[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

The Benzenesulfonyl Derivatives of 1-Amino-2,3-dibromopropane and 2-Amino-1,3-dibromopropane

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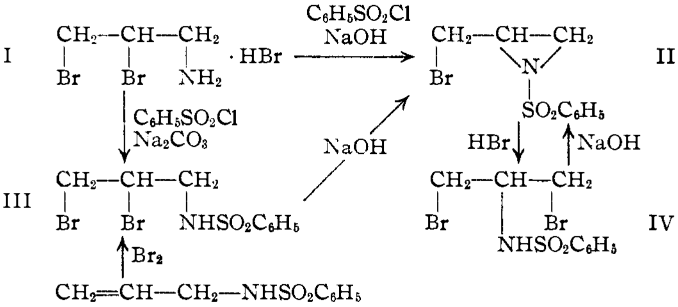
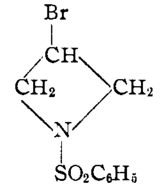
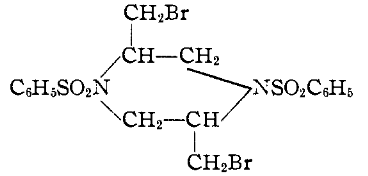
It was reported recently[1] that the action of benzenesulfonyl chloride with 1-amino-2,3-dibromopropane hydrobromide (I) in sodium hydroxide solution resulted in the formation of an alkali insoluble material which furnished analytical figures agreeing not with those calculated for 1-benzenesulfonamido-2,3-dibromopropane (III) but for III minus a molecule of hydrogen bromide. The structure of 1-benzenesulfonyl-2-bromomethylethyleneimine (II) was proposed for this compound. The present report is concerned with the reactions involved in the formation of II, and the demonstration of its structure.

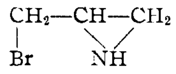


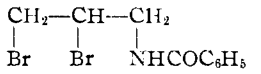
It was found that III, the normal benzenesulfonyl derivative, could be obtained from the reaction of I and benzenesulfonyl chloride by the use of sodium bicarbonate, or better sodium carbonate, in place of sodium hydroxide. The same compound was formed on the addition of bromine to N-(benzenesulfonyl)-allylamine. Compound III was insoluble in carbonate or bicarbonate solution and could be recovered unchanged after exposure to these reagents. However, when III was treated with dilute sodium hydroxide, a clear solution resulted, which after a few seconds suddenly became milky and deposited a crystalline solid. This solid was identical with the product (II) obtained directly from 1-amino-2,3-dibromopropane.[2]

The facts that 1-benzenesulfonamido-2,3-dibromopropane could be obtained from 1-amino-2,3-dibromopropane under conditions milder than those used in the direct conversion of 1-amino-2,3-dibromopropane to II, and that 1-benzenesulfonamido-2,3-dibromopropane could be converted to II under the same conditions as those in the direct conversion, constituted permissive evidence in favor of the probable course of the reaction, I → [III] → II. It was necessary, however, to consider an alternate course in which 1-amino-2,3-dibromopropane could first cyclize to form 2-bromomethylethyleneimine (VII), which would then react with benzenesulfonyl chloride to yield the product II. To test this possibility 1-amino-2,3-dibromopropane hydrobromide was added to an excess of sodium hydroxide solution. The mixture was allowed to stand for a period equal to the reaction time allowed in the direct formation of II, and under the same conditions. Benzoyl chloride was then added to effect a benzoylation of either the cyclized molecule, VII, or the unchanged starting material. It was found that the product was the derivative of the starting material, 1-benzamido-2,3-dibromopropane, VIII (96% yield, m. p. 125–127°; 66% yield after purification, m. p. 129–129.5°) and not the cyclized form IX. Since no cyclization occurred in the benzoylation experiment, no cyclization to VII was possible in the benzenesulfonation reaction; and therefore in the direct formation of II from 1-amino-2,3-dibromopropane, the reaction path, I → [VII] → II, could be eliminated.

