(±)-*cis*-2-Phenylcyclopropylamine was less active in inhibiting the plasma enzyme than the (±)-*trans* isomer. Harmine again made a poor showing. It inhibited the deamination of benzylamine by beef plasma MAO to only 10% at 3.2×10^{-5} *M*. Higher concentrations could not be measured spectrophotometrically[17] because of the interference of optical absorption by the alkaloid.

The tertiary 2-phenylcyclopropylamine derivative II and the propargylamine III, which inhibit the mitochondrial enzyme at very low concentrations (Table III), did not affect the deamination of benzylamine by beef plasma MAO below 8 and 4×10^{-4} *M*, respectively. At higher concentrations of these two compounds, an apparent reversal of inhibition values was observed repeatedly in our test system.[17]

Acknowledgment.—We acknowledge with pleasure helpful suggestions and advice by Professor Kerry T. Yasunobu in the course of our work. We are grateful to the National Institute of General Medical Sciences, National Institutes of Health, for financial support.

Notes

Potential Antiradiation Agents.[1a] Preparation and Polymerization of Monomeric Thiazolidines[1b,c]

C. G. OVERBERGER, H. RINGSDORF, AND B. AVCHEN[1d]

Department of Chemistry, Institute of Polymer Research, Polytechnic Institute of Brooklyn, Brooklyn, New York 11201

Received May 17, 1965

Because the major shortcoming of present radioprotective agents is their relatively short-lived protection, we have undertaken to prepare compounds that may act as sources of molecular entities of proven protective capacity; that is, compounds so designed that they would slowly release moieties such as 2-mercaptoethylamine and cysteine under physiological conditions, and in so doing provide a long-lasting source of radioprotective agent in nontoxic amounts.

Since the thiazolidine heterocycle is readily cleaved to α-amino-β-thiols under mild hydrolytic conditions,[2] we herein report the preparation of polymeric thiazolidines of 2-mercaptoethylamine and cysteine. The synthetic method employed is outlined in Scheme I.

2,2-Dimethylthiazolidine (I) was prepared by treating a solution of ethylenimine in acetone with gaseous hydrogen sulfide according to the method of Bestian.[3] 4-Carbomethoxy-2,2-dimethylthiazolidine (VII) was prepared by the more conventional method of condensing cysteine methyl ester hydrochloride with acetone, followed by liberation of the free amine with aqueous sodium carbonate.[4]

N-Acrylyl-2,2-dimethylthiazolidine (II) and N-acrylyl-4-carbomethoxy-2,2-dimethylthiazolidine (VIII) were prepared by acylation of I and VII, respectively, with acrylyl chloride in the presence of trimethylamine as the acid acceptor. The yields of the acrylamide were 61.5 and 60%, respectively. Treatment of I with S-β-chloroethyl chlorothiolformate[6] afforded a 71.5% yield of IV which readily underwent dehydrochlorination with 1 molecular equiv. of potassium *t*-butoxide in *t*-butyl alcohol to afford the S-vinylmonothiolcarbamate V.

The monomeric thiazolidines (II, V, and VIII) thus prepared were homopolymerized to high conversion using α,α′-azobisisobutyronitrile as initiator. While the polymeric acrylamides III and IX may conceivably act as a source of 2-mercaptoethylamine and cysteine, respectively, the polymeric monothiolcarbamate VI may be expected to undergo metabolic hydrolysis with the formation of polyvinylmercaptan (itself a radioprotective agent[7,8]) as well as resulting in the liberation of 2-mercaptoethylamine.

It has been determined that polyvinylpyrrolidone is capable of complexing toxic radiation products and hastening excretion in the urine.[9] The monomeric thiazolidines were therefore copolymerized with N-vinylpyrrolidone in the hope that the copolymers might combine effects with the absorptive ability exhibited by polyvinylpyrrolidone. A further desirable feature of the copolymers is their water solubility.

It is worthy of note that after this research was begun a report was published[10] relating to the fact that some thiazolidines were as effective in protecting against ionizing radiation as is 2-mercaptoethylamine. Indeed, it has been found[11] that a copolymer consisting of 18 mole % V and 82 mole % N-vinylpyrrolidone was effective in protecting experimental rats at a dosage of 150 mg./kg. of body weight.

