Dithiols. Part XVIII. Some Water-soluble Derivatives Containing the Sulphonic Acid Group.*

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The syntheses of water-soluble salts of 2 : 3-dimercaptopropanesulphonic acid and of a 2′ : 3′-dimercaptopropylbenzenesulphonic acid are described. Pure prop-2-ene-1-sulphonic acid has been prepared.

THE syntheses of water-soluble derivatives of 2 : 3-dimercaptopropanol (BAL), described in some of the earlier papers in this series, have been mainly concerned with polyhydroxy-compounds. The present investigation had as its initial object the synthesis of 2 : 3-dimercaptopropanesulphonic acid, which either as free acid or sodium salt (IV) would be

* Part XVII, preceding paper.

expected to possess the antiarsenical properties associated with the presence of the vicinal dithiol grouping, and to be readily soluble in water.

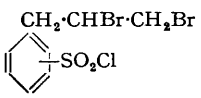
No dimercaptoalkanesulphonates have hitherto been reported. Lipovich (*Zhur. priklad. Khim.*, 1945, **18**, 718) described the formation, in solution, of three simple sodium monomercaptoalkanesulphonates, but the only compound of this type claimed to have been isolated is sodium 4-mercaptobutane-2-sulphonate (Helberger, Manecke, and Heyden, *Annalen*, 1949, **565**, 22); the purity of the latter, however, was not stated and cannot be assessed in the absence of any recorded thiol value, because the presence of even a considerable proportion of the corresponding disulphide would have little effect on the carbon and hydrogen figures, which were the only analyses given.

Because the free dimercapto-acid would probably lactonise to form the thio-sultone, experiments were directed towards the synthesis of the sodium and the potassium salt. Sodium prop-2-ene-1-sulphonate (I), as prepared by interaction of allyl bromide and sodium sulphite (Belous and Postovskii, *Chem. Abs.*, 1951, **45**, 2391), is obtained as a double salt with sodium bromide, from which the halide can be removed only by tedious recrystallisation. The crude material, however, although insoluble in aprotic solvents is soluble in acetic acid, and it then reacts smoothly with bromine to give sodium 2 : 3-dibromopropanesulphonate (II), which is relatively easily freed from the accompanying

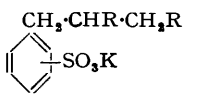
$CH_2{:}CH{\cdot}CH_2{\cdot}SO_3Na$ (I)

$CH_2R{\cdot}CHR{\cdot}CH_2{\cdot}SO_3Na$ (II; R = Br) (III; R = SAc) (IV; R = SH)

$EtO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}SO_2Et$ (V)



(VI)



(VII; R = Br) (VIII; R = SH)

sodium bromide. When this product was treated with sodium thiolacetate in boiling ethanol, a mixture of sodium salts was obtained, from which the newly-formed sodium bromide was again removed by fractional crystallisation. The bromide-free material so obtained was not the pure bisthiolacetate (III), but was contaminated with the partly deacetylated compound, a circumstance which was not a serious hindrance as the product could be used as such for the final stage of deacetylation. This was rapid in ethanolic sodium ethoxide, but the free dithiol could not be separated from other sodium salts either by crystallisation or by ion-exchange methods. Deacetylation with hot aqueous hydrochloric acid was also unsuccessful, owing to the formation of some sodium chloride which could not be entirely removed, but by hydrolysis of the bisthiolacetate with aqueous acetic acid the pure sodium 2 : 3-dimercaptopropanesulphonate (IV) was obtained.

Only two alkenesulphonic acids have been obtained in the free state, *viz.* ethylenesulphonic acid (*inter al.*, U.S.P. 2,619,452, *Chem. Abs.*, 1953, **47**, 9342; Snyder, Anderson, and Hallada, *J. Amer. Chem. Soc.*, 1951, **73**, 3258) and prop-1-ene-1-sulphonic acid (Lambert and Rose, *J.*, 1949, 46). We have now obtained prop-2-ene-1-sulphonic acid by hydrolysis of its acid chloride, prepared from the crude sodium salt (I); the pure sodium and potassium salts are thus made easily available by subsequent neutralisation of the acid. Addition of bromine to a solution of the potassium salt in acetic acid afforded potassium 2 : 3-dibromopropanesulphonate, which with potassium thiolacetate behaved similarly to the sodium analogue and gave a bisthiolacetate mixed with partly deacetylated material. Complete deacetylation was effected by mild acid hydrolysis, though in this case the free dithiol was not obtained pure.

