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N-[(ARYL SUBSTITUTED ADAMANTANE)ALKYL] 2-MERCAPTOACETAMIDINES, THEIR CORRESPONDING DISULFIDES AND S-PHOSPHOROTHIOATES

Chung Chyi Tseng, Indra Handa, Ashraf N. Abdel-Sayed and Ludwig Bauer*
Department of Medicinal Chemistry
College of Pharmacy, University of Illinois at Chicago
P.O. Box 6998, Chicago, Illinois 60680, U.S.A.
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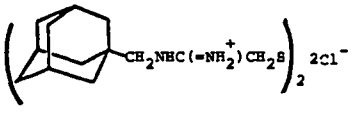
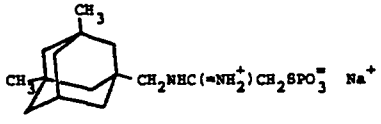
Abstract Syntheses of a number of (aryl substituted adamantane)alkylamines are described. (1-Aryl-2-adamantane)methyl- and ethylamines were prepared in good yields from 4-protoadamantanone. In another sequence, 4-epoxymethyleneprotoadamantane was converted to 1-amino-2-(2-phenyl-1-adamantyl)ethane. p-(1-Adamantane)benzyl- and phenethylamines were synthesized from 1-(p-bromophenyl)adamantane and 1-(p-tolyl)adamantane, respectively. Reaction of chloroacetonitrile with the above amines furnished N-substituted 2-chloroacetamidine hydrochlorides, which were the precursors of 2-mercaptoacetamidines and related derivatives.

Among the best radioprotectors were some mono-N-substituted 2-mercaptoacetamidines and their corresponding disulfides and phosphorothioates. Particularly effective against otherwise lethal doses of γ-radiation in mice were the adamantane derivatives, 1 and 2.[1]

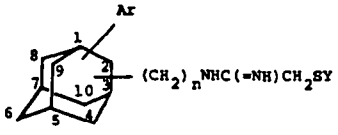


1 (WR-155,419)



2 (WR-159,243)

We were interested in the synthesis of a number of potential radioprotectors which were to be N-(aryl substituted adamantane)alkyl 2-mercaptoacetamidines and derivatives. It was therefore necesary to synthesize a number of (aryl substituted adamantane)alkylamines. In designing these amines, an aryl substituent on the adamantane ring was in relatively close proximity to a short aliphatic chain carrying a mercaptoacetamidine group. Structure 3 broadly represents this type of compound in which the aryl substituent is located either 1,2 or 1,3 to a relative short aliphatic chain (n = 1 or 2) carrying the mercaptoacetamidine moiety. In another series, the adamantane ring was to be separated from the mercaptoacetamidine group by a 1,4-phenylene spacer (4).



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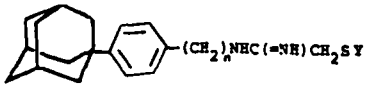
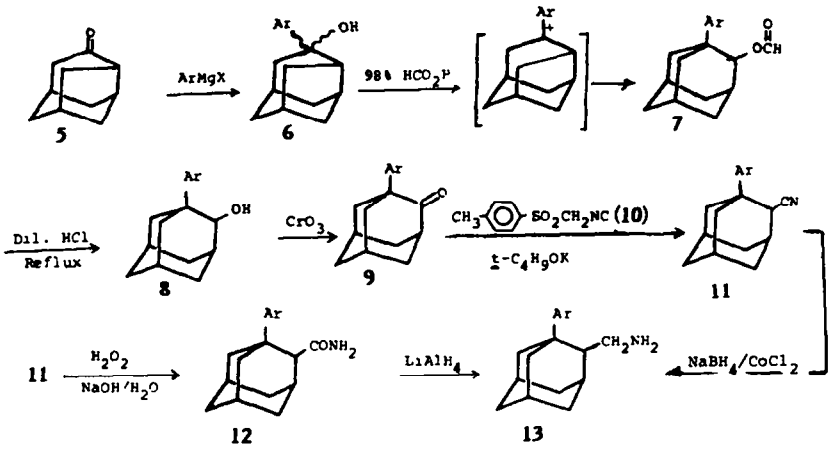


4

1-Aryl-2-(aminoalkyl)adamantanes. Syntheses of adamantanes bearing an aryl group at C-1 and a suitable functional group at C-2 commenced with the reaction of organometallic reagents with 4-protoadamantanone (5). Reactions of 5 with phenyllithium or a Grignard reagents generated from either bromobenzene, p-fluorobromobenzene, p-bromoanisole or p-bromothioanisole yielded a mixture of epimeric alcohol, 6. These alcohols were not purified but were rearranged immediately by various acids to furnish 1,2-disubstituted adamantanes.[2,3]

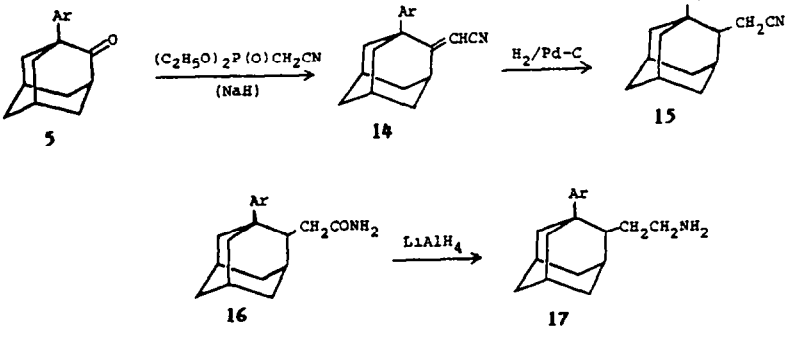
For example, the reaction of 6 (R = C_6H_5) with hydrogen chloride or bromide provided good yields of either 2-chloro-1-phenyl- or 2-bromo-1-phenyladamantane. Formic acid rearranged 6 to the formates 7 which were hydrolyzed to the corresponding 2-adamantanols, 8.[2,3] Attempts to displace the halo group in 1-phenyl-2-haloadamantanes, or for that matter, the p-toluenesulfonate of 8, by cyanide ion failed under a number of relatively stringent conditions and only starting materials were recovered.



