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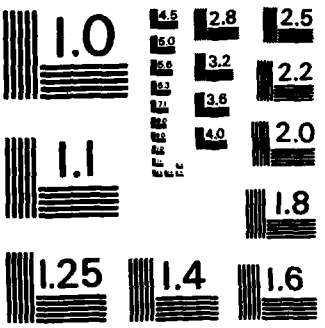

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SYNTHESIS OF NEW PROPHYLACTIC ANTIRADIATION DRUGS

Progress Report No. 1

By

Ludwig Bauer, Ph.D.

August 1980

(For the period 1 March 1980-31 July 1980)

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Department of Medicinal Chemistry
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Synthesis of 1,3-di(ω-aminoalkyl)adamantanes, and their 2-mercaptoacetamidines.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The synthesis of 1,3-di(2-aminoethyl)adamantane is described. Attempts to convert this diamine to the corresponding 1,3-bis-(2-mercaptomethylcarboxamidine)ethyl adamantane are delineated.

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Summary

The synthesis of new mercaptoacetamidines, $HSCH_2C(=NH)NHR$, and derivatives, as potential antiradiation drugs, has been initiated. The initial series of compounds is based on 1,3-disubstituted ω-aminoalkyladamantanes. Starting from the known 1,3-adamantanediacetic acid, the corresponding 1,3-di-(2-aminoethyl)adamantane was prepared. Using this diamine as the amino component, the bis Bunte Salt type $RNH-C(=\overset{+}{N}H_2)CH_2S_2O_3^-$ was synthesized where R is part of the 1,3-disubstituted adamantane system. Further work is planned to reach the target compounds which will be submitted for testing at Walter Reed Army Institute of Research.

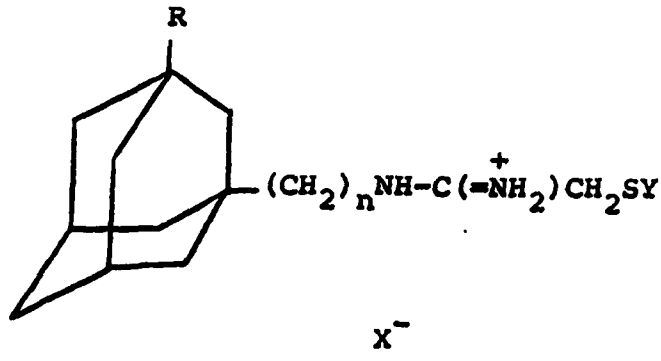
Foreword:

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

Table of Contents

Introduction

This report describes the initial work carried out between March 1, and July 31, 1980 on the synthesis of some 1,3-disubstituted adamantane derivatives of general structure, 1, as potential new antiradiation drugs.



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The work concentrated on the procurement of suitable starting materials needed for the synthesis of 1,3-di(aminomethyl) and 1,3-di(aminoethyl)adamantanes, 7 and 14, respectively. These diamines are essential ingredients for the preparation of the α-chloroacetamidinium salts and then the corresponding Bunte salts. Subsequent conversions of the Bunte salts to a thiol and a disulfide are indicated. Schemes I and II summarize our efforts for the 1,3-di(aminomethyl and 1,3-di(aminoethyl)adamantane series. The reactions which are yet to be carried out, carry the words "projected" under the arrows.

At this point it has been possible for us to convert 1-bromoadamantane, 2, to 1,3-adamantanedicarboxylic acid, 5, using literature procedures. The acid was converted to the corresponding diamide, 6 which was reduced to the diamine, 7. The overall yield

from 2-7 needs improvement. A particularly poor yield reaction was the acid-catalyzed disproportionation of 1-adamantanol, 3 to 1,3-adamantanediol, 4. Since the homologous diacetamide, 13, was available in better yield, we shall explore the Hofmann degradation route of 13 to 7.

