Potential Antiradiation Agents.[1] Preparation and Polymerization of N-Vinyl-2-thiazolidinone[2,3]

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N-Vinyl-2-thiazolidinone (VI) has been prepared both by the Cope degradation of N-(2-dimethylethylamino)-2-thiazolidinone (IV) and by dehydrohalogenation of N-(2-chloroethyl)-2-thiazolidinone (V). VI is readily polymerized by radical catalysts to a white solid which softens at about 275°. Attempts to hydrolyze the polymer to poly[N-(2-mercaptoethyl)vinylamine] proved unsuccessful. VI was copolymerized with N-vinylpyrrolidone and reactivity ratios were calculated. The Alfrey–Price equations were used to determine Q- and e-values for VI.

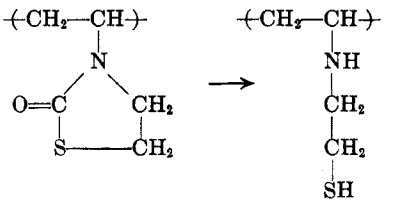
2-Aminoethanethiol and several of its S-substituted derivatives,[6] such as S-2-aminoethyl thiosulfuric acid, are well known type structures which protect against ionizing radiation in experimental animals, as are the corresponding S-3-aminopropyl derivatives.[7,8] The need for effective agents possessing longer duration of protective action has prompted the synthesis and study of structural variations of these known active compounds.

Very few polymers have been prepared as potential radioprotective agents. It has been shown in this laboratory, however, that synthetic polythiols which are effective in reactivating enzymes inactivated by chemical oxidation are relatively good protective agents for mice exposed to lethal doses of X-ray radiation. Specifically, a copolymer of *p*-vinylphenyl thiol acetate[9] and methyl methacrylate, hydrolyzed to liberate the free sulfhydryl groups, was found to be effective, as was the hydrolyzed copolymer of vinylene carbonate and vinyl thiol acetate.[10]

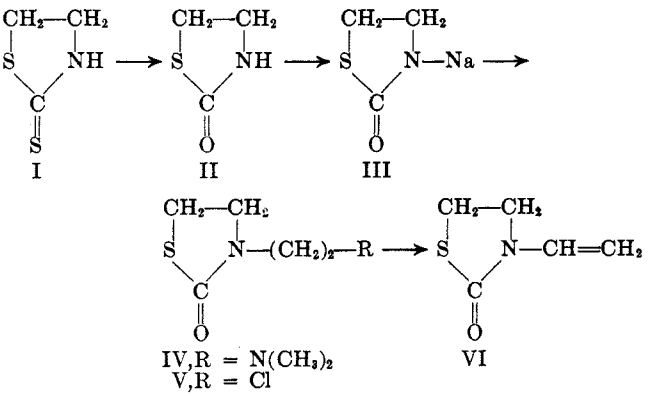
In the hope of increasing the protection without increasing toxicity, we have undertaken the preparation of polymeric analogs of 2-mercaptoethylamine and 3-mercaptopropylamine.

Although a variety of synthetic polythiols[11] and polyamines[12] have been prepared, there are no known polymers incorporating both these functional groups. An obvious approach to synthetic polymeric mercaptoamines, then, would consist in the copolymerization of a monomer containing the sulfhydryl group which is protected by a subsequently removable blocking group with a monomeric amine or protected amine. This method is considered undesirable, however, for it would yield a polymeric material in which the position and environment of the sulfhydryl and amine residues relative to one another could in no way be predetermined. Further it would be virtually impossible in this way to prepare a polymer in which the two functional groups were in a β-position to each other. It was deemed desirable then, to prepare a monomeric heterocycle of sulfur and nitrogen—a heterocycle which was amenable to ring opening in such a way as to result in the formation of the 2-aminoethanethiol moiety. This paper describes the preparation and polymerization of N-vinyl-2-thiazolidinone (VI).

Schöberl[13] and co-workers have reported that the parent compound, 2-thiazolidinone (II), is readily hydrolyzed to 2-aminoethanethiol on treatment with mineral acid. It seemed reasonable to assume, then, that hydrolysis of poly(N-vinyl-2-thiazolidinone) could yield a polymeric mercaptoamine in which the amino group is covalently bound to the main chain and in a β-position to the sulfhydryl function.



