152. *Isethionic Acid.*

By Alan A. Goldberg.

A new method of preparation of isethionic acid and its salts is described together with some sodium *O*-acylisethionates.

Isethionic acid, $CH_2(OH)\cdot CH_2\cdot SO_3H$, has been prepared by the action of solid sulphur trioxide on ethyl alcohol (Magnus, *Annalen*, 1833, **6**, 163; *Ann. Physik*, 1839, **47**, 509), on ethyl hydrogen sulphate (Meves, *Annalen*, 1867, **143**, 196), and on diethyl ether (Hübner, *ibid.*, 1884, **223**, 210), by the interaction of ethylene or ethyl alcohol with sulphur trioxide dissolved in liquid sulphur dioxide (F.P. 716,914; B.P. 378,895), by the action of aqueous sodium hydrogen sulphite on ethylene chlorohydrin at 180° (Collmann, *Annalen*, 1868, **148**, 107) and by the passage of ethylene oxide into aqueous sodium hydrogen sulphite, giving the sodium salt in good yield (Lauer and Hill, *J. Amer. Chem. Soc.*, 1936, **58**, 1873; Rumpf, *Bull. Soc. chim.*, 1938, **5**, 877).

Since difficulties are encountered in working with sulphur trioxide, and ethylene oxide is not always accessible, a new method has been found in the reaction between ethyl sulphate and fuming sulphuric acid at a low temperature with production of ethyl hydrogen sulphate and ethionic acid; when the product is boiled with water, these compounds are hydrolysed, the former into sulphuric aicd and alcohol and the latter into sulphuric acid and isethionic acid. By removing the sulphuric acid as calcium sulphate the calcium salt of isethionic acid may be obtained easily and in excellent yield; other salts can be produced by double decomposition in aqueous solution.

Sodium *O*-acylisethionates are obtained by heating acyl chlorides with finely divided anhydrous sodium isethionate with or without a neutral diluent such as xylene. They are extremely soluble in water and are hydrolysed very slowly at the neutral point, more rapidly at low p_H values, and very rapidly in strongly alkaline solutions. Long-chain acylated isethionic acids in the form of their sodium salts have been used as wetting agents and detergents which function in acid liquors (B.P. 366,916). Because of the high solubility of sodium acylisethionates and their ability to hydrolyse into the corresponding acyl acid and the relatively non-toxic sodium isethionate, the latter would appear to possess desirable properties as a solubilising group for therapeutically active insoluble organic acids which may not be used in the form of their sodium salts owing to immediate precipitation by the gastric juice of the insoluble free carboxylic acid. It would, in addition, appear probable that the esterification of the carboxylic acid with sodium isethionate inhibits to some extent the normal detoxifying process occurring in the liver and kidney of conjugating the carboxylic acid with glycine which results not only in detoxification but in loss of therapeutic activity. *Sodium* O-*phenylacetylisethionate*, *sodium* O-β-*phenylpropionylisethionate* and *sodium* O-*acetylmandelylisethionate* have been prepared for examination as urinary disinfectants when administed 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 20—24 g.

Experimental.

Calcium Isethionate.—Fuming sulphuric acid containing 60% of free sulphur trioxide (150 g.; 77 c.c.) was added during 2½ hours with slow stirring to ethyl sulphate (100 g.; 85 c.c.) in a strong freezing mixture at such a rate that the temperature did not exceed 10°. After standing overnight at room temperature, the dark liquid was poured into water (1 l.) and refluxed for 10—12 hours. Calcium carbonate (150 g.) in the form of a thin milk with water was added, and the calcium sulphate separated and washed with boiling water. The acid filtrate and the washings were evaporated to *ca.* 1 l. and refluxed for 10—12 hours in order to complete the hydrolysis of the ethyl hydrogen sulphate and ethionic acid. Calcium carbonate (50 g.) was then added, the calcium sulphate removed and washed with boiling water, the combined filtrates and washings evaporated, and the calcium sulphate which crystallised removed (charcoal) by filtration (*). The filtrate was evaporated on the water-bath to *ca.* 110 c.c. and kept on ice for 12 hours; it then set to a semi-solid crystalline mass of calcium isethionate, which was well drained (pump). The filtrate was further evaporated, seeded, and kept on ice; the further heavy crop of calcium isethionate obtained was drained. The combined crops were dehydrated on the water-bath in a vacuum, pure anhydrous calcium isethionate (118 g.) being obtained as a fine white powder. The mother-liquor from the second crop was still rich in calcium isethionate. A sample was recrystallised from the minimum amount of boiling water and separated into two fractions (i) and (ii), which were dehydrated at 115°/5 mm., for 3 hours [Found: Ca, (i) 13·7, (ii) 13·6. Calc. for $C_4H_{10}O_8S_2Ca$: Ca, 13·8%]. 10 Parts of calcium isethionate dissolve in 16 parts of water at 25° and in just less than 10 parts at 100°.

