[CONTRIBUTION FROM THE RESEARCH LABORATORIES, COLGATE-PALMOLIVE CO.]

Dipolar Ions Related to Taurine

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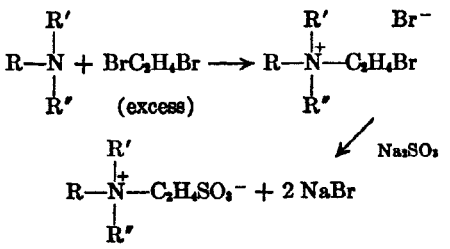
Quaternization of tertiary amines with excess ethylene bromide yields substituted 2-bromoethylammonium bromides. Treatment of these quaternary ammonium salts with sodium sulfite yields *N,N,N*-trisubstituted taurine derivatives (taurine betaines).

The literature on *N,N,N*-trisubstituted taurine derivatives (taurine betaines) is limited, only the trimethyl,[1] the dibenzylmethyl,[2] the dimethyloctadecyl,[3] and a group of methylbis(alkylbenzyl) derivatives[2] having been reported.

Compounds of this type display interesting physical properties. They are neutral inner salts of strong acids and strong bases, and in solution, maintain a dipolar character over a wide *p*H range. Solutions of the compounds are nonconducting although the concentration of electrically charged sites in the solutions may be varied widely by appropriate dilution.

This paper reports a simple general method of synthesis of taurine betaines. The scope of the method is wide and may be judged by the variety of compounds reported here.



Step 1 involves the treatment of a tertiary amine with an excess of ethylene halide,[4,5] the excess minimizing the formation of the bisquaternary compound.

Step 2 involves the treatment of the quaternary salt with sodium sulfite.[6]

The tertiary amines which could not be purchased were synthesized by the reductive alkylation of the appropriate primary amine,[7] or by the reaction of the alkyl bromide with dimethylamine.

That the final products are indeed dipolar ions containing both quaternary ammonium and sulfonate groups was proved in two ways. First, the products in solution affect the *p*H of the solution no more than a typical strong neutral electrolyte. Second, the conductivity of the solutions of the products is essentially zero. Table I shows the specific conductance of three taurine betaines. Relative to that of a simple strong electrolyte, the conductivity of the taurine derivatives is negligible. Even this low order of conductivity may be due to traces of sodium bromide by-product in the betaines. Table I also shows the solubility of a number of taurine betaines in water.

TABLE I

CONDUCTANCE AND SOLUBILITY OF TAURINE BETAINES

Compound	Conductance[a] × 10^5	Solubility[b]
Cyclohexyldimethyltaurine betaine	1.30	42.4
Hexyldimethyltaurine betaine	—	65.5
Decyldimethyltaurine betaine	—	0.22
Dodecyldimethyltaurine betaine	—	0.01
Docosyldimethyltaurine betaine	—	<0.01
β-Hydroxyethyldimethyltaurine betaine	—	52.7
Benzyldimethyltaurine betaine	0.08	13.2
1-(2'-Sulfoethyl)pyridinium betaine	—	69.7
4-Methyl-4-(2'-sulfoethyl)morpholinium betaine	0.93	34.3
Potassium chloride	460	—

[a] Specific conductance in ohms^{-1} cm.$^{-1}$ of 0.25% solutions at 25°. [b] Grams per 100 g. of water at 30°.

Tables II and III contain analytical data, reaction conditions, and yields of the quaternary intermediates and the taurine betaines, respectively.

EXPERIMENTAL

Tertiary amines. Trimethylamine, cyclohexyldimethylamine, dimethylethanolamine, benzyldimethylamine, *N*-methylmorpholine, and pyridine were purchased. Hexyldimethylamine, b.p., 144–146°/760 mm., 58% yield, and dodecyldimethylamine, b.p., 95°/1.1 mm., 73% yield, were prepared by the reductive alkylation of hexylamine and dodecylamine.[7]

Decyldimethylamine. Decyl bromide, 177 g., 0.8 mole, and dimethylamine, 144 g., 3.2 moles, were dissolved in 1600 ml.

(1) J. W. James, *J. Chem. Soc.*, 47, 367 (1885); R. Kuhn and W. Brydowna, *Ber.*, 70, 1333 (1937).

(2) R. D. Stayner, U. S. Patent 2,697,116 (1954).

(3) F. B. Downing and F. W. Johnson, U. S. Patent 2,129,264 (1938).

(4) J. G. Erickson, U. S. Patent 2,774,786 (1956); S. Frankel and K. Nussbaum, *Biochem. Z.*, 182, 424 (1927).

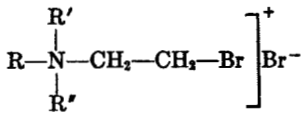
(5) Ethylene bromide is the halide of choice. It reacts readily and yields easily crystallized quaternary salts. Several of the corresponding chlorides are more hygroscopic and more difficult to crystallize.

