In other experiments it was shown that virtually no alkylation occurred at −78° and that the precipitate formed at −20° was identical to that formed from **3** at −20° in the absence of alkyl halide.

Reaction of the Lithio Derivative 4 with Benzophenone

To a solution of **4**, generated from 1.00 g (7.35 mmoles) of butane-1,4-sultone in 30 ml of tetrahydrofuran at −78° were added 1.30 g (7.2 mmoles) of solid benzophenone. The reaction mixture was stirred at −78° for 10 min and then worked up as described above. Recrystallization of the crude solid adduct from methylene chloride – pentane gave 1.44 g (63%) colorless needles, m.p. 182–182.5°. The i.r. spectrum ($CHCl_3$) showed peaks at 3550 (m), 1350 (s), 1165 (s), and 955 (m) cm^{-1}. The n.m.r. peaks ($CDCl_3$) occurred at 1.6–2.6 (m, 4H), 4.12 (s, 1H), 4.2–4.7 (m, 2H), and 7.1–7.7 p.p.m. (10H).

Anal. Calcd. for $C_{17}H_{18}O_4S$: C, 64.14; H, 5.70; S, 10.06. Found: C, 64.23; H, 5.87; S, 10.11.

Dehydration of 315 mg of the above adduct under the usual conditions furnished 263 mg (89%) of unsaturated sultone **8**, m.p. 172–173.5° (needles from methylene chloride – pentane). The i.r. spectrum ($CHCl_3$) showed peaks at 1360 (s), 1170 (s), and 970 (m) cm^{-1}. The n.m.r. bands ($CDCl_3$) occurred at 1.9–2.2 (m, 2H), 2.8–3.0 (m, 2H), 4.60 (t, J = 5.5 c.p.s., 2H), and 7.1–7.5 p.p.m. (m, 10H).

Anal. Calcd. for $C_{17}H_{16}O_3S$: C, 67.99; H, 5.37; S, 10.66. Found: C, 68.31; H, 5.45; S, 10.91.

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S-[(*N*-Terpenoid carboxamidinium)methyl] thiosulfates (Bunte salts) as potential antiradiation agents

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The synthesis of a number of α-acetamidinium Bunte salts, substituted on one of the nitrogen atoms by a terpenoid moiety, is reported.

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It has been shown that a number of *S*-[(*N*-substituted carboxamidinium)methyl] thiosulfates, $^{-}O_3SSCH_2C(=NH_2^{+})NHR$, **1**, are promising radiation-protective compounds in mice (1, 2). This paper describes the synthesis of derivatives of **1** in which one of the amidine nitrogen atoms bears a highly condensed aliphatic structure. It has been observed in a series of *N*-(ω-cycloalkane)-alkyl derivatives of **1** [R = *cyclo*-C_nH_{2n-1}—$(CH_2)_m$] that good activity was retained up to R = 4-(cyclohexyl)butyl, (3). In a recent report, it was disclosed that those *S*-2-aminoethyl thiosulfates, $HO_3S_2CH_2CH_2NHR$, bearing similarly constituted (cycloalkane)alkyl substituents on nitrogen, were among the best radiation-protective substances (4). The project described at present was designed to modify the polar character of **1** by introducing highly condensed aliphatic systems into the molecule. By attaching bi- and tricyclic aliphatic ring systems to the amidine function of **1**, it was hoped to impart additional lipid solubility and possibly facilitate transport of these substances through living systems. Toward this end, derivatives of **1** bearing either terpenoid or adamantane substituents were synthesized and their structures are listed in Table I.

