Benzothiazoline Derivatives. I. Reaction of 2-Benzothiazolinethione with Ethylene Oxide. (1)

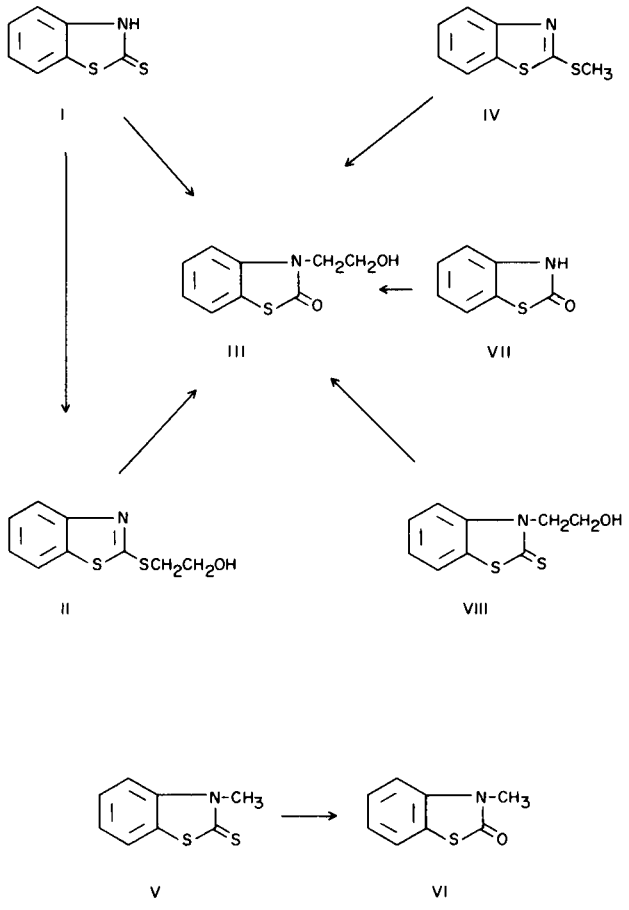
Paul Sohar, George H. Denny, Jr., and Robert D. Babson

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc.

Treatment of 2-benzothiazolinethione with excess ethylene oxide in acetic acid resulted in *N*-hydroxyethylation and thiono-oxo replacement to give 3-(2-hydroxyethyl)-2-benzothiazolinone. This product was also obtained when *S*-alkylthiobenzothiazoles were treated in this way. Similar treatment of the *N*-substituted compounds 3-methyl-2-benzothiazolinethione and 3-(2-hydroxyethyl)-2-benzothiazolinethione gave simple thiono-oxo replacement.

2-Benzothiazolinethione (I) customarily undergoes *S*-alkylation under a variety of conditions, exceptions being Mannich-type reactions (2) and vinyl additions (3,4,5) both of which lead to *N*-substituted derivatives. In a recent publication (6), it was shown that additions of various 4-thiazoline-2-thiones to activated vinyl compounds take place at either the *S*- or *N*-atom, or at both, in accordance with suitable modifications of the reaction conditions. Ethylene oxide is known to effect the *S*-hydroxyethylation of I in dioxane or diethyl carbitol (7), as predicted on the basis of its demonstrated reactivity with thiols (8) and thiol acids (9). We now wish to report an interesting instance of *N*-hydroxyethylation of 2-benzothiazolinethione (I) by ethylene oxide in acetic acid accompanied by replacement of the exocyclic sulfur atom by oxygen to give 3-(2-hydroxyethyl)-2-benzothiazolinone (III).

This was accomplished by using a ten-fold molar excess of ethylene oxide in solution at room temperature overnight. Shortening of the reaction time to one hour or the use of an equimolar amount of ethylene oxide gave the known 2-hydroxyethylthio compound II (7, 10, 11), as did the use of methanol as the solvent. To substantiate structure III, 2-benzothiazolinone (VII) was refluxed with 2-bromoethanol in the presence of aqueous sodium hydroxide. The resultant product III (21% yield) was identical with the sample obtained from compound I. A strong absorption at 6.05 μ (C=O) in the infrared spectrum supported the structural assignment of the product.