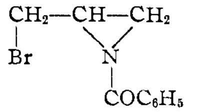
V 

 VI

VII 

 VIII

$CH_2Br{-}CHBr{-}CH_2NHCOC_6H_5$

 IX

Assignment of the structure of 1-benzenesulfonyl-2-bromomethylethyleneimine (II) for the alkali insoluble compound required proof since at least two other structures, V and VI, could be regarded as reasonably possible. The bimolecular piperazine derivative, VI, was eliminated on the basis of a molecular weight determination, while

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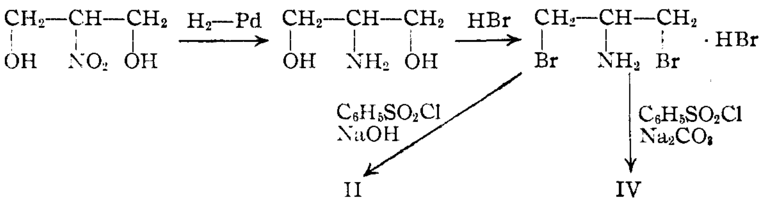
(1) Gensler, THIS JOURNAL, **69**, 1966 (1947).

(2) Similar reactions have been reported before. Adams and Cairns, THIS JOURNAL, **61**, 2464 (1939), converted 1-*p*-bromobenzenesulfonamido-2-methyl-2-chloropropane to 1-*p*-bromobenzenesulfonyl-2,2-dimethylethyleneimine; and Kharasch and Priestley, *ibid.*, p. 3425, obtained N-(*p*-toluenesulfonyl)-styreneimine from 1-*p*-toluenesulfonamido-1-phenyl-2-bromoethane.

the choice of II over V rested on the following two lines of evidence.

Rupture of the ring in the symmetrical trimethyleneimine V with the addition of hydrogen bromide can lead to only one product, 1-benzenesulfonamido-2,3-dibromopropane (III). The unsymmetrical ethyleneimine structure II on the other hand can yield either III or the isomeric compound, 2-benzenesulfonamido-1,3-dibromopropane (IV). On carrying out the experiment using 48% hydrobromic acid there was obtained only one addition product (68% yield) which proved to be not III but IV. The unsymmetrical structure for II was therefore indicated. The structure assigned to IV was supported by its smooth reconversion to II on treatment with alkali.

Conclusive proof was furnished by an unequivocal synthesis of II as well as IV. Hydrogenation of 2-nitro-1,3-dihydroxypropane according to Schmidt and Wilkendorff[3] yielded 2-amino-1,3-dihydroxypropane. Treatment with strong hydrobromic acid at 165–175° converted the aminoglycol to 2-amino-1,3-dibromopropane hydrobromide (X) which was isomeric with compound I. From the reaction of X and benzenesulfonyl chloride in the presence of sodium hydroxide it was possible to obtain a product II identical with the alkali insoluble compound derived from I. The use of sodium carbonate in place of sodium hydroxide resulted in the formation of 2-benzenesulfonamido-1,3-dibromopropane (IV) identical with the addition product of II and hydrogen bromide. These identities constitute a demonstration of structure, since it is possible to write only the structures of 1-benzenesulfonyl-2-bromomethylethyleneimine (II) and 2-benzenesulfonamido-1,3-dibromopropane (IV) for the compounds derived from 2-amino-1,3-dibromopropane X.



X

Discussion

The reaction of 1-benzenesulfonamido-2,3-dibromopropane, or 2-benzenesulfonamido-1,3-dibromopropane with alkali to form 1-benzenesulfonyl-2-bromomethylethyleneimine is interpreted on the basis of a nucleophilic attack of the sulfonamide anion on a *beta* carbon atom with the elimination of bromide ion. The dibromo compounds are stable in acidic or weakly alkaline medium since the unshared electron pair on the nitrogen of the undissociated sulfonamide grouping is unavailable for the displacement. At higher pH's a proton is removed from the sulfonamide group, and the strongly nucleophilic nitrogen reacts rapidly.

The formation of II rather than V from 1-benzenesulfonamido-2,3-dibromopropane shows that the attack of the sulfonamide anion on the number two carbon is much more rapid than on the number three. Freundlich and Kroepelin[4] have found that the first order rate constants for the cyclization of β-bromoethylamine and γ-bromopropylamine are 0.036 and 0.0005, respectively. If these figures give some measure of the relative tendency of a free unshared electron pair on nitrogen to displace bromide ion from the two- and from the three-positions, then only 1–2% of the four-membered ring compound, V, would be expected in the product from 1-benzenesulfonamido-2,3-dibromopropane. This small amount would be lost in the purification procedure.