The synthesis employed to prepare these compounds was as described previously (1–3). Methyl α-chloroacetimidate is generated *in situ*

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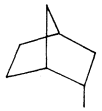
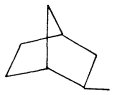
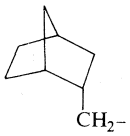
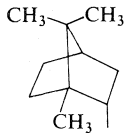
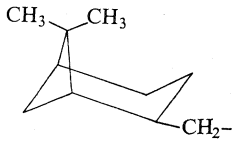
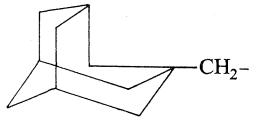
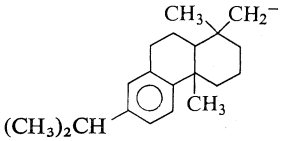
TABLE I

S-[*N*-(Substituted carboxamidinium)methyl] thiosulfates, $^{-}O_3S_2CH_2C(=NH_2^{+})NHR$, **1**

R in **1**	Yield %	Melting point (°C)	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found	S% Calcd.	S% Found
 *endo*-2-Norbornyl	27	165	$C_9H_{16}N_2O_3S_2$	40.91	40.79	6.10	6.30	10.60	10.48	24.23	24.09
 *exo*-2-Norbornyl	28	168–170	$C_9H_{16}N_2O_3S_2$	40.91	40.89	6.10	6.07	10.60	10.65	24.23	24.40
 *endo*-2-Norbornanemethyl	36	150–153	$C_{10}H_{18}N_2O_3S_2$	43.16	43.21	6.52	6.66	10.07	10.21	23.00	22.98
 Bornyl	40	168	$C_{12}H_{22}N_2O_3S_2$	47.05	47.36	7.24	7.10	9.15	9.25	20.89	21.02

 *cis*-Myrtanyl	80	162–165	$C_{12}H_{22}N_2O_3S_2$	47.05	47.44	7.24	7.38	9.15	9.45	20.89	20.83
 1-Adamantanemethyl	79	175–179	$C_{13}H_{22}N_2O_3S_2$	49.05	49.36	6.97	6.90	8.80	8.80	20.10	19.53
 Dehydroabietyl	57	202–205	$C_{22}H_{34}N_2O_3S_2$	60.24	60.28	7.81	7.73	6.39	6.24	14.62	14.70

from the base-catalyzed addition of methanol to chloroacetonitrile. Addition of a primary amine hydrochloride leads to the intermediate α-chloroacetimidinium chloride, $ClCH_2C(=NH_2^+)NHR\ Cl^-$. In the present series, only two of these chloroacetamidinium chlorides could be isolated as crystalline solids (see Experimental). The rest were transformed directly by thiosulfate ion to the corresponding Bunte salt. The crystalline *N*-(1-adamantanemethyl)-α-chloroacetamidinium chloride was converted *via* the phosphorothioate method (5) to the corresponding α-mercaptoacetamidinium chloride.

The procedure for ascertaining *in vivo* activity of these compounds in mice was described in detail previously (2, 4, 6). Of the compounds tested, the *N*-bornyl and *N*-(*cis*-myrtanyl) derivatives of **1**, when administered orally or intraperitoneally 15 min prior to irradiation (800–1000 R, X-rays) showed a high survival rate at one-half to one-quarter of the toxic (LD_{50}) dosage.

Experimental

Melting and boiling points are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois. Some nitrogen analyses were obtained by (the late) Mr. Leo Horner in this Department, using a Coleman model D-29. Proton magnetic resonance (p.m.r.) spectra were recorded by means of a Varian A-60 spectrometer, with tetramethylsilane and sodium 3-(trimethylsilyl)-1-propanesulfonate as internal standards in organic and aqueous media, respectively. Chemical shifts are recorded in p.p.m. (δ) downfield from these internal references and multiplicities are indicated by the usual abbreviations.

Starting Materials

The following chemicals were purchased from Aldrich Chemical Co.: chloroacetonitrile, norbornylene, (−)-β-pinene, 2-norbornanecarbonitrile, 1-adamantanecarbonitrile, 2-norboranamine hydrochloride and dehydroabietylamine. 2-Bornanamine [m.p. 159–169°, lit. (7) m.p. 163°] was purchased from K & K Laboratories and converted to the hydrochloride by passing HCl gas through a chilled solution of the amine in dry ether.

exo-2-Norbornanamine Hydrochloride

The procedure to prepare the amine was adapted from a recent literature method (8), except that hydroboration of norbornylene was accomplished here by generating diborane *in situ* (9). The hydrochloride was obtained by adding a slight excess of concentrated HCl to a solution of the free base in methanol, followed by evaporation to dryness. The yield was 25%; p.m.r. (D_2O) δ 3.29 (m, 1, *endo* H), 2.44 (broad s, 2, bridgehead H), 0.97–2.12 (m, 8, methylene H). The *N*-acetyl derivative of the amine melted at 138–140° [lit. (10) m.p. 139°].

