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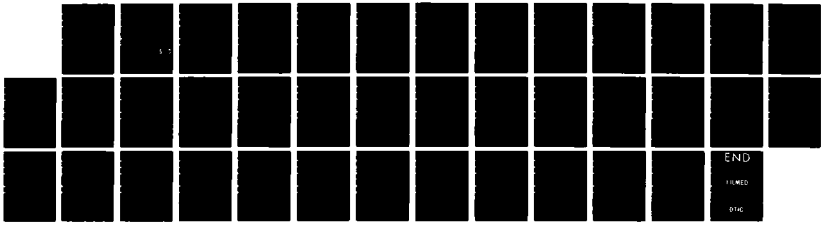

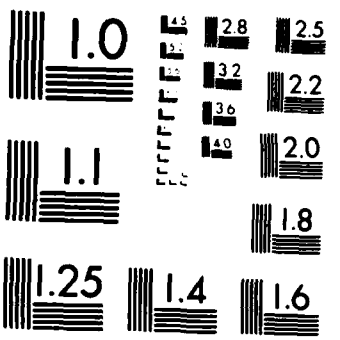

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Synthesis of New Prophylactic Antiradiation Drugs

Annual Report

Ludwig Bauer, Ph.D.
Indra Handa, Ph.D.

August 1982

(For Period August 1, 1981 through July 31, 1982)

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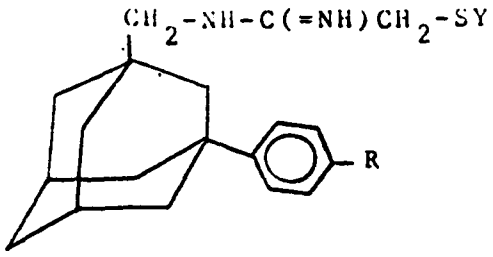
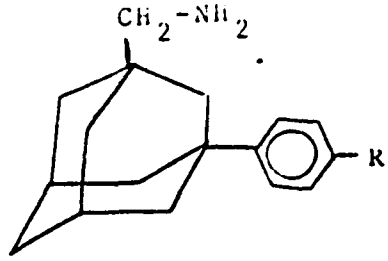
Abstract:

A series of N-(3-aryl-1-adamantanemethyl)-α-mercaptoacetamidines and derivatives, represented by the general formula, A, was synthesized.



A

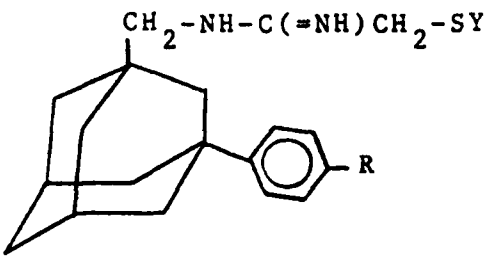


B

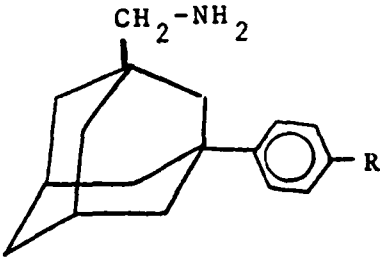
A number of 3-aryl-1-adamantanemethylamines, B, were synthesized first. These amines would become part of the N-substituent of the amidine function, R'NH-C(=NH)-CH_2SY. The specific α-mercaptoacetamidines and derivatives, A, which were prepared, were those in which R=CH_3, and SY is $S_2O_3^-$ (Bunte Salt), SPO_3^{-2} and S-S(disulfide); R=OCH_3, and SY is SH, S-S(disulfide), SPO_3^{-2}; R=F, and SY is SH, S-S(disulfide), SPO_3^{-2}; as well as R=SCH_3, where SY is $S_2O_3^-$ (Bunte Salt), or SPO_3^{-2}. Of the 10 compounds sent to Walter Reed Army Institute for Research, 6 were evaluated for radiation protective potency in mice. The compounds showed some protective activity but did not show unusual promise, in part due to their relatively high toxicity.

I. Synthesis of N-(3-Aryl-1-adamantanemethyl)-α-Mercaptoacetamidines and Derivatives

This report summarizes the work carried out during the period of August 1, 1981-July 30, 1982. It describes the syntheses of a number N-(3-aryl-1-adamantanealkyl)-α-merecaptoacetamidines, and derivatives thereof, summarized by the general structure, A.



A

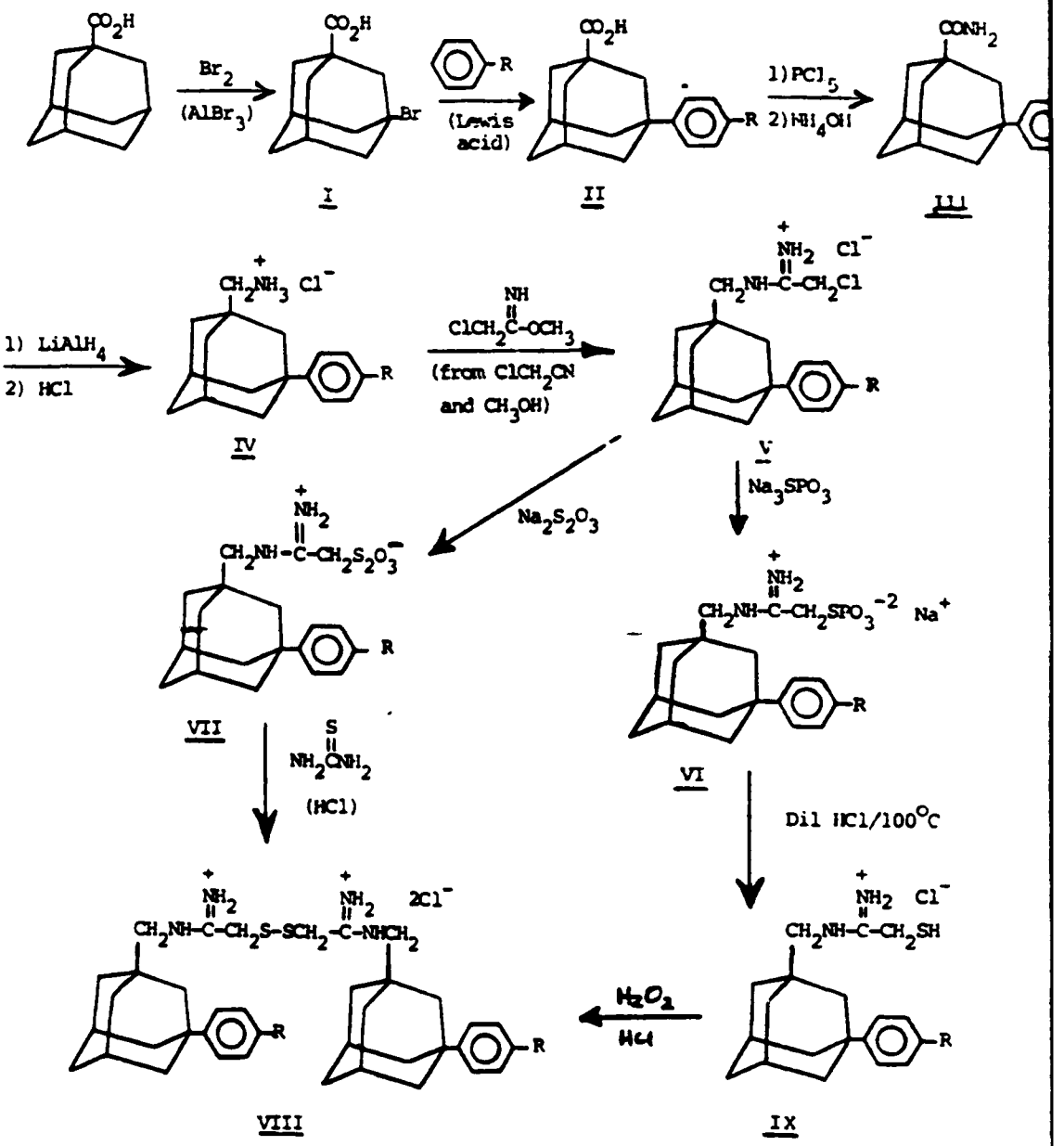


B

The series, A, is based on 3-aryl-1-adamantanemethylamines where the aromatic group on C-3 of the adamantane ring consists of a number of p-substituted arenes. The group R in A (or B) was varied among such substituents as methyl, methoxy, fluoro and methylthio. The sulfur-bearing group, SY, was either mercaptan (SH), disulfide (S-S), thiosulfate ($S-SO_3H$) or phosphorothioate (SPO_3H_2). Although the major thrust was to prepare the mercaptan, in some instances this was not practical. Since phosphorothioates had previously been relative good antiradiation drugs in our earlier N-(adamantanealkyl)-α-mercaptoacetamidine series (7), attempts were made to obtain these derivatives, also. Synthetic sequences are summarized in **Scheme I.**

The aluminum halide catalyzed bromination of 1-adamantanecarboxylic acid produced the essential starting material, namely 3-bromo-1-adamantanecarboxylic acid, I. Substitution of aluminum chloride for aluminum bromide (which was originally recommended in the literature) proved equally effective for this bromi-