N-Vinyl-2-thiazolidinone was prepared by the reaction sequence shown. 2-Thiazolidinone (II) was prepared in 50% yield by oxidation of commercially available 2-thiazoline-2-thiol (I) with yellow mercuric oxide in glacial acetic acid. Conversion of II to N-sodio-2-thiazolidinone (III) on treatment with a molecular equivalent of sodium sand was found to occur quite



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(3) This is the 27th in a series of papers concerned with the preparation and properties of new monomers and polymers; for the previous paper in this series, see C. G. Overberger and W. H. Daly, *J. Org. Chem.*, **29**, 757 (1964).

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(5) This article is taken from the dissertation of B. Avchen submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy (chemistry).

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(11) For a review, see C. G. Overberger, J. J. Ferraro, P. V. Bonsignore, F. W. Orttung, and N. Vorchheimer, *Pure Appl. Chem.*, **4**, 521 (1962).

(12) C. E. Schildknecht, "Vinyl and Related Polymers," John Wiley and Sons, Inc., New York, N. Y., 1952.

(13) A. Schöberl, M. Kawohl, and G. Hansen, *Ann.*, **614**, 83 (1958).

readily in anhydrous tetrahydrofuran. Treatment of III with N,N-dimethyl-2-chloroethylamine resulted in precipitation of sodium chloride with the formation of N-(2-dimethylethylamino)-2-thiazolidinone (IV).

Alkylation of IV with methyl iodide in ether afforded the quaternary methiodide in 90% yield. An initial attempt to degrade the methiodide according to standard Hofmann degradation procedures[14] with silver oxide resulted in extensive decomposition with no product formation. Similarly, decomposition occurred when an ion-exchange resin (Amberlite IRA-400) was used to generate the quaternary hydroxide. These results are interpreted as being due to hydrolysis of the thiazolidinone heterocycle under the basic conditions of pyrolysis.

N-(2-Dimethylethylamino)-2-thiazolidinone (IV) was converted to its N-oxide with 30% hydrogen peroxide in methanol solution. Evaporation of the solvent and pyrolysis of the resultant viscous sirup under vacuum afforded a 15% yield of N-vinyl-2-thiazolidinone (VI). That the yield of the monomer is as low as it is may be due in part to a competitive oxidation whereby the ring sulfur is oxidized to a sulfone by the hydrogen peroxide. Gaul and Fremuth[15] have in fact reported that 2-oxa-3-thiazolidinepropionamide is converted to 2-oxa-3-thiazolidinepropionamide 1,1-dioxide in 14.5% yield on treatment with 30% hydrogen peroxide.

Reaction of III with 1-bromo-2-chloroethane gave a 35% yield of N-(2-chloroethyl)-2-thiazolidinone (V) which was found to be contaminated with a small amount of N-(2-bromoethyl)-2-thiazolidinone, determined by sodium fusion. Repeated vacuum distillation failed to result in analytically pure V. Preparative vapor phase chromatography proved impractical for purposes of separation because of the comparative nonvolatility of the liquid. V was easily dehydrohalogenated by the dropwise addition of an equimolar solution of potassium *t*-butoxide in *t*-butyl alcohol to give the monomeric thiazolidinone (VI) in 35% yield. The over-all yield from I is 6%.

VI polymerized readily in the presence of radical initiators in bulk or in solution. Azobisisobutyronitrile was the most effective initiator tried, giving nearly quantitative conversions in twenty hours when the monomer was polymerized at 60° in bulk. Bulk polymerizations catalyzed by benzoyl peroxide generally gave conversions of less than 50%; solution polymerizations in benzene using azobisisobutyronitrile as initiator resulted in precipitation after a few hours at 60°.

The polymer isolated is a white solid, softening at 265–285°. It is totally insoluble in water, although similar homopolymers of N-vinyl-2-oxazolidinone of molecular weights up to 100,000 are reported[16] to be water soluble. This polymer, in fact, is found to be soluble in dimethylformamide and concentrated sulfuric acid only.