The p.m.r. spectrum of commercial 2-norbornanamine hydrochloride (D_2O) was as follows: δ 3.63 (m, 1, *exo* H), 2.42 (m, 2, bridgehead H), 0.87–2.17 (m, 8, methylene H). Since the α-methine and bridgehead hydrogens showed distinct signals from those of the synthetic *exo* compound, it was concluded that the purchased material is the *endo* isomer. There is no indication that either sample was a mixture of isomers.

cis-Myrtanylamine

This amine was prepared by a combination of the literature procedures for hydroboration of (−)-β-pinene (9) and amination of the resulting dialkylborane (8). The free base had b.p. 60–70° at 2–3 mm [lit. (8) b.p. 60–61° at 2 mm]; p.m.r. ($CDCl_3$) δ 2.67 (broad d, 2, J = 6.1 Hz, CH_2N), 1.25–2.50 (m, 9), 1.17 (s, 3, CH_3), 1.05 (s, NH), 0.97 (s, 3, CH_3). The yield was 15%.

The *N*-benzoyl derivative had m.p. 103.5–104.5° [lit. (8) m.p. 105–106°].

endo-2-Norbornanemethylamine Hydrochloride

This compound has previously been obtained from the corresponding phthalimido derivative (11, 12).

A solution of 2-norbornanecarbonitrile (24 g) in dry tetrahydrofuran (40 ml) was added during 1 h to a stirred suspension of $LiAlH_4$ (7.6 g) in dry tetrahydrofuran (350 ml) under a nitrogen atmosphere. The mixture was heated under reflux for 1 h and cooled. The excess hydride was decomposed by the dropwise addition of water (10 ml), and 10% NaOH solution (30 ml) was added with vigorous stirring. The mixture was filtered and the filtrate was dried over anhydrous Na_2SO_4, decanted, and evaporated *in vacuo* at 40–50°. The residual amine was dissolved in methanol and treated with a slight excess of concentrated HCl. Evaporation of the solvents *in vacuo* and recrystallization of the residue from 2-propanol gave 21.3 g of the hydrochloride (64%).

The *N*-benzoyl derivative was prepared directly from the hydrochloride using pyridine as solvent and melted at 99–101.5° [lit. (12) m.p. 99.5–101.5°; the *exo N*-benzoyl isomer reportedly has m.p. 116–117°]. From the m.p. of the derivative it was concluded that the commercially available nitrile used for this reduction was the *endo* isomer.

1-Adamantanemethylamine

This compound has previously been prepared by reduction of 1-adamantanecarboxamide (13).

A suspension of $LiAlH_4$ (4.2 g, 0.11 mole) in dry tetrahydrofuran (200 ml) was stirred in a nitrogen atmosphere and a solution of 1-adamantanecarbonitrile (16.1 g, 0.1 mole) in dry tetrahydrofuran (45 ml) was added during 0.5 h. The mixture was heated under reflux for 2.5 h, cooled, and treated dropwise with water (15 ml) and then 20% NaOH (25 ml). The mixture was filtered, and the filtrate was dried over anhydrous Na_2SO_4, decanted, and evaporated *in vacuo* at 40–50°. The residual amine was distilled to yield 11.6 g (70%) of product, $b.p._{.4}$ 95–97° [lit. (13) $b.p._3$ 83–85°], p.m.r. ($CDCl_3$) δ 2.30 (s, 2, CH_2—N), 1.97 (broad s, 3, bridgehead H), 1.73 (6 H), 1.47 (6 H), 1.10 (s, NH).

The *N*-benzoyl derivative had m.p. 144–145° [lit. (13) m.p. 142°].

S-(Carboxamidinium)methyl Thiosulfates 1

A 1 *M* solution of methyl α-chloroacetimidate was

prepared by adding distilled chloroacetonitrile to the required amount of a stock solution of $NaOCH_3$ (0.1 *N* in methanol), e.g., 20 mmole to 20 ml. Formation of the imidate is readily followed by p.m.r. (14) and was found to be complete in 15 min under these conditions.