(6) A. Strecker, *Ann.*, 148, 90 (1868); R. M. Reed and H. V. Tartar, *J. Am. Chem. Soc.*, 57, 570 (1935).

(7) R. A. Reck *et al.*, *J. Org. Chem.*, 12, 517 (1947).

TABLE II

2-BROMOETHYL(SUBSTITUTED)AMMONIUM BROMIDES



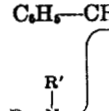
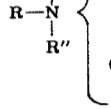
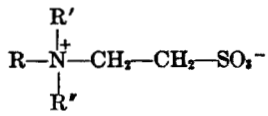
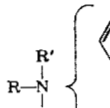
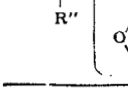
Substitution			Reaction Conditions		Recrystallization Solvent	Yield, %	Formula	Nitrogen, %		Ionic Bromide, %	
R	R′	R″	Temp.	Time, hr.				Calcd.	Found	Calcd.	Found
CH_3	CH_3	CH_3	30	96	Ethyl acetate	86	$C_5H_{13}Br_2N$	5.67	5.65	32.36	32.43
	CH_3	CH_3	30	96	Acetonitrile	75	$C_{10}H_{21}Br_2N$	4.45	4.48	25.36	25.11
n-C_6H_{13}	CH_3	CH_3	30	96	Methanol–ethyl acetate	85	$C_{10}H_{22}Br_2N$	4.42	4.40	25.20	25.41
n-$C_{10}H_{21}$	CH_3	CH_3	30	96	Ethyl acetate–acetonitrile	75	$C_{14}H_{31}Br_2N$	3.75	3.75	21.41	21.47
n-$C_{12}H_{25}$	CH_3	CH_3	30	96	Ethyl acetate–acetonitrile	80	$C_{16}H_{35}Br_2N$	3.49	3.51	19.92	19.93
n-$C_{22}H_{45}$	CH_3	CH_3	55	8	Ethanol–ethyl acetate	82	$C_{26}H_{56}Br_2N$	2.59	2.57	14.76	14.72
HO—C_2H_4	CH_3	CH_3	60	15	Methanol–ethyl acetate	89	$C_6H_{15}Br_2NO$	5.06	5.08	28.85	28.95
C_6H_5—CH_2	CH_3	CH_3	70	8	Acetonitrile	83	$C_{11}H_{17}Br_2N$	4.34	4.34	24.73	24.53
			70	13	Acetonitrile	87	$C_7H_9Br_2N$	5.25	5.29	29.94	30.20
			70	7	Methanol–ethyl acetate	60	$C_7H_{15}Br_2NO$	4.85	4.85	27.65	27.92

TABLE III

TAURINE BETAINES



Substitution			Recrystallization Solvent	Yield, %	Formula	Nitrogen, %		Sulfur, %	
R	R′	R″				Calcd.	Found	Calcd.	Found
CH_3	CH_3	CH_3	Ethanol-water	81	$C_5H_{13}NO_3S$	8.38	8.37	19.17	19.20
	CH_3	CH_3	Isopropyl alcohol	57	$C_{10}H_{21}NO_3S$	5.95	6.07	13.62	13.52
n-C_6H_{13}	CH_3	CH_3	Ethanol–isopropyl alcohol	57	$C_{10}H_{22}NO_3S$	5.90	5.88	13.51	13.63
n-$C_{10}H_{21}$	CH_3	CH_3	Water	84	$C_{14}H_{31}NO_3S$	4.77	4.83	10.92	10.84
n-$C_{12}H_{25}$	CH_3	CH_3	Water	90	$C_{16}H_{35}NO_3S$	4.36	4.32	9.98	9.96
n-$C_{22}H_{45}$	CH_3	CH_3	Butanone-2-water	50	$C_{26}H_{56}NO_3S$	3.03	2.97	6.94	6.98
HO—C_2H_4	CH_3	CH_3	Ethanol	60	$C_6H_{15}NO_4S$	7.10	7.14	16.25	16.25
C_6H_5—CH_2	CH_3	CH_3	Ethanol-water	67	$C_{11}H_{17}NO_3S$	5.76	5.70	13.18	13.03
			Ethanol	82	$C_7H_9NO_3S$	7.48	7.51	17.13	17.17
			Ethanol-water	68	$C_7H_{15}NO_4S$	6.70	6.69	15.32	15.34

of methanol and warmed at 50° for 6 hr. under a Dry Ice condenser. The solvent and excess dimethylamine were then removed by evaporation. The residue was shaken with 1000 ml. of 5% aqueous sodium hydroxide and the mixture extracted with ether. After drying the extract and evaporating the ether, the residue was distilled, yielding 96 g. (64%) of decyldimethylamine, b.p., 103°/10 mm., n_D^{25} 1.4297.

Anal. Calcd. for $C_{10}H_{27}N$: N, 7.56. Found: N, 7.63.