SCHEME I



WHERE (a) R = CH_3, the Lewis acid is $ZnCl_2$
(b) R = OCH_3, the Lewis acid is $AlCl_3$
(c) R = F, the Lewis acid is $FeCl_3$
(d) R = SCH_3, the Lewis acid is $ZnCl_2$

nation step and afforded I in yields which compared well to those reported in the literature (1). Friedel-Crafts alkylations of a number of arenes were attempted. The well-established reaction of 1-bromoadamantane with benzene in the presence of ferric chloride formed 1-phenyladamantane in about 60% yield (2). Fortunately, the carboxylic acid group in I did not interfere in the Friedel-Crafts reaction of 3-bromo-1-adamantanecarboxylic with benzene in the presence of aluminum bromide to form 3-phenyl-1-adamantanecarboxylic acid in 74% yield (3). An extension of this electrophilic substitution reaction to toluene, anisole, fluorobenzene and thioanisole provided the corresponding p-substituted 3-phenyl-1-adamantanecarboxylic acids, II, in good yields (**Scheme I**). In these reactions, the arene also served as the solvent. Two of these acids, namely the 3-(p-tolyl) and 3-(p-anisyl) derivatives, IIa, and IIb, have been described previously (4, 5), and were isolated by us in 71 and 60% yield, respectively. No o-isomers were present in the isolated products. With fluorobenzene as the aromatic substrate, the alkylation with I in the presence of aluminum chloride formed IIc in 62% yield. The Friedel-Crafts alkylation of thioanisole by I presented somewhat of a problem. We had hoped to avoid using this relatively expensive and foul-smelling thioether as a solvent for the Friedel-Crafts alkylation. When Friedel-Crafts reactions with thioanisole were carried out either in carbon disulfide ($AlCl_3$ catalyst) or in 1,2-dichloroethane ($AlCl_3$ catalyst), no IId was isolated. The best reaction was the one using excess thioanisole, which resulted in the isolation of IId in 35% yield, if zinc chloride was the Lewis catalyst, and 30% when ferric chloride was used as the catalyst.

Few Friedel-Crafts reactions have been reported on thioanisole. It has been speculated (6) that the thioether group complexes with the catalyst, e.g. aluminum chloride possibly precipitating the thioether as an insoluble complex. Even excess aluminum chloride would not help if the arene complexes and the ring becomes deactivated due to some sulfonium ion character imposed on the substituent:

$$C_6H_5\text{-}S\text{-}CH_3 + AlCl_3 \longrightarrow C_6H_5\text{-}\overset{+}{S}(CH_3)\text{-}\overset{-}{AlCl_3}.$$

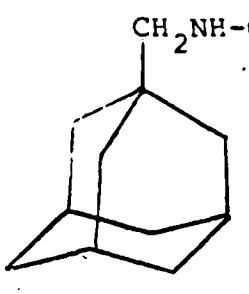
The routine conversion of the acids, II, by phosphorus pentachloride and then ammonium hydroxide produced the amides, III. These amides were sparingly soluble in tetrahydrofuran but were reduced by $LiAWlH_4$ to the amines, IV upon prolonged boiling. These amines were the essential amino components for the amidine synthesis. The established synthetic routes (7) to the corresponding α-mercapto acetamidines and derivatives were applied and are summarized in **Scheme I.**

Chloroacetonitrile was converted to its imidate, in situ, which was reacted with the amine hydrochlorides, IV, to afford α-chloroacetamidine hydrochlorides, V. Nucleophilic displacement reactions with various sulfur-bearing nucleophiles enabled us to obtain the mercaptan or its various derivatives.

The synthesis of α-mercaptoacetamidine hydrochlorides, IX, was achieved best by reacting the chloride, V, first with sodium phosphorothioate to form the corresponding S-alkyl phosphorothioate, VI. It was found that in this series, the phosphorothioates were quite insoluble in water or aqueous alcoholic media and could be recrystallized satisfactorily. These phosphorothioates, VI, were submitted for evaluation as antiradiation agents. Dilute hydrochloric acid hydrolyzed VI to the corresponding thiol, IX. Oxidation of these mercaptans with dilute hydrogen peroxide in dilute hydrochloric acid led to the disulfides, VII. An alternate synthesis of the disulfides was to react V first with sodium thiosulfate to obtain the Bunte salts, VII, which reacted with thiourea in an acid medium to form VIII (8).

Identification of the various sulfur-bearing amidinium salts were made by elemental analyses and ^1H NMR spectral data. The chemical shifts **(Table I)** for the methylenes next to the thiol (SH), disulfide (S-S), Bunte salt (S_2O_3) and

Table I: Chemical Shifts of Methylene Protons (DMSO-d_6) Attached to Sulfur-Bearing Functional Groups in N-(3-Aryl-1-Adamantanemethyl)-α-Mercapto Amidines and Derivatives in Scheme I

Compounds in Scheme I	Sulfur-Bearing Groups			
	CH_2SH[a] IX	CH_2S-S[a] VIII	$CH_2S_2O_3^{-}$[a] VII	$CH_2SPO_3^{-2}$[d] VI
p-Tolyl Series (a)	——	4.08	3.93	3.47[b] 3.87[c]
p-Methoxyphenyl Series (b)	3.52	4.05	——	Ins. in DMSO-d_6 3.90[c]
p-Fluorophenyl Series (c)	3.58	4.09	——	3.47[b] 3.88[c]
p-Methylthiophenyl Series (d)	——	——	3.92	3.45[b] 3.80[c]
 CH_2NH-C(=NH_2^+)CH_2SY X^-	3.53	4.05	3.92	——

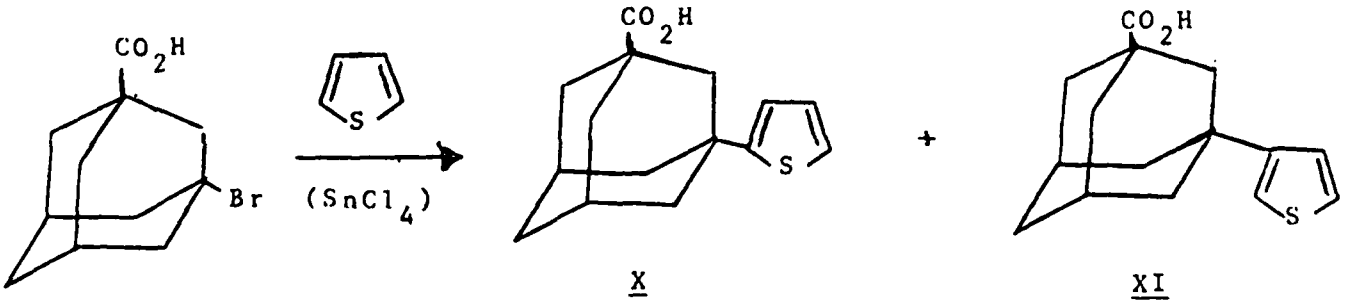
[a]Singlets; [b]In DMSO-d_6, J_{P-SCH}=15.7 Hz; [c]In CD_3CO_2D, J_{P-SCH} is 16.4-16.5 Hz; [d]Doublet.

phosphorothioate (SPO_3^{-2}) were sufficiently characteristic and different in the same solvent. The ^1H NMR spectra of most of these compounds were recorded in DMSO-d_6. However, several of the phosphorothioates were only soluble in CD_3CO_2D and their spectra were obtained in that solvent. The characteristic doublet due to long-range coupling of phosphorus through sulfur with the CH_2 protons (J = 15.5-16.5 Hz) was useful in distinguishing the phosphorothioate, VI, from their hydrolysis products, the thiols, IX. Again, the chemical shifts of the methylene groups next to the mercaptan (eg. IX) was sufficiently different from that attached to the disulfide group (eg. VIII) to permit identification of the product. Table I summarizes the shift data.

II. Other Attempted Syntheses

A. Synthesis of 3-(2- and 3-Thienyl)-1-Adamantanecarboxylic Acids.

Another series of 3-aryl-1-adamantanecarboxylic acids is under investigations. In it, the 3-aryl group is 2- or 3-thienyl. Friedel-Crafts alkylation of thiophene by 1-bromoadamantane has been reported to yield a mixture of 2- and 3-1-adamantyl-2- and 3-thiophenes (9). When this reaction was extended to 3-bromo-1-adamantanecarboxylic acid, a mixture of X and XI was obtained (45%).



X XI

Separation of the acids, their ethyl esters, or amides by a number of different methods has thus far proved to be fruitless. Analytical gas chromatography on the methyl esters suggest the ratio of X and XI to be 2:1. Column chromatography or

HPLC methods have failed to separate the isomers satisfactorily, at this point. Further experiments are planned to separate and utilize these acids in reactions which are outlined in **Scheme I.** Full details of all the successful methods will be provided in the next Report.

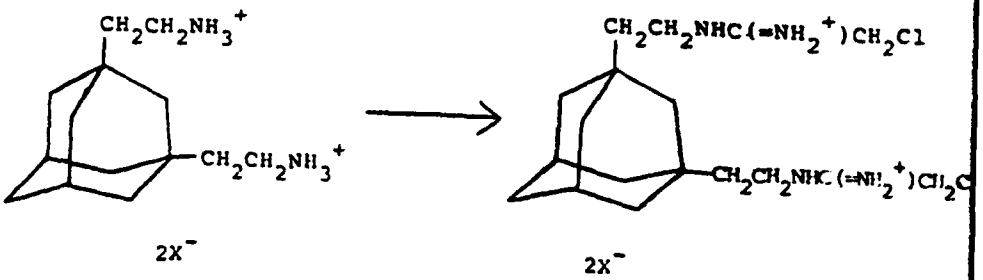
B. Attempted Synthesis of 15-Membered Bis-Amidinium Disulfide, XV.

This part of the Report summarizes our recent attempts to convert the diamine bis-salt, XII, to the cyclic amidine disulfide salt, XV **(Scheme II).** The route we had outlined and pursued previously proceeded via the α-chloro amidinium salt, XIV. The plan also called for the conversion of XIII to the thiol, XIV (Y= . Oxidative cyclization in dilute solutions should lead to the cyclic disulfide, I Starting from the amine (or its salt), XII, to all the subsequent amidines had, as usual, HCl as the accompanying acid.