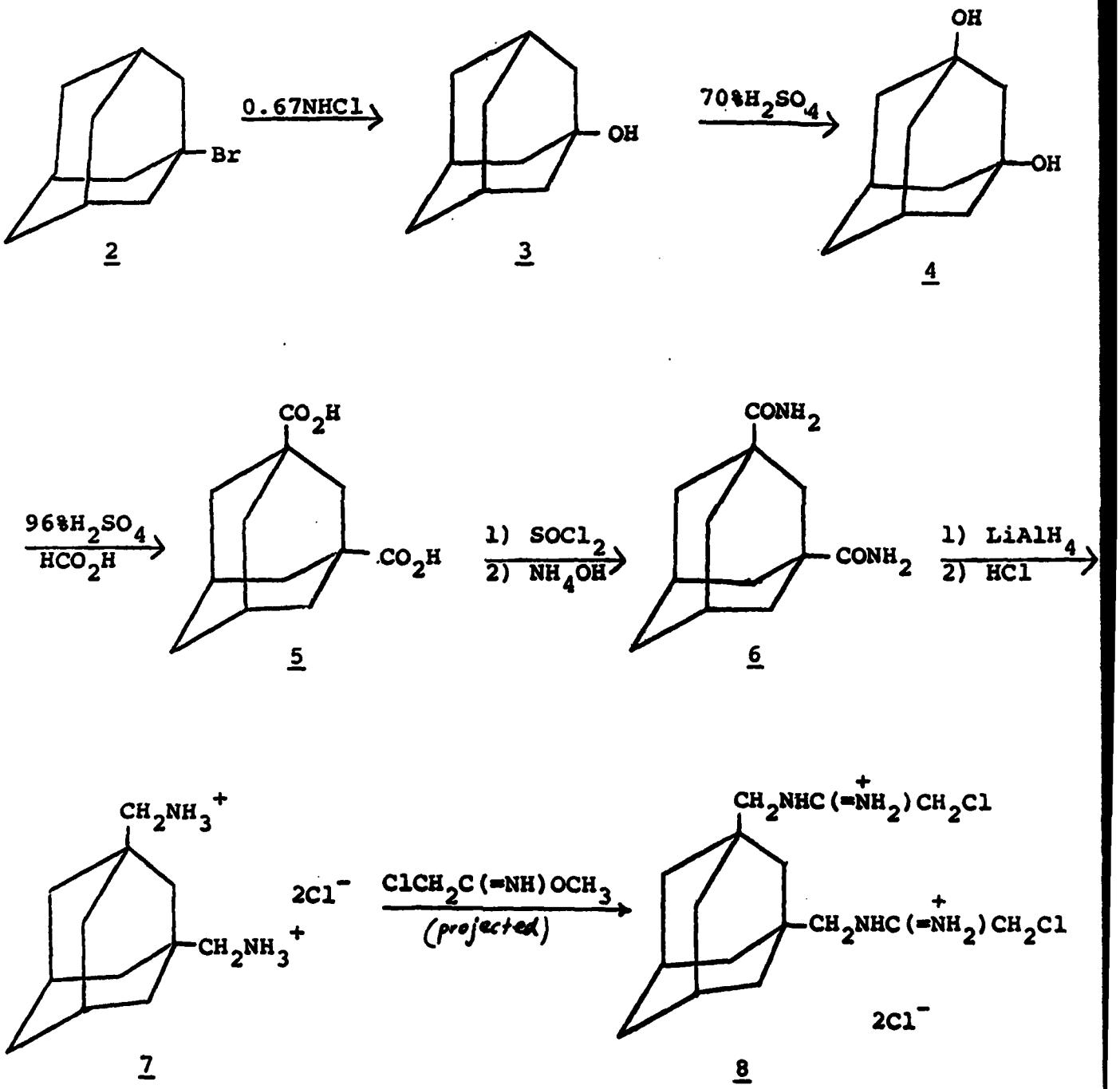
A large effort was expended in starting the synthesis from the available 1,3-adamantanediacetic acid, 12. The preparation of 12 from 1-bromoadamantane and 1,1-dichloroethene and sulfuric acid proceeded in 70% yield. The diamide, 13 was prepared in 50% from the dicarboxylic acid, 12. Reduction of 13 to 14 proceeded in 50%. The diamine readily yielded the corresponding α-chloroacetamidinium chloride, 15 (90%). Further reaction with sodium thiosulfate converted 15 to the Bunte salt, 16, in 90% yield. We are presently scaling up the preparations in order to carry out experiments leading to such target compounds as 17 and 18. Work will also continue on the corresponding "methylamine" series, Scheme I, leading to 10 and 11.

