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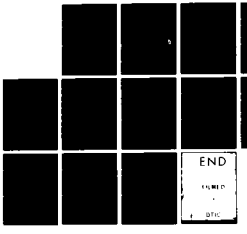

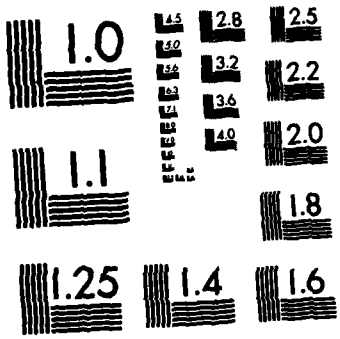

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SYNTHESIS OF NEW PROPHYLACTIC ANTIRADIATION DRUGS

Progress Report No. 2

By

Ludwig Bauer, Ph.D.

August 1981

(For the period 1 August 1980-31 July 1981)

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Synthesis, N-[ω-(3-Aryl-1-adamantyl)alkyl]-α-mercaptoacetamidines and derivatives.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
This report presents details of the work done on the project (covered) during the last 12 months. Approaches to the synthesis of a number of 3-aryl 1-(ω-aminoalkyl)adamantanes is described. Their final incorporation in the preparation of N-(adamantylalkyl) α-mercapto acetamidines, and derivatives, as potential antiradiation drugs is projected.

(Continued on next page)

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Abstract Continued:

The report is divided into two major sections. The first deals with the preparation of 1,3-bis(2-aminoethyl)adamantane and its conversion to the disulfide of 1,3-bis[2-(mercaptomethylcarboxamidino)ethyl]-adamantane. The next section describes the synthesis of some 3-aryl-1-adamantanecarboxylic and acetic acids, 12 (n=0 or 1, respectively). These are the vital precursors needed for the synthesis of the essential 3-aryl(1-adamantylmethyl and ethylamines), 11, which will be a part of the N-substituent of the target α-mercaptoacetamidines and derivatives, Adm$(CH_2)_n$HNC(=NH)CH_2SH. (Adm standing for a 3-aryl-1-adamantyl group).

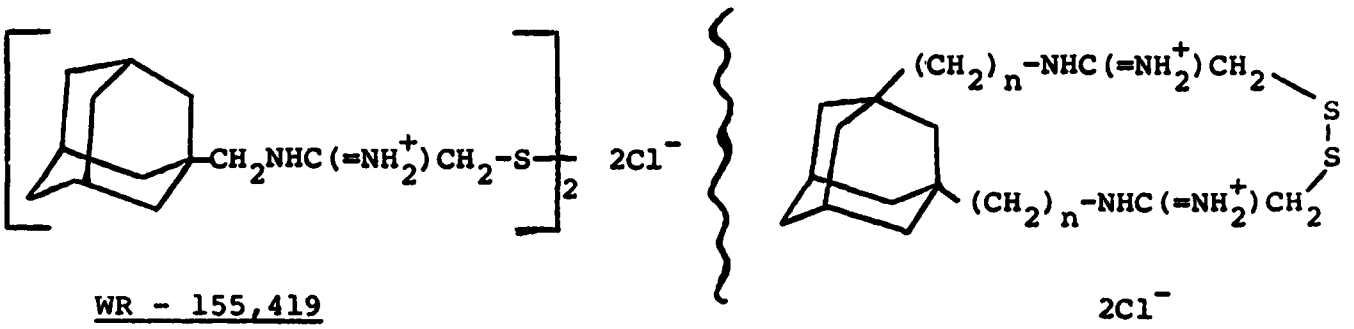
Foreword:

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

Part I: Synthesis of the Disulfide of 1,3-Bis[2-mercaptomethyl-carboxamidino)ethyl]adamantane

Based on the good radioprotective properties of WR-155,419,[1] the synthesis of large cyclic amidine disulfide was attempted. The general formula of such a cyclic disulfide is shown below where n could be 1 or 2.



WR - 155,419

The first disulfide to be chosen was based on 1,3-bis(2-aminoethyl)adamantane, (n-2, see Scheme I). This starting diamine, 4, was prepared by modified literature procedures starting from adamantane, 1.[2] The reaction of 1 with vinylidene chloride and t-butyl alcohol, fuming sulfuric acid, boron trifluoride etherate in cyclohexane between 10-20°C furnished 1,3-adamantanediacetic acid, 2, in 60-70% yield.[2] Conversion of 2 to the diamide, 3,[2] and subsequent $LiAlH_4$ reduction afforded the diamine, 4. The conversion of this diamine to the bis(chloroacetamidine), 5, was accomplished by our published procedure.[1] Addition of methanol to chloroacetonitrile proceeds to generate methyl chloroacetimidate in situ. This reaction can be followed by the ^1H nmr spectra in methanol: the methylene singlet of $ClCH_2CN$ appears at 4.46 ppm (downfield from $(CH_3)_4Si$); during the addition of methanol, this singlet diminishes with the rapid appearance of

a new CH_2 singlet due to $ClCH_2C(=NH)OCH_3$ at 4.13 ppm. This addition was monitored and deemed complete in about 1 hour. The reaction of the diamine (as the hydrochloride) with the imidate gave the bis-amidine which was isolated as a gummy hydrochloride, 5. Attempts to crystallize this salt proved futile, but this salt was readily converted to a crystalline bis-Bunte salt, 6, with sodium thiosulfate.[1] The latter analyzed perfectly for the elements and gave the expected ^1H nmr spectrum.

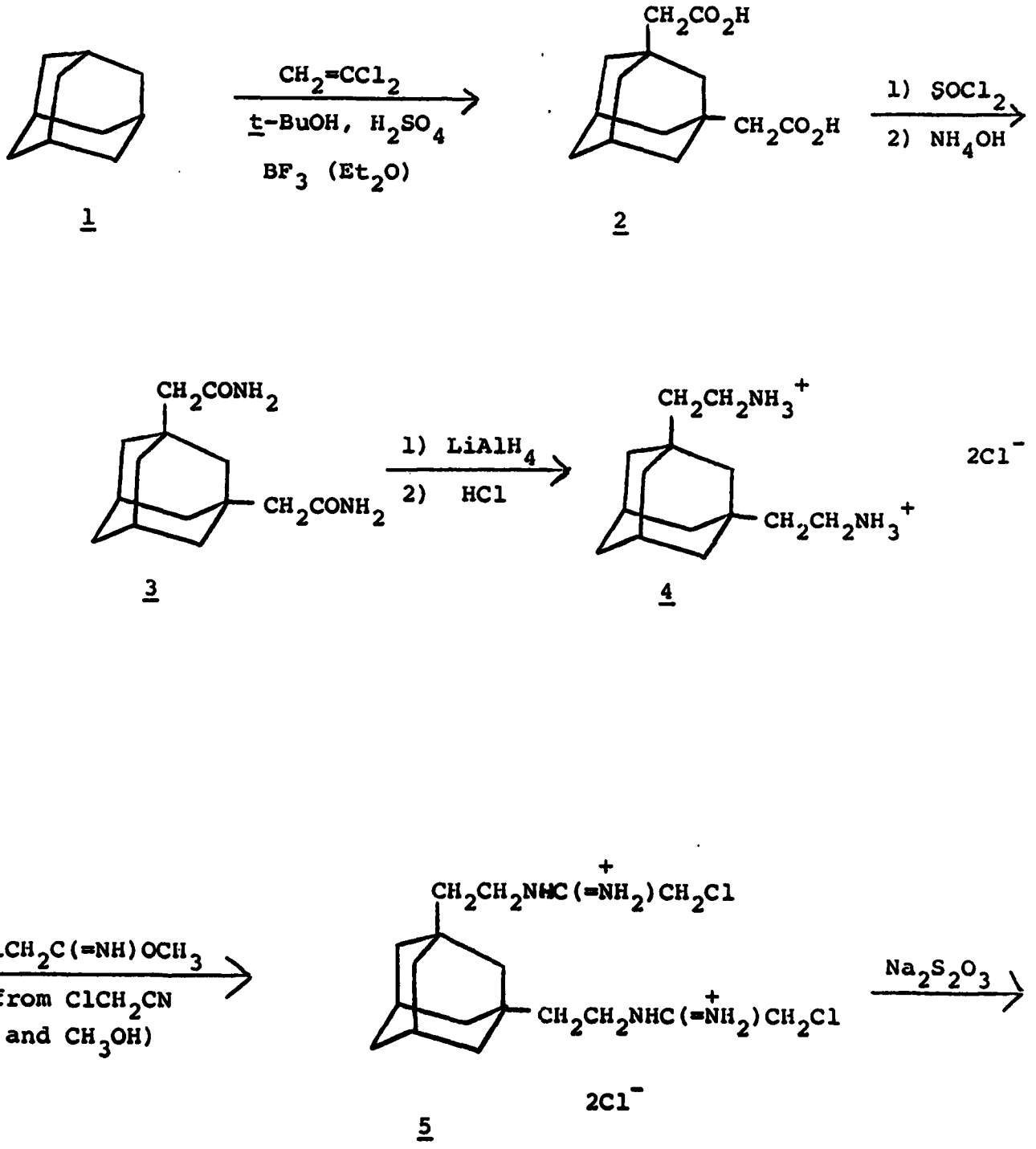
Reaction of 6 with thiourea and hydrochloric acid provided the disulfide 7 as had been demonstrated previously.[1] The disulfide was isolated as the hydrochlorides and analyzed correctly. At present, it is assumed to be cyclic 15-membered ring structure, 7, rather than the dimeric form, 8.