(1) (a) Supported by Contract No. DA-49-193-MD-2032 from the United States Army Medical Research and Development Command, Office of the Surgeon General. (b) Presented at the 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962. (c) This is 28th 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, H. Ringsdorf, and B. Avchen, *J. Org. Chem.*, **30**, 232 (1965). (d) 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).

(2) E. D. Bergmann, *Chem. Rev.*, **53**, 309 (1953).

(3) H. Bestian, *Ann.*, **566**, 210 (1950).

(4) Acetone was chosen as the condensing agent in each case because of the reported[5] greater ease of fission of 2,2-dimethylthiazolidines (as opposed to 2-phenylthiazolidines, for example).

(5) "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, Chapter 25.

(6) H. Ringsdorf and C. G. Overberger, *Makromol. Chem.*, **44**, 418 (1961).

(7) C. G. Overberger and A. Lebovits, *J. Am. Chem. Soc.*, **77**, 3675 (1955).

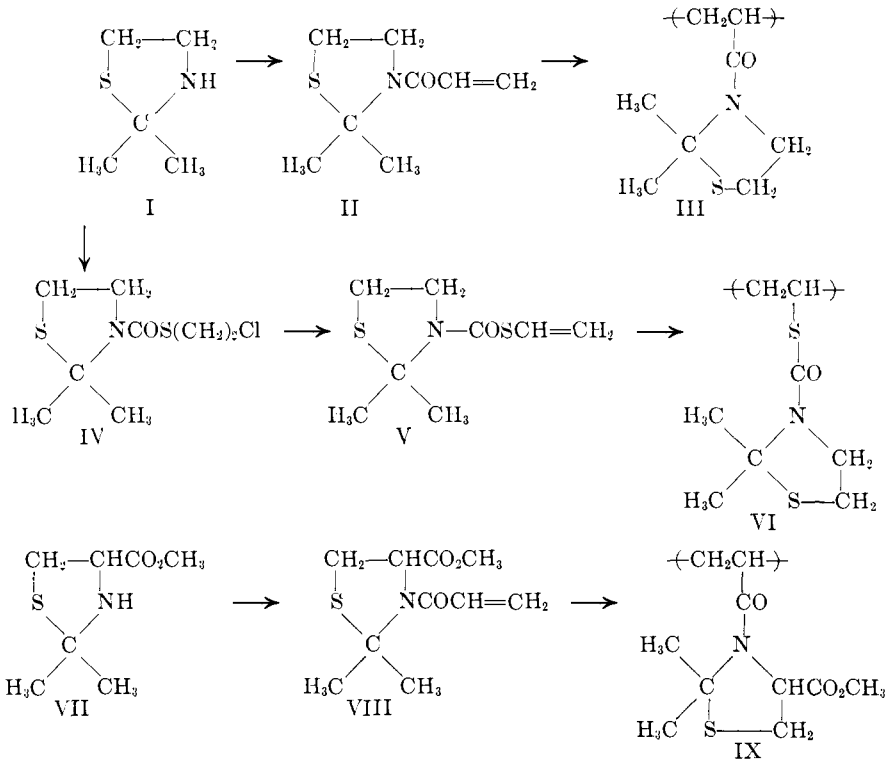
(8) C. G. Overberger, H. Biletch, and R. G. Nickerson, *J. Polymer Sci.*, **27**, 381 (1958).

(9) L. Sukyasyan, *Probl. Gematol. i. Pereliv. Krovi*, **4**, 48 (1959).

(10) A. Kaluszyner, P. Czerniak, and E. D. Bergmann, *Radiation Res.*, **14**, 23 (1961).

(11) Private communication to the authors from Dr. P. Coad, Walter Reed Army Institute of Research, Department of Medicinal Chemistry.

SCHEME I



Experimental Section[12]

N-Acrylyl-2,2-dimethylthiazolidine (II).—To a solution of 24.0 g. (0.20 mole) of 2,2-dimethylthiazolidine and 20.7 g. (0.20 mole) of triethylamine in 150 ml. of anhydrous ether and cooled to 0°, there was added dropwise a solution of 18.5 g. (0.20 mole) of acrylyl chloride in 50 ml. of ether. The reaction mixture was stirred overnight at room temperature and the precipitated triethylamine hydrochloride was filtered off and washed with additional solvent. The combined filtrates were washed with two 50-ml. portions of cold 2 *N* H_2SO_4, neutralized with dilute $NaHCO_3$ solution, washed again with water, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was distilled under reduced pressure; yield 21.6 g. (61.5%), b.p. 60° (0.1 mm.), $n^{24}D$ 1.5329.