In the addition of hydrogen bromide to 1-benzenesulfonyl-2-bromomethylethyleneimine to form 2-benzenesulfonamido-1,3-dibromopropane a solvolysis mechanism is unlikely since it would involve the formation of a primary carbonium ion. On the other hand, by analogy with the behavior of related three-membered ring systems,[5] it is reasonable to regard the reaction as a bimolecular displacement of the sulfonamido group by bromide ion. The electron attracting properties of the sulfonamido group polarize the bond between the nitrogen and carbon of the ring placing the positive end of a dipole at the carbon atom. The resulting low electron density at the carbon together with the normal strain in the three-membered ring would allow a ready attack by bromide ion.

In analogy with related cases the displacement occurs at the methylene rather than at the methine carbon.[6] In this connection it should be pointed out that this mode of ring cleavage is by no means the rule, and that a number of examples

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(3) Schmidt and Wilkendorff, *Ber.*, **52**, 389 (1919).

(4) Freundlich and Kroepelin, *Z. physik. Chem.*, **122**, 39 (1926).

(5) In the formation of 1-chloro-2-hydroxy-3-halopropane from aqueous hydrogen halide and epichlorohydrin, an oxygen analog, Brönsted, Kilpatrick and Kilpatrick [THIS JOURNAL, **51**, 428 (1929)] have shown that the rate of reaction is dependent on the halide ion–epichlorohydrin concentration product and also on the halide ion–epichlorohydrin–hydronium ion concentration product. Freundlich and Neumann [*Z. physik. Chem.*, **87**, 69 (1914)] have found that in the reaction of ethyleneimine with excess hydrobromic acid to form β-bromoethylamine, the rate depends on the product of the bromide ion and ethyleneimine (ethyleneimmonium ?) concentrations. In these cases a nucleophilic displacement mechanism of halide ion on a carbon atom is in agreement with the observed kinetics. Further, a displacement process by various donor groups on the ring-carbons of an intermediate quaternary ethyleneimmonium salt has been used satisfactorily to interpret the reaction kinetics of the nitrogen mustards (Ph.D. theses, Harvard University, 1944, by C. Gardner Swain and by Sidney D. Ross).

(6) For example, in the addition of hydrogen bromide [Gabriel and Ohle, *Ber.*, **50**, 815 (1917)] and of hydrogen chloride [Smith and Platon, *ibid.*, **55**, 3143 (1922)] to propyleneimine; and in the addition of the halogen acids to the oxygen analogs, epichlorohydrin and epibromohydrin ["Beilstein," 4th ed., Vol. XVII, pp. 7–8.]

are known in which the process occurs at the more highly, rather than the less highly, substituted carbon atom of the ethyleneimine ring.[7]

Experimental

1-Benzenesulfonamido-2,3-dibromopropane (III) from 1-Amino-2,3-dibromopropane (I).—To a vigorously stirred solution of 1.20 g. of 1-amino-2,3-dibromopropane hydrobromide[8] (0.0040 mole) in 10 ml. of water was added 0.6 ml. of benzenesulfonyl chloride (0.0047 mole) followed immediately by a solution of 1.2 g. of sodium carbonate (0.011 mole) in 10 ml. of water. After the mixture had been stirred for forty-five minutes at room temperature it was filtered, and the solids washed and pressed on the funnel. This material, dried in the air, weighed 1.33 g. (92%) and had m. p. 91–97° (sintering at 85°). It was crystallized from 8 ml. of carbon tetrachloride to yield 1.05 g. (73%) of 1-benzenesulfonamido-2,3-dibromopropane in the form of fine needle-like crystals, m. p. 97–99°.

Two further crystallizations from alcohol brought the melting point to 98–100°.

Anal. Calcd. for $C_9H_{11}NSO_2Br_2$: C, 30.3; H, 3.1. Found: C, 30.6; H, 3.2.

1-Benzenesulfonamido-2,3-dibromopropane (III) from N-(Benzenesulfonyl)-allylamine.—The product of the reaction of benzenesulfonyl chloride and allylamine in aqueous alkali was readily purified by distillation. The fraction which boiled at 156–158° (2 mm.) and solidified to a white solid, m. p. 39.5–41.5°, was taken as N-(benzenesulfonyl)-allylamine.[9]

Twenty-five milliliters of chloroform containing 4.05 g. of bromine (0.025 mole) was added over a period of one and three-quarters hours to a cold (10°) vigorously stirred solution of 5.00 g. of N-(benzenesulfonyl)-allylamine (0.025 mole) in 50 ml. of chloroform. After the addition was complete the reaction mixture, from which crystals of the product had separated, was allowed to stand at 10–15° for one hour. The solvent was then removed, with only slight warming, by distillation under reduced pressure. To the residue was added 15 ml. of alcohol and again all volatile material was removed with suction. Crystallization of the crude product from alcohol yielded 7.48 g. (83%) of white crystals, m. p. 97.5–101.5°, which showed no depression in mixed melting point with the 1-benzenesulfonamido-2,3-dibromopropane from 1-amino-2,3-dibromopropane. Further crystallizations did not improve the melting point.