An alternate synthesis of 7 appeared to be feasible. The reaction of 5 with sodium phosphorothioate gave rise to a gummy carboxamidinium phosphorothioate, 9, which defied crystallization and plausible purification. Mild acid hydrolysis of 9 produced a gummy mercaptoacetamidine hydrochloride, 10, which was converted by mild oxidation to the disulfide, 7.

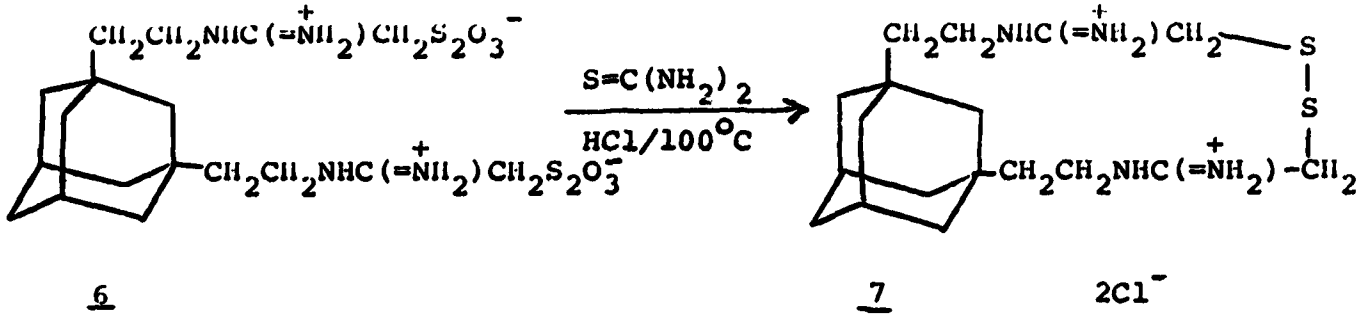
However, rigorous proof of 7 will be sought. Attempts to gently hydrolyze the carboxamidino disulfide to the corresponding carboxamide has resulted in destruction of the whole molecule. Further work will be developed to prove the structure of 7 beyond doubt. At present, production of 2-5 g of this disulfide is in progress.

All the aforementioned reactions are summarized in Scheme I:

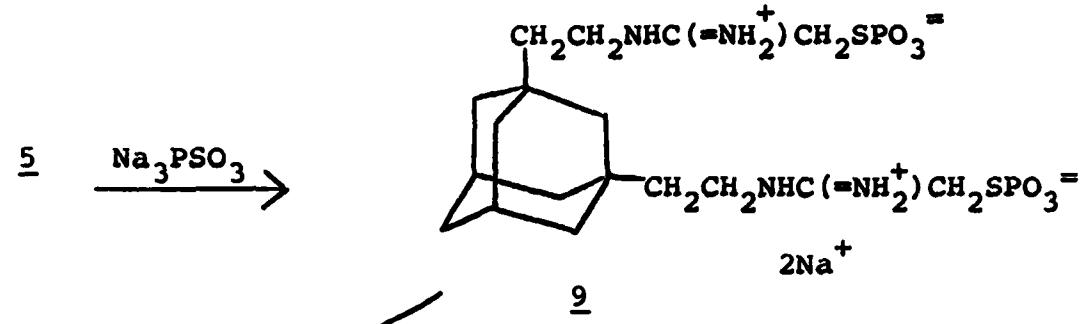
Scheme I



1 2 3 4 5



6 7 $2Cl^-$



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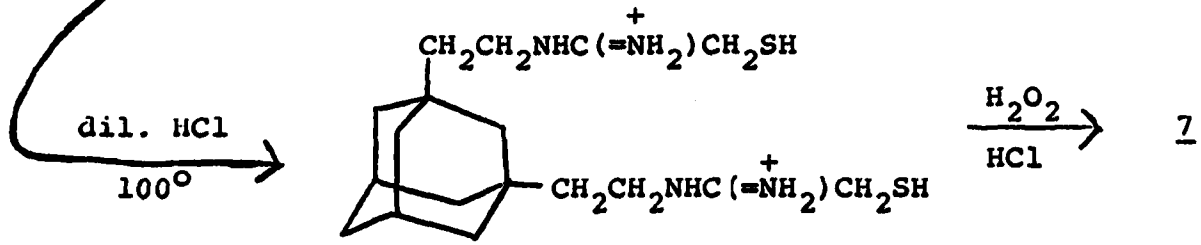
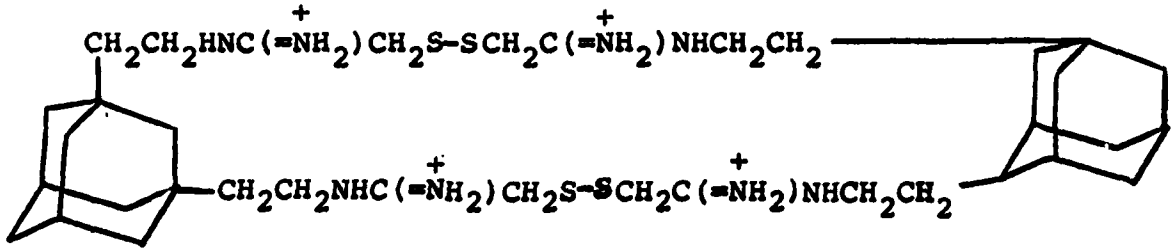


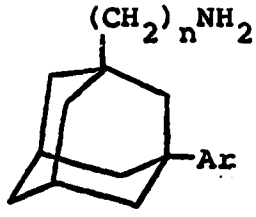
10 $2Cl^-$



8 $4Cl^-$

Part II: Syntheses of N-[ω-(3-Aryl-1-adamantyl)alkyl] α-Mercaptoacetamidine and Derivatives

This part of the Report deals with the attempted and successful syntheses of some 3-aryl-(1-adamantyl methyl- and ethylamines), 11, (n=1 or 2) which would become part of N-substituent in $HSCH_2C(=NH_2^+)NHR\ Cl^-$ and derivatives.