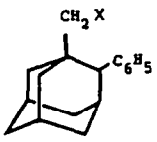
where a, Ar = C_6H_5; b, Ar = 4-FC_6H_4; c, Ar = 4-$CH_3OC_6H_4$; d, Ar = 4-$CH_3SC_6H_4$

In order to introduce the carbon side chain at C-2 of **8**, a number of different approaches were explored. Oxidation of the secondary alcohols (**8**) with Jones' reagent[4] provided the ketones, **9**.[2,3] Alternate methods were sought for the oxidation of the p-methylthiophenyl alcohol **8** (Ar = p-$CH_3SC_6H_4$). To avoid oxidation of the sulfide, this alcohol was oxidized by dimethyl sulfoxide and trifluoroacetic anhydride[5] to provide the corresponding ketone in 96% yield. Ketones were converted readily either to the corresponding methyl- or ethylamines. Reductive cyanation of **9** in a base-catalyzed reaction with p-toluenesulfonylmethyl isocyanide (TOSMIC, van Leusen reagent, **10**)[6] furnished the nitriles **11**. The aryl group at C-1 caused no particular steric hindrance towards this reaction. Reduction of nitriles **11** with lithium aluminum hydride or borane-dimethyl sulfide complex[7,8] tended to be capricious. The most reproducible route to reduce **11** to the primary amines, **13**, was to convert **11** first to the corresponding amides **12** by alkaline hydrogen peroxide.[9-11] Smooth reduction of **12** with lithium aluminum hydride led to **12**. An alternative procedure, using sodium borohydride and cobaltous chloride reduced the nitriles directly to the primary amines.[12]

Introduction of the aminoethyl side-chain at C-2, commenced with a Wittig reaction on **9** with diethyl cyanomethylphosphonate to furnish cyanomethylene derivatives **14**. Catalytic reduction of the alkene in **14** led to cyanomethyl compounds, **15**. These nitriles were reduced either directly by sodium borohydride and cobaltous chloride or converted first to amides, **16**, which were then reduced by lithium aluminum hydride to **17**.



2-Aryl-1-(ω-aminoalkyl)adamantanes. Amines in this series were not as readily accessible. We have already described the synthesis of 1-hydroxymethyl-2-phenyladamantane (**18**) from 4-epoxymethyleneprotoadamantane.[13]



18 X = OH

19 X = Br

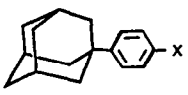
20 X = CN

21 X = CH_2NH_2

The alcohol **18** was converted by hydrobromic acid to the bromide **19.** Although rearrangements of this neopentyl type system to a homoadamantane could be anticipated,[14,15] this was avoided by carrying out this reaction under thermodynamic conditions in boiling 48% hydrobromic acid.[14,15] Bromide **19** was not purified but was reacted directly with sodium cyanide in dimethyl sulfoxide to provide nitrile **20** which was subsequently reduced to the amine **21.**

(3-Aryl-1-adamantyl)alkylamines. The synthesis of a number of these amines had been described previously.[16] These amines were utilized in the preparation of the required compounds as is described below.

[p-(1-Adamantyl)phenyl]alkylamines. Several amines in this series were prepared. Carbonation of the Grignard reagent from 1-(p-bromophenyl)adamantane (**22**)[17] yielded the corresponding acid (**23**) which was converted to the amide (**24**). Reduction of **24** with lithium aluminum hydride afforded the methylamine (**25**). In order to obtain the corresponding ethylamine the following sequence was employed: Free-radical bromination of 1-(p-tolyl)adamantane (**26**) yielded the bromomethyl derivative (**27**). Reaction with potassium cyanide produced nitrile **28** which was reduced to the required amine, **29.**



22 X = Br

23 X = CO_2H

24 X = $CONH_2$

25 X = CH_2NH_2

26 X = CH_3

27 X = CH_2Br

28 X = CH_2CN

29 X = $(CH_2)_2NH_2$

Synthesis of 2-mercaptoacetamidines and derivatives. Syntheses of the target compounds followed the sequences outlined in **Scheme I.**[1] Sodium methoxide-catalyzed addition of methanol to chloroacetonitrile (**30**) generated methyl chloroacetimidate (**31**). Reaction of **31** with amine hydrochlorides yielded the corresponding 2-chloroacetamidine hydrochlorides, **32.** These and other amidinium salts which proved to be powerful vesicants have to be handled with extreme care, particularly, avoiding contact with the skin. The initial aim was to convert **32** to S-alkyl phosphorothioates, (**33, 34**) since these were the most active compounds in prior series.[1] Therefore, **32** was reacted with trisodium phosphorothioate to form S-alkyl phosphorothioates which were isolated either as the sodium hydrogen salts, **33,** or upon careful neutralization with cold dilute mineral acids, as phosphorothioic acids, **34.** The phosphorothioates in these particular series were quite insoluble and could be purified sometimes by extraction with hot solvents. If purification of either **33** or **34** proved too tedious, or if they failed to crystallize, they could be hydrolyzed relatively quickly by hot dilute hydrochloric acid to mercaptoacetamidine hydrochlorides, **35.** Some of these thiols (**35**) were too difficult to purify and were oxidized by hydrogen peroxide in dilute hydrochloric acid to provide the very stable disulfides **36.**