Other approaches to some of the intermediates were investigated. The attempted conversion of prop-2-ene-1-sulphonyl chloride into the ester, by reaction with ethanol in excess of pyridine, gave only water-soluble products, but when only one mol. of pyridine was used the ethyl ester was obtained in excellent yield; it underwent very rapid hydrolysis when heated with water. Reaction of the sulphonyl chloride in ether with ethanol and potassium hydroxide resulted in addition to the double bond and gave ethyl 3-ethoxypropanesulphonate (V). With bromine in carbon tetrachloride, ethyl prop-2-ene-1-sulphonate gave ethyl 2 : 3-dibromopropane-1-sulphonate; the reaction occurred readily

only in bright sunlight. When the dibromo-ester reacted with potassium thiolacetate, the ester group was destroyed, and the product contained only potassium salts, a result clearly due to the alkylating properties of sulphonic esters.

Attention was next turned to the synthesis of an aromatic analogue. Chlorosulphonation of 2′ : 3′-dibromopropylbenzene gave an analytically pure 2′ : 3′-dibromopropylbenzenesulphonyl chloride (VI) as a liquid, possibly a mixture of isomers. Hydrolysis of the acid chloride with boiling aqueous ethanol did not affect the dibromide group, and neutralisation of the resulting acid afforded a pure potassium 2′ : 3′-dibromopropylbenzenesulphonate (VII). With potassium thiolacetate this gave a potassium 2′ : 3′-bisacetylthiopropylbenzenesulphonate, from which a potassium 2′ : 3′-dimercaptopropylbenzenesulphonate (VIII) was obtained by deacetylation with aqueous acetic acid.

All the sodium and the potassium sulphonates encountered in this investigation were freely soluble in water, and the main experimental difficulty was in effecting their complete separation from accompanying inorganic salts.

Experimental

Sodium 2 : 3-*Dibromopropanesulphonate.*—To a solution of crude sodium prop-2-ene-1-sulphonate (Belous and Postovskii, *Chem. Abs.*, 1951, **45**, 2391) (15 g.) in acetic acid (50 c.c.), bromine (17 g.) in acetic acid (50 c.c.) was added dropwise during 30 min. at 10—15°. The solution, which still contained free bromine, was concentrated under reduced pressure and then stirred with ether (100 c.c.) to precipitate the dibromide (29·5 g.). This contained some sodium bromide, but recrystallisation of a portion from 90% *iso*propanol gave *sodium* 2 : 3-*dibromopropanesulphonate* as hard crystals, decomp. *ca.* 250°, readily soluble in water, methanol, and ethanol (Found : C, 11·8; H, 1·9; Br, 52·4; Na, 7·5. $C_3H_5O_3Br_2SNa$ requires C, 11·85; H, 1·7; Br, 52·6; Na, 7·6%).

Sodium 2 : 3-*Bisacetylthiopropanesulphonate.*—The dibromide (24 g.), sodium thiolacetate (20 g.), and ethanol (120 c.c.) were boiled under reflux for 6 hr. Filtration of the hot solution removed sodium bromide (6 g.); the cooled solution deposited the crude bisthiolacetate (17 g.) containing a little sodium bromide, most of which was removed by solution of the solid in boiling dry methanol (125 c.c.), concentration to about half bulk, and addition of dry ethanol (70 c.c.). One further crystallisation of the precipitated solid from methanol gave material which was free from halogen, but the bisthiolacetate contained a small amount of free thiol (Found : C, 26·3; H, 3·8; thiol-S, 1·9. Calc. for $C_7H_{11}O_5S_3Na$: C, 28·6; H, 3·8%). Repeated recrystallisation resulted only in further deacetylation.

