protein binding, 54; CD_{50} >400 mg/kg. *Anal.* ($C_{15}H_{21}N_3O_4S_2$) C, H, N.

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Potential Antiradiation Agents. III.[1] N-Substituted Aminoethanethiosulfuric Acids

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A series of N-monoalkyl-substituted 2-aminoethanethiosulfuric acids was prepared for testing as potential antiradiation agents. The compounds were synthesized by the direct alkylation of the sodium salt of 2-aminoethanethiosulfuric acid with primary alkyl bromides, by the reaction of the appropriate *N*-alkylaminoethyl halide hydrohalides with sodium thiosulfate, or by the ring opening of 1-substituted aziridines with ammonium thiosulfate. Excellent radioprotective activity (>70% survival) was obtained with those 2-aminoethanethiosulfuric acids which were N-substituted by methyl, *n*-octyl, 2-octyl, *n*-nonyl, 2-nonyl, 3-nonyl, *n*-decyl, 2-decyl, 3-decyl, 3,7-bimethyloctyl, 4-phenylbutyl, and 5-phenylpentyl groups.

In an earlier paper[2] we described the synthesis and radioprotective properties of a series of aminoalkanethiosulfuric acids possessing a primary amino group. It was shown that optimal activity was obtained when the NH_2 and SSO_3H functions were separated by two CH_2 groups. The high antiradiation activity shown by many *N*-alkylaminoethanethiols[3] suggested that 2-aminoethanethiosulfuric acids which were N-substituted also might be useful as potential antiradiation drugs.

In this paper we report on the antiradiation properties of a series of N-monoalkyl-substituted 2-aminoethanethiosulfuric acids, the synthesis of many of which was described by us previously.[4]

Chemistry

The previously unreported *N*-alkylaminoethanethiosulfuric acids (Table I) were prepared by two general methods. Method A involved the direct alkylation of 2-aminoethanethiosulfuric acid as the Na salt with a primary alkyl bromide in EtOH–H_2O. The dialkylated by-product was separated from the desired monoalkylated 2-aminoethanethiosulfuric acid by repeated recrystallizations.

$$RBr + H_2NCH_2CH_2SSO_3^- \longrightarrow RNHCH_2CH_2SSO_3H + Br^-$$

Method B utilized the reaction of sodium thiosulfate with an *N*-alkylaminoethyl halide hydrohalide in H_2O or EtOH–H_2O. The *N*-alkylaminoethanol precursors were prepared either by the direct alkylation of 2-aminoethanol by the method of Wright, *et al.*,[5] or by the reaction of a carboxylic acid with 2-aminoethanol to yield an *N*-(2-hydroxylethyl)amide which was reduced with LAH in THF. The resultant N-substituted aminoethanols were converted into the amino halide form by treatment with $SOCl_2$ or 48% HBr.

$$R\overset{+}{N}H_2CH_2CH_2X\ X^- + SSO_3^{2-} \longrightarrow RNHCH_2CH_2SSO_3H + 2X^-$$

Results and Discussion

Compounds **1**–**18** constitute a homologous series of aminoethanethiosulfuric acids N-substituted with unbranched alkyl groups. The first five members were the most water soluble and the least toxic. However, any appreciable radioprotective activity was limited to those compounds substituted with Me (**1**) or Et (**2**), while slight activity was shown by the Pr compound (**3**). Increased toxicity and absence of activity marked compounds **4**–**6**, but activity was restored to the series with the heptyl-substituted compound (**7**) and rose steadily, reaching a peak effect with **10**. Compound **10** not only conferred a high degree of protection to the mice, but did so at a considerably smaller dose (5 mg/kg) than that required by most radioprotective thiosulfuric acids. In contrast to 2-mercaptoethylamine (MEA), whose duration of maximum radioprotective activity extends to 15 min and then diminishes rapidly thereafter,[6] the duration of activity of **10** extends close to 1 hr. Compound **10**, while effective when given parenterally and moderately protective when given subcutaneously, is ineffective when given orally. Other agents in this class, which protected after parenteral injection, also failed to protect when administered by intubation. Attempts to induce absorption included acidification of the intestinal contents of the mouse and the use of ethylenediaminetetraacetic acid which promotes the absorption of a wide variety of poorly

(1) Part II: D. L. Klayman, M. M. Grenan, and D. P. Jacobus, *J. Med. Chem.*, **12**, 723 (1969).