1-Benzenesulfonyl-2-bromomethylethyleneimine (II) from 1-Amino-2,3-dibromopropane (I).—A solution of 1.20 g. of 1-amino-2,3-dibromopropane hydrobromide (0.0040 mole) in 5 ml. of water was mixed with 0.70 ml. of benzenesulfonyl chloride (0.0054 mole). Five milliliters of sodium hydroxide solution, containing 0.97 g. or 0.024 mole of sodium hydroxide, was added without delay and with vigorous stirring. Immediately after the addition of the alkali the mixture became almost entirely clear, but after a few seconds a heavy turbidity suddenly developed which soon gave way to a precipitate. After the mixture had been stirred at room temperature for thirty-five minutes, the solids were collected, washed with water, and finally air-dried. The crude product, which weighed 0.95 g. (86%) and melted at 86–88.5°, was purified by crystallization from ethyl alcohol, and furnished 0.82 g. (74%) of 1-benzenesulfonyl-2-bromomethylethyleneimine, m. p. 89–90° (faint sintering at 86°). This material gave no depression in mixed melting point with the analytical sample of the material previously prepared,[1] while the mixed melting point with 1-benzenesulfonamido-2,3-dibromopropane was 76–91°.

A Rast molecular weight determination gave values lying between 272 and 281. The calculated molecular weight for II is 276.

1-Benzenesulfonyl-2-bromomethylethyleneimine (II) from 2-Amino-1,3-dibromopropane (X).—The procedure employed was the same as that described above for the reaction with 1-amino-2,3-dibromopropane. The same product was obtained (melting point and mixed melting point, 89–90°) in 76% yield.

1-Benzenesulfonyl-2-bromomethylethyleneimine (II) from 1-Benzenesulfonamido-2,3-dibromopropane (III).—A solution of 1.4064 g. of 1-benzenesulfonamido-2,3-dibromopropane (0.00394 mole) in 10 ml. of alcohol was added in one portion to 50.00 ml. of 0.099 *N* sodium hydroxide (0.00495 equivalent). The addition was made as complete as possible by rinsing the flask with two 5-ml. portions of alcohol. The stirred solution remained perfectly clear for about fifteen seconds and then suddenly became milky. After the addition of 25 ml. of water the mixture was cooled in an ice-bath and filtered. The time which elapsed between the addition and the filtration was no longer than fifteen minutes. The solids, washed thoroughly on the funnel with approximately 50 ml. of water, pressed, and air-dried, weighed 1.02 g. (94%) and showed m. p. 88.5–90° (sintering at 85°). One crystallization from alcohol afforded 0.76 g. (70%) of pure 1-benzenesulfonyl-2-bromomethylethyleneimine, with melting point and mixed melting point, 89–90°.

The aqueous alkaline filtrate, together with the wash water, was titrated with 9.50 ml. of 0.100 *N* hydrochloric acid to the disappearance of the red color of phenolphthalein. This revealed that the amount of sodium hydroxide consumed in the cyclization process was 0.0040 equivalents, in good agreement with the theoretical value of 0.00394.

1-Benzenesulfonyl-2-bromomethylethyleneimine (II) from 2-Benzenesulfonamido-1,3-dibromopropane (IV).—The cyclization of IV followed essentially the directions given for the cyclization of III. However, it was noted in this case that the addition of the alcoholic solution of the 1,3-dibromide to the aqueous alkali did not result in a clear solution, but in an immediate turbidity. The crude air-dried product (m. p. 87–89°; 99% yield) was crystallized from alcohol, and furnished pure 1-benzenesulfonyl-2-bromomethylethyleneimine, m. p. 89–89.5°, in 81% yield. Mixed melting point determinations with II, III, and IV established the identity of the product.