Sodium 2 : 3-*Dimercaptopropanesulphonate.*—A solution of the bisthiolacetate (1 g.) in 15% acetic acid (30 c.c.) was heated on the steam-bath for 40 hr. in nitrogen, the thiol value then having risen to 84% of the theoretical. The solution was freeze-dried at 0·05 mm., and the residue was triturated with ethanol (10 c.c.); the solid (0·6 g.) was collected and dried in vacuum (P_2O_5) (Found : C, 18·1; H, 3·8; Na, 10·9; thiol-S, 23·6%). A portion (175 mg.) was dissolved in water (0·5 c.c.) containing a trace of acetic acid, and the solution filtered, diluted with ethanol (3 c.c.), and cooled to 0°; a solid (60 mg.), which crystallised, had a low thiol content and was rejected. The residual solution was concentrated in a vacuum desiccator (NaOH), and was then stirred with ethanol (3 c.c.) and a trace of acetic acid, giving leaflets of the *dithiol* (55 mg.), which were collected by centrifugation, washed with ethanol, and dried (P_2O_5) (Found : C, 17·6; H, 3·7; Na, 11·0; thiol-S, 31·0. $C_3H_7O_3S_3Na$ requires C, 17·1; H, 3·35; Na, 10·9; thiol-S, 30·5%).

Prop-2-ene-1-sulphonyl Chloride.—A mixture of crude sodium prop-2-ene-1-sulphonate (100 g.) and phosphorus oxychloride (170 g.) was boiled under reflux with occasional shaking for 3 hr. Most of the remaining oxychloride was then removed on the steam-bath at 120 mm., and the residue, suspended in pure chloroform (250 c.c.), was gradually treated with crushed ice (200 g.). The washed and dried chloroform layer on evaporation gave the sulphonyl chloride, which distilled as a colourless oil (58·5 g., 61%), b. p. 74—76°/15 mm., n_D^{20} 1·4767. Belous and Postovskii (*loc. cit.*), who obtained a 33% yield, reported b. p. 73—75°/12·5 mm., n_D^{14} 1·4730.

Prop-2-ene-1-sulphonic Acid.—When the acid chloride (15 g.) was heated and stirred with water (50 c.c.) on the steam-bath, the mixture became homogeneous in 30 min. It was cooled, extracted once with ether (the extract being rejected), and then evaporated under reduced pressure to give the *sulphonic acid* as a viscous, hygroscopic liquid (12 g.), which could be

distilled in gram portions at *ca.* 180° (bath)/0·0001 mm.; it then had n_D^{20} 1·4620 (Found: C, 29·45; H, 5·2. $C_3H_6O_3S$ requires C, 29·5; H, 4·95%). Neutralisation in aqueous solution with pure potassium hydroxide, and evaporation to dryness, gave the *potassium salt*, which crystallised from methanol in shining leaflets, decomp. *ca.* 240° (Found: C, 22·5; H, 3·2; K, 25·0. $C_3H_5O_3SK$ requires C, 22·5; H, 3·1; K, 24·4%).

Potassium 2 : 3-*Dibromopropanesulphonate.*—The above potassium salt (20 g.) was treated in acetic acid (100 c.c.) with bromine (24 g.) in acetic acid (50 c.c.), and the product was isolated as for the sodium compound. It was crystallised first from methanol–ethanol (1 : 1), and then from methanol, to give the *dibromide*, decomp. *ca.* 260° (Found: C, 11·9; H, 1·9; Br, 49·6. $C_3H_5O_3Br_2SK$ requires C, 11·3; H, 1·6; Br, 49·95%). Unlike the sodium compound it was only sparingly soluble in ethanol.

Potassium 2 : 3-*Bisacetylthiopropanesulphonate.*—Reaction of the dibromide (10 g.) with potassium thiolacetate (8·5 g.) in boiling ethanol (60 c.c.), as for the sodium salt, gave a solid (8·4 g.) containing some potassium bromide; the latter was removed by recrystallisation from ethanol, but the resulting bisthiolacetate was partly deacetylated (Found: C, 25·7; H, 3·7; K, 15·4; thiol-S, 3·9. Calc. for $C_7H_{11}O_5S_3K$: C, 27·1; H, 3·6; K, 12·6%).