Anal. Calcd. for $C_8H_{13}NOS$: C, 56.10; H, 7.65; N, 8.18; S, 18.72. Found: C, 56.37; H, 7.61; N, 7.98; S, 18.52.

Poly(N-acrylyl-2,2-dimethylthiazolidine) (III).—A thick-walled Pyrex cappable tube was charged with 8.0 g. (47 mmoles) of II and 27 mg. of α,α'-azobisisobutyronitrile dissolved in 15 ml. of dry benzene. The polymerization tube was alternately evacuated and flushed with dry nitrogen three times and then sealed under vacuum. The solution was heated at 60° for 3 hr. An additional 30 ml. of benzene was added to the polymer mass and the polymer was precipitated by adding dropwise to a 10:1 excess of cold pentane. Purification was effected in like manner. The reprecipitated polymer weighed 6.5 g. (81%) and softened at 235–250°, [η] 0.72 determined in benzene at 29.2°.

Anal. Calcd. for $(C_8H_{13}NOS)_n$: C, 56.10; H, 7.65. Found: C, 56.20; H, 7.61.

Condensation of I with S-β-Chloroethyl Chlorothiolformate (IV).—The procedure described for the preparation of II was employed. Treatment of 23.4 g. (0.20 mole) of I with 31.8 g. (0.20 mole) of S-β-chloroethyl chlorothiolformate[6] in the presence of 20.2 g. (0.20 mole) of triethylamine afforded 34.3 g. (71.5%) of IV as a water white liquid, b.p. 90° (0.1 mm.), $n^{25}D$ 1.5560.

Anal. Calcd. for $C_8H_{14}ClNOS_2$: C, 40.07; H, 5.89; Cl, 14.78; N, 5.84; S, 26.74. Found: C, 39.97; H, 5.70; Cl, 14.72; N, 5.99; S, 26.54.

S-Vinyl(2,2-dimethylthiazolydyl)monothiolcarbamate (V).—To a solution prepared by dissolving 5.1 g. (0.13 g.-atm.) of potassium in 250 ml. of absolute *t*-butyl alcohol, heated to 60°, there was added dropwise a solution of 31.2 g. (0.13 mole) of IV in 100 ml. of *t*-butyl alcohol. The resultant slurry was stirred at 50° overnight. The precipitated KCl was filtered and washed with additional solvent. The combined filtrates were made neutral with glacial acetic acid and the solvent was removed *in vacuo*. The viscous residue was distilled under reduced pressure to give 16.9 g. (64%) of colorless liquid which solidified in the receiver; b.p. 85° (0.15 mm.), m.p. 44–45°.

Anal. Calcd. for $C_8H_{13}NOS_2$: C, 47.25; H, 6.44; N, 6.89; S, 31.54. Found: C, 47.28; H, 6.32; N, 6.74; S, 31.38.

Poly[S-vinyl(2,2-dimethylthiazolydyl)monothiolcarbamate] (VI).—A polymerization tube was charged with 13.1 g. of V and 58.6 mg. of α,α'-azobisisobutyronitrile. The polymerization tube was alternately evacuated and flushed with nitrogen three times and then sealed under vacuum. The charged tube was maintained in an oil bath for 30 hr. at 60°. The resultant polymer plug was triturated with ethanol to separate unreacted monomer and then dissolved in 50 ml. of benzene. The polymer solution was added dropwise to a 10:1 excess of cold pentane. The precipitated polymer was filtered and reprecipitated. The product, 10.2 g. (78%), was a white solid, softening at 170–180°, [η] 0.21 determined in benzene at 29.2°.

Anal. Calcd. for $(C_8H_{13}NOS_2)_n$: C, 47.25; H, 6.44. Found: C, 47.15; H, 6.42.