1-Benzamido-2,3-dibromopropane (VIII).—The benzoylation of 1-amino-2,3-dibromopropane was carried out by following essentially the directions for the preparation of 1-benzenesulfonyl-2-bromomethylethyleneimine from 1-amino-2,3-dibromopropane. From the reaction of 1.20 g. of the amino-dibromide hydrobromide (0.0040 mole), 0.62 ml. of benzoyl chloride (0.0054 mole), and a solution of 0.98 g. of sodium hydroxide, there was obtained 1.18 g. (91%) of washed and air-dried product, m. p. 128–129°. One crystallization of this material from alcohol yielded 0.79 g. (61%) of 1-benzamido-2,3-dibromopropane, m. p. 129–129.5°. Two further crystallizations were carried out to obtain the analytical sample, m. p. 129.5–130°.[10]

Anal. Calcd. for $C_{10}H_{11}NOBr_2$: C, 37.4; H, 3.5. Found: C, 37.5; H, 3.4.

Repetition of this experiment with the one difference of stirring the mixture of amino-dibromide hydrobromide in the sodium hydroxide solution for thirty-five minutes at room temperature before the addition of the benzoyl

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[7] This is the case in the formation of 1-*p*-toluenesulfonamido-2-phenyl-2-bromoethane from N-(*p*-toluenesulfonyl)-styreneimine and hydrobromic acid [Kharasch and Priestley, THIS JOURNAL, **61**, 3425 (1939)]; in the formation of 1-amino-2-methylpropanol-2 from isobutyleneimine and dilute sulfuric acid [Cairns, *ibid.*, **63**, 871 (1941)]; and in the action of hydrogen chloride with isobutyleneimine and with 2,2-diphenylethyleneimine to form the tertiary chlorides [Campbell and Campbell, reported at the New York Meeting of the American Chemical Society, September, 1947].

[8] Paal and Hermann, *Ber.*, **22**, 3076 (1889).

[9] Ginzberg, *Ber.*, **36**, 2703 (1903), reported m. p. 40.5–41° for N-(benzenesulfonyl)-allylamine.

[10] Bergmann, Dreyer and Radt, *Ber.*, **54**, 2139 (1921), reported m. p. 135° for this compound. Abderhalden and Paquin, *ibid.*, **53**, 1125 (1920), who prepared the compound without recognizing its structure, found m. p. 130°.

chloride gave practically the same results. There was obtained 1.24 g. (96%) of dry unpurified product, m. p. 125–127°, and after crystallization, 0.85 g. (66%) of white crystals, m. p. 129–129.5°. There was no depression in the mixed melting point with 1-benzamido-2,3-dibromopropane.

2-Benzenesulfonamido-1,3-dibromopropane (IV) from 1-Benzenesulfonyl-2-bromomethylethyleneimine (II).—A stirred mixture of 63 ml. of 48% hydrobromic acid and 3.40 g. of 1-benzenesulfonyl-2-bromomethylethyleneimine (0.012 mole) was heated on the steam-bath under a condenser for three and one-half hours. After the addition of 100 ml. of water, the reaction mixture was cooled in an ice-bath and the solids collected, washed with cold water, and finally air-dried. This material (3.38 g. melting at 91–94.5°) was crystallized from carbon tetrachloride (decolorizing carbon used) to yield 3.0 g. (68%) of well-formed pure white crystals of 2-benzenesulfonyl-1,3-dibromopropane, m. p. 93–93.5°. The melting point was not raised by further recrystallization.

Anal. Calcd. for $C_9H_{11}NO_2SBr_2$: C, 30.3; H, 3.1. Found: C, 30.2; H, 3.0.

The mixed melting point with 1-benzenesulfonamido-2,3-dibromopropane was 70–80°; the mixed melting point with the starting material was 66–78°.

2-Benzenesulfonamido-1,3-dibromopropane (IV) from 2-Amino-1,3-dibromopropane (X).—The directions for the preparation of 1-benzenesulfonamido-2,3-dibromopropane from the corresponding amino-dibromide were followed. However, in this case the water-insoluble material formed in the reaction mixture was only semi-solid after forty-five minutes of stirring. The material was taken up in ether, the ethereal solution washed with water and dried over magnesium sulfate. Removal of all solvent left a colorless mobile oil possessing a strong odor of benzenesulfonyl chloride. The oil crystallized partially on standing; it was found that the addition of low-boiling petroleum ether containing a small amount of ether dissolved only the oily portion and allowed the solids to be collected. There was obtained white crystals, m. p. 87–94.5° (sintering at 65°) in 14% yield. Two crystallizations of this material from carbon tetrachloride yielded pure 2-benzenesulfonamido-1,3-dibromopropane (10%), which melted alone or mixed with the material prepared from 1-benzenesulfonyl-2-bromomethylethyleneimine at 93–93.5°. The mixed melting points with 1-benzenesulfonamido-2,3-dibromopropane and with 1-benzenesulfonyl-2-bromomethylethyleneimine were depressed 17° and 23°, respectively.