An alternate synthesis of disulfides **36** from **33** has been described.[1] The reaction of **32** with sodium thiosulfate usually produced highly crystalline and easy to purify Bunte salts, **37.** These were converted to **36** using thiourea in hot dilute mineral acid.[1]

Table I: Synthesis and Physical Properties of 1-Substituted, 1,2- and 1,3-Disubstituted Adamantanes

Substituents on the Adamantane Ring		Method[a]	Yield,	mp,	Recrystn.	Formula
X at C-1	Y, at other ring carbons		%	°C	Solvent[b]	
C_6H_5	2-OH	A	79	70-73[c]	MeOH-H_2O	---
4-FC_6H_4	2-OH	A	67	89.5-91.5	hexane	$C_{16}H_{19}FO$
4-$CH_3OC_6H_4$	2-OH	A	74	99.5-101.5	hexane	$C_{17}H_{22}O_2$
4-$CH_3SC_6H_4$	2-OH	A	67	122.5-124	Et_2O-hexane	$C_{17}H_{22}OS$
C_6H_5	2 (=O)	B	87	138-139[d]	hexane	--
4-FC_6H_4	2 (=O)	B	94	162.5-164.5	Et_2O-hexane	$C_{16}H_{17}FO$
4-$CH_3OC_6H_4$	2 (=O)	B	87	88-92	hexane	$C_{17}H_{20}O_2$
4-$CH_3SC_6H_4$	2 (=O)	C	96	87-89	CH_2Cl_2-hexane	$C_{17}H_{20}OS$
C_6H_5	2-CN	D	72	112-113	EtOH-H_2O	$C_{17}H_{19}N$
4-$CH_3SC_6H_4$	2-CN	D	59	90.5-93	CH_2Cl_2-hexane	$C_{18}H_{21}NS$
C_6H_5	2 (=CHCN)	E	92	94-94.5	hexane	$C_{18}H_{19}N$
4-FC_6H_4	2 (=CHCN)	E	97	84-85	hexane	$C_{18}H_{18}FN$
4-$CH_3OC_6H_4$	2 (=CHCN)	E	86	160.5-162.5	Et_2O-hexane	$C_{19}H_{21}NO$
C_6H_5	2-CH_2CN	F	96	81-82	hexane	$C_{18}H_{21}N$
CH_2CN	2-C_6H_5	G	95	67-68	---	$C_{18}H_{21}N$
4-FC_6H_4	2-CH_2CN	F	98	66.5-70.5	hexane	$C_{18}H_{20}FN$
4-$CH_3OC_6H_4$	2-CH_2CN	F	89	129-130.5	Et_2O-EtOAc-hexane	$C_{19}H_{23}NO$
C_6H_5	2-$CONH_2$	H	78	160-161	MeOH	$C_{17}H_{21}NO \cdot H_2O$
C_6H_5	2-CH_2CONH_2	H	95	152-153.5	Et_2O-hexane	$C_{18}H_{23}NO$
CH_2CONH_2	2-C_6H_5	H	79	145-146	Et_2O-H_2O	$C_{18}H_{23}NO$
4-FC_6H_4	2-CH_2CONH_2	H	83	140.5-142.5	Et_2O-pet. ether	$C_{18}H_{22}FNO$
4-$CH_3OC_6H_4$	2-CH_2CONH_2	H	92	151.5-153.5	THF-hexane	$C_{19}H_{25}NO_2$
C_6H_5	2-$CH_2NH_2 \cdot HCl$	I	72	300-302 (dec.)	---	$C_{17}H_{23}N \cdot HCl$
4-$CH_3SC_6H_4$	2-$CH_2NH_2 \cdot HCl$	I	63	316-320 (dec.)	---	$C_{18}H_{25}NS \cdot HCl$
C_6H_5	2-$(CH_2)_2NH_2 \cdot HCl$	I	100	267-269	MeOH-Et_2O	$C_{18}H_{25}N \cdot HCl$
$(CH_2)_2NH_2$ HCl	2-C_6H_5	I(J)	87(83)	252-254 (dec.)	EtOH-Et_2O	$C_{18}H_{25}N \cdot HCl$

Table I (Continued)

