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2. *Taurine.*

By Alan A. Goldberg.

A new synthesis of taurine is described together with some sodium acylamidoethanesulphonates.

Taurine has been prepared by Gabriel (*Ber.*, 1888, **21**, 2667; 1899, **22**, 1152), Knorr and Rossler (*Ber.*, 1903, **36**, 1281), and in better yields by Ward (*J. Amer. Chem. Soc.*, 1935, **57**, 914) and Cortese (*ibid.*, 1936, **58**, 191); see also Rumpf (*Bull. Soc. chim.*, 1938, **5**, 877).

It has now been found that β-aminoethyl hydrogen sulphate (easily and rapidly obtained from ethanolamine) reacts smoothly with aqueous sodium sulphite with production of taurine and sodium sulphate. The replacement of halogens by the sulphonic acid group effected by heating alkyl halides with aqueous sodium hydrogen sulphite is well known, but it is remarkable that an alkyl sulphate undergoes a similar reaction in which the carbon–oxygen link in the latter is ruptured and a carbon–sulphur link established. The reaction may be compared with the formation of ethylthiol by the interaction of sodium ethyl sulphate with potassium hydrogen sulphide in aqueous solution (Klason, *Ber.*, 1887, **20**, 3411). At the boiling point under atmospheric pressure (105—108°) the reaction between aminoethyl hydrogen sulphate and sodium sulphite requires *ca.* 30 hours for completion, but under pressure at about 140° reaction is complete in *ca.* 15 hours. The taurine is separated from inorganic salts by means of its high solubility in concentrated hydrochloric acid.

N-Acyl derivatives of taurine in the form of their alkali-metal salts may be readily obtained by the interaction of the acyl chloride with aqueous taurine in the presence of the alkali hydroxide. These compounds, which may be regarded as ethylamides of the acylating acid bearing a sulphonic radical in the ethylamido-group, are extremely soluble in water and highly resistant towards hydrolysis by mineral acids or alkalis. Long-chain acylated taurines in the form of their sodium salts have been used as wetting, emulsifying, and detergent agents which function in liquors of all pH values (B.P. 389,543). Since bacteriostatic aromatic acids such as benzoic and phenylacetic acids, when administered orally or parenterally, undergo detoxication in the liver and kidney by conjugation with natural aminocarboxylic acids (usually glycine), it was of interest to examine the *in vivo* activity of some aromatic acylated taurines in which the acylating aromatic acid is conjugated with a natural amino-sulphonic acid. The sodium salts of the *phenylacetyl*, *phenylpropionyl*, and *acetylmandelyl* derivatives of taurine have been synthesised for examination as urinary disinfectants when administered by the oral and intravenous routes; the pharmacological results will be published separately.

The median lethal dosages (LD_{50}) recorded are for a single subcutaneous injection into 6—8 weeks old white mice weighing 22—24 g.

Experimental.

β-Aminoethyl Hydrogen Sulphate (cf. Fränkel and Cornelius, *Ber.*, 1918, **51**, 1660).—Fuming sulphuric acid (20% SO_3; 100 c.c.) was added (3 hours) with stirring to ethanolamine (50 c.c.) in an ice–salt bath, the temperature never being allowed to exceed 10°. The semi-solid product was kept in the ice-chest overnight, ground with absolute ether (300 c.c.), drained (pump) on sintered glass, dissolved in boiling water (300 c.c.), and quickly filtered (charcoal). The filtrate was poured into rectified spirit (1000 c.c.) and kept for several hours; the aminoethyl hydrogen sulphate separated in lustrous white leaves, which were washed with a small quantity of absolute alcohol and dried in a vacuum. Yield 102 g., 89% (Found : S, 22·6; N, 10·0. Calc. for $C_2H_7O_4NS$: S, 22·7; N, 9·9%).