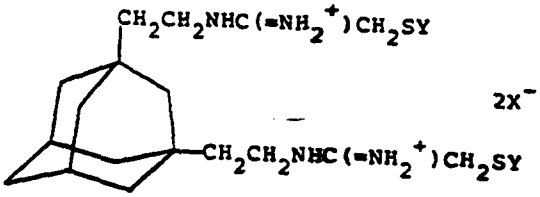
The only crystalline and clearly identifiable product emerging from this project to date was the Bunte salt, XII ($Y=SO_3^-$) (see Report No. 2, Ann. Summary Report, 8/1/80-7/31/81 for its preparation). However, testing data indicated that this compound was far too toxic and did not prove to be a good radioprotective drug.

The whole series, XII XV, was plagued with a number of practical problems. Most of the salts proved difficult to handle and crystallize. And, above all, they appeared very difficult to purify as judged from their poor elemental analyses. Since the hydrochlorides in this series were relatively soluble and difficult to handle, we examined the plausibility of using other acids to form more crystalline and perhaps more readily purifiable salts. p-Toluenesulfonates were chosen (HX = p-$CH_3C_6H_4SO_3H$). Although less soluble salts (XII, XIII) were encountered, the overall synthetic route was fraught with too many problems to assure reasonable success. There still remained problems of purification and identification. Synthe

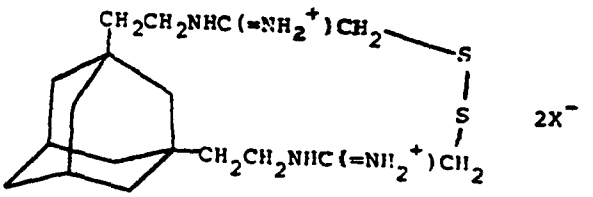
Scheme II



XII VIII



XIV



XV

ses in this area have been temporarily abandoned in order to concentrate on the more productive work described in Part I.

C. Attempted Synthesis of N-Cyano-α-Mercaptoacetamidines.

It might have been interesting to prepare a few N-cyano amidines based on the α-mercaptoacetamidine system. N-Benzyl-N-cyano-α-chloroacetamidine, $ClCH_2C(=N-C\equiv N)NHCH_2C_6H_5$, was prepared by literature methods (10). However, reaction of this halo amidine with $Na_2S_2O_3$ (usual reagent for Bunte salt preparations) produced a black tar after 10 minutes of the reaction on the steam bath. Again, thiourea, which usually reacts with an aliphatic halo group to form an S-isothiuronium salt, produced a black tar from the halo amidine after 5 minutes at 90 °. No further work was carried out or is planned in this area.

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(7) R.D. Westland, M.M. Merz, S.M. Alexander, L.S. Newton, L. Bauer, T.T. Conway, J.M. Barton, K.K. Khullar, P.B. Devdhar and M.M. Grenan, J. Med. Chem. 15, 1313 (1972).

(8) B. Milligan and J.M. Swan, J. Chem. Soc., 2172 (1962).

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Submission of Compounds and Testing Data

The ten (10) compounds which are listed in **Table II** have been submitted for testing in at least 2-g quantities. Six of these compounds have been screened for radioprotective properties in mice. In general, it was found that these compounds were relatively toxic, in the range 7.5–30 mg/Kg. They were also relatively difficult to formulate into an injectionable solution of suspension.

The results of radioprotective evaluation are summarized in **Table II.** The highest non-toxic drug dose ranged from 6 to 16 mg/Kg for 5 of 6 compounds tested, WR-250022 was nontoxic at 30 mg/Kg. It was found that none of those 6 compounds were considered to be "particularly promising" (quoted from Progress Report No. 7, prepared by Dr. Jacob J. Chement, of the Arthur D. Little, Inc., Company on May 10, 1982).

A note on drug toxicities on a millimole/Kg basis might be appropriate (see **Table IV).** It would appear that WR-250021, (Mol. Wt.=759) which is a disulfide (injected i.p.) protected 90% irradiated mice for 30 days at a dose of 15 mg/Kg which is equivalent to 0.020 mmoles/Kg. These data appear favorable when compared to $\left[H_2N\text{-}C(=NH_2^+)CH_2SH\right]_2SO_4^{-2}$ (Mol. Wt. = 278) which protected up to 100% at 12.5 mg/Kg which is equivalent to 0.045 mmoles/Kg (Ref. 7). The phosphorothioate, WR-25022 (Mol. Wt. = 518) was non-toxic at 30 mg/Kg, (equivalent to 0.058 mmoles/Kg), and provided 60% protection at this dose. This phosphorophioate is compared to the 3,5-dimethyl-1-adamantanemethyl analog with an LD_{50} of 0.26 mmoles/Kg but affords 93% protection at 0.017 mmoles/Kg (Ref. 7).

It appears essential to synthesize less toxic substances to those in **Table III.**

Table II

Compounds Submitted For Testing

March 1, 1981 - July 31, 1982.

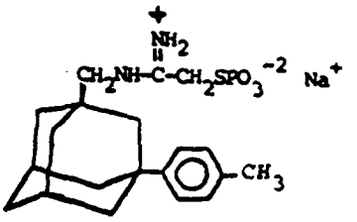
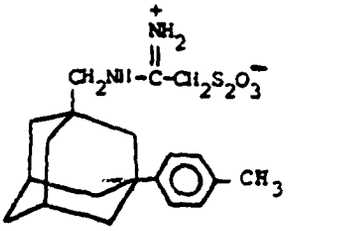
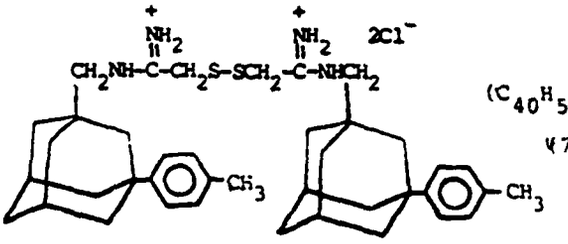
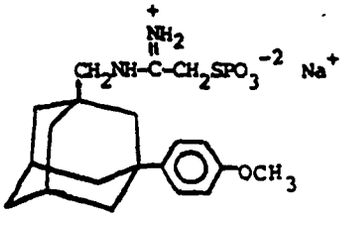
Code Numbers (Date sent)	Structure	(Molecular Formu (Mol. Weight)
IH-276 WR-249914 (11/17/81)		($C_{20}H_{28}N_2O_3PSNa$) (430.22)
IH-292 WR-249939 (12/17/81)		($C_{20}H_{28}N_2O_3S_2$) (408.22)
IH-275 WR-249915 (11/24/81)		($C_{40}H_{56}Cl_2N_4S_2$) (763.45)
IH-2-26 WR-250022 (2/11/82)		($C_{20}H_{28}N_2O_4PSNa \cdot 4H$) (519.29)

Table II Continued

Compounds Submitted For Testing

March 1, 1981 - July 31, 1982.

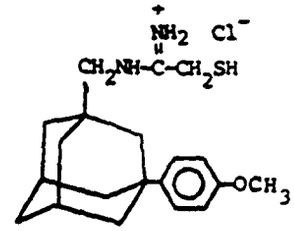
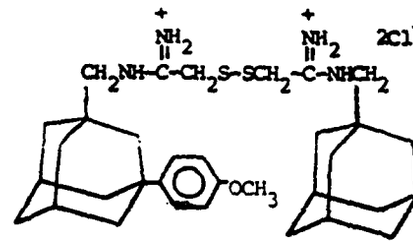
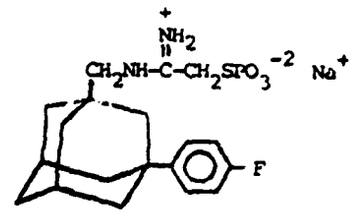
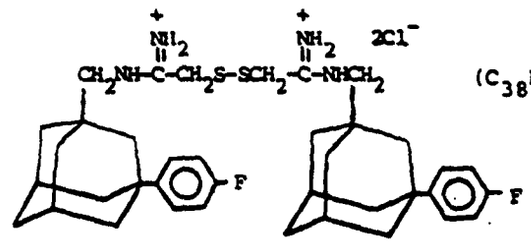
Code Numbers (Date sent)	Structure	(Molecular Formula) (Mol. Weight)
IH-2-19 WR-250023 (2/11/82)		$(C_{20}H_{29}ClN_2OS)$ (380.73)
IH-2-20 WR-250021 (2/11/82)		$(C_{40}H_{56}Cl_2N_4O_2S_2)$ (759.46)
IH-35A (3/17/82)		$(C_{19}H_{25}FN_2O_3PSNa\cdot 1.5H_2O)$ (461.22)
IH-2-36 (3/17/82)		$(C_{38}H_{50}F_2Cl_2N_4S_2)$ (735.40)

Table II Continued

Compounds Submitted For Testing

March 1, 1981 - July 31, 1982.