The possibility that the transformation I → III may proceed by way of the intermediate II suggested that the latter be subjected to the same conditions. This gave III with either excess or approximately equimolar amounts of ethylene oxide. After standing overnight alone in acetic acid, compound II was recovered unchanged, thereby eliminating the possibility of direct solvent interaction at this stage. Simple heating of II was reported by

Sexton (10) to give 2-benzothiazolinone (VII). This has been confirmed in attempts to bring about thermal rearrangement of II under various conditions. Pathways to III involving VII as an intermediate were eliminated by treating VII with ethylene oxide in acetic acid, as described, or in ethanol. After treatment, VII was recovered unchanged in either case. Experiments designed to ascertain the form in which sulfur was eliminated during the ethylene oxide reactions were largely inconclusive, principally due to the formation of polymeric residues which probably contain the sulfur-bearing by-products. It was determined, however, that the volatile portion of the reaction mixtures contained no hydrogen sulfide or thiol compounds. Apparently, if such compounds formed they reacted further with either the solvent or the excess ethylene oxide present in the reaction mixtures. Oxidative hydrolysis is known (12) to convert I to its corresponding oxo analog VII, suggesting that the thiono-oxo replacement (I → III) may have occurred during purification. Attempts to preserve the exocyclic sulfur function during hydroxyethylation by treatment of the reaction mixture with aqueous solutions of either sodium sulfide or sodium hydrosulfide did not alter the course of the reaction. In this connection it may be noted that compound VIII (13), a possible intermediate, was converted to III under the conditions of the reaction.

The generality of the ethylene oxide reaction was further demonstrated by its application to the isomeric *S*- and *N*-methyl derivatives, IV and V (14). In this way, the *S*-methyl compound (IV) was converted to compound III in 29% yield. Compound V, under the same conditions, gave its oxo analog VI in 88% yield (acetic acid alone had no effect on I, IV, V, or VIII). The latter reaction demonstrates the ability of ethylene oxide to function as a reagent for the replacement of exocyclic sulfur by oxygen in the *N*-substituted benzothiazolinethione series.

EXPERIMENTAL (15)

3-(2-Hydroxyethyl)-2-benzothiazolinone (III).

Method A.

A stirred suspension of 50.0 g. (0.299 mole) of 2-benzothiazolinethione (I) in glacial acetic acid (1 l.) was cooled to 10° and to this was added 150 ml. (3.0 moles) of ethylene oxide which had been condensed at the temperature of a dry ice-acetone bath. The temperature was allowed to rise to room temperature (1 hour), resulting in a clear solution. After stirring overnight the excess ethylene oxide was driven off (nitrogen) and the solvent removed *in vacuo*. The oily residue was next partitioned between equal volumes (1.5 l.) of water and ether. The aqueous layer was back extracted and the combined ether layers dried (saturated aqueous sodium chloride), decolorized (Darco G-60), and dried again (sodium sulfate). The gum obtained after solvent removal was triturated with petroleum ether (30-60° b.p.) to give 52 g. of crude solid. This was dissolved in 2 l. of warm ether, treated with Darco G-60, and the filtrate carefully reduced in volume to 150 ml. by warming and stirring the solution at atmospheric pressure. The resultant slurry was chilled for two hours, then collected by filtration to give 34.7 g. (yield 60%), m.p. 89-92°; nmr (pyridine-d_5); τ 2.5-3.1 (multiplet, 4-H, C_6H_4), 3.4-3.8 (singlet, 1-H, hydroxyl, exchanged with deuterium oxide), 5.6-6.1 ppm (A_2B_2 multiplet, 4-H, CH_2CH_2): ultraviolet spectrum; λ max (MeOH), 215 (ϵ, 44,000), 246 (ϵ, 5,680), 283 (ϵ, 2,790), 290 mμ (ϵ, 2,830); infrared spectrum: 2.85, 6.05, 6.25, 7.50, 13.10 μ.