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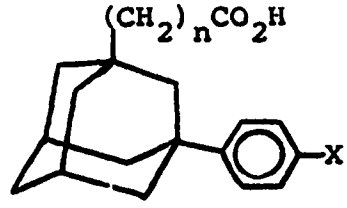
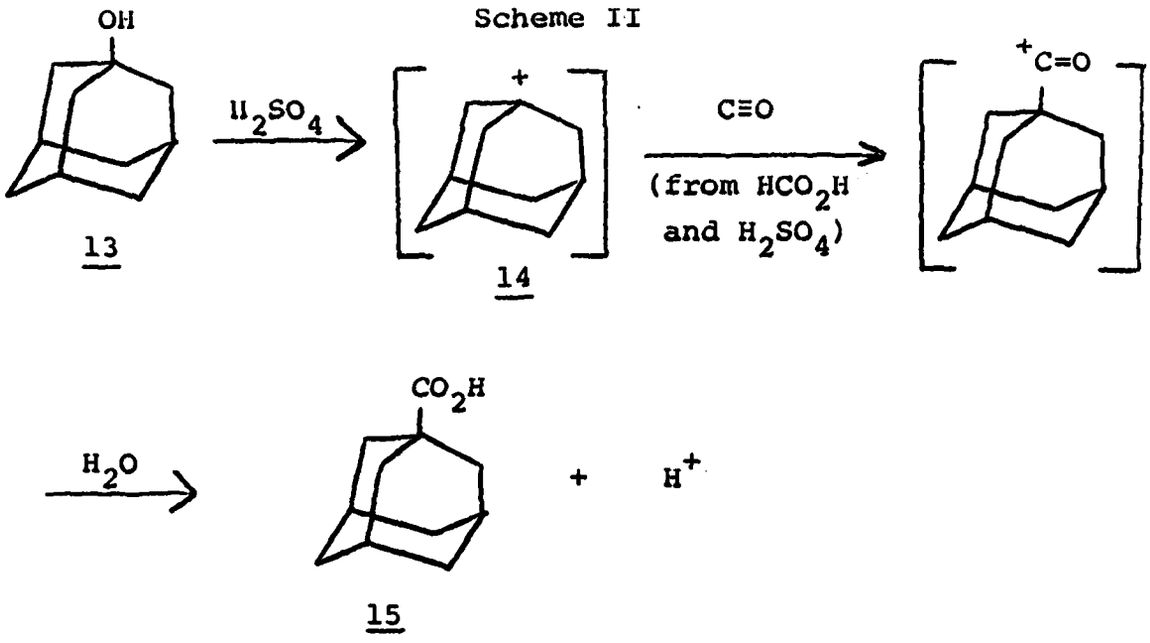


12

Typical precursors for 11 would be the carboxylic acids, 12, where n=0 or 1. 1-Adamantanecarboxylic acids, 12, (n=0) are synthesized usually by the Koch-Haaf reaction[3,4] which is shown in Scheme II.

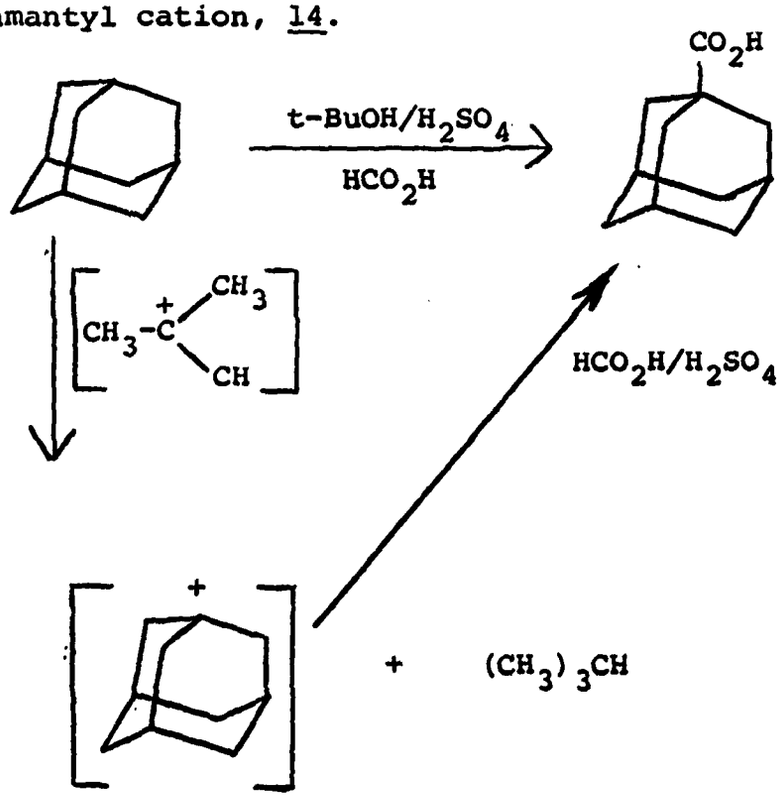
This reaction proceeds particularly well on adamantane[3] or 1-adamantanol, 13,[4] and even 1-bromoadamantane[16] to provide 1-adamantanecarboxylic acid; 15. Apparently in such systems, the 1-adamantyl cation is generated readily to react with carbon monoxide liberated *in situ* from the action of conc. sulfuric acid upon formic acid. The reaction from adamantanol is shown below:

Scheme II

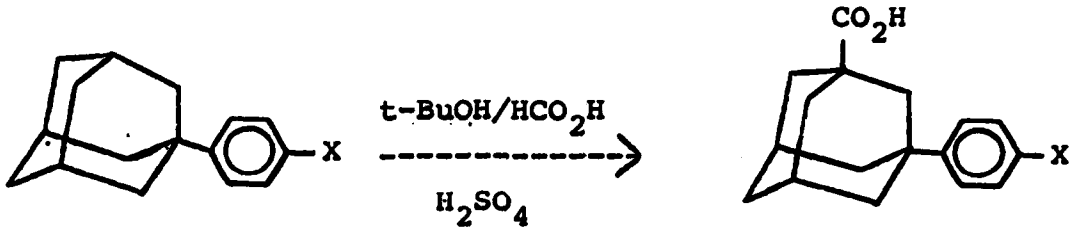


13 14 15

In order to generate the 1-adamantyl cation from adamantane, a t-butyl cation is generated first during the reaction. Apparently the bridgehead protons are sufficiently acidic that one of them is neutralized by the t-butyl cation, in situ, to generate the 1-adamantyl cation, 14.

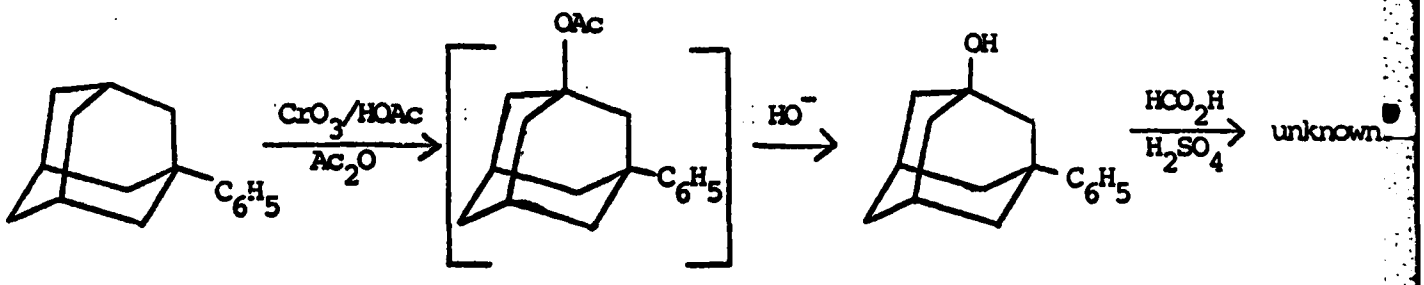


Much to our surprise, 1-aryladamantanes, 16, did not participate readily in the Koch-Haaf reaction to furnish the required acids, 17.