Table I lists the compounds in hand.

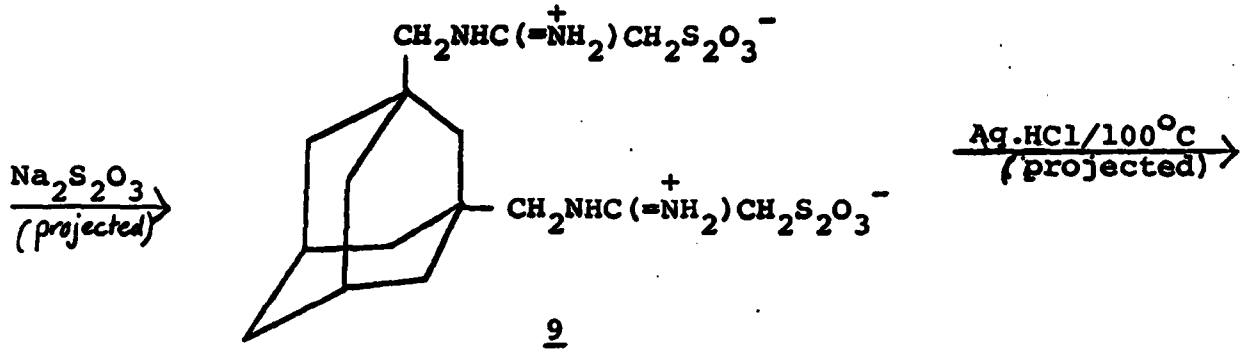
Submission of Compounds

It is projected that some 3 to 6 compounds (2 to 5 g each) will be submitted prior to the end of the contract year, early 1981.

Scheme I : Synthesis of 1,3-di(Aminomethyl)adamantane and Related Amidino Derivatives



Scheme I , cont'd:



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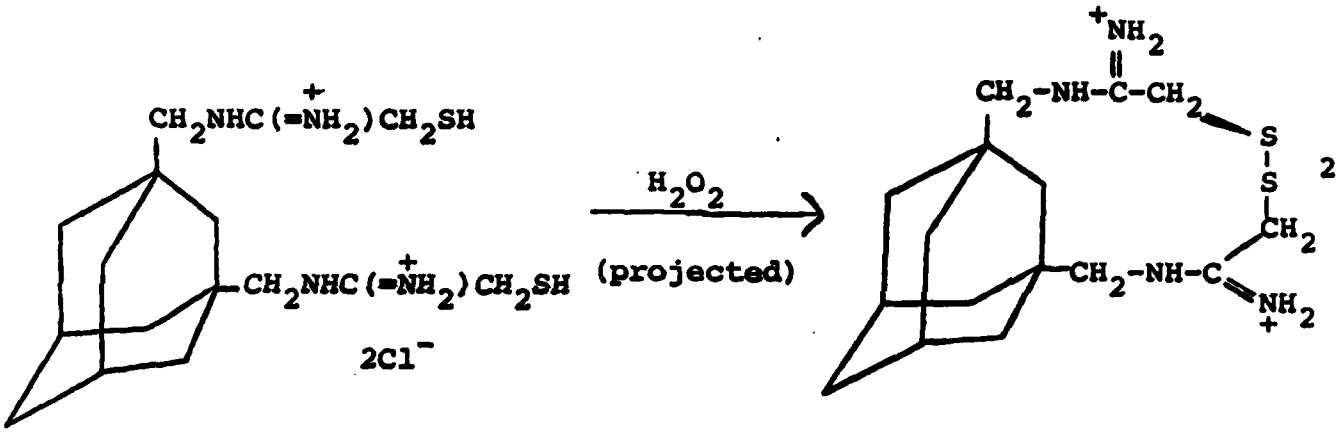