Attempts at improving the yield by allowing a longer period for reaction resulted in an oily mixture from which only a small amount of 1-benzenesulfonyl-2-bromomethylethyleneimine could be isolated. A longer reaction period, using bicarbonate instead of carbonate to preclude ring closure, yielded an oil from which no solid product could be obtained.

2-Amino-1,3-dibromopropane Hydrobromide (X).—A warm solution of 5.0 g. of barium hydroxide octahydrate (0.016 mole) in 40 ml. of water was added with stirring to a warm solution of 4.0 g. of 2-amino-1,3-dihydroxypropane oxalate[3] (containing 0.0294 mole of the aminoglycol) in 30 ml. of water. The mixture was filtered and the barium oxalate rinsed thoroughly with water. To remove the excess barium the combined filtrate and washings were saturated with carbon dioxide, then boiled for ten minutes to decompose bicarbonate, and filtered. After acidification of the filtrate with 5 ml. of 48% hydrobromic acid, all the solvent was removed by distillation under reduced pressure. More hydrobromic acid was added and again removed. The residual material dissolved in 23 ml. of hydrobromic acid was saturated at 0° with gaseous hydrogen bromide, and heated in a Carius tube for three hours at 165–175°.

The resulting dark-colored mixture, in which some carbonized material was present, was diluted with 200 ml. of water and treated with decolorizing carbon (Nuchar) to obtain a water-white solution. This was taken to dryness under reduced pressures on the steam-bath, absolute alcohol was added to the crystalline residue, and the volatile matter again removed. The crude product was dissolved in absolute alcohol, and after a small amount of insoluble ammonium bromide was removed, the solution was concentrated to the first appearance of solid and diluted with an excess of ethyl acetate. The white crystalline product was removed from the cooled mixture, washed with ethyl acetate and dried on the steam-bath. 2-Amino-1,3-dibromopropane hydrobromide, m. p. 152–157°, was obtained in a yield of 6.55 g. (75%). One crystallization from absolute alcohol–ethyl acetate (1 to 5) furnished 4.57 g. (52%) of crystals melting at 154–158° (preliminary sintering); a second crystallization gave 3.4 g. (39%) with m. p. 158–162° (preliminary sintering). The material in the mother liquors could be recovered and reworked.

A number of further recrystallizations, involving much loss of material, was necessary before constant melting point of 162–162.5° was reached.

Anal. Calcd. for $C_3H_8NBr_3$: C, 12.1; H, 2.7. Found C, 12.4; H, 2.9.

2-Amino-1,3-dibromopropane hydrobromide differed from the isomeric 1-amino-2,3-dibromopropane hydrobromide (m. p. 167–169.5°) in the crystal form and in solubility behavior (the former was very soluble in absolute alcohol, while the latter could be recrystallized from this solvent); the mixed melting point was depressed 30°.

The attempts at forming 2-amino-1,3-dibromopropane by boiling the amino-glycol with 48% hydrobromic acid and concentrated sulfuric acid, or with hydrobromic acid according to the directions for the conversion of ethanolamine to β-bromoethylamine hydrobromide,[11] failed.

Summary

1-Amino-2,3-dibromopropane and 2-amino-1,3-dibromopropane react with benzenesulfonyl chloride in the presence of aqueous sodium carbonate to form the normal derivatives, 1-benzenesulfonamido-2,3-dibromopropane and 2-benzenesulfonamido-1,3-dibromopropane, respectively. With free alkali the product from either amino-dibromide and benzenesulfonyl chloride, or from either normal benzenesulfonyl derivative is 1-benzenesulfonyl-2-bromomethylethyleneimine.

CAMBRIDGE, MASS. RECEIVED SEPTEMBER 9, 1947

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[11] Cortese, "Org. Syn.," Coll. Vol. II (1943), p. 91.