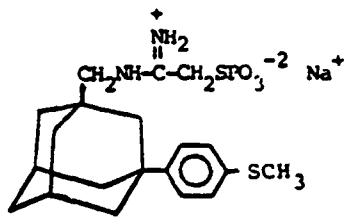
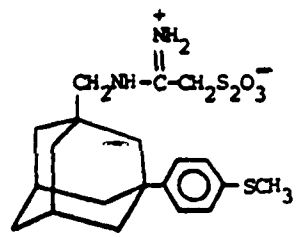
Code Numbers (Date sent)	Structure	(Molecular Formula) (Mol. Weight)
III-124 (7/15/82)		$(C_{20}H_{28}N_2O_3PSNa \cdot 3H_2O)$ (516.27)
IH-2-128 (7/15/82)		$(C_{20}H_{28}N_2O_3S_3)$ (440.22)

Table III:

RADIOPROTECTANT ACTIVITY OF ADAMANTYL-AMIDINIUM COMPOUNDS

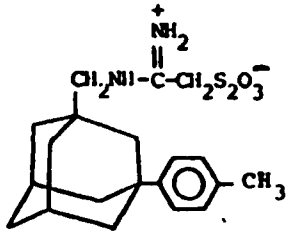
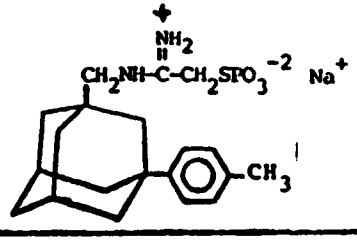
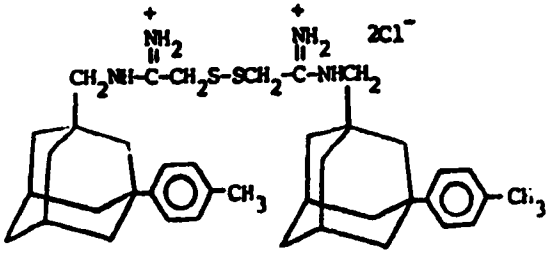
Compound	Structure	Drug Dose mg/kg	Drug Toxcicity	30-Day Survivors
WR 249939		16 8 4 2 0	6/10	30% 80% 10% 30% 0%
WR 249914		30 15 7.5 0	1/10	40% 70% 30% 5%
WR 249915		30 15 7.5 0	10/10 2/10	0% 10% 20% 5%

Table III Continued:

RADIOPROTECTANT ACTIVITY OF ADAMANTYL-AMIDINIUM COMPOUNDS (CONT'D)

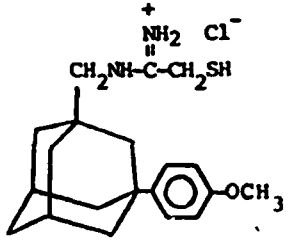
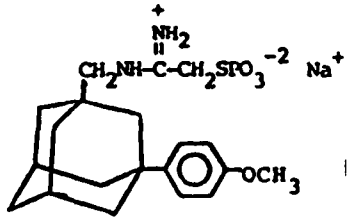
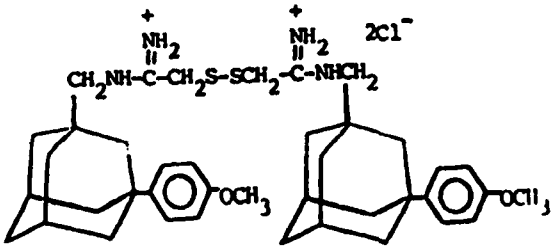
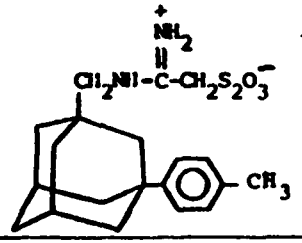
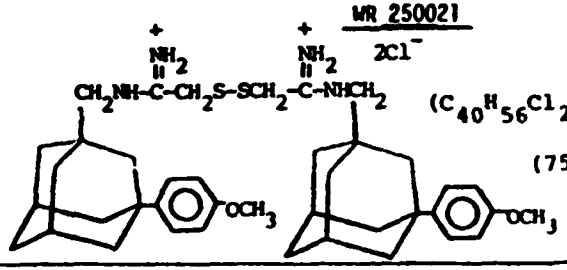
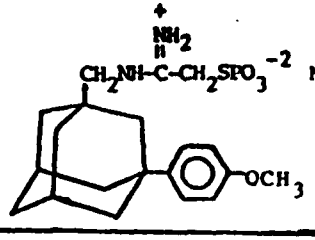
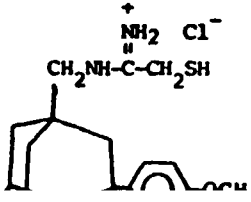
Compound	Structure	Drug Dose mg/kg	Drug Toxicity	30-Day Survivors
WR 250023		16 8 4 2 0		50% 30% 0% 0% 0%
WR 250022		60 30 15 7.5 0	7/10	20% 60% 30% 0% 0%
WR 250021		60 30 15 7.5 0	8/10 10/10	10% 0% 90% 20% 0%

Table IV: DRUG TOXICITY OF AMIDINIUM RADIOPROTECTORS

Compound	Vehicle	Dose* (mg/kg)	Rte of Admin	Deaths	30 Day Survivors
 WR 249939 $(C_{20}H_{28}N_2O_3S_2)$ (408.22)	20% ETOH + TW80	600 300 150 75 37.5 18.75 9.38	ip	5/5 5/5 5/5 5/5 5/5 3/5 0/5	0% 0% 0% 0% 0% 40% 100%
 WR 250021 $2Cl^-$ $(C_{40}H_{56}Cl_2N_4O_2S_2)$ (759.46)	20% ETOH + TW80	600 300 150 75	ip	5/5 5/5 5/5 5/5	0% 0% 0% 0%
 WR 250022 Na^+ $(C_{20}H_{28}N_2O_4PSNa\cdot 4H_2O)$ (518.29)	20% ETOH + TW80	600 300 150 75	ip	5/5 5/5 5/5 3/5	0% 0% 0% 40%
 WR 250023 Cl^- $(C_{20}H_{29}ClN_2OS)$ (380.71)	10% ETOH + TW80	600 300 150 75 37.5 18.75 9.38	ip	5/5 5/5 5/5 5/5 5/5 3/5 0/5	0% 0% 0% 0% 0% 40% 100%

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. ^1H 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, br, s, d, t and m refer to broad, singlet, doublet triplet, and multiplet, respectively.

Thin layer chromatograms (tlc) were developed on 8 x 4 cm slides coated with silica gel containing a fluorescent indicator (Eastman Chromagram Sheets, No. 6060). Spots were visualized by UV light and/or exposure to iodine vapor. The general statement "that solvents were removed or distilled in vacuo", implies that low boiling solvents were evaporated by means of a rotary flash evaporator using a hot water bath (40-90 °C) at 20-30 Torr. All pure samples were dried at room temperature, in vacuo, over $CaCl_2$ or P_2O_5.

Starting materials.— Chloroacetonitrile was purchased from Aldrich Co., Milwaukee, Wisconsin. Trisodium phosphorothioate was made from thiophosphoryl chloride (obtained from Alfa Products, Danver, Ma, 01923) by reaction with sodium hydroxide, according to the method of S. Akerfeldt [Acta. Chem. Scand., 16, 1897 (1962)].

3-Bromo-1-adamantanecarboxylic Acid (I). Bromine (34 ml, 99.55 g, 0.62 mole) and aluminum bromide (20 g, 0.075 mole) were placed in a 3-necked flask equipped with a stirrer, a reflux condenser carrying a $CaCl_2$ tube and a nitrogen

inlet tube. The mixture was cooled for 1 hr in an ice-water bath. To this stirred cold mixture was added 1-adamantanecarboxylic acid (9.0 g, 0.05 mole) in small portions over a period of 4 hr. The mixture was allowed to stand at room temperature overnight and was then heated for 2 hr at 60-70 °C. The reaction mixture was cooled, poured onto ice and then chloroform (200 ml) was added. With constant stirring, sodium bisulfite was added to the mixture until the bromine color had disappeared. The chloroform layer was separated and the aqueous layer extracted twice with 50 ml protions of chloroform. The chloroform layer was washed with water and dried (Na_2SO_4). The solid obtained upon evaporation of the chloroform solution was recrystallized from cyclohexane to give 10.50 g (81%) of 3-bromo-1-adamantanecarboxylic acid, m.p. 143-144 °C [lit. m.p. 146.5 °C; H. Stetter and J. Mayer, Chem. Ber. 95, 667 (1962)]; ^{1}H NMR ($CDCl_3$) δ 1.70 to 2.49 (m, 14H, adamantane protons); 10.20 (br s, 1H, COOH).

Series Starting From 3-(p-Tolyl)-1-adamantanecarboxylic Acid, IIa

3-(p-Tolyl)-1-adamantanecarboxylic Acid (IIa). A mixture of 3-bromo-1-adamantanecarboxylic acid (10.4 g, 0.04 mole), toluene (60 ml) and anhydrous zinc chloride (6.0 g, 0.044 mole) was refluxed for 2 hr. The reaction mixture was cooled, poured into water and the organic layer separated. The aqueous layer was extracted with benzene and the combined organic layer was washed with water and dried (Na_2SO_4). After evaporating solvents, in vacuo, the residue was recrystallized from benzene to give 7.2 g (71%) of IIa, m.p. 175-176 °C [lit. m.p. 175-176 °C; G.I. Danilenko, V.I. Votyakov, O.T. Andreeva, E.I. Broeko, L.V. Denisova, M.N. Shashikhina, M.N. Timofeeva, E.I. Dikolenko, and T.N. Utochka, Khim. Farm. Zh.

10, 737 (1976)]; ^{1}H NMR ($CDCl_3$) δ 1.74 to 2.13 (m, 14H, adamantane protons); 2.31 (s, 3H, CH_3); 7.17 (br s, 4H, aromatic protons).

3-(p-Tolyl)-1-adamantanecarboxamide (IIIa). 3-(p-Tolyl-1-adamantanecarboxylic acid (8.5 g, 0.031 mole), phosphorus pentachloride (6.46, 0.031 mole) and carbon tetrachloride (60 ml) were refluxed for 1 hr. Volatile liquids were removed by vacuum evaporation by means of a flash evaporator. The residue was extracted 3 times with 20 ml of carbon tetrachloride. After distillation of this solution, in vacuo, the residue was dissolved in anhydrous tetrahydrofuran (30 ml). This solution was added with stirring to ice-cold 28% ammonium hydroxide (80 ml). After stirring overnight, the solid which formed was filtered off and recrystallized from ethanol. The yield was 6.5 g (76%), m.p. 124-125 °C. [lit. m.p. 127-128 °C; G.I. Danilenko et al., Khim. Farm. Zh. 10, 737 (1976)].