Substituents on the Adamantane Ring		Method[a]	Yield,	mp,	Recrystn.	Formula
X at C-1	Y, at other ring carbons		%	°C	Solvent[b]	
4-FC_6H_4	2-$(CH_2)_2NH_2 \cdot HCl$	I	79	244-245.5	EtOH-hexane	$C_{18}H_{24}FN \cdot HCl$
4-$CH_3OC_6H_4$	2-$(CH_2)_2NH_2 \cdot HCl$	I	85	255-257	EtOH-Et_2O	$C_{19}H_{27}NO \cdot HCl$
C_6H_5	2-$CH_2NHC(=NH)CH_2Cl \cdot HCl$	K	78	270-272 (dec.)	MeOH-Et_2O	$C_{19}H_{25}ClN_2 \cdot HCl$
4-$CH_3SC_6H_4$	2-$CH_2NHC(=NH)CH_2Cl \cdot HCl$	K	81	214-216 (dec.)	EtOH-pet. ether	$C_{20}H_{27}ClN_2S \cdot HCl$
C_6H_5	2-$(CH_2)_2NHC(=NH)CH_2Cl \cdot HCl$	K	95	216-218 (dec.)	EtOH-Et_2O	$C_{20}H_{27}ClN_2 \cdot HCl$
$(CH_2)_2NHC(=NH)CH_2Cl \cdot HCl$	2-C_6H_5	K	87	179-181 (dec.)	2-PrOH-Et_2O	$C_{20}H_{27}ClN_2 \cdot HCl$
4-FC_6H_4	2-$(CH_2)_2NHC(=NH)CH_2Cl \cdot HCl$	K	73	203.5-204.5 (dec.)	EtOH-pet. ether	$C_{20}H_{26}ClFN_2 \cdot HCl$
4-$CH_3OC_6H_4$	2-$(CH_2)_2NHC(=NH)CH_2Cl \cdot HCl$	K	97	206.5-208.5 (dec.)	EtOH-Et_2O	$C_{21}H_{29}ClN_2O \cdot HCl$
4-$C_6H_4CONH_2$	--	Q	75	200-202	EtOH	$C_{17}H_{21}NO$
4-$C_6H_4CH_2NH_2 \cdot HCl$	--	I	78	304-305	EtOH-H_2O	$C_{17}H_{23}N \cdot HCl$
4-$C_6H_4CH_2NHC(=NH)CH_2Cl \cdot HCl$	--	K	84	148-150	EtOH-H_2O	$C_{19}H_{25}ClN_2 \cdot HCl$
4-$C_6H_4CH_2NHC(=NH)CH_2SPO_3HNa$	--	L	75	120-121	EtOH-Et_2O	$C_{19}H_{26}N_2NaO_3PS \cdot 2H_2O$
4-$C_6H_4CH_2NHC(=NH)CH_2S]_2 \cdot 2 HCl$	--	P	86	255-260	EtOH-Et_2O	$C_{38}H_{50}N_4S_2 \cdot 2HCl$
4-$C_6H_4CH_2CN$	--	R	77	114-116	---	$C_{18}H_{21}N$
4-$C_6H_4(CH_2)_2NH_2 \cdot HCl$	--	J	78	308-310	2-PrOH	$C_{18}H_{25}N \cdot HCl \cdot 0.5H_2O$
4-$C_6H_4(CH_2)_2NHC(=NH)CH_2Cl \cdot HCl$	--	K	87	268-269	EtOH-Et_2O	$C_{20}H_{27}ClN_2 \cdot HCl$
4-$C_6H_4(CH_2)_2NHC(=NH)CH_2S]_2 \cdot 2 HCl$	--	P	60	236-237	EtOH-Et_2O	$C_{40}H_{54}N_2S_2 \cdot 2HCl$
C_6H_5	2-$CH_2NHC(=NH)CH_2SPO_3H_2$	L	87	217-219 (dec.)	---	$C_{19}H_{27}N_2O_3PS$
4-$CH_3SC_6H_4$	2-$CH_2NHC(=NH)CH_2SPO_3H_2$	L	42	201-204 (dec.)	2-PrOH-$C_6H_5CH_3$-Et_2O	$C_{20}H_{29}N_2O_3PS_2$
C_6H_5	2-$(CH_2)_2NHC(=NH)CH_2SH \cdot HCl$	M	85	191-193 (dec.)	EtOH-Et_2O	$C_{20}H_{28}N_2S \cdot HCl$
C_6H_5	2-$(CH_2)_2NHC(=NH)CH_2S_2O_3H$	O	89	155-157	EtOH-Et_2O	$C_{20}H_{28}N_2O_3S_2$
C_6H_5	2-$(CH_2)_2NHC(=NH)CH_2S]_2 \cdot 2HCl$	P	65	201-203	2-BuOH-Me_2CO-Et_2O	$C_{40}H_{54}N_4S_2 \cdot 2HCl$
$(CH_2)_2NHC(=NH)CH_2SPO_3H_2$	2-C_6H_5	L	91	158-162 (dec.)	---	$C_{20}H_{29}N_2O_3PS \cdot 0.25H_2O$
$(CH_2)_2NHC(=NH)CH_2SH \cdot HCl$	2-C_6H_5	M	92	88-95 (dec.)	---	$C_{20}H_{28}N_2S \cdot HCl$
4-FC_6H_4	2-$(CH_2)_2NHC(=NH)CH_2SPO_3H_2$	L	52	175-178 (dec.)	EtOH-Et_2O	$C_{20}H_{28}FN_2O_3PS \cdot H_2O$
4-$CH_3OC_6H_4$	2-$(CH_2)_2NHC(=NH)CH_2SPO_3H_2$	L	48	170-172	EtOH-Et_2O	$C_{21}H_{31}N_2O_4PS \cdot H_2O$

Table I (Continued)