16 17

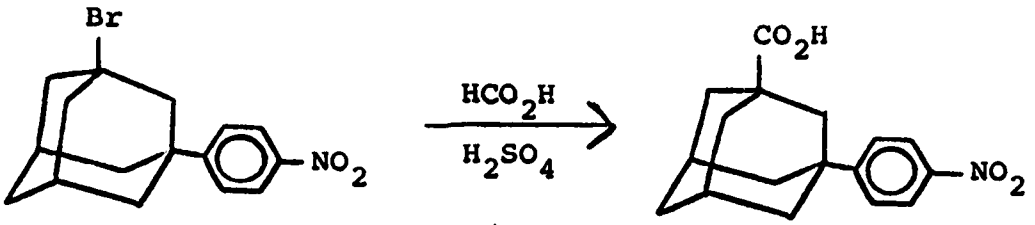
Under standard conditions,[3] 1-phenyladamantane (16, X-H) was recovered in 85% and no acid was detected. The p-bromophenyl analog, (16, X=Br) behaved similarly. Since the Koch-Haaf reaction could not be carried out on 1-phenyladamantane, presumable because the corresponding adamantyl cation is not formed, it seemed reasonable to assume that the required carbocation would be generated more readily from the corresponding alcohol. Therefore, using literature methods, 3-phenyl-1-adamantanol, 18, was prepared.[5] However, when reacted with formic and sulfuric acid (under conditions under which 1-adamantanol reacts) 3-phenyl-1-adamantanol, 18, provided a neutral high melting and (to date) unknown compound. This approach was then abandoned.



18

Since the Koch-Haaf method also works on 1-adamantyl halides, one of the known 3-aryl-1-adamantyl bromides was subjected to this reaction.

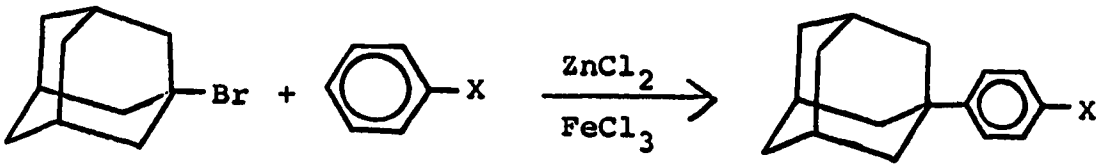
3-p-Nitrophenyl-1-adamantyl bromide 19[6] became available, furnished via a literature Koch-Haaf procedure the expected p-nitrophenyl acid, 20.[6]



19 20

However, the presence of the nitro group is bothersome since further steps in our procedure calls for the $LiAlH_4$ reduction of an amide, $CONH_2$, in the presence of the nitro group would would also be reduced (not necessarily to an amino group). Certainly, in any drug one would want to avoid the presence of either a nitro or an aromatic amino group.

Many 1-aryladamantanes are available from typical Friedel-Crafts procedures:[7]

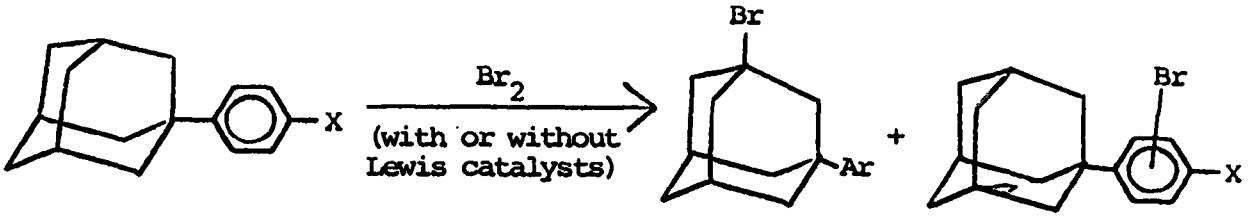


21 22

It was possible to prepare the phenyl (22, X=H), p-bromophenyl (22, X=Br) and p-methoxyphenyladamantanes (22, $X=OCH_3$) in good yields. When bromobenzene or amisole were used as substrates,

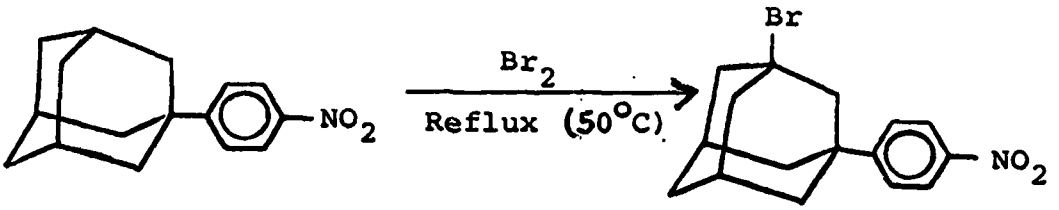
only p-(1-adamantyl) arenes 22 were obtained. With t-butylbenzene, a mixture of aryladamantanes was produced as evidence from nmr and tlc data.

Bromination of such aryladamantanes bearing electron releasing substituents such as halo, alkoxy and alkyl were bound to produce both arene and adamantyl ring substituted products:



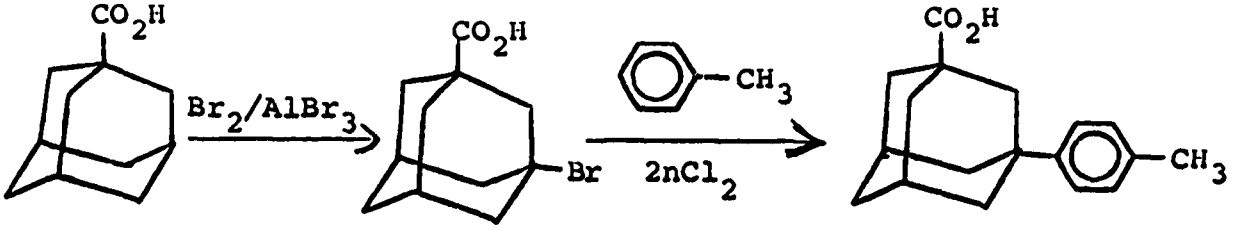
22

Only when the substituent a strong deactivation like NO_2, the predominant product was the desired adamantyl bromide:[6]



(79%)

Another approach to 3-aryl-1-adamantanecarboxylic acids was explored. Bromination of 1-adamantanecarboxylic acid has been reported in the literature.[8] Without a Lewis catalyst, no substitution took place. But, with $AlBr_3$, 3-bromo-1-adamantane-carboxylic acid was obtained.