(2) Part I: D. L. Klayman, M. M. Grenan, and D. P. Jacobus, *ibid.*, **12**, 510 (1969).

(3) Annual Report, FY 1964, Walter Reed Army Medical Center, Walter Reed Army Institute of Research, Division of Medicinal Chemistry, Washington, D. C. Available through the Defense Documentation Center, Cameron Station, Alexandria, Va. 22315, as Report AD 601934.

(4) D. L. Klayman and W. F. Gilmore, *J. Med. Chem.*, **7**, 823 (1964).

(5) J. B. Wright, E. H. Lincoln, R. V. Heinzelmann, and J. H. Hunter, *J. Amer. Chem. Soc.*, **72**, 3536 (1950).

(6) Z. M. Bacq, "Chemical Protection Against Ionizing Radiation," Charles C. Thomas, Springfield, Ill., 1965, pp 126–129.

Table I

N-Alkyl- and *N*-Aralkylaminoethanethiosulfuric Acids

Compd	Formula[a]	Method of synthesis	Mp, °C	% yield[b]	Recrystn solvent
20	$C_6H_{13}NO_3S_2$	B[c]	184–186 dec	30	MeOH
22	$C_7H_{15}NO_3S_2$	B[c]	212–213	50	H_2O
23	$C_7H_{15}NO_3S_2$	B[c]	188–189 dec	47	H_2O–MeOH
25	$C_9H_{18}NO_3S_2$	B	202–203	92	EtOH–H_2O
35	$C_{10}H_{21}NO_3S_2$	B[c]	203–205 dec	38	EtOH–H_2O
38	$C_{12}H_{25}NO_3S_2$	B	205–206 dec	67	EtOH–H_2O
41	$C_{30}H_{57}NO_3S_2$	B[c]	187–189 dec	92	EtOH–H_2O
44	$C_{12}H_{19}NO_4S_2$	A	146–147	19	H_2O
45	$C_{12}H_{19}NO_3S_2$	B[c]	168–169	58	EtOH–H_2O
46	$C_{12}H_{19}NO_3S_2$	B[d]	181–182	88	H_2O–EtOH
47	$C_{19}H_{21}NO_3S_2$	B[c]	188–189 dec	68	95% EtOH
48	$C_{14}H_{23}NO_3S_2$	A[e]	173–174	47	CH_3CN
49	$C_{20}H_{25}NO_3S_2$[f]	B[c]	216–217 dec	62	EtOH
50	$C_{19}H_{33}NO_3S_2$[g]	B[c]	194–196	20	MeOH
51	$C_{15}H_{24}N_2O_3S_2$[h]	A	244–245	93	[i]
53	$C_{11}H_{17}NO_3S_2$	B[c]	178–178.5 dec	72	MeOH–H_2O

[a] All compounds were analyzed for C, H, N, S. [b] Yields are based on the final step only. [c] The N-substituted aminoethanols, used as precursors of the aminoalkylhalide hydrohalides, were made by the reaction of carboxylic acids with 2-aminoethanol, followed by reduction of the resultant *N*-(2-hydroxyethyl)amide with LAH. [d] 4-Phenylbutylamine was treated with $(CH_2)_2O$ to give 2-(4-phenylbutylamino)ethanol. [e] *Cf.* Experimental Section for the preparation of 6-phenylhexylbromide. [f] Calcd: S, 15.00; found, 14.55. [g] Calcd: H, 8.58; found, 8.18. [h] Calcd: S, 19.18; found, 18.69. [i] Purified by washing with H_2O.

absorbed agents when administered in high doses (100–500 mg/kg) in rats.[7]

When a lethal dose of **10** (10 mg/kg) was administered and followed in 15 min by a dose of MEA (25 mg/kg), the toxic effects of **10** were reversed and all mice survived with no apparent adverse effects. When **10** was given at the radioprotective dose (5 mg/kg) 30 min prior to irradiation, followed by the administration of 75 mg/kg of MEA 15 min prior to irradiation, the antiradiation effect of **10** was completely antagonized by the latter compound.