Substituents on the Adamantane Ring		Method[a]	Yield, %	mp, °C	Recrystn. Solvent[b]	Formula
X at C-1	Y, at other ring carbons					
4-$CH_3C_6H_4$	3-$CH_2NHC(=NH)CH_2Cl \cdot HCl$	K	85	130-132 (dec.)	EtOH-H_2O	$C_{20}H_{27}ClN_2 \cdot HCl$
4-FC_6H_4	3-$CH_2NHC(=NH)CH_2Cl \cdot HCl$	K	95	120-122 (dec.)	EtOH-H_2O	$C_{19}H_{24}FClN_2 \cdot HCl$
4-$CH_3OC_6H_4$	3-$CH_2NHC(=NH)CH_2Cl \cdot HCl$	K	96	184-186	EtOH-H_2O	$C_{20}H_{27}ClN_2O \cdot HCl$
4-$CH_3SC_6H_4$	3-$CH_2NHC(=NH)CH_2Cl \cdot HCl$	K	90	145-148 (dec.)	EtOH-H_2O	$C_{20}H_{27}ClN_2S \cdot HCl$
2-C_4H_3S[e]	3-$CH_2NHC(=NH)CH_2Cl \cdot HCl$	K	92	216-218 (dec.)	EtOH-H_2O	$C_{17}H_{23}ClN_2S \cdot HCl \cdot H_2O$
4-$CH_3C_6H_4$	3-$CH_2NHC(=NH)CH_2S_2O_3H$	N	84	184-186	EtOH-Et_2O	$C_{20}H_{28}N_2O_3S_2$
4-$CH_3C_6H_4$	3-$CH_2NHC(=NH)CH_2SPO_3HNa$	L	65	125-128 (dec.)	MeOH-Et_2O	$C_{20}H_{28}N_2NaO_3PS$
4-$CH_3C_6H_4$	3-$CH_2NHC(=NH)CH_2S\frac{1}{2}_2 \cdot 2HCl$	P	45	176-178	MeOH-Et_2O	$C_{40}H_{54}N_4S_2 \cdot 2HCl \cdot 2H_2O$
4-FC_6H_4	3-$CH_2NHC(=NH)CH_2SPO_3HNa$	L	50	98-100	MeOH-Et_2O	$C_{19}H_{25}FN_2NaO_3PS \cdot 1.5H_2O$
4-FC_6H_4	3-$CH_2NHC(=NH)CH_2SH \cdot HCl$	M	47	198-200	EtOH-Et_2O	$C_{19}H_{25}FN_2S \cdot HCl \cdot 1.5H_2O$
4-FC_6H_4	3-$CH_2NHC(=NH)CH_2S\frac{1}{2}_2 \cdot 2HCl$	P	83	216-218 (dec.)	EtOH-H_2O	$C_{38}H_{48}F_2N_4S_2 \cdot 2HCl$
4-$CH_3OC_6H_4$	3-$CH_2NHC(=NH)CH_2SPO_3HNa$	L	75	125-127	MeOH-Et_2O	$C_{20}H_{28}N_2NaO_4PS \cdot 4H_2O$
4-$CH_3OC_6H_4$	3-$CH_2NHC(=NH)CH_2SH \cdot HCl$	M	78	174-176 (dec.)	EtOH-Et_2O	$C_{20}H_{28}N_2OS \cdot HCl$
4-$CH_3OC_6H_4$	3-$CH_2NHC(=NH)CH_2S\frac{1}{2}_2 \cdot 2HCl$	P	78	230-232 (dec.)	EtOH-Et_2O	$C_{40}H_{54}N_4O_2S_2 \cdot 2HCl$
4-$CH_3SC_6H_4$	3-$CH_2NHC(=NH)CH_2S_2O_3H$	N	71	178-180 (dec.)	MeOH-H_2O	$C_{20}H_{28}N_2O_3S_3$
4-$CH_3SC_6H_4$	3-$CH_2NHC(=NH)CH_2SPO_3HNa$	L	81	105-108	MeOH	$C_{20}H_{28}N_2NaO_3PS_2 \cdot 3H_2O$
2-C_4H_3S[e]	3-$CH_2NHC(=NH)CH_2SPO_3HNa$	L	81	118-120	EtOH-Et_2O	$C_{17}H_{24}N_2NaO_3PS_2 \cdot 6H_2O$
2-C_4H_3S[e]	3-$CH_2NHC(=NH)CH_2SH \cdot HCl$	M	75	185-187 (dec.)	EtOH-H_2O	$C_{17}H_{24}N_2S_2 \cdot HCl$

[a] For general methods, see the Experimental Section. Combustion analyses for C, H, N (and frequently for S) were submitted in the original draft for consideration by the referees.

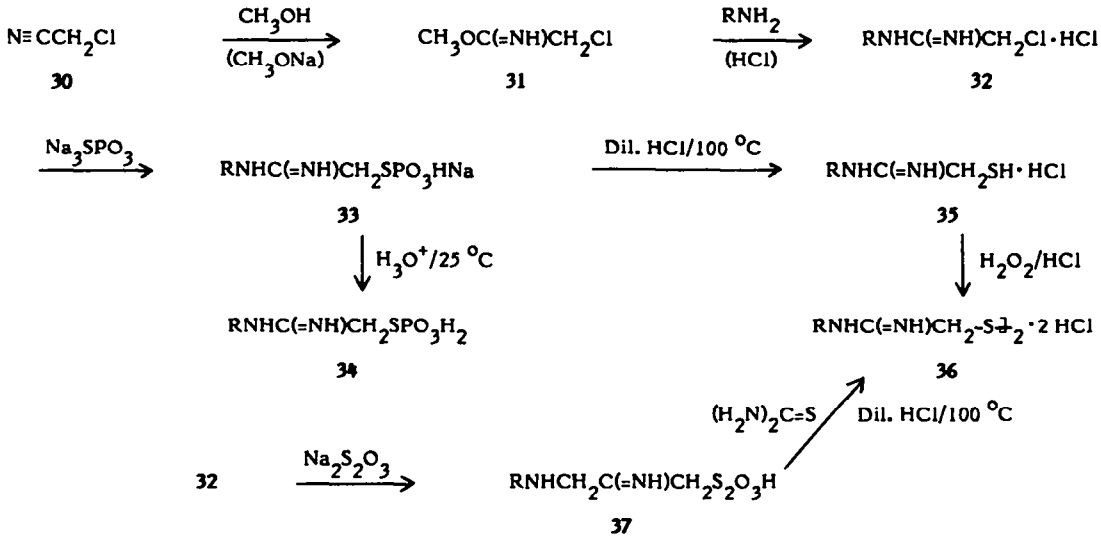
[b] The following abbreviations are used: MeOH for methanol, EtOH for ethanol, 2-PrOH for 2-propanol; 2-BuOH for 2-butanol; Et_2O for ether, THF for tetrahydrofuran; Me_2CO for acetone; EtOAc for ethyl acetate.