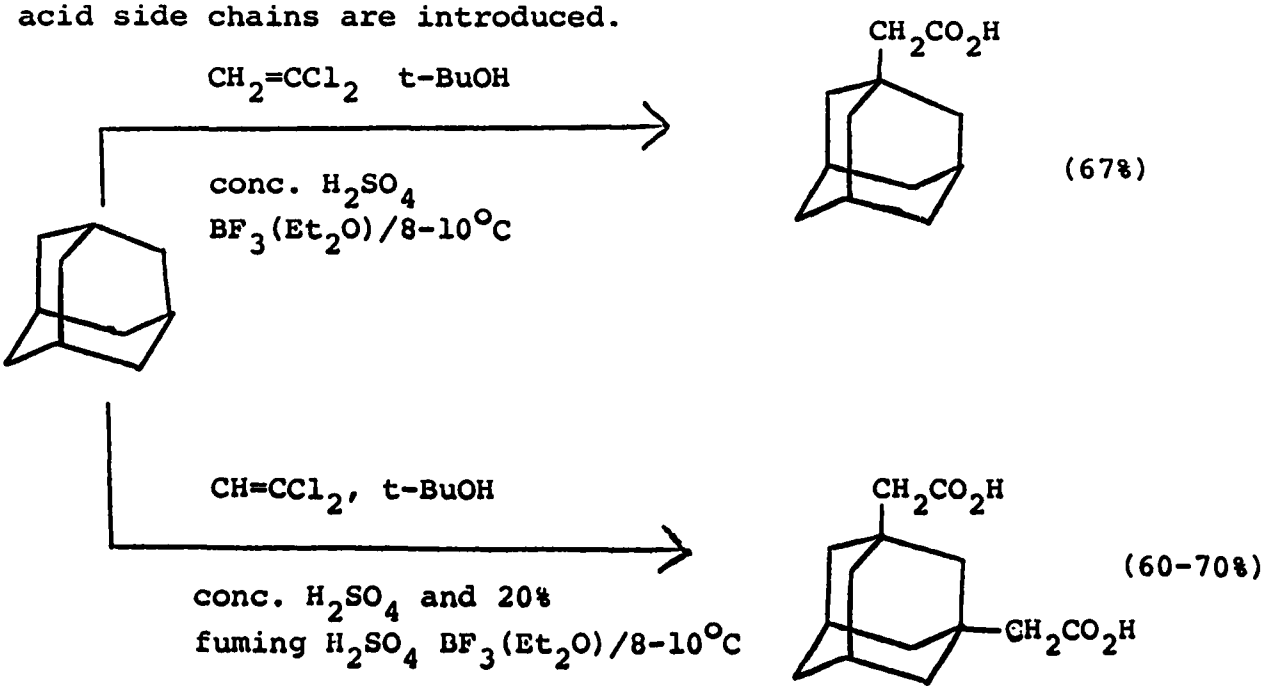


15 23 24

Unfortunately, the melting point for the bromo acid described in the literature was 146-147°C and our porudct melted at 197-200°C. But, a Friedel-Crafts reaction of 23 with toluene, that is one our higher melting bromo acid produced the correct 3-(p-tolyl)-1-adamantanecarboxylic acid, 24.[9]

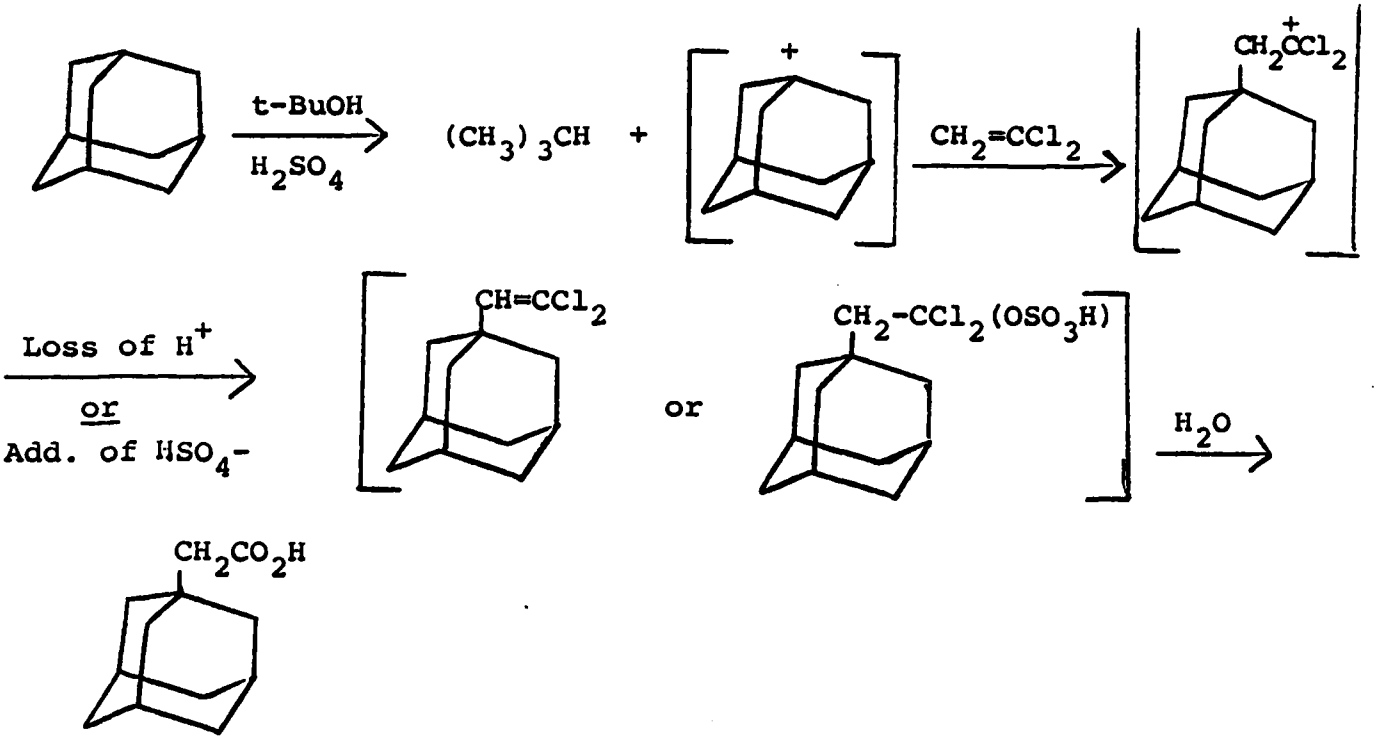
To summarize this section, it would appear that 3-aryl-1-adamantanecarboxylic acids can be made by a Friedel-Crafts reaction of 3-bromo-1-adamantanecarboxylic acids. This approach will be examined further in this laboratory.

In view of the inherent difficulty of introducing the carboxylic acid group via the conventional Koch-Haaf reaction, we turned out attention to the introduction of an acetic acid side chain at the bridgehead position of an aryladamantane. A standard method[2] is to treat adamantane with vinylidene chloride in the presence of t-butyl alcohol, conc. or fuming sulfuric acid and boron trifluoride etherate. In this manner, either one or two acetic acid side chains are introduced.

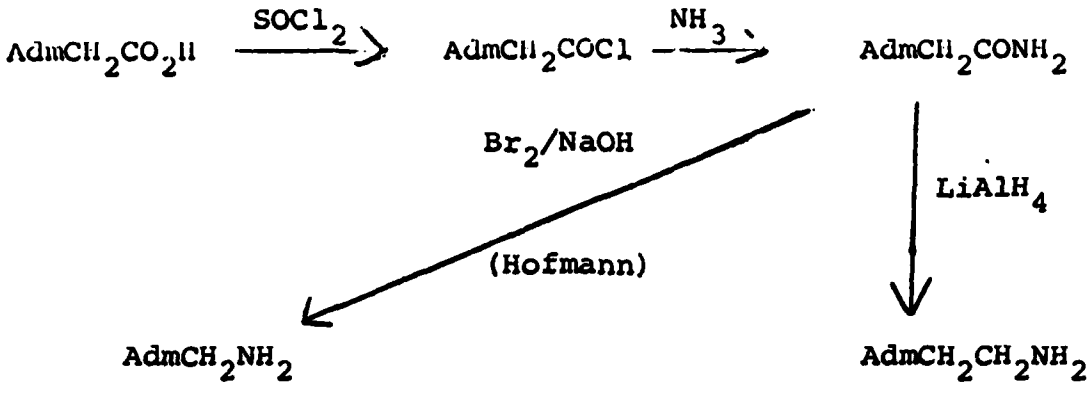


The mechanism postulated for this complex series of events again has the t-butyl cation neutralize a bridgehead proton to form an 1-adamantyl carbocation. This electrophilic species adds to the alkene to form a dihalocarbocation. Such an electrophilic center can lose a proton to form an dihaloalkene or pick up a nucleophile to create a potential orthocarboxylic acid derivative by having three heteroatoms on the same sp^3-hybridized carbon. Either intermediate hydrolyses to the acid during the aqueous workup (see Scheme III).