4-Carbomethoxy-2,2-dimethylthiazolidine (VII).—Cysteine methyl ester hydrochloride[13] (83.3 g., 0.49 mole) was suspended in 2 l. of acetone, and the slurry was refluxed overnight. The reaction mixture was cooled to room temperature and filtered to give 76.5 g. (74%) of VII·HCl as a powdery white solid, m.p. 154–156° (lit.[14] 162°).

The free amine was liberated as follows. The hydrochloride was dissolved in a minimum amount of water and the solution was covered with twice the volume of ether. Sodium carbonate was then added in small portions until CO_2 evolution had ceased. The ethereal layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Vacuum distillation of the residue gave the free amine as a water white liquid, b.p. 66° (0.80 mm.), $n^{25}D$ 1.4960, $[\alpha]^{25}D$ −185.71° (*c* 4.61, $CHCl_3$).

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

(13) M. Joullie, M. Laarre, G. Maillard, P. Muller, and R. Zoul, French Patent 1,241,102; *Chem. Abstr.*, **55**, 25782*f* (1961).

(14) E. Abderhalden and W. Geidel, *Fermenforschung*, **13**, 97 (1931).

N-Acrylyl-4-carbomethoxy-2,2-dimethylthiazolidine (VIII).—The procedure described for the preparation of II was used. Treatment of 15.3 g. (0.09 mole) of VII with 8.1 g. (0.09 mole) of acrylyl chloride in the presence of 9.1 g. (0.09 mole) of triethylamine afforded a yellow solid which was recrystallized from ether to give 12.5 g. (60%) of white prisms, m.p. 87.5–88.5°, $[\alpha]^{25}D$ −71.70° (*c* 5.54, $CHCl_3$).

Anal. Calcd. for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59; N, 6.11; S, 13.99. Found: C, 52.36; H, 6.53; N, 6.20; S, 13.74.

Poly(N-acrylyl-4-carbomethoxy-2,2-dimethylthiazolidine) (IX).—A polymerization tube was charged with 8.0 g. of VIII and 29 mg. of α,α'-azobisisobutyronitrile dissolved in 15 ml. of dry benzene. The polymerization tube was alternately evacuated and flushed with dry nitrogen three times and then sealed under vacuum. The solution was heated at 60° for 2 hr. An additional 25 ml. of benzene was added to the polymer mass and the polymer was precipitated by adding dropwise to a 10:1 excess of cold pentane. The polymer was purified by repeating this procedure. The reprecipitated polymer weighed 6.9 g. (86.3%) and softened at 215–225°, $[\eta]$ 0.63 determined in benzene at 29.2°.

Anal. Calcd. for $(C_{10}H_{15}NO_3S)_n$: C, 52.38; H, 6.59. Found: C, 52.19; H, 6.63.

Acknowledgment.—The authors gratefully acknowledge the support of this work from the U. S. Army Medical Research and Development Command, Office of the Surgeon General, under Contract No. DA-49-193-MD-2032.

Substituted 2-Aminothiosulfuric Acids Derived from α-Amino Acids[1]

HERMAN GERSHON[2] AND RAYMOND RODIN

Pfister Chemical Works, Inc., Ridgefield, New Jersey

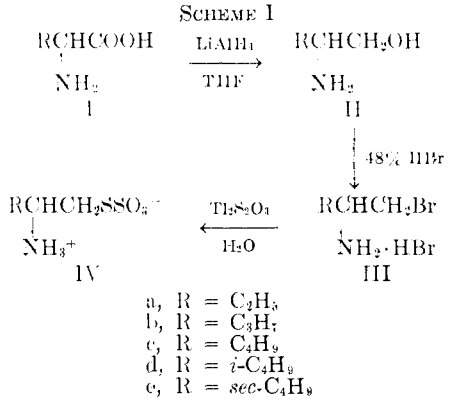
Received April 8, 1965

The discovery[3] of the protective effect of cysteine against acute radiation toxicity has led to the examination of simple mercaptoalkylamines and their derivatives, some of which are more effective than cysteine in reducing the toxic effect of radiation.[4] The most promising compounds contain a basic group and a free or potential sulfhydryl group separated by two or three carbon atoms.[5]

The replacement of the carboxylate function of α-amino acids by the methylenethiosulfonate group ($CH_2SSO_3^-$) would yield products having an amino group and a potential sulfhydrly group separated by two carbons. This transformation has been carried out on a number of racemic amino acids.