[c] Ref. 2 and 3 report the mp, 70-72 °C.

[d] After crystallization (hexane), the pure ketone (TLC, IR, ^1H NMR, MS) melted at 138-139 °C, while the lit.[2,3] report a mp of 152-153 °C.

[e] 2-C_4H_3S = 

SCHEME I



R = Substituted (adamantane)lalkyl

The structure of all products were substantiated by microanalysis and spectral analyses. Proton NMR spectra readily distinguished between thiols **35**, disulfides **36** and phosphorothioates such as **33** and **34**. In DMSO-d_6, the CH_2-S proton signal of either **33** or **34** appeared as a doublet around 3.40 ppm, showing long-range coupling with phosphorus of about 15 Hz. This doublet uniquely distinguishes the phosphorothioates from the thiols or disulfides. In DMSO-d_6 the chemical shifts for the methylene protons of CH_2-SH of **35** was around 3.35 ppm and that of the CH_2-S-S-CH_2 protons of **36**, appeared as a singlet between 3.60 and 4.00 ppm.

The biological activities of a number of the compounds described in this paper will be reported elsewhere.

Experimental[18]

Method A: Synthesis of 1-Aryl-2-adamantanols (8)

After the reaction of **5** with Grignard reagents, the intermediate 4-aryl-4-protoadamantanols were were rearranged immediately with formic acid and the formate hydrolyzed as described in this typical example.

1-(4-Fluorophenyl)-2-adamantanol: A solution of 4-protoadamantanone[19] (6.06 g, 4.03 mmol) in THF (50 mL) was added to the Grignard reagent prepared from magnesium turnings (1.03 g, 42.3 mmol) and 1-bromo-4-fluorobenzene (7.78 g, 44.5 mmol) in THF (50 mL). The mixture was refluxed (4 h) and then quenched with a saturated aq. NH_4Cl solution, and extracted with ether (3 x 100 mL). The combined ether layers were washed with saturated $NaHCO_3$ (100 mL) then water (2 x 100 mL) and dried ($MgSO_4$). Solvents were removed, in vacuo, and the residue was refluxed with 98% formic acid (200 mL) for 30 min. After evaporating solvents in vacuo, the residue was dissolved in acetone (200 mL) and was boiled with 1 N HCl (80 mL, 2 h). Volatile materials were distilled, in vacuo, and the residue was extracted with ether (3 x 100 mL). The extract was washed with $NaHCO_3$ (3 x 100 mL), water (2 x 100 mL) dried ($MgSO_4$) and evaporated in vacuo. The oil was triturated with petroleum ether to furnish a beige powder (6.64 g, 67%), mp 87-90 °C, which was recrystallized repeatedly (hexane) to produce colorless prisms, mp 89.5-91.5 °C; IR (KBr) 3424 cm^{-1} (OH); ^1H NMR (60 MHz, $CDCl_3$) δ 7.81-6.77 (AA'XX' system, 4H, Ar), 3.97 (br s, 1H, CH-O), 3.01-0.83 (m, 14H, AdH).

1-Aryl-2-adamantanones (9), Typical examples:

Method B: 1-(4-Fluorophenyl)-2-adamantanone: Jones reagent[4] (18.5 mL) was added dropwise to a prechilled solution (-10 °C) of 1-(4-fluorophenyl)-2-adamantanol (10 g, 40.6 mmol) in acetone (185 mL) and water (30 mL). The mixture was stirred at 15 °C for 3.5 h. Excess oxidant was destroyed by adding methanol (30 mL). Low boiling materials were distilled, in vacuo, the residue diluted with water (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (5 x 200 mL), saturated $NaHCO_3$ (2 x 200 mL), water (2 x 200 mL) and were dried ($MgSO_4$). Colorless prisms (9.27 g, 94%) mp 160-

163.5 °C were obtained after solvents were removed, in vacuo. The product was recrystallized from ether-hexane, mp 162.5-164.5 °C; IR (KBr) 1712 cm^{-1} (C=O); ^1H NMR (60 MHz, CCl_4) δ 7.28-6.68 (m, 4H, Ar), 2.60 (br s, 1H, CHC=O), 2.70-1.85 (m, 12H, AdH).