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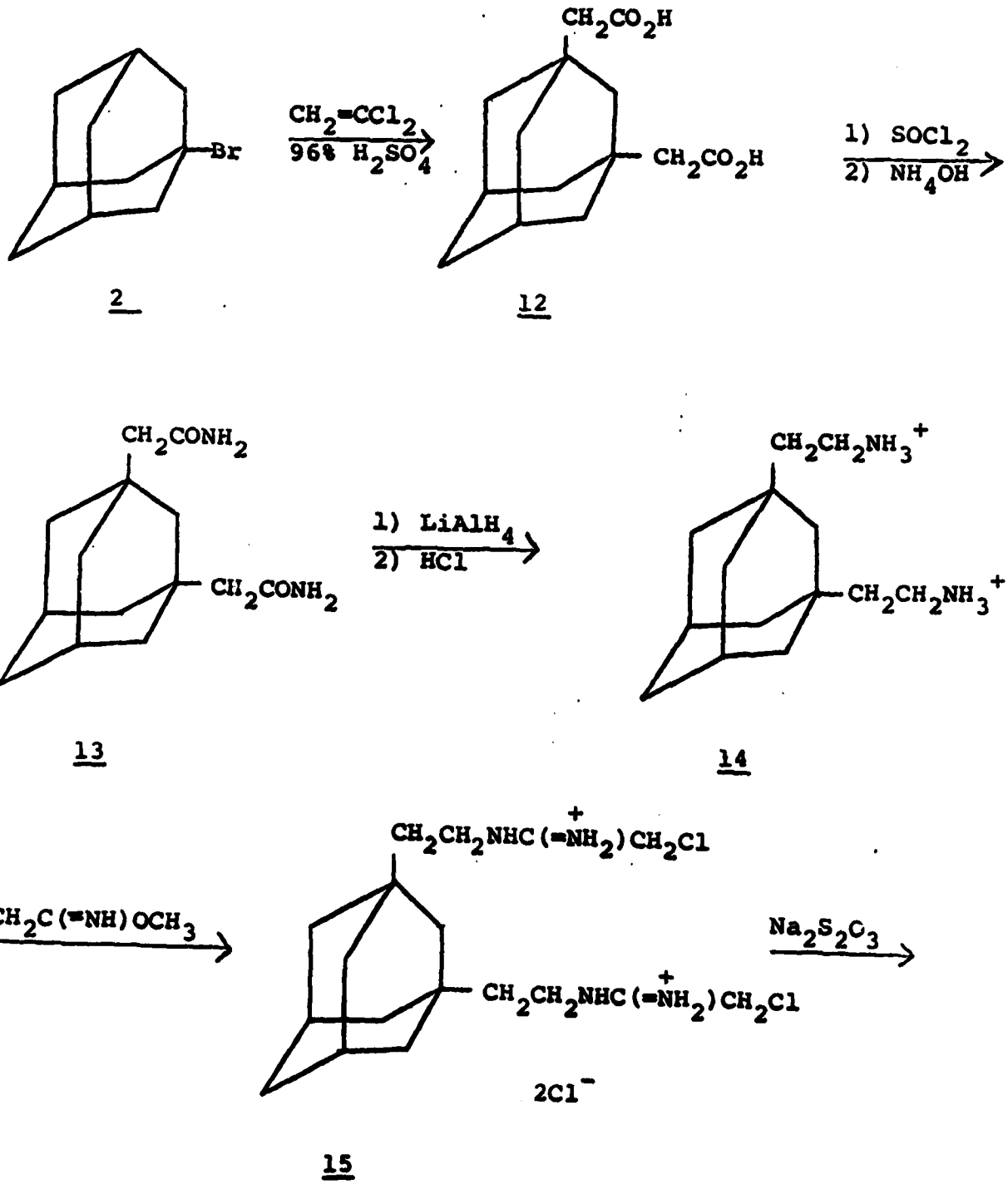
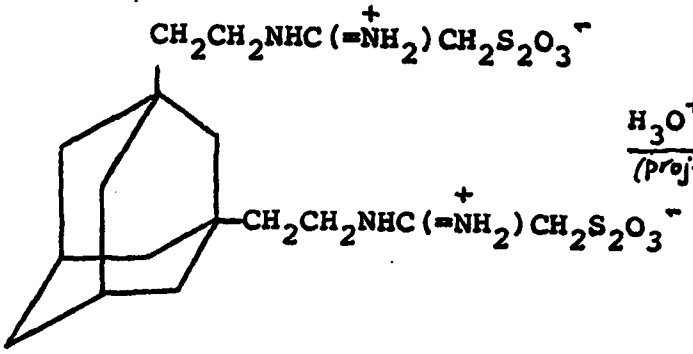
Scheme II: Synthesis of 1,3-di(Aminoethyl)adamantane and Related Amidine Derivatives



