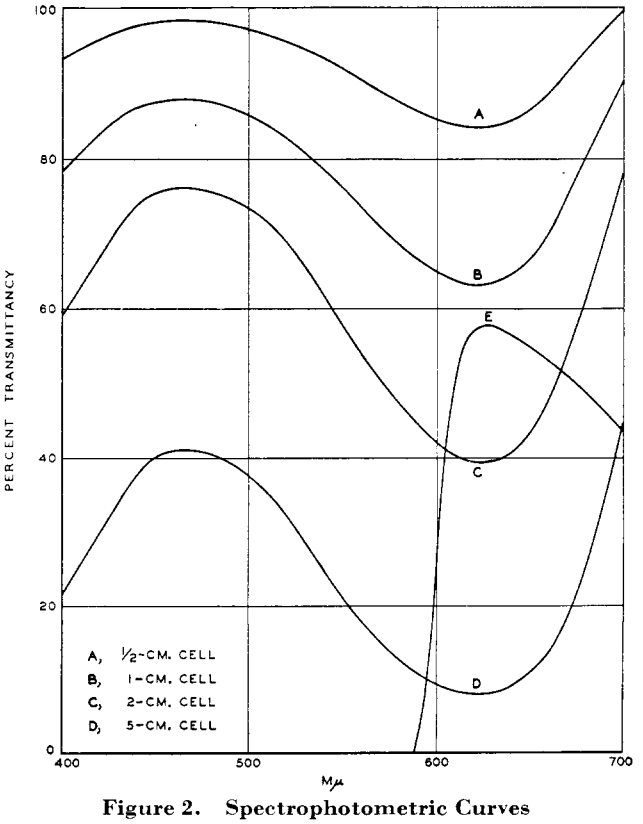


Figure 2. Spectrophotometric Curves

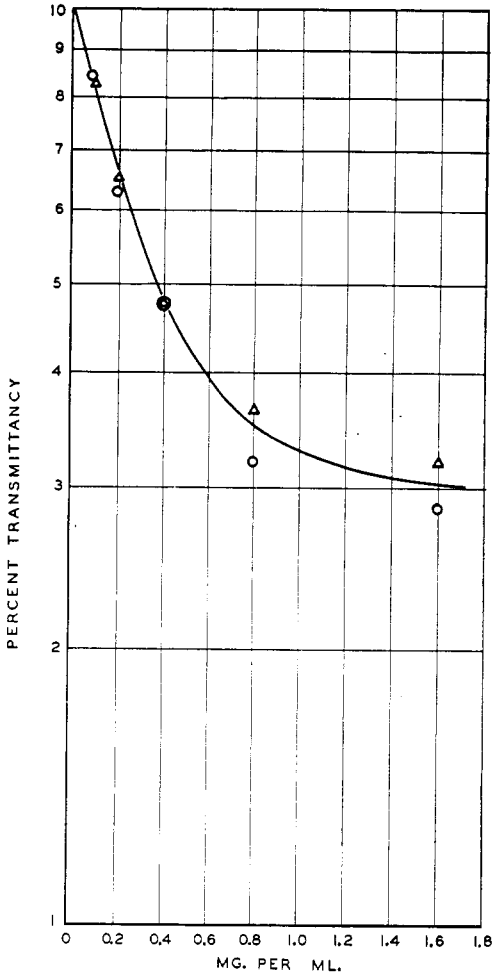


Figure 3. Calibration Curve

ml. volumetric flask to which 5 ml. of a 1% phenol solution were added. The remainder of the 25 ml. of the flask was filled with distilled water. The flask was tipped several times to ensure homogeneity, and then about 0.1 gram of calcium hypochlorite was added. The flask was quickly shaken to wash down particles adhering to the sides and was placed immediately in boiling water and permitted to remain exactly 3 minutes. The color began to appear in 30–45 seconds and continually darkened. At the end of 3 minutes the flask was quickly placed under a stream of cold water in order to arrest the color development as soon as possible. A cell (1.0 cm.) from the photelometer was rinsed with a small portion of the cold filtered solution, and the cell was filled. The cell was placed in the previously standardized photelometer (the instrument should read 100% transmittancy when a 1.0-cm. cell is introduced), and the per cent transmittancy was recorded.

Per cent transmittancy was plotted against concentration on semilogarithmic paper. The results in Table V were plotted to give the average curve in Figure 3.

Close agreement of the readings indicate reproducibility. The readings should be taken immediately, however, for the per cent transmittancy changes one unit in 2–5 minutes. The average time for a determination was 10 minutes. The accuracies of concentration determinations were within 5% of the actual concentration, as long as the concentration was small enough so that the photelometric readings fell on the nearly linear portion of the curve.

PREPARATION OF *N*-METHYLTAURINE

ANHYDROUS METHYLAMINE PROCESS. Fifty grams of sodium 2-chloroethane-1-sulfonate were reacted with 100 ml. of anhydrous methylamine and 2.0 grams of cuprous chloride in a nickel-lined stationary autoclave at 150° C. for 2 hours. The excess methylamine was permitted to escape, and the residue was taken up in 300 ml. of concentrated hydrochloric acid. After filtration of the insoluble salts, the remaining solution was concentrated to one third its original volume. Four volumes of 95% ethanol were added, and the total solution was cooled in an ice bath. A straw-colored crystalline product was obtained which weighed 10.0 grams; this indicated a 38% yield.

Other experimental trials were attempted in which the temperatures and times of reaction were varied. The results are given in Table VI.

AQUEOUS METHYLAMINE (30–40%) PROCESS. Twenty-five grams of crude sodium 2-chloroethane-1-sulfonate were dissolved in 200 ml. of 30–40% aqueous methylamine and heated in a nickel-lined stationary autoclave at 120–130° C. for 5 hours. After cooling the autoclave, the solution was removed and concentrated to one fourth its original volume. Four hundred milliliters of concentrated hydrochloric acid were added, and the solution was filtered to remove the insoluble salts. The solution was concentrated to one fourth its original volume, and then four volumes of 95% ethanol were added. The total solution was cooled in an ice bath. Five grams (38%) of a crystalline product were obtained.

TABLE V. TRANSMITTANCY *vs.* CONCENTRATION

Org. Concn., Mg./Ml.	Taurine Soln., Ml.	H_2O Added, Ml.	1% Phenol, Ml.	Total Vol., Ml.	Final Concn., Mg./Ml.	Readings 1st detn.	Readings 2nd detn.
2.00	20	..	5	25	1.60	28.5	32
1.00	10	10	5	25	0.80	34	36.5
0.50	5	15	5	25	0.40	47	47
0.31	3	17	5	25	0.25	59	..
0.25	2.5	17.5	5	25	0.20	63	65
0.10	1	19	5	25	0.08	84	82

TABLE VI. EFFECTS OF TEMPERATURE AND TIME ON YIELD OF *N*-METHYLTAURINE

Expt.	Temp., °C.	Time, Hr.	*N*-Methyltaurine[a], Grams	Yield, %
90	150	2	4.5	16
91	200	14	22.0	80
93	190–200	6	10.0	38

[a] Kjeldahl nitrogen analysis of *N*-methyltaurine: experimental, 9.87%; calculated, 10.07%.

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