Compounds **11** and **12**, having one and two CH_2 groups greater than **10**, respectively, were completely inactive. Compounds **13–15** exhibited marginal activity, but further extension of the alkyl chain (**16–18**) gave agents exhibiting no radioprotective properties.

Included in the group of compounds **19–39** are *N*-substituted aminoethanethiosulfuric acids in which the alkyl substituent is branched, in which the linkage of the amino group with the alkyl chain occurs on other than the terminal carbon, and in which N-substitution is by cycloalkyl or cycloalkylmethyl.

Like their straight chain isomers, **19–23** were inactive. While **7** protected 50% of the mice, the 2-heptyl (**24**) and cycloheptyl (**25**) derivatives were ineffective. In the octyl series (**26–30**), a high degree of protection was obtained when substitution was in the 2-position (**26**). The others in the series produced diminished but nevertheless good activity.

In the nonyl series, **31–35**, the 2- and 3-nonyl variants (**32**, **33**) afforded protection similar to the unbranched analog (**9**). The other members (**31**, **34**) showed moderate–fair protection, while **35** had poor activity.

The decyl series, **36–38**, was the most effective. Like the unbranched isomer, **10**, >80% protection was obtained with each of these at a low dose. However, **10** proved to be a more potent radioprotector than the other members of the decyl series.

Compound **39**, in contrast to the related unbranched *N*-alkyl derivative (**11**) which lacked any activity, showed good activity. This improvement may be attributed to its semblance to **10** further substituted with Me in the 1-position of the *n*-decyl chain.

In the phenylalkyl series (**40–50**) the number of CH_2 groups separating the phenyl ring from the amino function ranged from 1 to 6 and 11. The best activity was possessed by **43**, **46**, and **47**, which gave survival values of 40, 94, and 83%, respectively. The presence of *m*-CH_3O on the phenyl ring of **43** resulted in **44** with virtually no activity. Similarly, modification of the structure of **43** by the addition of two phenyl groups in the 3-position of the propyl chain produced **49** devoid of activity.

2-(9-Acridylamino)ethanethiosulfuric acid (**51**) lacked activity presumably because of its unusually poor solubility characteristics. Compounds **52** and **53** in which the phenoxy groups are substituted at the 2-carbon of Et and Pr groups, respectively, also failed to show activity.

Many N-substituted aminoethanethiosulfuric acids in this series have been found to produce a generalized vasoconstriction and myocardial depression in the dog, which resulted in hypertension, slowed heart rate, and narrowed pulse pressure.[8] In addition to these, **10** was found to possess β-adrenergic blocking activity.

Experimental Section

Biological Methods.—A detailed procedure for the preparation and administration of potential antiradiation agents and the irradiation of mice has been given in an earlier report.[7] The minor deviations from this procedure which were followed in this study are given below.

Female Bagg Swiss mice, 5–6 weeks of age, obtained from the Walter Reed mouse colony were used exclusively in these experiments. Minor changes in radiation sensitivity of the mouse strain which occurred over the 5-year period in which these experiments were performed were compensated for by the alteration of the radiation dose. Using the ^{60}Co source, the dose ranged from 925 to 1000 R, and with the X-ray source, 800 to 825 R.

(7) L. S. Shanker and J. M. Johnson, *Biochem. Pharm.*, **8**, 421 (1961).

(8) M. H. Beiffer, R. L. Mundy, G. E. Demaree, D. P. Jacobus, and R. L. Brockenton, manuscript in preparation.