2 12 13 14 15

Scheme II, cont'd:



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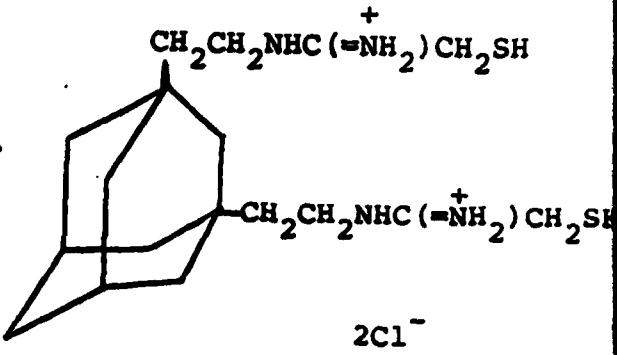
$H_3O^+Cl^-$ (projected)



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H_2O_2 (projected)

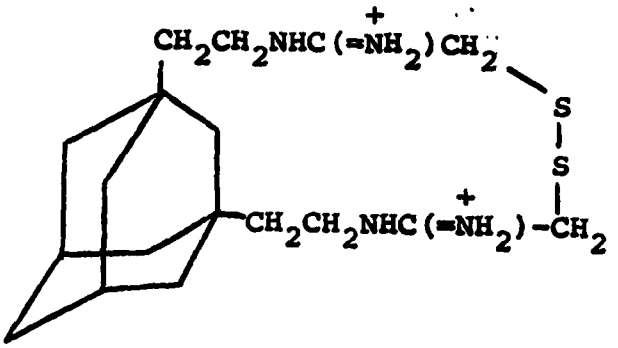

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TABLE I: Adamantane Derivatives Synthesized Thus Far

Compound No. (Schemes I and II)	Yield, %	m.p., °C	Lit. m.p. °C	Solvent for Crystallization	Re
3	90	282-284 (sealed tube)	283-285	Water	1
4	25	320-325	325-330	EtOAc-EtOH (9:1)	2
5	40	275-278	276-278	MeOH-Water	3
6	40	253-255	255	EtOH	5
7	60	356-359 (dec)	>300	MeOH-Water	6
12	70	228-230	234-236	MeOH-Water	6
13	50	181-183	181.5-183	THF-EtOH (4:1)	6
14	50	410-414 (dec) (sealed tube)	new	EtOH-Water	-
15	90	238-240 (dec)	new	EtOH-Water	-
16	95	210-212 (dec)	new	EtOH-Water	-

EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover Unimelt apparatus up to 240°C, and over 240°C on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois. ^{1}H Nmr spectra were obtained on a Varian T60A spectrometer equipped with a Nicolet TT-7 Fourier Transform Accessory. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. The abbreviations s, d, t and m refer to singlet, doublet, triplet, and multiplet. Mass spectra were obtained by Mr. Richard Dvorak using a Hitachi Perkin-Elmer RMU-D6 single focusing mass spectrometer. Spectra were recorded at 70 eV. Relative abundances are reported in general for fragments over 5% of the base peak.

Thin layer chromatographs (tlc) were developed on 8 x 4 cm slides coated with silica gel and a fluorescent indicator (Eastman Chromagram Sheet 6060). Spots were visualized by UV light and/or exposure to iodine vapor. The general statement on the removal of solvents *in vacuo* implies that low boiling solvents were removed in a rotary flash evaporator between 40-90°C at 20-30 Torr.

Synthesis of Starting Material by Literature Methods

1-Adamantanol was prepared in 90% yield by the hydrochloric acid catalyzed hydrolysis of 1-bromoadamantane (1).

1,3-Adamantanediol was prepared by the method of Geluk and Schlaturan (2). It involved the disproportionation of 1-adamantanol by 70% sulfuric acid into 1,3-adamantanediol and adamantane. The yield of the diol was 25% and one of the experimental problems was

to separate the starting alcohol from the required diol.