The possibility of hydrolyzing poly(N-vinyl-2-thiazolidinone) to poly[N-(2-mercaptoethyl)vinylamine] was studied in some detail. After refluxing a 10% slurry of the polymer in 10% hydrochloric acid for several hours the polymer was recovered essentially unchanged. Similar treatment in constant-boiling or concentrated hydrochloric acid also resulted in no carbon dioxide evolution and the polymer was again recovered. Treatment of a solution of the polymer in dimethylformamide with a concentrated sodium hydroxide solution at room temperature failed to result in any reaction; at elevated temperatures (50°) a quantitative yield of what proved to be sodium formate precipitated from the solution.

N-Vinyl-2-thiazolidinone (M_1) was copolymerized with N-vinylpyrrolidone (M_2). Conversions were kept low in order that reactivity ratios could be calculated.[17] As a result of these copolymerizations it was determined that $r_1 = 0.52 \pm 0.10$ and $r_2 = 0.62 \pm 0.07$.

The Alfrey–Price equations[18] were used to calculate the Q- and e- values for VI[19]; values of $Q = 0.10$ and $e = 0.80$ were obtained.[20]

Experimental[21]

2-Thiazolidinone (II).—An intimate mixture of 59.6 g. (0.50 mole) of 2-thiazoline-2-thiol and 108.3 g. (0.50 mole) of yellow mercuric oxide was added to 2.0 l. of glacial acetic acid. The reaction mixture immediately turned white. The mild exotherm was allowed to subside and the addition was repeated three times. The reaction mixture was held at reflux for 24 hr. After 10 min. of heating, the suspension turned black. The mixture was vacuum filtered and the filtrate was concentrated to a viscous sirup from which crystals had begun to separate. The crude 2-thiazolidinone was distilled under reduced pressure. The distilled product, b.p. 86° (0.04 mm.), solidified in the receiver and weighed 102 g. (49.5%). The white solid melted at 51–53° (Crawhall and Elliott[22] give m.p. 54° and b.p. 160° at 20 mm., while Michels and Gever[23] report m.p. 50–52° and b.p. 138–138.5° at 2.5 mm.).

N-(2-Dimethylethylamino)-2-thiazolidinone (IV).—To freshly prepared sodium sand[24] (9.0 g., 0.39 g.-atom) suspended in 500 ml. of anhydrous tetrahydrofuran there was added 40.7 g. (0.39 mole) of 2-thiazolidinone in 300 ml. of tetrahydrofuran at such a rate that the temperature did not rise above 40°. When the exotherm had subsided there was added all at once 42.0 g. (0.39 mole) of freshly distilled N,N-dimethyl-2-chloroethylamine and the resultant slurry was refluxed overnight. The precipitated sodium chloride was removed by filtration and washed with additional solvent. The combined filtrates were concentrated under vacuum; the residue was distilled under reduced pressure to give 27.7 g. (41%) of pure product, b.p. 80° (0.07 mm.), $n^{25}D$ 1.5218.

Anal. Calcd. for $C_7H_{14}N_2OS$: C, 48.24; H, 8.10; N, 16.08; S, 18.40. Found: C, 48.24; H, 7.75; N, 15.68; S, 18.94.

N-(2-Dimethylethylamino)-2-thiazolidinone Methiodide.—A solution of methyl iodide (14.2 g., 0.10 mole) in 40 ml. of ether was added to a solution of IV (17.3 g., 0.099 mole) in 60 ml. of ether and the solution was stirred at room temperature overnight. The precipitated salt was suction filtered, washed with ether, and dried under vacuum giving 28.4 g. (90%) of methiodide, m.p. 134.5–136° dec. (from ethanol).

Anal. Calcd. for $C_8H_{17}IN_2OS$: C, 30.39; H, 5.42. Found: C, 30.30; H, 5.37.

N-Vinyl-2-thiazolidinone (VI).—**A. From IV.**—A solution of N-(2-dimethylethylamino)-2-thiazolidinone (5.2 g., 30 mmoles)

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(16) E. K. Drechsel, *ibid.*, **22**, 849 (1957).