3-(p-Tolyl)-1-adamantanemethylamine Hydrochloride (IVa). A suspension of 3-(p-tolyl)-1-adamantanecarboxamide (8 g, 0.29 mole) in anhydrous ether (150 ml) was added dropwise to a well-stirred suspension of lithium aluminium hydride (5.8 g, 0.15 mole) in anhydrous ether (400 ml). The reaction was carried in a 3-necked flask equipped with an efficient water-cooled condenser carrying a calcium chloride tube, a dropping funnel and a magnetic stirrer. After the addition was complete, the reaction mixture was heated under reflux for 24 hr. The reaction mixture was then cooled to 0 °C and water (5.9 ml) was added dropwise, followed by 10% sodium hydroxide (17.7 ml) and then more water (5.9 ml). This procedure is designed to produce a filterable form of alumina. The precipitate was filtered and washed with three 50 ml portions of ether. The combined ether layers were dried over anhydrous magnesium sulfate and concentrated to dryness, in vacuo. The residue was dissolved in dry ether (50 ml), filtered from a small amount of insoluble material and treated with dry hydrogen chloride gas. The hydrochloride was filtered and recrystallized from aqueous ethanol to

give 6.4 g (75%), m.p. 214-216 °C; ^{1}H NMR (DMSO-d_6) δ 1.57 to 1.75 (m, 12H, six CH_2's of the adamantane ring), 2.16 (s, broad, 2H, bridgehead protons), 2.26 (s, 3H, CH_3), 2.54 (s, broad, 2H, CH_2N) 7.17 (s, 4H, aromatic), 7.97 (s, broad, 3H, NH's).

Anal. Calcd. for $C_{18}H_{26}NCl$: C, 74.06; H, 8.97; N, 4.79. Found: C, 74.23; H, 8.93; N, 4.77.

N-[3-(p-Tolyl)-1-adamantanemethyl]-α-chloroacetamidine Hydrochloride (Va). Chloroacetonitrile (1.13 g, 0.015 mole) was added to a solution of sodium methoxide [prepared from 0.034 g of sodium in methanol (9 ml)] and stirred at room temperature for 1 hr. A solution of 3-(p-tolyl)-1-adamantanemethylamine hydrochloride (4.37 g, 0.015 mole) in methanol (20 ml) was added and the pH adjusted to 4 by adding methanolic HCl. The pH was tested by means of wet ALKACID^{R} Test paper (Fisher Scientific Co.). The reaction mixture was stirred at room temperature for 2 hr. Solvents were evaporated, in vacuo, at room temperature and the residue was triturated with acetone. The colorless powder (4.7 g, 85%) was recrystallized from aqueous ethanol, m.p. 130-132 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 1.59 to 1.76 (m, 12H, six CH_2's of adamantane ring), 2.17 (s, broad, 2H, bridgehead protons), 2.25 (s, 3H, CH_3), 3.15 (s, 2H, CH_2N) 4.54 (s, 2H, CH_2-Cl), 7.17 (s, 4H, aromatic) and 9.59 (s, broad, 3H, NH-C=$\overset{+}{N}H_2$).

Anal. Calcd. for $C_{20}H_{28}N_2Cl_2$: C, 65.31; H, 7.61; N, 7.62. Found: C, 64.91; H, 7.66; N, 7.31.

Sodium S-{N-[3-(p-Tolyl)-1-adamantanemethyl]carboxamidiniummethyl} Phosphorothioate (VIa). A solution of N-[3-(p-tolyl)-1-adamantylmethyl]-α-chloroacetamidine hydrochloride (3.6 g, 0.01 mole) in 50% ethanol (20 ml) was added to a solution of freshly prepared trisodium phosphorothioate (1.8 g, 0.01 mole) in water (15 ml) and the reaction mixture was stirred for 30 min at room temperature in an atmosphere of nitrogen. During this time a heavy precipitate was formed

which was filtered, and washed first with water, then with ethanol, and dried in a vacuum desiccator over P_2O_5. It weighed 2.8 g (65%). It was recrystallized from methanol and ether, m.p. 125-128 °C; ^{1}H NMR (CD_3COOD) 1.70 to 1.83 (m, 12H, six CH_2's of adamantane ring), 2.03 (s, 2H, bridgehead protons), 2.27 (s, 3H, CH_3), 3.15 (2H, CH_2N), 3.87 (d, 2H, CH_2-S-P, J_{P-H} = 16.4 Hz) 7.17 (s, 4H, aromatic); IR (KBr) showed $\delta(C=NH_2)$ and $\gamma(C=N)$ absorptions at 1680 and 1650 cm^{-1}, respectively.

Anal. Calcd. for $C_{20}H_{28}N_2O_3NaSP$: C, 55.81; H, 6.52; N, 6.51, S, 7.41. Found: C, 55.83; H, 7.23; N, 6.20; S, 7.26.

A 2-gram sample was prepared and sent for testing on 11/17/81.

S-{ N- [3-(p-Tolyl)-1-adamantanemethyl]carboxamidiniummethyl} Thiosulfate (VIIa). To a solution of N- [3-(p-tolyl)-1-adamantanemethyl]-α-chloroacetamidine hydrochloride (3.67 g, 0.01 mole) in 50% ethanol (20 ml) was added an aqueous solution of sodium thiosulfate pentahydrate (2.48 g, 0.01 mole in 10 ml). The mixture was stirred at 80-85 °C for 1 hr. The reaction mixture was concentrated, in vacuo, to a small volume when a solid separated which was collected, washed with water and dried. The product, 3.42 g (84%), was recrystallized from ethanol-ether, m.p. 184-186 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 1.55-1.75 (m, 12H, six CH_2's of adamantane ring), 2.13 (s, broad, 2H, bridgehead protons), 2.25 (s, 3H, CH_3), 3.04 (s, 2H, CH_2N), 3.93 (s, 2H, CH_2-S) 7.16 (s, 4H, aromatic) and 8.65 (s, broad, 3H, NH-C=$\overset{+}{N}H_2$); IR (KBr) showed $\delta(C=NH_2^+)$ and $\nu(C=N)$ at 1690 and 1640 cm^{-1}, respectively.

Anal. Calcd. for $C_{20}H_{28}N_2S_2O_3$: C, 58.79; H, 6.91; N, 6.85; S, 15.70. Found: C, 59.14; H, 6.90; N, 6.70; S, 16.15.

A 2-gram sample was submitted for testing on 12/17/81.

N-[3-(p-Tolyl)-1-adamantanemethyl]carboxamidiniummethyl Disulfide Dihydrochloride (VIIIa). A mixture of the Bunte Salt (VIIa, 4 g, 0.01 mole), thiourea

(0.76 g, 0.01 mole) and 1N HCl (25 ml) was heated at 90-95 °C for 2.5 hr. The reaction mixture was then cooled. The white solid was filtered and washed with water. The product was dissolved in cold methanol and filtered again to remove some sulfur which had coprecipitated. These reactions are known to produce some sulfur as by-product; for an example, see B. Milligan and J.M. Swan, J. Chem. Soc., 2172 (1962). The methanol solution was concentrated, in vacuo, and the product crystallized upon adding a small amount of ether. The yield was 1.60 g (45%), m.p. 176-178 °C (dec); ^{1}H NMR (DMSO-d_6) 1.60 to 1.69 (m, 24H, twelve CH_2's of adamantane ring), 2.11 (s, 4H, bridgehead protons), 2.24 (s, 6H, two CH_3's) 3.11 (s, br, 4H, two CH_2N's), 4.08 (s, 4H, $C\underline{H}_2S\text{-}S\underline{C}H_2$) 7.15 (s, 8H, aromatic), 10.05, 9.63, 9.10, (broad NH-C=NH_2); IR (KBr) showed the typical medium $\delta(C{=}NH^+_2)$ and strong $\gamma(C{=}N^+)$ absorption at 1695 and 1650 cm^{-1}, respectively.

Anal.: Calcd. for $C_{40}H_{56}N_4Cl_2S_2 \cdot 2H_2O$: C, 62.87; H, 7.92; N, 7.33; S, 8.38. Found: C, 62.89; H, 7.41; N, 7.19; S, 7.79.

Series Starting from 3-(p-Methoxyphenyl)-1-adamantanecarboxylic Acid

3-(p-Methoxyphenyl)-1-adamantanecarboxylic Acid (IIb). 3-Bromo-1-adamantanecarboxylic acid (10.5 g, 0.04 mole) was added to a mixture of aluminium chloride (13.25 g) and dry anisole (120 ml) at -10 °C over a period of 1 hr. The reaction mixture was stirred at room temperature for 24 hr and then poured into a mixture of ice-water (375) and conc. hydrochloric acid (40 ml). Sodium chloride was added to the mixture until the aqueous phase was saturated. The organic material was extracted with four-100 ml portions of ethyl acetate. The extracts were treated with 2 N sodium carbonate solution (60 ml) and saturated sodium chloride solution (140 ml). Since the sodium salt of this high molecular weight

was insoluble in water and in organic solvents, this method separated this acid from neutral components and the starting acid, I, whose sodium salt was soluble in this medium. The sodium salt of IIb was filtered from the aqueous-ethyl acetate mixture. The salt was suspended in dilute HCl to effect double decomposition to release the acid, IIb, which was extracted by CH_2Cl_2. The CH_2Cl_2 solution was washed with water and dried (Na_2SO_4). After solvents were evaporated, the acid was recrytstallized from methanol to yield 6.8 g (60%), m.p. 165-166 °C [lit. m.p. 167-168.5 °C, ref. is the one quoted below for the NMR data]; ^1H NMR ($CDCl_3$) δ 1.73-2.02 (m, 12H, six CH_2's of adamantane ring), 2.22 (br, s, 2H, bridgehead H's), 3.78 (s, 3H, OCH_3), 6.83 and 7.27 (m, 4H, parts of the AA'BB' pattern of arene), 10.04 (s, 1H, CO_2H). [The NMR spectra in $CDCl_3$ is in agreement with the one reported in the literature; V.W. Fischer, C.A. Grob and H. Katayama, Helv. Chim. Acta, 59, 1953, (1976).]