Deacetylation. The crude bisthiolacetate (2 g.) was heated with acetic acid (3 c.c.) and water (17 c.c.) for 48 hr. at 100° in nitrogen. The thiol content reached only 61% of the theoretical (cf. the corresponding sodium salt) and fractional crystallisation of the isolated salt gave material (Found: C, 17·7; H, 3·4; S, 37·9; thiol-S, 22·5; K, 18·2. Calc. for $C_3H_7O_3S_3K$: C, 15·9; H, 3·1; S, 42·5; thiol-S, 28·3; K, 17·3%) which could not be completely purified.

Ethyl Prop-2-ene-1-sulphonate.—Dry pyridine (7·9 g.) in pure chloroform (10 c.c.) was slowly added (15 min.) to a stirred solution of prop-2-ene-1-sulphonyl chloride (13·9 g.) in dry ethanol (5 g.) and pure chloroform (15 c.c.) at −5°. The mixture was kept at −5° for a further 15 min., then warmed to 20° and kept for 20 min. After the addition of crushed ice (20 g.) the chloroform layer was separated, washed once with water, dried ($CaCl_2$), and evaporated to an oil, which on distillation furnished the *ethyl ester* (12·6 g.), b. p. 53—55°/0·1 mm., 80—82°/0·5 mm., n_D^{25} 1·4410 (Found: C, 40·0; H, 6·9; S, 21·15. $C_5H_{10}O_3S$ requires C, 40·0; H, 6·7; S, 21·3%). This was insoluble in cold water, but was rapidly decomposed by boiling water.

Ethyl 3-*Ethoxypropanesulphonate.*—Finely powdered potassium hydroxide (1·5 g.) was added in small portions to a stirred mixture of prop-2-ene-1-sulphonyl chloride (1·4 g.), dry ethanol (0·48 g.), and dry ether (15 c.c.) at 0° to −5°. Stirring was maintained for a further 2 hr. at 0°, and the mixture was then set aside at room temperature overnight. Ice (5 g.) was added, and the ether layer was separated, dried (Na_2SO_4), and evaporated to an oil (0·35 g.), consisting essentially of *ethyl* 3-*ethoxypropanesulphonate*, b. p. 126—132°/18 mm., n_D^{22} 1·4352 (Found: C, 42·6; H, 7·9; S, 17·1; EtO, 42·6. $C_7H_{16}O_4S$ requires C, 42·85; H, 8·2; S, 16·3; OEt, 45·9%). The material was slightly unsaturated and the analytical figures are compatible with the presence of 5—10% of the unsaturated ethyl ester.

Ethyl 2 : 3-*Dibromopropanesulphonate.*—Bromine (11 g.) in carbon tetrachloride (25 c.c.) was added to ethyl prop-2-ene-1-sulphonate (10 g.) in carbon tetrachloride (25 c.c.) in strong sunlight. The reaction (which in the absence of sunlight was very slow) was complete in 3 hr., and evaporation of the solvent and distillation of the residue gave the *dibromo-ester* (18·9 g.), b. p. 114—118°/0·001 mm., n_D^{21} 1·5182, n_D^{32} 1·5142 (Found: C, 19·7; H, 3·35; Br, 51·4. $C_5H_{10}O_3Br_2S$ requires C, 19·4; H, 3·25; Br, 51·6%).

Reaction with potassium thiolacetate. The dibromo-ester (6·2 g.), potassium thiolacetate (5·5 g.), and ethanol (25 c.c.) were boiled under reflux for 4 hr. Most of the ethanol was then removed under reduced pressure and the residue was shaken with water (15 c.c.) and chloroform (40 c.c.). The chloroform layer was removed and the aqueous portion was extracted once more with chloroform. Evaporation of the combined extracts gave a sticky solid (0·9 g.) which was extracted with boiling ethanol (40 c.c.). An insoluble residue (0·2 g.) was rejected, and the filtrate was cooled; a pale yellow hygroscopic solid (0·7 g.) was deposited. This had unusual solubility properties, being soluble in water and in chloroform, but insoluble in cold ethanol. It was probably a mixture of the potassium salts of 2 : 3-bisacetylthio- and 3-acetylthio-2-bromopropanesulphonic acids (Found: C, 22·0; H, 3·0; S, 23·6; Br, 13·6; K, 15·1. Calc. for $C_7H_{11}O_5S_3K$: C, 27·1; H, 3·6; S, 31·0; K, 12·6. Calc. for $C_5H_8O_4BrS_2K$: C, 19·05; H, 2·6; Br, 25·35; S, 20·3; K, 12·4%).