One equivalent of the appropriate amine hydrochloride was then added, and stirring was continued for 30–45 min (see below for exception). A solution of one equivalent of $Na_2S_2O_3 \cdot 5H_2O$ in an equal volume of water was then added, and methanol was evaporated *in vacuo* at 25° or under a gentle stream of filtered air at 25°. Some dark tar generally separated, and evaporation was continued until solids began to separate. The supernatant liquid was then decanted and chilled to obtain the product. The tar was extracted once with hot water to recover any product trapped therein, and the combined product was recrystallized either from water, ethanol or a mixture thereof. Details are listed in Table I. Yields are based on chloroacetonitrile.

N-(1-Adamantanemethyl)-α-chloroacetamidine Hydrochloride

1-Adamantanemethylamine (3.3 g, 0.02 mole) was converted to the hydrochloride by treatment with excess concentrated HCl in methanol followed by evaporation of the solvent. Chloroacetonitrile (1.5 g, 0.02 mole) was then stirred for 25 min with $NaOCH_3$ solution (20 ml), and the amine hydrochloride was added. The mixture was stirred for 2 h at room temperature. Some of the product (2.5 g) which had precipitated, was filtered off and the filtrate was diluted with dry ether (100 ml) to yield another 1.4 g of product, m.p. 274–276°. The p.m.r. spectra of the two samples were identical, and the product was recrystallized from absolute ethanol. The total yield was 3.9 g (70%), and the product proved to be sparingly soluble in water; p.m.r. (CF_3CO_2H) δ 4.38 (s, 2, $ClCH_2$), 3.13 (broad d, 2, J = 5.0 Hz, CH_2N), 2.06 (broad d, 2, bridgehead H), 1.80, 1.67 (broad singlets, 12 total, methylene H.)

Anal. Calcd. for $C_{13}H_{22}Cl_2N_2$: C, 56.28; H, 7.97; N, 10.20. Found: C, 56.50; H, 8.06; N, 10.27.

S-[N-(Dehydroabietyl)carboxamidinium)methyl] Thiosulfate

Dehydroabietylamine hydrochloride was precipitated by passing dry HCl through a solution of the free amine (mixed isomers) in dry ether. A solution of the amine hydrochloride (12.2 g) in methanol (50 ml) was added to 40 ml of 1 *M* methyl α-chloroacetimidate (see above). After 45 min, concentrated HCl (1 ml) was added, and most of the solvent was evaporated. Ether was added to precipitate inorganic solids, which were removed by filtration. The solvents were again evaporated, the residue was dissolved in methanol (15 ml), and water was added in small portions until solids began to separate. After several hours, 9.4 g were collected, m.p. 138–146°. The intermediate defied recrystallization from H_2O, organic solvents, and mixtures thereof.

A 2.0 g sample of the solid was dissolved in warm mixture of water (25 ml) and 95% ethanol (5 ml), and $Na_2S_2O_3 \cdot 5H_2O$ (1.25 g) in water (5 ml) was added with stirring. The mixture was cooled, and the precipitate was collected and washed with hot water. The dry weight was 2.0 g. Additional details are listed in Table I.

N-(1-Adamantanemethyl)-α-mercaptoacetamidine Hydrochloride

N-(1-Adamantanemethyl)-α-chloroacetamidine hydrochloride (5.54 g) was suspended in a solution of Na_3SPO_3 (5) (4.0 g) in water (60 ml). The mixture was stirred vigorously for 30 min. The flask was then flushed with nitrogen, and 6*N* HCl (35 ml) and 2-propanol (30 ml) were added. The mixture was stirred, heated to 80–90° for 20 min, and cooled. The product was collected, 5.0 g (91%), m.p. 220.5–222.5° (decomp.). Recrystallization from water did not alter the decomposition range.

Anal. Calcd. for $C_{13}H_{23}ClN_2S$: C, 56.79; H, 8.43; N, 10.19; S, 11.66. Found: C, 56.35; H, 8.36; N, 10.25; S, 11.04.

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