3-(p-Methoxyphenyl)-1-adamantanecarboxamide (IIIb). 3-(p-Methoxyphenyl)-1-adamantanecarboxylic acid (2.36 g, 0.01 mole), phosphorus pentachloride (2.08, 0.01 mole) and carbon tetrachloride (20 ml) were refluxed for 1 hr. Volatile materials were distilled in a flash evaporator and the residue was triturated three times with 20 ml carbon tetrachloride. After distilling off carbon tetrachloride, in vacuo, the residual oil was dissolved in dry benzene (30 ml). This solution was added to a stirred ice-cold 28% ammonium hydroxide solution (80 ml). After stirring overnight, the powder was filtered off and was recrystallized from methanol. The yield was 2.3 g (82%) m.p., 145-146 °C; IR (Nujol), 1650 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.73 to 1.96 (m, 12H, six CH_2's of adamantane ring); 2.23 (m; 2H, bridgehead protons), 3.78 (s, 3H, CH_3O); 5.60 (br, s, 2H, NH_2) 6.84 and 7.27 (AA'BB', 4H aromatic, p-substituted phenyl system).

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 75.74; H, 8.12; N, 4.90. Found: C, 75.53; H, 7.98; N, 4.85.

3-(p-Methoxyphenyl)-1-adamantanemethylamine Hydrochloride (IVb). A suspension of 3-(p-methoxyphenyl)-1-adamantanecarboxamide (6 g, 0.021 mole) in anhydrous ether (100 ml) was added dropwise to a well stirred suspension of lithium aluminium hydride (5.0 g, 0.13 mole) in anhydrous ether (400 ml). The reaction was carried in a 3-necked flask equipped with an efficient water-cooled condenser carrying a calcium chloride tube, a dropping funnel and a magnetic stirrer. After the addition was complete the reaction mixture was heated under reflux for 24 hr. It was then cooled to 0 °C and water (5.0 ml) was added dropwise, followed by 10% sodium hydroxide (15.0 ml) and finally another 5.0 ml water. Solids were filtered off and the insoluble material was washed with three 50 ml portions of ether. The combined ether filtrates were dried ($MgSO_4$) and concentrated to dryness, in vacuo. Dry ether (50 ml) was added to the residue, a small amount of insoluble material filtered off, and the filtrate was treated with dry hydrogen chloride gas. The hydrochloride was filtered and recrystallized from aqueous ethanol to give 5.0 g (77%), m.p. 237-238 °C; ^{1}H NMR (DMSO-d_6) δ 1.56 to 1.76 (m, 12H, six CH_2's of the adamantane ring), 2.12 (s, broad, 2H, bridgehead protons), 3.72 (s, 3H, OCH_3) 2.55 (s, broad, 2H, CH_2N) 6.84-7.28 (complex m, p-substituted phenyl, 4H, aromatic), 8.06 (s, broad, 3H, NH's).

Anal. Calcd. for $C_{18}H_{26}NClO$: C, 70.19; H, 8.51; N, 4.54. Found: C, 69.94; H, 8.30; N, 4.40.

N-[3-(p-Methoxyphenyl)-1-adamantanemethyl]-α-chloroacetamidine Hydrochloride (Vb). Chloroacetonitrile (1.10 g, 0.014 mole) was added to a solution of sodium methoxide [prepared from 0.033 g of sodium in methanol (9 ml)] and stirred at room temperature for 1 hr. A solution of 3-(p-methoxyphenyl)-1-

adamantanemethylamine hydrochloride (4.50 g, 0.014 mole) in methanol (15 ml) was added and the pH was adjusted to 4 by adding methanolic HCl. The reaction mixture was stirred at room temperature for 2 hr. Solvents were evaporated, in vacuo, at room temperature and residue was triturated with ether to give a colorless powder (5.1 g, 96%), which was recrystallized from aqueous ethanol, m.p. 184-186 ^{o}C (dec.); ^{1}H NMR (DMSO-d_6) δ 1.59 to 1.68 (m, 12H, six CH_2's of adamantane ring), 2.11 (s, broad, 2H, bridgehead protons), 3.72 (s, 3H, OCH_3) 3.15 (s, 2H, CH_2N), 4.55 (s, 2H, CH_2Cl), 7.29-6.85 (complex m, p-substituted phenyl, 4H, aromatic) and 8.86 (s, broad, 3H, NH-C=NH_2); IR (Nujol), δ(C=NH_2) and ν(C=N) at 1700 and 1650 cm^{-1}, respectively.

Anal. Calcd. for $C_{20}H_{28}N_2Cl_2$: C, 62.62; H, 7.36; N, 7.30. Found: C, 62.25; H, 7.35; N, 7.63.

Sodium S-[N-[3-(p-Methoxyphenyl)-1-adamantanemethyl]carboxamidiniummethyl] Phosphorothioate (VIb). A solution of N-[3-(p-methoxyphenyl)-1-adamanthyl-methyl]-α-chloroacetamidine hydrochloride (2.85 g, 0.0074 mole) in 50% ethanol (10 ml) was added to a solution of trisodium phosphorothioate (1.34 g, 0.0074 mole) in water (22 ml) and the reaction mixture was stirred at room temperature in an atmosphere of nitrogen. After 30 min, a solid was formed which was filtered, washed with water and dried. The salt was dissolved in cold methanol, filtered from a small amount of insoluble material and precipitated by adding ether. The proudct was filtered and dried, m.p. 125-127 ^{o}C (dec.). The yield was 2.5 g (75%); ^{1}H NMR (CD_3COOD), 1.70 to 1.89 (m, 12H, six CH_2's of adamantane ring) 2.19 (s, broad, 2H, bridgehead protons), 3.15 (s, 2H, CH_2NH), 3.75 (s, 3H, OCH_3) 3.90 (d, 2H, CH_2-S-PO_3, J=16.5 Hz), 6.84-7.29 (complex m, p-substituted phenyl, 4H, aromatic); IR (KBr) showed δ(C=NH_2) and ν(C=N) at 1670, 1640 cm^{-1}, respectively.

Anal. Calcd. for $C_{20}H_{28}N_2SPO_4Na \cdot 4H_2O$: C, 46.30; H, 7.00; N, 5.40; S, 6.17. Found: C, 46.32; H, 6.75; N, 5.33; S, 6.20.

(A 2-gram sample of this compound has been sent for testing.)

N-[3-(p-Methoxyphenyl)-1-adamantanemethyl]-α-mercaptoacetamidinium Chloride (IXb). A solution of N-[3-(p-methoxyphenyl)-1-adamantanemethyl]-α-chloroacetamidine hydrochloride (3.83 g, 0.01 mole) in 50% ethanol (15 ml) was added to a solution of trisodium phosphorothioate (1.8 g, 0.01 mole) in water (30 ml) and the mixture was stirred for 30 min (nitrogen atmosphere). The salt, VIb, was not isolated but was hydrolyzed by 6N hydrochloric acid (17 ml) at 85-90 °C for 20 min. The mixture was cooled, concentrated to about half its volume, in vacuo, and the aqueous layer was decanted from a gum. This gum was dissolved in ethanol, filtered and the product precipitated by adding ether. The colorless solid weighed 3.0 g (78%), m.p. 174-176 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 1.59-1.67 (m, 12H, six CH_2's of adamantane ring), 2.12 (s, broad, 2H, bridgehead protons) 3.06 (s, broad, 2H, CH_2N) 3.52 (s, 2H, CH_2S), 3.72 (s, 3H, OCH_3), 6.81-7.27 (complex m, p-substituted phenyl, 4H), 9.47, 8.89 (br, s, 3H, NH-C=NH_2) IR (KBr) shows δ(C=NH_2) and ν(C=N) at 1690, 1650 cm^{-1}, respectively.

Anal. Calcd. for $C_{20}H_{29}ClN_2OS$: C, 63.01; H, 7.67; N, 7.35; S, 8.40. Found: C, 62,83; H, 7.58; N, 7.12; S, 8.15.

(A 2-gram sample of this compound was prepared and has been sent for testing.)

N-[3-(p-Methoxyphenyl)-1-adamantanemethyl]carboxamidiniummethyl Disulfide Dihydrochloride (VIIIb). Hydrogen peroxide (3%, 11.5 ml) was added dropwise over a period of 1.5 hr to a stirred mixture of the mercaptan (IXb, 1.9 g, 0.005 mole), methanol (5 ml) and hydrochloric acid (1:1, 10 ml). The reaction mixture was stirred at room temperature for another 1.5 hr, concentrated in vacuo, and filtered. The product was recrystallized from ethanol-ether, m.p. 230-

232 °C (dec.). it weighed 0.90 g (78%); ^{1}H NMR (DMSO-d_6) δ 1.61-1.64 (m, 24H, twelve CH_2's) of adamantane ring), 2.10 (s, broad, 4H, bridgehead protons), 3.11 (s, broad, 4H, two CH_2N), 3.71 (s, 6H, two OCH_3's) 4.05 (s, 4H, CH_2S-SCH_2), 6.84-7.26 (complex m, p-substituted phenyl, 8H, aromatic) 9.01, 9.56, 9.96 (s, broad, 6H, two NH-C=NH_2's); IR (KBr), δ(C=NH_2) and ν(C=N) at 1690 and 1640 cm^{-1}, respectively.