Docosyldimethylamine. Docosyl bromide[8] 50 g., 0.13 mole, and dimethylamine, 39 g., 0.9 mole, were dissolved in 260 ml. of ether, sealed in glass tubes and warmed at 50° for 18 hr. The reaction mixtures were then removed from the tubes, combined and extracted with 250 ml. of 5% aqueous sodium hydroxide. The bulk of the excess dimethylamine boiled off during this operation. After drying the extract, the ether was evaporated yielding 38 g. of a pale yellow waxy mass which resisted all attempts to recrystallize it. Its hydrochloride was equally intractable. The crude base was used, therefore, in the quaternization step.

2-Bromoethyl(substituted)ammonium bromides The appropriate tertiary amine was dissolved in a tenfold excess of ethylene bromide and treated as recorded in Table II. In several cases, addition of methanol was required to affect homogeneity. The excess ethylene bromide and solvent were then removed in a flash evaporator *in vacuo* at 40°. The crystalline residue was washed with cold ethyl acetate, collected, and dried and stored out of contact with moisture. These materials were of sufficient purity for use directly in the next step (the docosyldimethyl derivative is an exception). Analytical samples were prepared by recrystallization from the solvents shown in Table II.

Taurine betaines. The appropriate 2-bromoethyl(substituted)ammonium bromide was treated in aqueous solution (the docosyldimethyl derivative required 25% ethanol) with a 5% molar excess of sodium sulfite for 5–10 hr at 85°. The reaction mixture was then concentrated to a moist residue in a flash evaporator and triturated with 1 l. of cold concd. hydrochloric acid per mole of quaternary used in the reaction. Just as with taurine,[9] the taurine betaines are soluble in this medium while the inorganic salts are only slightly soluble. The trituration mixture was filtered through a sintered glass funnel and the clear filtrate was concentrated *in vacuo* at 50° to a thick sirup. Addition of ethanol or isopropyl alcohol caused the taurine betaine to precipitate. In the cases of the decyl, dodecyl, and docosyl derivatives, the concentration and trituration steps were unnecessary because the products precipitated directly from the reaction mixtures on cooling.

The crude products were recrystallized from the solvents listed in Table III.

The infrared spectra of the products, measured with a Perkin-Elmer Model 21 spectrophotometer, contained strong bands near 8.4 and 9.6 μ characteristic of the sulfonate group.

Titrations with acid and base. Samples of each taurine betaine were titrated in aqueous or aqueous ethanolic solution with 0.1*N* hydrochloric acid and with 0.1*N* sodium hydroxide with the aid of a *p*H meter. No buffer capacity was observed between *p*H 3 and 11.

Conductivity. The specific conductance of 0.25% solutions of three taurine betaines was determined at 25° using a Henry cell and a Leeds and Northrup catalog No. 4866 conductance bridge (60 cycles/sec). The results are shown in Table I together with the value for a typical strong electrolyte, potassium chloride.

Solubility. Solubility was determined at 30° in a constant temperature bath. Suspensions of taurine betaines in 0.5 g. of water were prepared and diluted dropwise with water at 24-hr. intervals until the solids dissolved. The solubilities are recorded in Table I.

Acknowledgment. The author wishes to express his appreciation to Mr. E. W. Blank and staff for the microanalyses and infrared measurements and to Mr. Conrad Jakob for the conductivity and solubility measurements.

JERSEY CITY, N. J.

(8) J. von Braun *et al.*, *Ann.*, **472**, 121 (1929).

(9) F. Cortese, *Org. Syntheses*, Coll. Vol. II, 564 (1943)

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY]

The Structure of Helvolic Acid. III[1,2]

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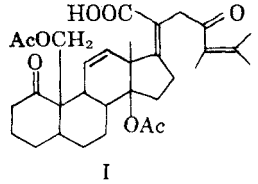
Chemical and spectroscopic studies, taken in conjunction with earlier data, have led to a tentative formulation of the structure of helvolic acid as that shown in VI.

Helvolic acid, an antibiotic isolated from the mold *Aspergillus fumigatus*, has been the subject of fairly extensive chemical and biological studies.[4] Attempts to summarize the available data in 1956 yielded a tentative structure (I)[1,4] for the compound.



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The structure of helvolic acid has now been further investigated, and additional evidence has been obtained. While the actual structure still has not been established with certainty, a good deal more has been learned about it.

The empirical formula deduced earlier is still regarded as correct, as is the presence of the indi-

(1) Paper II, N. L. Allinger, *J. Org. Chem.*, 21, 1180 (1956).

(2) This research was supported by a grant (E-2267) from the U. S. Public Health Service, National Institutes of Health.

(3) Ethyl Corp. Research Fellow, 1958–1959.

(4) For a summary of the earlier literature and references, see D. J. Cram and N. L. Allinger, *J. Am. Chem. Soc.*, 78, 5275 (1956).