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(18) T. Alfrey, J. J. Bohrer, and H. Mark, "Copolymerization," Interscience Publishers, Inc., New York, N. Y., 1952, Chapters 3 and 4.

(19) Q- and e- values of 0.093 and −1.17, respectively, were used for the comonomer, N-vinylpyrrolidone.[20]

(20) J. F. Bork and L. E. Coleman, *J. Polymer Sci.*, **43**, 413 (1960).

(21) All melting points are uncorrected; analyses are by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., and by Alfred Bernhardt, Mikroanalytisches Laboratorium in Max-Planck-Institut fur Kohlenforschung, Mülheim (Ruhr), West Germany.

(22) J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 3094 (1952).

(23) J. G. Michels and G. Gever, *J. Am. Chem. Soc.*, **78**, 5349 (1956).

(24) R. Kempf, "Houben-Weyl, Methoden der Organischen Chemie," Vol. 2, E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1925, p. 748.

in 10 ml. of methanol was cooled to 0° and 30% hydrogen peroxide (10.2 g., 90 mmoles) was added over a period of 30 min. The solution was allowed to come to room temperature and stand for 24 hr., at the end of which time it was neutral to Universal Indicator. To the solution there was then added 0.25 g. of platinum asbestos, and stirring was continued for 24 hr. The slurry was filtered and the filtrate was subjected to vacuum distillation. The water and methanol were removed at 30–40° (10–100 mm.) resulting in a viscous sirup. The temperature was then carefully raised to 130–140° (3–4 mm.) at which point decomposition ensued. The pyrolysate was distilled under reduced pressure giving 0.6 g. (15%) of water-white liquid, b.p. 55° (0.10 mm.), $n^{25}D$ 1.5625. An infrared spectrum of the product showed strong N-vinyl absorption at 1645 cm.$^{-1}$.

Anal. Calcd. for C_5H_7NOS: C, 46.49; H, 5.46; N, 10.84; S, 24.82. Found: C, 46.40; H, 5.60; N, 10.89; S, 24.80.

B. From V.—To freshly prepared sodium sand (11.5 g., 0.50 g.-atom) suspended in 800 ml. of anhydrous tetrahydrofuran there was added 51.6 g. (0.50 mole) of II in 300 ml. of tetrahydrofuran at such a rate that the temperature did not rise above 40°. When the exotherm had subsided there was added all at once 143.4 g. (1.0 mole) of 1-bromo-2-chloroethane. After the initial mild exotherm had subsided, the reaction mixture was refluxed for 24 hr. The slurry was vacuum filtered and the filter cake was washed with additional solvent. The combined filtrates were concentrated under vacuum; the residue was distilled under reduced pressure. The fraction distilling at 100–110° (0.5 mm.) was collected and used as such, 29 g. (35%). To a solution of 52 g. (0.31 mole) of N-(2-chloroethyl)-2-thiazolidinone dissolved in 100 ml. of absolute *t*-butyl alcohol and warmed to 60° there was slowly added a previously prepared solution of 13 g. (0.33 g.-atom) of potassium metal in 600 ml. of *t*-butyl alcohol. The reaction mixture was heated at reflux overnight, neutralized with glacial acetic acid, and filtered. The filter cake was washed with ether and the combined filtrates were concentrated under vacuum. The residue was distilled under reduced pressure to give 14 g. (35%) of product with physical constants and infrared spectrum identical to that obtained *via* the Cope degradation of IV.

Poly(N-vinyl-2-thiazolidinone). A. Polymerization in Bulk.—A thick-walled, Pyrex, cappable tube was charged with 10 g. (0.08 mole) of freshly distilled N-vinyl-2-thiazolidinone and 50 mg. (0.5 wt. %) of α,α'-azobisisobutyronitrile. The polymer tube was alternately evacuated and flushed with dry nitrogen three times and then sealed under vacuum. The charged tube was maintained at 60° in an oil bath for 24 hr. The resultant polymer plug, which was triturated with ethanol to separate unreacted monomer, was dissolved in 50 ml. of dimethylformamide, reprecipitated by adding dropwise to a 10:1 excess of methanol, filtered, and dried under vacuum. The product, 9.7 g. (97%), was a white solid: softening range 265–285°; $[\eta]$ 0.35, determined in dimethylformamide at 29.2°.