TABLE II

PROTECTION OF MICE AGAINST X OR γ RADIATION BY N-SUBSTITUTED AMINOETHANETHIOSULFURIC ACIDS, $RNHCH_2CH_2SSO_3H$

Compd	R	LD_{50}, mg/kg[a]	Drug dose, mg/kg[a]	Time interval, min[b]	Radiation dose, R[c]	% survival (30-day)
1[d,e]	Me	350	300	15	800	70
2[d]	Et	525	300	30	1000	55
3[d]	*n*-Pr	350	225	15	925	30
4[d,e]	*n*-Bu	300	200	15	1000	7
5[d]	*n*-Pentyl	200	50	30	1000	0
6[d]	*n*-Hexyl	85	75	15	1000	0
7[d]	*n*-Heptyl	125	75	30	1000	50
8[d]	*n*-Octyl	125	15	30	1000	80
9[d]	*n*-Nonyl	40	15	30	1000	87
10[d]	*n*-Decyl	13	5	30	975	90
11[d]	*n*-Undecyl	8	5	15	1000	0
12[d]	*n*-Dodecyl	10	5	30	1000	0
13[d]	*n*-Tridecyl	15	5	30	1000	40
14[d]	*n*-Tetradecyl	10	5	30	1000	20
15[d]	*n*-Pentadecyl	40	30	30	1000	7
16[d]	*n*-Hexadecyl	150	40	30	825	0
17[d]	*n*-Heptadecyl	200	100	30	800	0
18[d]	*n*-Octadecyl	400	250	30	800	0
19[d]	*i*-Pr	270	250	30	800	0
20	Cyclopropylmethyl	300	150	15	1000	0
21[d]	*t*-Bu	250	200	15	825	10
22	2,2-Dimethylpropyl	475	200	15	1000	0
23	Cyclobutylmethyl	180	100	15	1000	0
24[d]	2-Heptyl	175	75	15	1000	0
25	Cycloheptyl	75	50	15	1000	0
26[d]	2-Octyl	138	75	30	1000	100
27[d]	3-Octyl	125	75	30	1000	40
28[d]	4-Octyl	140	75	15	800	33
29[d]	Cyclooctyl	150	100	15	800	33
30[d]	2-Ethyl-1-hexyl	180	120	15	1000	53
31[d]	Isononyl	140	40	15	1000	47
32[d]	2-Nonyl	50	22.5	30	825	94
33[d]	3-Nonyl	125	50	15	825	80
34[d]	4-Nonyl	200	75	15	800	20
35	3,5,5-Trimethylhexyl	100	20	30	1000	13
36[d]	2-Decyl	25	15	30	1000	94
37[d]	3-Decyl	100	25	15	800	80
38	3,7-Dimethyloctyl	125	30	30	1000	87
39[d]	2-Undecyl	20	10	30	825	53
40[d]	Benzyl	250	150	30	1000	0
41	4-Methoxybenzyl	180	100	15	1000	0
42[d]	Phenethyl	150	50	15	800	0
43[d]	3-Phenylpropyl	125	50	15	1000	40
44	3-(*m*-Methoxy)phenylpropyl	150	50	15	825	7
45	2-Phenylbutyl	125	50	30	1000	13
46	4-Phenylbutyl	300	120	30	825	94
47	5-Phenylpentyl	130	70	15	825	83
48	6-Phenylhexyl	38	25	30	1000	27
49	3,3,3-Triphenylpropyl	140	5	30	1000	0
50	11-Phenylundecyl	25	7.5	30	1000	0
51	9-Acridyl	50	25	30	825	0
52[d]	2-Phenoxyethyl	175	50	30	1000	0
53	2-Phenoxypropyl	150	50	15	1000	7

[a] Intraperitoneal administration. [b] Administration prior to irradiation. [c] ^{60}Co γ-irradiation at 925–1000 R (dose rate 50–100 R/min); all other doses were delivered by a 300-kvp X-ray (dose rate 45 R/min). [d] Synthesis of this compound reported previously; *cf.* ref 4. [e] Also prepared by the ring-opening of aziridines with ammonium thiosulfate; *cf.* D. L. Klayman, W. F. Gilmore, and T. R. Sweeney, *Chem. Ind.* (London), 1632 (1965).

All compounds were administered by the intraperitoneal route unless noted otherwise.

The principles of laboratory care as promulgated by the National Society for Medical Research were observed.