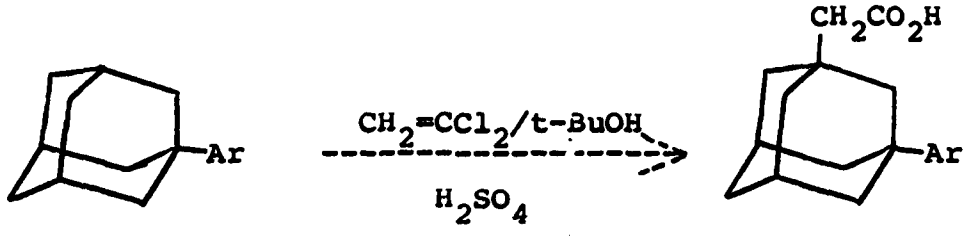
Scheme III



The availability of a series of 3-aryl-1-adamantaneacetic acids would be most acceptable since such acids could be precursors for either the methyl- or ethylamine required for the amidine syntheses. The availability of these amines can be summarized by these reactions:

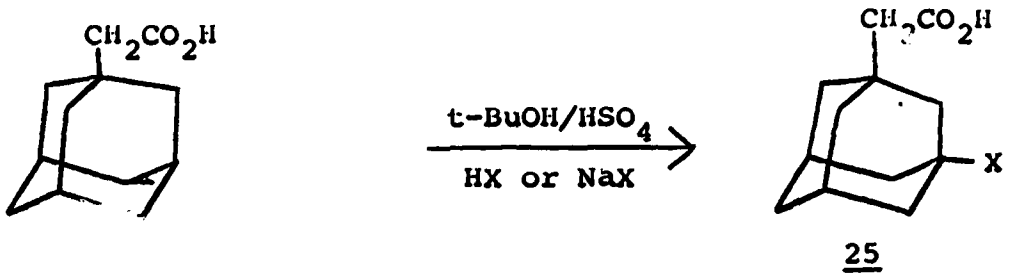


Unfortunately, just like the Koch-Haaf reaction, a number of 1-aryladamantanes failed to react with vinylidene chloride under the above-stated conditions.[2]



Again, an alternate route was sought. Like the precursors for the Koch-Haaf reaction, halo or hydroxyadamantanes might give rise to the adamantyl carbocation more readily. The alternate would be a Friedel-Crafts reaction on 3-halo-1-adamantaneacetic acids.

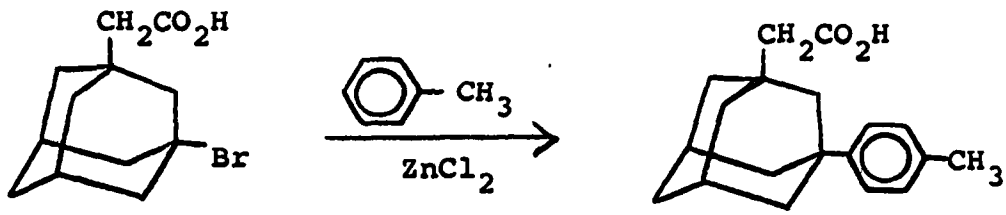
In a recent patent and communication,[10] Inamoto utilized the concept of the intermediacy of an adamantyl cation in preparing 3-halo-1-adamantaneacetic acids. In treating 1-adamantaneacetic acid with t-butyl alcohol, conc. sulfuric acid and either hydrogen halides or sodium halides, he was able to prepare 3-halo-1-adamantaneacetic acids, 25.



25

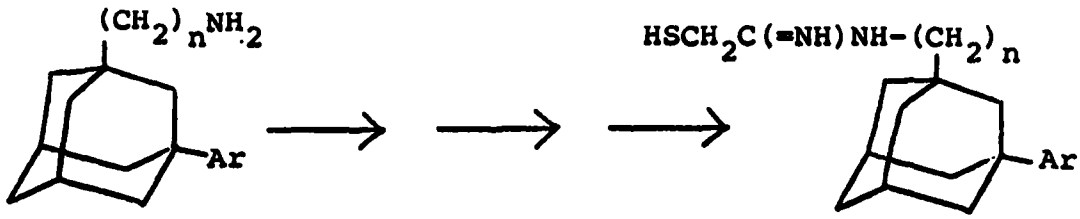
Using either hydrogen chloride gas or sodium bromide, we were able to prepare these halo acids 25 where X was Cl or Br.

Subsequent Friedel-Crafts reaction on 25 with toluene yielded the new 3-(p-tolyl)-1-adamantaneacetic acid, 26.



26

It is hoped to continue to explore this last type of reaction to synthesize several other 3-aryl-1-adamantaneacetic acids. Subsequently, these acids will be a source of amines of type alluded to above, namely, capable of incorporation into the α-mercaptoacetamidine synthesis.



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, br, s, d, t and m refer to broad, singlet, doublet, triplet, and multiplet, respectively. 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. Only relevant ions are reported.

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.

Part I: Synthesis of the Disulfide of 1,3-Bis[mercaptomethyl-carboxamidinium)ethyl]adamantane, 7

1,3-Adamantanediacetic Acid, 2. This acid was prepared essentially by the lit. method.[2] A slightly larger amount of fuming sulfuric acid was used by us (1.5 times that of lit.) and ensured a relatively good yield of diacid. Also, vigorous stirring is essential to the reproducibility of this experiment.

Adamantane (Aldrich Gold Label, 13.6 g, 0.1 mole), conc. sulfuric acid (160 ml), freshly distilled boron trifluoride etherate (42 ml), and cyclohexane (100 ml) was placed in a 1-liter 3-necked flask fitted with condenser (calcium chloride tube), stirrer and two self-regulating pressure-equalized addition funnels. One dropping funnel contained tert-butyl alcohol (57.7 ml, 0.60 mole) and vinylidene chloride (97 ml, 1.25 mole). In the other separatory funnel was placed 20-23% fuming sulfuric acid (100 ml). To the vigorously stirred (overhead stirrer) mixture in the flask maintained between 12-15°C, the contents of the two separatory funnels were added simultaneously over 2 hours. After these additions, the mixture was continued to be stirred vigorously for another 2 hours at the same temperature (12-15°C). The reaction mixture was then poured onto ice (600 ml). The solid was filtered and dissolved in 5% sodium hydroxide solution. This solution was extracted with ether (3 x 100 ml). The basic aqueous solution was warmed on a steambath to expel dissolved ether, cooled, and acidified with conc. hydrochloric acid. This solid was filtered and recrystallized from 70% methanol. The acid (13.90 g, 62%) melted between 230-234°C (lit.[2] mp 244-244.5°C).

1,3-Adamantanediacetamide, 3. A suspension of 2 (10.0 g, 0.04 mole) in thionyl chloride (127 ml) was refluxed for 24 hours (as suggested in the lit.[2]). Excess thionyl chloride was removed in vacuo and the residue was dissolved in dry benzene (32 moles). This solution was added to a vigorously stirred (mechanical stirrer is suggested) solution of 28% ammonium hydroxide (150 ml) over 1 hour and the mixture was stirred for another 6 hours. The crude

product (65%) was washed with ether and is sufficiently pure for the next step. It can be recrystallized from a mixture of tetrahydrofuran-ethanol. The yield was 5.0 g (50%), mp 181-183°C, lit.[2] mp 181.5-183°C; ^{1}H nmr (DMSO-d_6) δ 1.51 (br s, CH_2 protons), 1.85 (s, $C\underline{H}_2CO$), 1.96 (s, bridgehead CH's), 7.09, 6.58 (br, 4 protons of the 2 NH_2 groups).

1,3-Bis(2-aminoethyl)adamantane Dihydrochloride, 4. The free diamine was prepared in 83% yield by the catalytic hydrogenation of 1,3-adamantanediacetonitrile, using H_2/Raney Ni (W-6) at 115-120°C.[2] The present method uses chemical reduction.