Anal. Calcd. for $C_9H_9NO_2S$: C, 55.37; H, 4.65; N, 7.18; S, 16.42. Found: C, 55.12; H, 4.61; N, 7.27; S, 16.60.

Method B.

To a suspension of 28.0 g. (0.185 mole) of 2-benzothiazolinone (VII) in 250 ml. of ethanol was added 7.4 g. (0.185 mole) of sodium hydroxide in 70 ml. of water, followed by 46.4 g. (0.37 mole) of 2-bromoethanol. The resulting solution was heated under reflux for 2 hours and concentrated to dryness *in vacuo*. The residue was evaporated twice *in vacuo* with water and suspended in 500 ml. of water containing 7 g. of sodium hydroxide. The solid was collected, washed with water, and air-dried to give 7.8 g. of solid, m.p., 85-88°. Methylene chloride extraction of the combined aqueous mother liquors and washes gave an additional 8 g. of crude product. The combined crops were dissolved in methylene chloride (1 l.), washed with 1.4 *N* sodium hydroxide and saturated sodium chloride, then dried (sodium sulfate). The solution was concentrated *in vacuo* and the product dissolved in 500 ml. of ether. This was decolorized with Darco G-60 and the filtrate reduced in volume to the point of cloudiness (400 ml.). After cooling, the white crystals were washed with ether and petroleum ether, then dried to give 7.4 g. (yield 21%) of pure III; m.p. and mixture m.p. with material obtained by Method A: 89-92°. Samples obtained by the two methods had identical uv, ir, and nmr spectra.

Conversion of 2-(Methylthio)benzothiazole (IV) to 3-(2-Hydroxyethyl)-2-benzothiazolinone (III).

Freshly condensed ethylene oxide (5 ml., 0.1 mole) was added to a solution at 10° containing 0.8 g. (4.4 mmoles) of 2-(methylthio)benzothiazole (IV) in 40 ml. of glacial acetic acid. This was allowed to stand overnight at room temperature. Concentration *in vacuo* gave an oil, which was dissolved in methylene chloride, washed with 0.5 *N* sodium hydroxide, then with water, and dried over sodium sulfate. The solution was evaporated to dryness and the residue triturated with ether-petroleum ether to give 0.25 g. (yield 30%) of III, shown to be the same as an authentic sample by mixture melting point and comparison of infrared spectra.

Conversion of 3-Methyl-2-benzothiazolinethione (V) to 3-Methyl-2-benzothiazolinone (VI).

The procedure used was similar to that used for the conversion of IV to III, described above. One gram (5.5 mmoles) of V and 6 ml. (0.12 mole) of ethylene oxide in 40 ml. of glacial acetic acid gave 0.8 g. (yield 88%) (triturated with petroleum ether) of VI, m.p., 73-75°; lit., 74° (16). An authentic sample was prepared according to a literature method (16) and found to be identical by means of mixture melting point, and comparison of uv and ir spectra.

Conversion of 3-(2-Hydroxyethyl)-2-benzothiazolinethione (VIII) to 3-(2-Hydroxyethyl)-2-benzothiazolinone (III).

The procedure used was similar to Method A. One gram (4.7 mmoles) of VIII (13) and 5 ml. (0.10 mole) of ethylene oxide in 40 ml. of glacial acetic acid gave an oil which was partitioned

between 50 ml. of water and 100 ml. of ether. After back extraction and washing, the product was triturated with petroleum ether (30-60° b.p.) and petroleum ether-ether to give 0.6 g. (yield 71%) of III, identical to authentic material as indicated by mixture melting point, and comparison of uv and ir spectra.

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