Barium Isethionate.—In order to test more thoroughly the homogeneity of the product of the above reaction, one preparation (from 100 g. of ethyl sulphate) was converted into the barium salt by using the equivalent amount of barium carbonate in place of calcium carbonate for removal of the sulphuric acid. Barium isethionate has a much steeper solubility curve than has the calcium salt and therefore lends itself better to fractional crystallisation. The barium isethionate isolated (143 g.) was dissolved in boiling water (220 c.c.) and separated by fractionation into four fractions: (i) 9 g., (ii) 61 g., (iii) 39 g., and (iv) 25 g. The first two fractions were dehydrated at 120°/5 mm. for 3 hours and analysed as such and the last two fractions were recrystallised separately, dehydrated, and analysed [Found: Ba, (i) 35·3, (ii) 35·4, (iii) 35·3, (iv) 35·0. Calc. for $C_4H_{10}O_8S_2Ba$: Ba, 35·5%].

Potassium Isethionate.—To the solution of calcium isethionate obtained above (*) from 100 g. of ethyl sulphate, potassium carbonate (*ca.* 70 g.), dissolved in water, was added in portions until further small additions caused no more precipitation of calcium carbonate. The precipitate was removed, and the filtrate evaporated to a very small volume and cooled; the potassium isethionate then obtained in stout white needles was dehydrated at 110°/5 mm. (130 g.) (Found in recrystallised anhydrous salt: K, 23·8; S, 19·3. Calc. for $C_2H_5O_4SK$: K, 23·8; S, 19·5%). Potassium isethionate is much less hygroscopic than the sodium salt. 10 Parts of it dissolve in 12 parts of water at 25° and in less than 6 parts at 100°.

Sodium Isethionate.—This was obtained in small white tablets in the same manner as the potassium salt by using sodium carbonate (54 g.) in the place of potassium carbonate (70 g.). The yield of anhydrous sodium isethionate from 100 g. of ethyl sulphate was 111 g. (Found: Na, 15·4; S, 21·3. Calc. for $C_2H_5O_4SNa$: Na, 15·5; S, 21·6%). The median lethal dose is 8·8 g./kg. Sodium isethionate is hygroscopic and is rather more soluble than the potassium salt.

Sodium O-*Phenylacetylisethionate.*—An intimate mixture of anhydrous sodium isethionate (14·8 g.) and phenylacetyl chloride (17·0 g.) was heated at 130—140° (oil-bath) until no more hydrogen chloride was evolved (4 hours). The dark yellow oil was dissolved in boiling water (100 c.c.), filtered (charcoal), and extracted with ether to remove phenylacetic acid. The aqueous liquor was adjusted to p_H 7·2 with sodium hydroxide and evaporated under reduced pressure until incipient crystallisation took place. On cooling, it set to a white semi-solid mass, which was drained (pump) and recrystallised from boiling water (20—25 c.c.); *sodium* O-*phenylacetylisethionate* was then obtained (10·0 g.) in stellate clusters of white needles (Found in salt dehydrated at 100°/5 mm.: S, 12·2. $C_{10}H_{11}O_5SNa$ requires S, 12·0%). Median lethal dose, 3·3 g./kg. (LD_{50} of phenylacetic acid, 1·7 g./kg.).

Sodium O-β-*Phenylpropionylisethionate.*—β-Phenylpropionyl chloride (27 g.), anhydrous sodium isethionate (21 g.), and xylene (75 c.c.) were refluxed (140°) until no more hydrogen chloride was evolved (4 hrs.). The hot liquor was filtered and the residue was washed with a little ether, dissolved in boiling water (50 c.c.), filtered (charcoal), and kept on ice. The white crystalline precipitate, recrystallised from boiling water (30 c.c.), gave *sodium* O-β-*phenylpropionyl-*

isethionate (14 g.) in white flakes (Found in dehydrated salt: S, 11·1. $C_{11}H_{13}O_5SNa$ requires S, 11·4%). Median lethal dose, 2·0 g./kg. (LD_{50} for β-phenylpropionic acid, 1·1 g./kg.).

Sodium O-Acetylmandelylisethionate.—This was obtained in good yield in the same manner from acetylmandelyl chloride (*Org. Syn.*, **4**, 1) (21·2 g.), sodium isethionate (14·8 g.), and xylene (75 c.c.). It was extremely soluble in cold water and was obtained analytically pure only with difficulty by crystallisation from dilute methanol (Found in dehydrated salt: S, 9·4. $C_{12}H_{13}O_7SNa$ requires S, 9·9%). Median lethal dose, 6·5 g./kg. (LD_{50} for acetylmandelic acid, 5·5 g./kg.).

The author thanks Miss M. Derrington for assistance with the preparative work and Dr. F Scholl for the toxicity figures.

RESEARCH LABORATORIES, WARD, BLENKINSOP & CO., LTD.,
BRADFORD-ON-AVON.

[*Received, July 8th*, 1942.]