Chemistry.[9] ***N*-Alkylaminoethanethiosulfuric Acids. Method A.**—The procedure[4] for the direct alkylation of sodium 2-aminoethyl thiosulfate was improved by increasing the quantity of the latter compound relative to the primary alkyl bromide. In general, using a 2:1 ratio of amine to alkyl halide was found to appreciably diminish the yield of the dialkylated by-product.

6-Phenylhexyl Bromide.—To a solution of 12.2 g (0.05 mol) of

(9) Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Microanalyses were performed by Mr. Joseph F. Alicino, Metuchen, N. J. 08840, and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. 11377. Infrared spectra were determined as KBr pellets on a Beckman IR-5 spectrophotometer.

1,6-dibromohexane in 100 ml of THF maintained under N_2 at *ca.* −9° was added dropwise over 0.75 hr a solution of 42.5 ml of 20% PhLi solution (70:30 C_6H_6-Et_2O). The resultant solution was allowed to come to room temperature over a 20-hr period. H_2O (50 ml) was slowly added to destroy the unreacted PhLi. The two phases were separated, the aqueous phase was discarded and the organic phase was washed (H_2O) and dried ($CaCl_2$). The solvent was evaporated under reduced pressure and the residue was distilled by means of a spinning-band column. The product, bp 79–81° (0.45 mm) [lit.[10] bp 160–161° (17 mm)], $n^{25}D$ 1.5252–1.5285, weighed 4.13 g (34%). *Anal.* ($C_{12}H_{17}Br$) Br.

Method B.—Equimolar quantities of an *N*-alkylaminoethyl halide hydrohalide and $Na_2S_2O_3 \cdot 5H_2O$ in H_2O or H_2O-EtOH, depending on the solubility of the former reactant, were heated on a steam bath for *ca.* 0.5 hr. When the reaction was complete, as indicated by failure of S to precipitate from a strongly acidified aliquot, the thiosulfuric acids crystallized from the cooled and, in some instances, concentrated reaction mixtures. The *N*-alkylaminoethanethiosulfuric acids which were recrystallized until they were free of halide ion showed characteristic peaks in the ir near 8.15, 8.40, and 9.80 μ.

2-(5-Phenylpentylamino)ethanethiosulfuric Acid.—The following exemplifies the procedure used when a carboxylic acid was the precursor of the *N*-alkyl group. A mixture of 100 g (0.56 mol) of 5-phenylvaleric acid and 34.3 g (0.56 mol) of 2-aminoethanol was heated gently at first, followed by a gradual increase in the application of heat until the temperature was maintained at 160–200°. The H_2O which formed in the course of the reaction was collected in a Dean–Stark trap fitted atop a Vigreaux column. The crude *N*-2-hydroxyethyl-5-phenylvaleramide was used in the next step without further purification.

A THF solution (200 ml) of the *N*-2-hydroxyethyl-5-phenylvaleramide was added over 2.5 hr to a cooled and stirred slurry of 22.8 g (0.6 mol) of LAH and 500 ml of THF. After the mixture was heated under reflux for 11 hr, 250 ml of H_2O was cautiously added to the cooled and stirred mixture to destroy excess LAH. The $Al(OH)_3$ which formed was filtered from the mixture and washed (Et_2O). The aqueous phase of the filtrate was extracted (Et_2O), the ether and THF solutions were combined, and dried ($MgSO_4$), and the solvents were evaporated on a rotary evaporator. The residue was distilled at reduced pressure to give 52 g (50%) of 2-(5-phenylpentylamino)ethanol. Treatment of the latter with 48% HBr by the method of Cortese[11] gave 58 g (60%) of 2-(5-phenylpentylamino)ethyl bromide·HBr which was converted into the thiosulfuric acid by the reaction with $Na_2S_2O_3 \cdot 5H_2O$ in 1:1 H_2O-EtOH.

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(10) J. von Braun, *Ber.*, **44**, 2877 (1911).