Anal. Calcd. for $C_{40}H_{56}N_4Cl_2S_2O_2$: C, 63.20; H, 7.43 N, 7.37; S, 8.42. Found: C, 63.65; H, 7.52; N, 7.29; S, 8.34.

Series Starting from 3-(p-Fluorophenyl)-1-adamantanecarboxylic Acid

3-(p-Fluorophenyl)-1-adamantanecarboxylic Acid (IIc). A mixture of 3-bromo-1-adamantanecarboxylic acid (2.59 g, 0.01 mole), fluorobenzene (15 ml) and ferric chloride (1 g) was refluxed for a period of 3 hr. The reaction mixture was cooled and poured into ice-water (200 ml) and hydrochloric acid (15 ml). The organic layer was separated and the aqueous layer was extracted with ether (2x50 ml). The combined organic extract was washed with water, dried (Na_2SO_4) and solvent removed, in vacuo. The residue was recrystallized from methanol, m.p. 168-170 °C, and weighed 1.7 g (62%); ^{1}H NMR (CCl_4) δ 1.75-2.01 (m, 12H, six CH_2's of adamantane ring), 2.22 (s, broad, 2H, bridgehead protons), 6.76 to 7.29 (m, 4H, aromatic) 11.82 (s, 1H, COOH); IR (Nujol) showed the C=O stretching band at 1690 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}O_2F$: C, 74.41; H, 6.98. Found: C, 74.11; H, 6.90.

3-(p-Flurophenyl)-1-adamantanecarboxamide (IIIc). 3-(p-Fluorophenyl)-1-adamantanecarboxylic acid (8.22 g, 0.03 mole), phosphorus pentachloride (6.25 g, 0.03 mole) and carbon tetrachloride (80 ml) were refluxed for 1 hr. Solvents were distilled in vacuo. To remove some volatile phosphorus halides, portions of carbon

tetrachloride (20 ml) were added thrice and distilled in vacuo. The residue was then dissolved in anhydrous benzene (30 ml). This solution was added to stirred ice-cold 28% ammonium hydroxide (80 ml). After stirring overnight, the powder was filtered and was recrystallized from ethanol. The yield was 5.3 g (64%), m.p. 160-162 °C; ^{1}H NMR ($CDCl_3$) δ 1.74-1.97 (m, 12H, six CH_2's of adamantane ring), 2.22 (s, broad, 2H, bridgehead protons), 5.73 (s, broad, 2H, $CONH_2$) and 6.82-7.44 (m, 4H, aromatic). IR (Nujol), C=O stretching band at 1670 cm^{-1}.

Anal. Calcd. for $C_{17}H_{28}FNO$: C, 74.68; H, 7.38; N, 5.12. Found: C, 74.49; H, 7.15, N, 5.08.

3-(p-Fluorophenyl)-1-adamantanemethylamine Hydrochloride (IVc). The reaction was carried out in a 3-necked flask equipped with an efficient water-cooled condenser, a calcium chloride tube and a dropping funnel and was stirred by means of a magnetic stirrer. A suspension of 3-(p-fluorophenyl)-1-adamantanecarboxamide (4.6 g, 0.016 mole) in anhydrous ether (75 ml) was added dropwise to a well-stirred suspension of lithium aluminium hydride (3.99 g, 0.10 mole) in anhydrous ether (300 ml). After the addition was complete, the reaction mixture was heated under reflux for 24 hr. After cooling to 0 °C, water (4.0 ml) was added dropwise, followd by 10% sodium hydroxide (12.0 ml) and again 4.0 ml water. Solids were filtered and washed with three 50 ml portions of ether. The combined ether filtrates were dried (anhydrous $MgSO_4$) and concentrated to dryness, in vacuo. The residue was redissolved in dry ether (50 ml), filtered from a small amount of insoluble material, and treated with dry hydrogen chloride gas. The hydrochloride was filtered and recrystallized from aqueous ethanol to give 3.8 g (76%), m.p. 208-210 °C; ^{1}H NMR (DMSO-d_6) δ 1.57 to 1.77 (m, 12H, six CH_2's of the adamantane ring), 2.14 (s, broad, 2H, bridgehead protons), 2.56 (s, broad, 2H, CH_2N) 6.95-7.55 (complex m, 4H, aromatic) 8.06 [s, broad, 3H, NH-C(=NH_2^+)].

Anal. Calcd. for $C_{17}H_{21}NFCl$: C, 68.99; H, 7.84; N, 4.73. Found: C, 69.03; H, 7.85; N, 4.65.

N-[3-(p-Fluorophenyl)-1-adamantanemethyl]-α-chloroacetamidine Hydrochloride (Vc). Chloroacetonitrile (1.17 g, 0.015 mole) was added to a stirred solution of sodium methoxide (prepared from 0.035 g of sodium in 9 ml methanol) at room temperature over 1 hr. A solution of 3-(p-fluorophenyl)-1-adamantanemethylamine hydrochloride (4.60 g, 0.015 mole) in methanol (10 ml) was added and the pH was adjusted at 4 by adding a small quantity of methanolic HCl. The reaction mixture was stirred at room temperature for 2 hr. Solvents were distilled off in vacuo at room temperature and the residue was triturated with ether. The insoluble colorless solid (5.5 g, 95%) was recrystallized from aqueous ethanol, m.p. 120-122 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 1.59 to 1.72 (complex m, 12H, six CH_2's of adamantane ring); 2.11 (br, s, 2H, bridgehead protons), 3.17 (br, s, $C\underline{H}_2N$), 4.58 (s, $C\underline{H}_2Cl$), 6.95-7.54, (complex m, 4H, arene H's), 9.01 (br, s, 3H, NH-C=NH_2^+); IR (Nujol), δ(C=NH_2) and ν(C=N) at 1700 and 1650 cm^{-1}, respectively.

Anal. Calcd. for $C_{19}H_{25}Cl_2FN_2$: C, 61.42; H, 6.78; N, 7.54. Found: C, 60.97; H, 7.00; N, 7.27.

Sodium S-{N[3-(p-Fluorophenyl)-1-adamantanemethyl]carboxamidiniummethyl} Phosphorothioate (VIc). A solution of N-[3-(p-fluorophenyl)-1-adamantylmethyl]-α-chloroacetamidine hydrochloride (2.95 g, 0.01 mole) in 50% ethanol (20 ml) was added to a solution of trisodium phosphorothioate (1.8 g, 0.01 mole) in water (32 ml) and the reaction mixture was stirred for 30 min at room temperature in an atmosphere of nitrogen. During this time a solid formed which was filtered, washed with water, then aqueous ethanol (50%), and dried (2.30 g). It was recrystallized from methanol-ether, m.p. 98-100 °C to yield 2.2 g (50%) of VIc; ^{1}H NMR (CD_3COOD) δ 1.68 to 1.83 (m, 12H, six CH_2's of adamantane ring), 2.18 (s, broad, 2H, bridgehead protons), 3.15 (s, 2H, CH_2N), 3.88 (d, 2H, CH_2-S-P, J=16.5

Hz) and 6.84-7.46 (complex m, 4H, aromatic); IR (KBr) δ ($C=NH_2$) and ν(C=N) at 1700 and 1630 cm^{-1}, respectively.

Anal. Calcd. for $C_{19}H_{25}N_2FO_3NaSP \cdot 1.5\ H_2O$: C, 49.43; H, 6.11; N, 6.07; S, 6.93. Found: C, 49.80; H, 6.47; N, 5.56; S, 6.25.

N-[3-(p-Fluorophenyl)-1-adamantanemethyl]-α-mercaptoacetamidinium Chloride (VIIc). A solution of N-[3-(p-fluorophenyl)-1-adamantylmethyl]-α-chloroacetamidine hydrochloride (3.2 g, 0.0086 mole) in 50% ethanol (10 ml) was added to an aqueous solution of trisodium thiophosphate 1.55 g, (0.0086 mole) in 25.8 ml water . The reaction mixture was stirred at room temperature (nitrogen atmosphere) for 10 min. Without isolating the intermediate VIc, 6 N hydrochloric acid (15.5 ml) was added and the reaction mixture was heated at 85-90 °C for 20 min. The mixture was concentrated, in vacuo, diluted with water and the solid filtered. Recrystallization from ethanol-ether provided IXc, 1.5 g (47%), m.p. 198-200 °C; ^1H NMR: (DMSO-d_6) δ 1.61 to 1.75 (complex m, 12H, six CH_2 of adamantane ring), 2.14 (s, broad, 2H), 3.17 (2H, CH_2-N) 3.58 (s, broad, 2H, CH_2S) 7.02 to 7.18 (m, 4H, aromatic) 10.50, 10.22, (s, 3H, NH-C=NH_2). IR (KBr) showed δ ($C=NH_2$) and ν(C=N) at 1640 and 1620 cm^{-1} respectively.

Anal. Calcd. for $C_{19}H_{26}N_2ClFS \cdot 1.5\ H_2O$: C, 57.61; H, 7.39; H, 7.07, S, 8.08. Found: C, 57.92; H, 6.68; N, 6.87; S, 8.38. Upon further recrystallization and reanalysis, the analytical data worsened. The thiol was then oxidized immediately to the disulfide, VIIIc.