Chlorosulphonation of 2′ : 3′-*Dibromopropylbenzene.*—The dibromo-hydrocarbon (Huston and Sagar, *J. Amer. Chem. Soc.*, 1926, **48**, 1955) (5 g.) in pure chloroform (20 c.c.) was added slowly (10 min.) to a stirred mixture of chlorosulphonic acid (10 c.c.) and pure chloroform (15 c.c.) at 0°. After being kept for an hour at room temperature, the solution was treated with ice (100 g.);

the chloroform layer was washed with water, dried (Na_2SO_4), and evaporated to a viscous oil, which on distillation furnished 2′ : 3′-dibromopropylbenzenesulphonyl chloride (possibly a mixture of isomers) (5 g.), b. p. 210—220° (bath)/0·0002 mm., n_D^{21} 1·6052 (Found : C, 28·6; H, 2·6; S, 8·55. Calc. for $C_9H_9O_2ClBr_2S$: C, 28·7; H, 2·4; S, 8·5%).

Potassium 2′ : 3′-Dibromopropylbenzenesulphonate.—A solution of the acid chloride (17 g.) in ethanol (100 c.c.) was boiled for 12 hr. under reflux. Water (20 c.c.) was then added, and the heating was maintained for a further 4 hr., after which the solution was evaporated under reduced pressure, the last traces of hydrochloric acid being removed by several evaporations from ethanol. The residual oil was dissolved in water (600 c.c.) and freed from a small amount of insoluble material by one extraction with ether (50 c.c.), the extract being discarded. The aqueous solution was then neutralised (phenolphthalein) with potassium hydroxide and evaporated to dryness at 15 mm.; the solid residue was triturated with ethanol (50 c.c.) and collected by filtration (yield, 10·6 g.). Recrystallisation from 90% ethanol gave pearly leaflets of the *potassium salt* (Found : Br, 40·0%. $C_9H_9O_3Br_2SK$ requires Br, 40·4%).

Potassium 2′ : 3′-Bisacetylthiopropylbenzenesulphonate.—The above dibromo-salt (7·8 g.) and potassium thiolacetate (5·8 g.) were boiled in ethanol (50 c.c.) for 6 hr. under nitrogen. The mixture was then diluted with ethanol (20 c.c.), heated to boiling, and filtered hot, and the solid was washed with hot ethanol (30 c.c.). Cooling the combined filtrates precipitated the crude product (3·3 g.), which contained a little potassium bromide; the latter was removed by crystallisation of the material from dry methanol, from which the bisthiolacetate separated as microcrystals (Found : C, 38·9; H, 3·8; K, 11·1. Calc. for $C_{13}H_{15}O_5S_3K$: C, 40·4; H, 3·9; K, 10·1%). The analytical figures indicate slight deacetylation.

Potassium 2′ : 3′-Dimercaptopropylbenzenesulphonate.—The bisacetylthio-compound (0·75 g.), acetic acid (2 c.c.), and water (18 c.c.) were heated under reflux on the steam-bath for 2 days under nitrogen, the thiol value of the solution then having attained 85% of the theoretical for complete deacetylation. The solution was then freeze-dried at 0·05 mm., and the residue was triturated with dry ethanol (3 c.c.). Filtration gave the *dithiol* (0·32 g.), a portion of which was recrystallised from ethanol–water–acetic acid (16 : 3 : 1) (Found : C, 35·8; H, 3·9; S, 32·0; K, 13·05; thiol-S, 18·8. $C_9H_{11}O_3S_3K$ requires C, 35·7; H, 3·7; S, 31·8; K, 12·9; thiol-S, 21·2%). The thiol value indicates slight oxidation to disulphide.

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