Taurine : Reaction between Aminoethyl Hydrogen Sulphate and Sodium Sulphite.—(i) *At atmospheric pressure.* A mixture of β-aminoethyl hydrogen sulphate (141 g.; 1 mol.), sodium sulphite heptahydrate (278 g., 1·1 mols.), and water (360 c.c.) was kept boiling (106—108°), in an oil-bath to prevent bumping, for 8 hours on each of two consecutive days. A further quantity of sodium sulphite (139 g.; 0·55 mol.) and water (100 c.c.) was added, the mixture boiled for two further periods of 8 hours, and then evaporated to dryness under reduced pressure. The solid residue was extracted on the water-bath (2 hours) with concentrated hydrochloric acid (1000 c.c.), the extract filtered through sintered glass, and the residue extracted with more concentrated hydrochloric acid (250 c.c.). The combined extracts were cooled, the precipitated sodium chloride removed, and the bulk of the hydrochloric acid distilled off under reduced pressure on the water-bath. Absolute alcohol (500 c.c.) was added to the residual glutinous liquid, crude taurine being precipitated as a white, spongy solid. This was collected, dissolved in the minimum amount of boiling water (200 c.c.), filtered (charcoal), and kept for several hours in the ice-chest, pure taurine crystallising in transparent, colourless needles. These were collected, and dried at 100°/5 mm.; yield 80 g., 63%. They were free from sulphate and chloride ions (Found : S, 25·5; N, 11·3. Calc. for $C_2H_7O_3NS$: S, 25·6; N, 11·2%). From the mother-liquor, which was very rich in taurine, a further quantity of impure taurine (*ca.* 10 g.) was isolated. The sodium sulphate produced during the reaction was found in the form of sulphuric acid in the alcoholic filtrate from the crude precipitated taurine.

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(ii) *Under pressure.* A solution of aminoethyl hydrogen sulphate (141 g.; 1 mol.) and anhydrous sodium sulphite (189 g.; 1·5 mols.) in water (700 c.c.) was heated in an autoclave for 20 hours at 140° (50 lb. pressure). The resulting solution was made slightly alkaline with sodium hydroxide, and air bubbled through in order to precipitate any iron. Ferric hydroxide was removed, the solution made just acid with hydrochloric acid and evaporated to dryness, and the residue treated as above described, whereupon pure taurine (78 g.; 62%) was obtained. The solution of a sample in water was free from sulphate and chloride ions (Found: S, 25·6; N, 11·4%). 11 Hours' heating with 1·25 mols. of sodium sulphite, the other conditions being the same as before, afforded only 63 g. (50%) of pure taurine.

Ten parts of taurine dissolve in 17 parts of boiling water and in 50 parts of water at 22°. Median lethal dose 6·0 g./kg.

Sodium Phenylacetamidoethanesulphonate.—Phenylacetyl chloride (15·4 g.) and 5N-sodium hydroxide (20 c.c.) were added during 30 minutes to a stirred, ice-cold solution of taurine (12·5 g.) in 5N-sodium hydroxide (20 c.c.) at such a rate that the pH value of the mixture, as shown by bromothymol-blue and phenolphthalein used as internal indicators, was maintained at 7·6—8·5. Stirring was continued for a further 1½ hours, and the semi-solid product chilled and drained (pump); evaporation of the filtrate gave a second crop of material. The combined solids (26 g.) were recrystallised from the minimum amount of boiling water (40 c.c.), pure *sodium phenylacetamidoethanesulphonate* (19 g.) being obtained in stellate clusters of white leaves (Found, in salt dried at 100°/2 mm. for 1 hour: S, 12·0. $C_{10}H_{12}O_4NSNa$ requires S, 12·1%). Median lethal dose: 8·0 g./kg. (LD50 for phenylacetic acid: 1·7 g./kg.).

Sodium β-Phenylpropionamidoethane sulphonate.—This was obtained in the same manner by adding β-phenylpropionyl chloride (16·8 g.) and 5N-sodium hydroxide (20 c.c.) to a solution of taurine (12·5 g.) in 5N-sodium hydroxide (20 c.c.). Recrystallisation of the crude product from the minimum amount of boiling water (37 c.c.) gave *sodium phenylpropionamidoethanesulphonate* (21 g.) in small white needles (Found in dehydrated salt: S, 11·3. $C_{11}H_{14}O_4NSNa$ requires S, 11·5%). Median lethal dose: 8·0 g./kg. (LD50 for phenylpropionic acid: 1·1 g./kg.).

Sodium Acetylmandelamidoethanesulphonate.—This was obtained in the same manner from acetylmandelyl chloride (21·2 g.) (*Organic Syntheses*, 1941, **21**, 12) and taurine (12·5 g.). The crude product (24 g.) was extremely soluble in water and on evaporation tended to form a "glass"; it was obtained pure by slow crystallisation from dilute methanol in white micro-leaves (Found in dehydrated salt: S, 9·8. $C_{12}H_{14}O_6NSNa$ requires S, 9·95%). Median lethal dose: 8·5 g./kg. (LD50 for acetylmandelic acid: 5·5 g./kg.).

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