1,3-Adamantanedicarboxylic acid was synthesized in 40% by reading the corresponding diol with formic acid in the presence of concentrated sulfuric acid (3,4). The dicarboxylic acid was converted to the corresponding diamide by reacting the acid with thionyl chloride to form the bis-acid chloride, followed by the addition of ammonia (5).

Reduction of 1,3-adamantanedicarboxamide with lithium aluminum hydride furnished 1,3-di(aminomethyl)adamantane (6).

The literature method was also utilized to synthesize 1,3-adamantanediacetic acid. The reaction of 1-bromoadamantane with 1,1-dichloroethene and conc. sulfuric acid were the reagents for this preparation (6). The corresponding diamide became available through the standard preparation, namely, first thionyl chloride, then ammonia.

Synthesis of new compounds are described in detail.

1,3-Di(ω-aminoethyl)adamantane Dihydrochloride, 14: 1,3-Adamantanediacetamide, 13: (1.90 g, 0.0076 mole) was added to a suspension of $LiAlH_4$ (1.73 g, 0.046 mole) in ether (80 ml). The mixture was refluxed for 24 hours, and then, excess $LiAlH_4$ destroyed by the careful addition of ice-water. The mixture was filtered and the insoluble precipitate washed with ether (3 x 50 ml). The filtrate was separated and the aqueous layer extracted with ether (3 x 50 ml). All ether solutions were combined, dried (Na_2SO_4) and evaporated to dryness. The resultant oil was dissolved in methanol (20 ml), and reacted with conc. hydrochloric acid (4 ml). Solvents were removed in vacuo

and the salt recrystallized from ethanol-water. It weighed 1.11 g (50%), mp, 410-414° (dec.) in sealed tube. Its ^{1}H nmr spectrum [$(CD_3)_2SO$] should signals at δ 8.07 (broad s, 6H, NH_3^+ protons), 2.74 (broad m, 4H, $C\underline{H}_2N$), 1.98 (broad s, 2H, bridgehead protons), 1.53 (s, 4H, $C\underline{H}_2CH_2N$), 1.36, 1.21 (two broad s, 12H, CH_2's in ring). Anal. Calcd for $C_{14}H_{28}N_2Cl_2$: C, 56.89; H, 9.48. N, 9.48. Found: C, 56.57; H, 9.39; N, 9.33.

Synthesis of 15. A solution of chloroacetonitrile (0.6 g, 0.008 mole) in methanol (8 ml) containing sodium methoxide (0.043 g, 0.0008 mole) was stirred at room temp. for 35 minutes. The amine hydrochloride, 14 (0.9 g, 0.0031 mole) in methanol (8 ml) was added. The pH of the mixture was adjusted to pH of 4 with a methanolic hydrogen chloride solution. After 40 minutes, solvents were removed in vacuo and the solid recrystallized from ethanol-water. The product (1.24 g, 90%) melted at 238-240°C(dec.), ^{1}H nmr [$(CD_3)_2SO$], δ 10.46, 9.73, 9.33 (broad singlets, 6H amidinium protons), 4.53 (s, 4H, $C\underline{H}_2Cl$), 3.31 (broad m, 4H, $C\underline{H}_2N$), 1.99 (broad s, 2H, bridgehead proton) 1.43 (broad s, 6H, CH_2's in ring). Anal. pending.

Synthesis of 16. To a solution of 15 (0.445 g, 0.001 mole) in methanol (7 ml) was added a solution of sodium thiosulfate pentahydrate (0.498 g) in methanol (7 ml) and water (1.3 ml). The mixture was stirred at room temperature for 6 hours. The precipitate was filtered, washed well with water. Recrystallization from methanol-water afforded the Bunte salt as a colorless solid (0.462 g, 95%), mp 210-212°C (dec.); ^{1}H nmr spectra in [$(CD_3)_2SO$] δ 8.93 (broad s, 6H, NH's) 3.85 (s, 4H, $C\underline{H}_2S$), 3.11 (broad m, 4H, $C\underline{H}_2N$), 2.00 (broad s, 2H, bridgehead protons), 1.43, 1.26 (broad s, 16H, all other CH_2's). Anal. Calcd for $C_{18}H_{32}N_4O_6S_4$: C, 40.91, H, 6.10, N, 10.60. Found: C, 40.94; H, 6.10; N, 10.58.

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