Anal. Calcd. for $(C_5H_7NOS)_n$: C, 46.49; H, 5.46; N, 10.84; S, 24.82. Found: C, 46.20; H, 5.50; N, 10.81; S, 24.59.

B. Solution Polymerization.—A solution of 1.0 g. of IV in 5.0 ml. of anhydrous benzene was polymerized at 60° with 5 mg. of α,α'-azobisisobutyronitrile as initiator. After a 3-hr. period, polymer had precipitated from solution. The insoluble material was filtered and washed with benzene. "Work-up" was effected as described to yield 0.55 g. (55%), η_{rel} (1% in dimethylformamide) 1.25.

Copolymerization of N-Vinyl-2-thiazolidinone with N-Vinylpyrrolidone.—The monomers were freshly distilled and weighed directly in the polymerization tubes which were then immersed in an acetone–Dry Ice bath and evacuated by means of an oil pump while intermittently flushing with dry nitrogen gas. The tubes were sealed under vacuum and then placed in a constant temperature bath (65°). α,α'-Azobisisobutyronitrile was employed as the free-radical source in a concentration of 0.3–0.4% by weight in each case. The contents of each tube was diluted to approximately one half its initial volume with anhydrous benzene. The polymers were precipitated by addition to cold anhydrous ether. Purification was effected by reprecipitation from dimethylformamide with the same precipitating nonsolvent. The purified polymers were dried under vacuum to constant weight, and the compositions were determined by elemental analysis. The reactivity ratios were calculated using the method of Mayo and Lewis.[17]

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trans,trans-2,8-*trans*-Bicyclo[8.4.0]tetradecadiene[1]

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trans,trans-2,8-*trans*-Bicyclo[8.4.0]tetradecadiene (**7**) has been prepared and characterized. It can be obtained in *ca.* 15% yield by zinc fragmentation of a mixture of 9,10-dibromo-*trans,syn,trans*-perhydroanthracenes.

We are here reporting a synthesis of *trans,trans*-2,8-*trans*-bicyclo[8.4.0]tetradecadiene (**7**), a study of which may contribute to our knowledge of the stereochemistry of acid-catalyzed cyclizations of 1,5-dienes.[2] It was anticipated that, unlike *trans,trans*-1,5-cyclodecadiene,[3] **7** would be thermally stable through degeneracy of the Cope rearrangement,[4] and the 1,5-cyclodecadiene moiety of **7** would therefore be susceptible to investigation under conditions not otherwise feasible. A discussion of the reactions of **7** will follow.

The projected synthesis was based on the possibility of fragmenting a 9,10-dibromo-*trans,syn,trans*-perhydroanthracene (*e.g.*, **4** → **7**) in a manner analogous to that reported for *cis*- and *trans*-1,4-dibromocyclohexanes, using metals, notably zinc.[5] Control over the stereochemistry of the double bonds formed in the fragmentation was anticipated from the choice of stereochemistry of the disubstituted perhydroanthracene.[5] Our preconception of the mechanism of fragmentation involved the formation of intermediate **6**[5] which is most simply derived from the corresponding *trans*(*e,e*) dibromide. The *cis*(*e,a*) dibromide **4** can also lead directly to **7** if the axial (but not the equatorial) bromine is replaced by zinc.[6] A convenient route to one or both of these dibro-

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(2) For reviews see W. S. Johnson, *Pure Appl. Chem.*, **7**, 317 (1963); A. Eschenmoser, D. Felix, M. Gut, J. Meier, and P. Stadler, *Ciba Found. Symp. Biosyn. Terpenes Sterols*, 217 (1959).

(3) C. A. Grob, H. Link, and P. W. Schiess, *Helv. Chim. Acta*, **46**, 483 (1963).

(4) Several examples of this phenomenon are discussed by W. von E. Doering and W. R. Roth, *Angew. Chem., Intern. Ed. Engl.*, **2**, 115 (1963).

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(6) Assuming configurational lability of the carbon–zinc bond.