Method C: 1-(4-Methylthiophenyl)-2-adamantanone: This oxidation is a modification of a known method.[5] A solution of trifluoroacetic anhydride (0.79 g, 3.75 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise to a solution of DMSO (0.36 mL, 5 mmol) in CH_2Cl_2 (3 mL) at -65 °C (under nitrogen) and the mixture was stirred at -65 °C for 10 min. A solution of 1-(4-methylthiophenyl)-2-adamantanol (0.69 g, 2.5 mmol) in CH_2Cl_2 (2 mL) was then added and the mixture was stirred between -65 and -78 °C for 5 min. Triethylamine (1 mL) was added and the stirred mixture was allowed to reach ambient temperature (40 min). The mixture was washed with water (2 x 10 mL), the organic layer was separated and dried ($MgSO_4$). Removal of solvents, in vacuo, followed by column chromatography (Alumina F-20, ethyl acetate-chloroform, 1:20) produced a colorless solid (0.65 g, 96%), mp 82-85 °C. Repeated recrystallization raised the mp to 87-89 °C; IR (KBr) 1717 cm^{-1} (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 7.19 (s, 4H, Ar), 2.46 (s, 3H, SCH_3), 2.75-1.50 (m, 13H, AdH).

Method D: 1-Aryl-2-adamantanecarbonitriles (11)

1-(4-Methylthiophenyl)-2-adamantanecarbonitrile: Potassium t-butoxide (20.45 g, 182.2 mmol) was added at once to a solution of tosylmethyl isocyanide, **10** (15.8 g, 80.7 mmol) in DMSO (95 mL) (ice-cooling). The mixture was stirred at ambient temperature for 5 min, followed by the addition of 1-(4-methylthiophenyl)-2-adamantanone (7.33 g, 26.9 mmol) in methanol (11 mL). The reaction was monitored for the disappearance of the starting ketone (TLC). The mixture was stirred at 25 °C (1 h), then at 45 °C (72 h), was cooled and poured into a solution of 0.5N HCl (200 mL). The mixture was extracted with CH_2Cl_2 (3 x 150 mL), the extract was washed with water (5 x 300 mL) and dried ($MgSO_4$). Solvents were removed, in vacuo and the residue purified by column chromatography [Alumina F-20, CH_2Cl_2-hexane (1:1) as eluent] to give a colorless solid (4.47 g, 59%); m.p. 84.5-89 °C. Repeated recrystallization from CH_2Cl_2-hexane gave colorless prisms, mp 90.5-93 °C; IR (KBr) 2232 cm^{-1} (C≡N); ^1H NMR (60 MHz, $CDCl_3$) δ 7.27 (s, 4H, Ar), 3.10 (br s, 1H, CHCN), 2.47 (s, 3H, SCH_3), 2.65-1.06 (m, 13H, AdH).

Method E: 1-Aryl-2-(cyanomethylene)adamantanes (14)

2-Cyanomethylene-1-phenyladamantane. A solution of diethyl cyanomethylphosphonate (354 mg, 2 mmol) in THF (3 mL) was added to a suspension of sodium hydride (50% in paraffin, 96 mg, 2 mmol) in ice-cold THF (3 mL). After stirring at 25 °C (10 min), 1-phenyl-2-adamantanone (453 mg, 2 mmol) in THF (5 mL) was added. The reaction was followed by the disappearance of the ketone (TLC). The clear supernatant was decanted and the residue was washed thoroughly with THF. The combined THF solutions were evaporated, in vacuo, and the residue was purified by column chromatography [silica gel, pentane (250 mL), followed by pentane-ether (4:1)]. Colorless prisms (460 mg, 92%) were obtained, mp 88-92 °C, mp 94-94.5 °C after recrystallization from hexane; IR (KBr) 2209 cm^{-1} (C≡N) and 1625 (C=C); ^1H NMR (60 MHz, CCl_4) δ 7.30 (s, 5H, ArH), 4.34 (s, 1H, alkene CH), 3.36 (m, CHCN), 2.60-1.70 (m, 12H); see Table I for analyses.

Such reactions can be carried out conveniently on a larger scale. If the reaction was incomplete after 20-24 h, the mixture was heated at 55 °C until all of the ketones had reacted.

Method F: (1-Aryl-2-adamantyl)acetonitriles (15)

2-(Cyanomethyl)-1-phenyladamantane. 2-(Cyanomethylene)-1-phenyladamantane (1.0 g, 4.0 mmol) in absolute ethanol (25 mL) was hydrogenated in a Parr apparatus in the presence of 10% Pd/C (0.20 g) under 40 psi hydrogen pressure at 25 °C (30 h). The catalyst was filtered off, washed with ethanol and solvents removed, in vacuo, to furnish a light orange solid (0.96 g, 96%). Colorless prisms were obtained after repeated recrystallizations from hexane, mp 81-82 °C; IR (KBr) 2246 (C≡N); ^1H NMR (CCl_4) δ 7.27 (s, 5H, ArH), 2.50-1.50 (m, 16H).