1,3-Adamantanediacetamide, 3 (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°C (dec.) in sealed tube. Its ^{1}H nmr spectrum [$(CD_3)_2SO$] showed signals at δ 1.21, 1.36 (br, s, CH_2's) 1.53 (m, $C\underline{H}_2CH_2N$), 1.98 (m, bridgehead protons) 2.74 (m, $CH_2C\underline{H}_2N$), 8.07 (br s, NH_3^+'s).

Please Note: EXTREME CAUTION MUST BE TAKEN IN HANDLING THE CHLORO, MERCAPTO, DISULFIDE, THIOSULFATE (BUNTE SALT) AND RELATED AMIDINES (5 → 8). EXPOSURE TO THEIR DUST, BE IT BY SKIN CONTACT OR BREATHING, MAY CAUSE SEVERE SKIN AND/OR ALLERGIC REACTIONS.

BESIDES USING GLOVES, HANDLERS ARE ADVISED TO WEAR ALSO FACE MASKS DURING HANDLING OF THESE COMPOUNDS AT ALL TIMES.

Synthesis of 5. 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 1 hour. The amine hydrochloride, 4 (0.9 g, 0.0031 mole) in methanol (8 ml) was added. The pH of the mixture was adjusted to pH of 4 by the dropwise addition of some methanolic hydrogen chloride solution. After 1 hour, solvents were removed in vacuo at temperatures no greater than room temperature. The residual gum was used in the next step without further purification. The ^1H nmr [$(CD_3)_2SO$], δ 10.46, 9.73, 9.33 (broad singlets, amidinium protons), 4.53 (s, $C\underline{H}_2Cl$), 3.31 (broad m, $C\underline{H}_2N$), 1.99 (broad s, bridgehead proton) 1.43 (broad s, CH_2's in ring).

Synthesis of 6. To a solution of 5 (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.); ^1H nmr spectra in [$(CD_3)_2SO$] δ 8.93 (broad s, NH's) 3.85 (s, $C\underline{H}_2S$), 3.11 (broad m, $C\underline{H}_2N$), 2.00 (broad s, bridgehead protons), 1.43, 1.26 (broad s, all other CH_2's).

Anal. Calcd for $C_{18}H_{32}N_4O_6S_4$: C, 40.91, H, 61.0, N, 10.60, S, 24.21. Found: C, 40.94; H, 6.10; N, 10.58; S, 23.53.

Synthesis of 7: A. From Bunte Salt, 6. A mixture of the Bunte Salt (0.150 g, 0.000284 mole) and thiourea (0.0216 g, 0.000284 mole) in 1 N HCl (2.5 ml) was heated in an oilbath at 96°C for 2 hours. After 30 minutes a solution was obtained. By the end of the reaction a jelly-like solid had deposited at the bottom of the flask. The solid was filtered, washed with cold acetone and recrystallized from methanol-water to yield 7 (0.020 g, 19%), mp 200-202°C (dec.)

Anal. Calcd. for $C_{18}H_{32}Cl_2N_4S_2 \cdot 2H_2O$; C, 45.49; H, 6.73; N, 11.78; S, 13.47. Found: C, 45.52; H, 7.05; N, 11.18, S, 13.50.

B. Synthesis of 7 via the Mercaptan 10.-Trisodium phosphorothioate was prepared by the method of Akerfelt.[11]

1,3-Bis(2-aminoethyl)adamantane dihydrochloride (0.9 g, 0.0031 mole) was converted to the α-chloroacetamidine derivative, 5 (as described above). A mixture of 5 and Na_3SPO_3 (1.08 g, 0.0062 mole) in water (6 ml) was stirred under N_2 for 30 minutes. Attempts to isolate the phosphorothioate, 9, did not result in a crystalline manageable salt. Therefore, in a subsequent identical reaction, the reaction mixture containing 9 was acidified with 6 N HCl (3 ml), diluted with 2-propanol (6 ml) and heated 20 minutes at 80-90°C. Salts were filtered and the filtrate evaporated in vacuo at room temperature. A gummy solid of 10, tending to change to a glass, was obtained which was not crystallized satisfactorily. It was readily soluble in 2-propanol and addition of ether provided a gummy material. It was best oxidized to 7 in the next step.

In a separate experiment, at the end of the acid hydrolysis of 9, 1% H_2O_2 (1 ml) was added and the mixture stirred at room

temperature for 2 hours. Evaporation of the solution in vacuo (room temperature) provided a solid which was recrystallized from methanol-ether (40% yield) mp 200-205°C (dec.). This material was identical to that prepared from the Bunte Salt.

Part II. Synthesis of 3-Aryl-1-(Adamantanecarboxylic and Acetic Acids)

1-Phenyladamantane: To a mixture of $FeCl_3$ (9.35 g) in 170 ml of thiophene free benzene, 33.27 g (0.155 mole) of 1-bromoadamantane in 255 ml benzene was added dropwise in 1 hour. The mixture was heated under reflux for 3.5 hours. Hydrogen bromide was evolved during the reaction period. At the end of the reaction, 450 ml of ice-water and 60 ml conc. HCl were added. The layers were separated. The aqueous layer was extracted with 200 ml of benzene three times. The benzene fractions were combined and washed with 200 ml of water (3 times). The organic layer was dried with $CaCl_2$ and solvents evaporated. The residue was recrystallized from methanol to give 20 g (60% yield) 1-phenyladamantane, mp 84-86°C lit.[12] mp 87-89°C.

1-(p-Bromophenyl)adamantane. 1-Bromoadamantane (33 g) was dissolved in bromobenzene (255 ml) and added dropwise to a suspension of ferric chloride (9.3 g) in bromobenzene (160 ml). The reaction mixture was refluxed for 3.5 hours, cooled and poured into cold water. The organic layer was separated and aqueous layer extracted several times with benzene. The combined organic layer was washed several times with water, dried over anhydrous calcium chloride and solvents were evaporated, in vacuo.

The residue (22 g) was chromatographed on alumina (600 g). Elution with petroleum ether (bp 40-60°C) provided 19 g (60%) mp 100-101°C (lit.[7] mp 101-102°C).

1-(p-Methoxyphenyl)adamantane. A solution of 1-bromoadamantane (12 g) in anisole (40 ml) was added to a stirred suspension of ferric chloride (2 g) in anisole (80 ml) over a period of one hour. The reaction mixture was stirred for another 3 hours at 70°C, cooled and poured on cold dilute HCl (100 ml). The aqueous layer was extracted with benzene. The organic layer was washed with water, dried (calcium chloride) and solvents evaporated in vacuo. The crude solid was chromatographed on silica gel using petroleum ether-ether (9:1) as eluant. The chromatographed product was recrystallized from methanol to afford 11 g (74%) of 1-(p-methoxyphenyl)adamantane, mp 81-82°C (lit.[13] mp 82-83°C).

1-(p-Nitrophenyl)adamantane. 1-Phenyladamantane (14 g) was dissolved in glacial acetic acid (280 ml) and was added with stirring to fuming nitric acid (280 ml) over a period of 30 minutes while maintaining the temperature between 30-40°C. The reaction mixture was stirred for another 30 minutes at this temperature and then stirred for 1 hour at room temperature. It was poured onto ice. The solid was filtered, washed with water and recrystallized from methanol to yield (12.6 g (76%) mp 128-129°C (lit.[14] mp 129-130°C).

1-(p-Nitrophenyl)-3-bromoadamantane. 1-(p-Nitrophenyl)-adamantane (6 g) was refluxed with 15 ml of bromine for 3 hours. The reaction mixture was cooled, dissolved in carbon tetrachloride and treated with a solution of sodium bisulfite until the CCl_4

layer was colorless. The organic layer was washed with water and dried over anhydrous sodium sulfate. Solvents were evaporated and the product was recrystallized from methanol. The yield was 5.9 g, (79%) mp 90-91°C (lit.[6] mp 92-93°C).