Scheme I presents the synthetic approach to the amino thiosulfuric acids derived from the neutral aliphatic amino acids. The reduction of this group of amino acids to amino alcohols (II) was accomplished by means of $LiAlH_4$ in tetrahydrofuran (THF) in 58–97% yields by the methods of Vogl and Pöhm.[6,7]

SCHEME I



a, R = C_2H_5
b, R = C_3H_7
c, R = C_4H_9
d, R = *i*-C_4H_9
e, R = *sec*-C_4H_9

The corresponding amino bromide hydrobromides (III) were prepared by treating the amino alcohols with 48% HBr.[8] In a number of cases, the products obtained were mixtures of the amino bromide hydrobromides and amino alcohol hydrobromides. Since a method of separation could not be worked out, the composition of the mixtures was determined from the bromine content, and the crude products were employed in the succeeding step without further purification. The mixtures contained from 80–95% bromide hydrobromide (58–82% yield). Upon treatment of III with thallous thiosulfate according to Lecher and Hardy,[9] the thiosulfuric acids (IV) were obtained in 60–83% yields.

The amino alcohols derived from the basic amino acids, ornithine and histidine, and the aromatic amino acid, tyrosine, could not be obtained directly by reduction with $LiAlH_4$. The preparation of L-tyrosinol from L-tyrosine was reported by Dornow, *et al.*,[10] but could not be reproduced.

The reactions employed in synthesizing the aminothiosulfuric acids from the basic and aromatic amino acids are summarized in Scheme II. L-Histidinol had been previously prepared[11] by reducing the ethyl ester of benzoyl-L-histidine with a large excess (18:1 mole) of $LiAlH_4$ in ethyl ether. In THF, an excess of $LiAlH_4$ reduced both the ester and amide functions and yielded benzylhistidinol (XIh). It seems that the reduction of the amide was temperature dependent since THF boils considerably higher than ether. When the ratio of $LiAlH_4$ to benzamido ester was 1:1 mole, a good yield of benzamido alcohol was obtained. To overcome the problem of nonselectivity during the reduction of the benzamido esters, the method of Stewart[12] was employed which depended on the selective reduction of ester functions by $LiBH_4$. The remainder of the synthetic sequence was similar to that of the aliphatic aminothiosulfuric acids, and the yield of Xf was 48%.

The infrared spectra of the thiosulfuric acids were characterized by peaks and bands at 1016–1040, 1065–1130, and 1180–1240 cm.$^{-1}$. These were in general agreement with the data reported by Simon and Kunath[13] for the sulfonate ion in alkylthiosulfates, and the crystal structure of compound IVa was de-

(1) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2161.

(2) To whom requests for reprints should be sent: Boyce Thompson Institute for Plant Research, Yonkers, N. Y. 10701.

(3) H. M. Patt, E. B. Tyree, R. L. Straube, and D. E. Smith, *Science*, **110**, 213 (1949).

(4) Z. M. Bacq, A. Herve, J. Lecompte, P. Fischer, J. Blavier, G. Dechamps, H. LeBihan, and P. Rayet, *Arch. intern. physiol.*, **59**, 442 (1951).

(5) A. Pihl and L. Eldjarn, *Pharmacol. Rev.*, **10**, 437 (1958).

(6) O. Vogl and M. Pöhm, *Monatsh.*, **83**, 541 (1952).

(7) O. Vogl and M. Pöhm, *ibid.*, **84**, 1097 (1953).

(8) F. Cortese, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 91.

(9) H. Z. Lecher and E. M. Hardy, *J. Org. Chem.*, **20**, 475 (1955).

(10) A. Dornow, G. Messwarb, and H. Frey, *Chem. Ber.*, **83**, 445 (1950).

(11) H. Bauer, E. Adamsr and H. Tabor, *Biochem. Prepn.*, **4**, 46 (1955).

(12) J. M. Stewart, *J. Org. Chem.*, **26**, 3360 (1961).

(13) A. Simon and P. Kunath, *Chem. Ber.*, **94**, 1980 (1961).