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

Antiviral Agents. I. Bicyclo[2.2.2]octan- and -oct-2-enamines

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The preparation of a number of bicyclo[2.2.2]octan- and -oct-2-enamines is described. Antiviral test data in mice are given and structure–activity relationships are discussed.

The discovery of antiviral activity for adamantan-1-amine (amantadine·HCl)[1] against several strains of influenza A virus in mice, chick embryos, and tissue culture[2] and the subsequent demonstration of its clinical efficacy against influenza A_2 in man[3] prompted us to synthesize other cage amines to explore their usefulness as antiviral agents.

This paper describes the synthesis of bicyclo[2.2.2]-octan-1-amines, bicyclo[2.2.2]oct-2-en-1-amines, bicyclo[2.2.2]octane-1-methylamines, and bicyclo[2.2.2]-oct-2-ene-1-methylamines[4] and presents a novel synthetic entry into the bicyclo[2.2.2]octane ring system. The results obtained from evaluation of these compounds as antiviral agents against influenza A/swine infections of mice are given.

Chemistry.—The syntheses of the required bicyclo[2.2.2]oct-2-ene- and -octane-1-carboxylic acids are outlined in Scheme I. Several of the alkyl α-pyrone-3-carboxylates (Ia,[5] Ic,[6] Id,[6] Ie, and If) were obtained by known methods.[5,6] The α-pyrones Ib,[6,7] Ig, and Ih were prepared by base condensation of the appropriate methyl ketone with diethyl ethoxymethylenemalonate, followed by cyclization of a postulated intermediate diethyl 3-acylethylidenemalonate. α-Pyrones Ic, If, and Ig were used without purification. The absorption bands of their spectra (ir) were as expected.

Reaction of the alkyl α-pyrone-3-carboxylates I with ethylene[5,7] at high pressure afforded the desired alkyl bicyclo[2.2.2]oct-2-ene-1-carboxylates II (see Scheme II). The esters (IV) were used without purification. Esters IIb and IIh have been reported previously.[8] In the reaction of ethylene with α-pyrones, the intermediate cyclohexadienes could usually be isolated by the use of lower temperatures or lower pressures.

We have observed that the ease of addition of ethylene to cyclohexadienes generally appears to increase

(1) Symmetrel®, E. I. DuPont De Nemours and Co.

(2) R. R. Grunert, J. W. McGahen, and W. L. Davies, *Virology*, **26**, 262 (1965). W. L. Davies, R. R. Grunert, R. F. Haff, J. W. McGahen, E. M. Neumayer, M. Paulshock, J. C. Watts, T. R. Wood, E. C. Hermann, and C. E. Hoffman, *Science*, **144**, 862 (1964). C. E. Hoffmann, E. M. Neumayer, R. F. Haff, and R. A. Goldsby, *J. Bacteriol.*, **90**, 623 (1965). E. M. Neumayer, R. F. Haff, and C. E. Hoffmann, *Proc. Soc. Exp. Biol. Med.*, **119**, 393 (1965). W. L. Davies, R. R. Grunert, and C. E. Hoffmann, *J. Immunol.*, **95**, 1090 (1966).

(3) For summaries see C. E. Hoffmann in "Annual Reports in Medicinal Chemistry," C. K. Cain Ed., Academic Press, New York, N. Y., 1967, p 118; 1968, p 117.

(4) J. C. Kauer, U. S. Patent 3,418,369 (1968). J. C. Kauer, Netherlands Patent Application 6,404,759 (1964); *Chem. Abstr.*, **62**, 14529 (1965).

(5) R. H. Wiley and A. J. Hart, *J. Amer. Chem. Soc.*, **76**, 1942 (1954).

(6) N. K. Kochetkov and L. I. Kudyashov, *J. Gen. Chem. USSR*, **27**, 277 (1957).

(7) P. R. Hills and F. J. McQuillin, *J. Chem. Soc.*, 4060 (1953).

(8) J. C. Kauer, Netherlands Patent Application 6,507,979 (1965); *Chem. Abstr.*, **64**, 15772 (1966).

(9) F. W. Baker and L. M. Stock, *J. Org. Chem.*, **32**, 3344 (1967).