3-(p-Nitrophenyl)-1-adamantanecarboxylic acid. A mixture of 1-(p-nitrophenyl)-3-bromoadamantane (3.36 g, 0.01 mole), conc. H_2SO_4 (25 ml), carbon tetrachloride (10 ml), and 98% HCOOH (0.1 ml) was cooled to 17-19°C in a three necked flask equipped with an efficient mechanical stirrer, fitted with a dropping funnel and a thermometer. A mixture of 3.8 ml of t-butyl alcohol and 98% formic acid (5.5 g) was added in a period of 2 hours. The reaction mixture was stirred at 17-25°C for another 30 minutes and then kept at room temperature for 17 hours without stirring, poured onto iced water (150 ml) and filtered. The product was dissolved in 5% NaOH solution, filtered to remove insoluble products. Acidification with conc. HCl, provided the solid, which was recrystallized from methanol. The yield was 1.92 g (64%), mp 200-201°C (lit.[6] mp 202-203°C).

3-Bromo-1-adamantanecarboxylic Acid. Bromine (34 ml) and aluminium bromide (20 g) were placed in a 3-necked flask equipped with an efficient stirrer and a $CaCl_2$ and a P_2O_5 drying tube, as well. The mixture was cooled for 1 hour (under N_2). 1-Adamantanecarboxylic acid (9 g, 0.05 mole) was added in portion over a period of 4 hours while the reaction mixture was stirred and chilled. The mixture was allowed to stand in ice-water for 48 hours and then stirred for 6 hours at room temperature.

The reaction mixture was slowly added to ice and 300 ml of chloroform. A solution of sodium bisulfite was also added with constant stirring until the color of bromine disappeared. The chloroform layer was separated and the aqueous layer extracted twice with 50 ml portions of chloroform. The combined chloroform extracts were washed with water, extracted with 5% NaOH solution. The sodium hydroxide solution was acidified with dilute HCl to give 8.0 g (62%) of the product which melted at 195-200°C (lit.[8] mp for 3-bromo-1-adamantanecarboxylic acid is 146-147°C). The mass spectrum of our acid shows a molecular ion peak for 3-bromo-1-adamantanecarboxylic acid. The product was used in the Friedel-Crafts with toluene. Without $AlBr_3$, the bromination did not take place and the starting material was recovered.

3-(p-Tolyl)-1-adamantanecarboxylic acid. A mixture of 3-bromo-1-adamantanecarboxylic acid (5.18 g, 0.02 mole), toluene (30 ml) and anhydrous zinc chloride was heated for 1 hour. The reaction mixture was cooled, poured into water and the organic layer separated. The aqueous layer was extracted with benzene and combined organic layers were washed with water, dried upon evaporating solvents, in vacuo. The residue (3 g, 55%) melted at 166-170°C (lit.[9] mp for the crystallized product is 175-176°C).

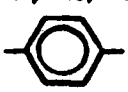
1-Adamantaneacetic acid. To a mixture of 95% sulfuric acid (120 ml), boron trifluoride etherate (37 g), adamantane (6.8 g, 0.05 mole) and cyclohexane (50 ml), kept between 8 and 10°, was added dropwise with efficient stirring a mixture of t-butyl alcohol (15 g, 0.2 mole) and vinylidene chloride (49 g, 0.5 mole) in a period of 40 minutes. The reaction mixture was stirred for another 2 hours at the same temperature. The reaction mixture

was poured onto 300 ml of ice-water and extracted with three 100 ml portions of ether. The ether layer was washed with water and then extracted with five 50 ml portions of 5% NaOH. The sodium hydroxide extract was acidified with conc. HCl. The white solid obtained was filtered and washed with water. Crystallization from 10% MeOH (aqueous) gave 6.5 g (67%) of the product mp 136-138°C (lit.[2] mp 137-139°C).

3-Chloro-1-adamantaneacetic Acid. A mixture of 1-adamantylacetic acid (4 g), carbon tetrachloride (75 ml), 96% sulfuric acid (200 g) was cooled to 5-10°C in a 3-necked flask equipped with an efficient mechanical stirrer. A mixture of t-butyl alcohol (12 g) and carbon tetrachloride (20 ml) was added dropwise over 30 minutes, while a fast stream of dry HCl gas was bubbled in. The reaction mixture was stirred for another 4 hours while passing of HCl continued. Then it was poured onto ice-water, CCl_4 layer separated and aqueous layer extracted with CCl_4. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4. Solvents were evaporated and the residue consisted of 4 g (66%) of the required product, mp 178-180°C (lit.[10] mp 182-183°C) after crystallization from methanol and water (7:3).

3-Bromo-1-adamantaneacetic Acid. Sodium bromide (42 g) were added in about 21 equal portions to a mixture of 1-adamantylacetic acid (4 g), carbon tetrachloride (80 ml) and 96% sulfuric acid (270 g) which was kept at 5-10°C by external cooling while thoroughly stirred (6 hours) while a mixture of t-butyl alcohol (12 g) and carbon tetrachloride (20 ml) was added dropwise over 30 minutes. The reaction mixture was poured onto 300 g of ice. The crystalline

precipitate was filtered, washed well with water and dried. On crystallization from water-methanol (3:7), the product (4 g, 70%) mp 195-196°C (lit.[15] mp 197-199°C), was obtained.

(3(p-Tolyl)-1-adamantaneacetic Acid. A mixture of 3-bromo-1-adamantaneacetic acid (40 g, 0.015 mile), toluene (22.5 ml) and anhydrous zinc chloride (2.25 g) were heated for 3 hours, cooled and then poured onto cold water (150 ml). The aqueous layer was extracted with benzene and the combined organic layers were washed with water, dried over calcium chloride and solvents evaporated in vacuo. The residue was treated with 5% NaOH solution but very little of it dissolved. The insoluble portion (in NaOH) appeared to be the sodium salt of the wanted acid as it was very high melting (>300°C). It was taken up in water and treated with HCl, when a white powdery solid separated. The product was filtered, washed with water and crystallized from methanol to give a white glassy crystals, (2.76 g, 65%) mp 138-139°C; ^{1}H nmr ($CDCl_3$) δ 1.52 to 1.87 (m. 1, six CH_2's of the adamantane ring), 2.18 (s, bridgehead protons and CH_2CO), 2.30 (s, CH_3), 7.01 to 7.29 (m, aromatic); the carboxylic acid proton was not unobserved). Its mass spectrum (70 eV) gave as major ions at 285 (21, M+1), 284 (100, M) 225 (2, M-CH_2COOH), 181 (86), 169 (41) 105 (53) 92 (41  CH_3). The ir spectrum (KBr) showed a strong C=O stretching band at 1670 cm^{-1} and broad OH stretching band between 2800 and 2900 cm^{-1}.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.51; H, 8.55.

Note: The reaction of 3-chloro-1-adamantaneacetic acid and toluene in the presence of $ZnCl_2$ or $FeCl_3$ provided the same 3-p-tolyl acid in 5[illegible]% yield.

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Compounds Submitted

The bis-Bunte salt, 6, was submitted and is being evaluated. The disulfide, 7, is being prepared in 2-5 g for submission in the near future.

Other compounds based on the N-(3-aryl-1-adamantyl)-α-mercaptoacetamidine system are also being worked upon.

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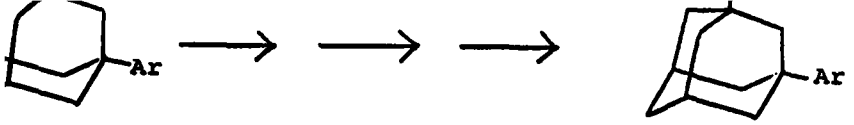

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