N-[3-(p-Fluorophenyl)-1-adamantanemethyl]carboxamidiniummethyl Disulfide Dihydrochloride. (VIIIc). Hydrogen peroxide (3%, 24 ml) was added dropwise over a period of 1.5 hr to a stirred mixture of the mercaptan (IXc), (3.68 g, 0.01 mole) in methanol (40 ml) and 1:1 hydrochloric acid (20 ml). The reaction mixture was stirred at 25 °C for another 1.5 hr., then concentrated, in vacuo, and the product filtered. The colorless solid was recrystallized from aqueous ethanol,

m.p. 216-218 °C (dec.). The yield was 3.0 g, (83%); ^{1}H NMR (DMSO-d_6) δ 1.62 to 1.75 (m, 24H, twelve CH_2's of adamantane ring), 2.15 (s, broad, 4H, bridgehead protons), 3.17 (s, broad, 4H, two CH_2N), 4.09 (s, broad, 4H, CH_2S-SCH_2), 7.11-7.41 (complex m, 8H, aromatic), 9.06, 9.58, 9.94 (br, s, NH's); IR (KBr), δ (C=NH_2) and ν(C=N) at 1670 and 1610 cm^{-1}, respectively.

Anal. Calcd. for $C_{38}H_{50}N_4Cl_2F_2S_2$: C, 62.00; H, 6.85; N, 7.61; S, 8.70. Found: C, 61.75; H, 6.95, N. 7.08, S, 8.78.

Series Starting from 3-(p-Methylthiophenyl)-1-adamantanecarboxylic Acid, IId

3-(p-Methylthiophenyl)-1-adamantanecarboxylic acid (IId). A mixture of 3-bromo-1-adamantanecarboxylic acid (10.30 g, 0.04 mole), anhydrous zinc chloride (11.88 g, 0.08 mole) and thioanisole (25 ml) were stirred at 95-100 °C for 3 hr. The reaction mixture was cooled and poured into ice-water (150 ml) containing conc. hydrochloric acid (10 ml). The mixture was extracted with 3 x 75 ml portions of benzene. The benzene extracts were washed with water and then treated with sodium hydroxide solution (10%, 150 ml) which had been saturated with sodium chloride. The sodium salt appeared at the interface and was filtered, and was washed with saturated sodium chloride solution. The salt was suspended in water (100 ml) and neutralized by the addition of conc. hydrochloric acid. The acid was filtered and washed with water. After recrystallization from methanol, the acid weighed 4.2 g (35%), m.p. 143-144 °C; ^{1}H NMR (DMSO-d_6) δ 1.68 to 1.82 (m, 12H, six CH_2's of adamantane ring) 2.15 (br, 2H, bridgehead protons); 2.44 (s, 3H, CH_3S); 7.25 (s, 4H, aromatic protons) in DMSO-d_6, the CO_2H proteon was not visible, but in CCl_4, a bad signal was observed at 10.85 p.p.m.; mass spectrum (70 eV) m/e (relative intensities), m/e 302 (M^+, 100).

Anal. Calcd. for $C_{18}H_{22}O_2S$: C, 71.48; H, 7.33. Found: C, 71.45; H, 7.27.

When the NaOH-NaCl filtrate was acidified, 0.8 g of the starting 3-bromo-1-adamantanecarboxylic acid was recovered.

Several experiments were carried out to improve the yield of IId. Experiments designed to use thioanisole and a solvent for the Friedel-Crafts reaction, e.g., carbon disulfide or 1,2-dichloroethane, at room temperature or refluxing temperature, or by replacing zinc chloride with aluminum chloride or ferric chloride, or an increase in reaction time always gave a smaller yield of IId.

3-(p-Methoxythiophenyl)-1-adamantanecarboxamide (IIId). A mixture of 3-(p-methylthiophenyl)-1-adamantanecarboxylic acid (3.02 g, 0.01 mole), phosphorus pentachloride (2.08 g, 0.01 mole) and carbon tetrachloride (30 ml) were refluxed for 1 hr. The solvents were evaporated, in vacuo, and the residue was treated thrice with 20 ml portions of carbon tetrachloride and evaporating after each addition, in vacuo. The residual oil was dissolved in anhydrous benzene and added slowly to stirred ice-cold ammonium hydroxide (60 ml). After 18 hrs, the organic layer was separated and aqueous phase extracted twice with benzene. The benzene extracts were washed with water and solvents removed, in vacuo. The residue was recrystallized from ethanol to furnish colorless crystals (2.0 g, 68%), m.p. 89-91 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.78 to 1.96 (m, 12H, six CH_2's of adamantane ring); 2.25 (br s, 2H, bridgehead protons); 2.45 (s, 3H, CH_3-S-); 5.98 (br s, 2H, $CONH_2$); 7.24 (s, 4H, aromatic protons).

Anal. Calcd. for $C_{18}H_{23}NOS$: C, 71.71; H, 7.69; N, 4.64. Found: C, 71.77; H, 7.82; N, 4.28.

3-(p-Methylthiophenyl)-1-adamantamemethylamine Hydrochloride (IVd). The amide (IIId, 5 g, 0.016 mole) obtained in the previous step was reduced as usual in a 3-necked flask fitted with condenser, dropping tube and $CaCl_2$ tube (see prep. of IVa), using lithium aluminum hydride (3.99 g) in anhydrous tetrahydrofuran (350 ml).

The amine was taken up in anhydrous ether and treated with HCl gas. The hydrochloride was filtered, washed with ether, and recrystallized from aqueous ethanol. The yield was 3.5 g (65%), m.p. 210-212 °C; ^{1}H NMR (DMSO-d_6) δ 1.56 to 1.77 (m, 12H, six CH_2's of adamantane ring; 2.14 (bs, 2H, bridgehead protons); 2.47 (br s, 2H, CH_2N); 2.44 (s, 3H, CH_3S), 7.26 (s, 4H, aromatic protons) and 7.86 (b, s, 3H, NH_3^+).

Anal. Calcd. for $C_{18}H_{26}NClS$: C, 66.72; H, 8.09; N, 4.32. Found: C, 66.42; H, 7.85; N, 4.16.

N-[3-(p-Methylthiophenyl)-1-adamantanemethyl]-α-chloroacetamidinium Hydrochloride (Vd). It was obtained in 90% (1.8 g) yield from the amine hydrochloride (IVd, 1.61 g, 0.005 mole), chloroacetonitrile (0.377 g, 0.005 mole) and sodium methoxide (prepared from 0.0115 g of sodium in 4 ml of methanol) following the standard procedure as outlined for Va (see above). After recrystallization from aqueous ethanol it melted at 142-145°C (dec.); ^{1}H NMR (DMSO-d_6) 1.59 to 1.70 (m, 12H, six CH_2's of adamantane ring); 2.10 (br, s, 2H, bridgehead protons); 2.44 (s, 3H, CH_3-S), 3.15 (s, 2H, CH_2N), 4.55 (s, 2H, CH_2Cl) and 7.25 (s, 4H, aromatic protons).

Anal. Calcd. for $C_{20}H_{28}.N_2Cl_2S$: C, 60.10; H, 7.06; N, 7.01; S, 8.01. Found: C, 59.65; H, 7.05; N, 6.81; S, 8.21.

S-{N-[3-(p-Methylthiophenyl)-1-adamantanemethyl]carboxamidiniummethyl} Thiosulfate (VIId). The chloro amidine hydrochloride (Vd, 0.79 g, 0.002 mole) was dissolved in 50% aqueous ethanol (5 ml) and was treated with our aqueous solution of sodium thiosulfate pentahydrate (0.496 g, 0.002 mole, in 1 ml). The reaction mixture was stirred at 85-90 °C for 1 hr. The solid was filtered and washed well with water. It was recrystallized from aqueous methanol to yield 0.7 g of VIId (71%), m.p. 178-180 °C (dec).; ^{1}H NMR (DMSO-d_6) δ 1.57 to 1.74 (m, 12H, six CH_2's of adamantane ring); 2.13 (br s, 2H, bridgehead protons); 2.4 (s, 3H, CH_3S),

3.04 (bs, 2H, CH_2N); 3.92 (s, 2H, CH_2S), 7.25 (s, 4H, aromatic protons), and 8.93 (br s, 3H, $NH-C=\overset{+}{N}H_2$).

Anal. Calcd. for $C_{20}H_{28}N_2O_3S_3$: C, 54.51; H, 6.41; N, 6.36; S, 21.80. Found: C, 54.39; H, 6.42; N, 6.36; S, 21.41.

Sodium S-{N-[3-(p-Methylthiophenyl)-1-adamantanemethyl]carboxamidiniummethyl} Phosphorothiaote (VId). A solution of N-[3-(p-methylthiophenyl)-1-adamantanemethyl]-α-chloroacetamidine hydrochloride (0.39 g, 0.001 mole) in 50% aqueous ethanol (3 ml) was added to a solution of trisodium phosphorothioate (0.18 g, 0.001 mole) in water (2 ml). The reaction mixture was stirred for 30 min at room temperature in an atmosphere of nitrogen. The precipitate was filtered, washed with water and recrystallized from methanol to yield 0.40 g, (81%), m.p. 105-108 °C. Its ^1H NMR spectrum in CD_3CO_2D was δ 1.72 to 2.06 (m, 14H, adamantane protons); 2.43 (s, 3H, CH_3-S); 3.17 (bs, 2H, CH_2N); 3.80 (d, 2H, CH_2SP, J_{P-CH_2} = 16.4 Hz); 7.26 (s, 4H, aromatic protons).

Anal. Calcd. for $C_{20}H_{28}N_2O_3PS_2Na \cdot 3H_2O$: C, 46.49; H, 6.60; N, 5.42; S, 12.39. Found: C, 46.27; H, 5.96; N, 5.39; S, 13.09.

Personnel Involved

The syntheses reported in this Annual Report were carried out full time (100% effort) by Dr. Indra Handa, August 1, 1981-July 31, 1982. The Principal Investigator is contributing about 15% of his time, at no charge.

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