Method G: 1-(Cyanomethyl)-2-phenyladamantane

1-(Hydroxymethyl)-2-phenyladamantane[13] (2.42 g, 10 mmol) was refluxed with 48% HBr (15 mL) (9 h). The reaction was monitored periodically by GC (SE-30, isothermal, 200 °C; retention times of the starting alcohol and the product are 3.2 and 4.2 min, respectively). The mixture was cooled, diluted with water (100 mL), and extracted with $CHCl_3$ (3 x 100 mL). The organic layer was washed with water, $NaHCO_3$ solution, brine and was dried ($MgSO_4$). The solvent was evaporated, in vacuo, to give 2.96 g (97%) of the bromide as a viscous liquid which solidified slowly to a waxy solid, mp 65-70 °C. GC/MS Analysis showed that the purity of the bromide is greater than 95%. The compound was used in the next step without further purification; ^1H NMR (360 MHz, $CDCl_3$) δ 7.42-7.18 (m, 5H, Ph), 3.06 and 2.99 (AB, 2H, CH_2Br, J_{AB} = 10.0 Hz), 2.94 (br s, 1H,

H-2), 2.34-1.62 (m, 13H, Adm); ^{13}C NMR (90 MHz, $CDCl_3$) δ 142.9 (Ph, C-i), 129.4 (Ph, C-o), 127.8 (Ph, C-m), 125.9 (Ph, C-p), 53.7 (C-2), 46.2 (CH_2Br), 43.4 (C-8), 39.5 (C-10), 37.5 (C-6), 36.2 (C-1), 36.0 (C-9), 35.0 (C-3), 30.4 C-1), 28.7 (C-7), 27.8 (C-5); MS, m/z (rel intensity) 306 and 304 (M^+, 28), 225 (M^+-Br, 56), 211 (19), 143 (11), 129 (12), 117 (14), 91 (100), 67 (10), 65 (10).

A mixture of the bromide, prepared above, (21.7 g, 70.9 mmol), NaCN (25 g), in dry DMSO (250 mL) was stirred at 80-100 °C (15 h), poured into ice-water (700 mL) and extracted with hexane (4 x 200 mL). The hexane extract was washed twice with water, 6 N HCl (to remove any isocyanide), dried ($MgSO_4$) and evaporated, in vacuo, to give 16.9 g (95%) of an oil which crystallized slowly (2 weeks) to colorless needles; mp 67-68 °C; GC retention time = 4.6 min (SE-30 column, isothermal, 200 °C); IR (film) 2242 (CN) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.44-7.22 (m, 5H, Ph), 2.94 (b s, 1H, H-2), 1.95 (s, 2H, CH_2CN), 2.28-1.57 (m, 13H, remaining adamantane ring H's); ^{13}C NMR (90 MHz, $CDCl_3$) δ 142.7 (Ph, C-i), 129.4 (Ph, C-o), 128.3 (Ph, C-m), 126.5 (Ph, C-p), 117.6 (CN), 54.8 (C-2), 44.6 (C-8), 39.5 (C-10), 37.3 (C-6), 36.7 (C-9), 35.1 (C-1), 34.8 (C-3), 30.3 (C-4), 29.6 ($\underline{C}H_2CN$), 28.8 (C-7), 27.8 (C-5); MS, m/z (rel intensity) 251 (M^+, 51), 211 (M^+-CH_2CN, 64), 160 (13), 129 (20), 119 (27), 91 (100), 79 (28), 65 (13).

Method H: The Conversion of Nitriles to Amides; Typical Example:

(2-Phenyl-1-adamantyl)acetamide: A mixture of (2-phenyl-1-adamantyl)acetonitrile (1.6 g, 6.37 mmol), methanol (15 mL), DMSO (0.5 mL), 30% H_2O_2 (1.1 mL), and 0.2 M NaOH (0.6 mL) was heated at 50-55 °C for 12 h. The reaction was monitored by GC; SE-30 column, isothermal, 200 °C, retention times of the starting nitrile and the amide are 4.6 and 8.8 min, respectively. The mixture was then diluted with water (100 mL) and extracted with $CHCl_3$ (3 x 75 mL). The organic layer was dried ($MgSO_4$) and evaporated, in vacuo. The residue was recrystallized from benzene-hexane and again from aqueous ethanol to give the amide (1.35 g, 79%), mp 145-146 °C; IR (KBr) 3313 and 3185 (NH_2), 1655 (C=O), cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.45-7.21 (m, 5H, Ph), 5.33 and 4.92 (2 br s, 2H, NH_2), 2.99 (s, 1H, H-2), 2.37-1.50 (a series of complex multiplets, 15H, adm and $C\underline{H}_2CO$). The DOUBTFULL NMR technique[20] was used to determine the chemical shift of the CH_2CO protons (dd, 2.05 and 1.85 ppm, J = 13.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.1 (C=O), 144.5 (Ph, C-i), 128.3 (Ph, C-o), 129.7 (Ph, C-o), 126.1 (Ph, C-p), 55.9 (C-2), 47.66 ($\underline{C}H_2C$=O), 44.9 (C-8), 39.8 (C-10), 38.4 (C-6), 37.8 (C-9), 35.9 (C-3), 35.7 (C-1), 29.2 (C-7), 28.3 (C-5); MS, m/z (rel intensity) 269 (M^+, 100), 252 (M^+-NH_3, 45), 224 (14), 211 (22), 210 (20), 178 (15), 136 (21), 119 (30), 115 (23), 91 (92), 79 (28), 77 (23), 67 (14), 65 (14).

Method I: Synthesis of Amines from Amides

1-Amino-2-[1-(4-Fluorophenyl)-2-adamantyl]ethane Hydrochloride: A solution of 1-(4-fluorophenyl)-2-adamantyl acetamide (4.2 g, 14.6 mmol) in THF (40 mL) was added dropwise to a suspension of $LiAlH_4$ (2.77 g, 73.0 mmol) in THF (110 mL) at 0-5 °C. The mixture was refluxed (24 h), cooled and treated successively with water (2.77 mL), 15% NaOH (2.77 mL), and water (8.31 mL). The mixture was refluxed for 10 min, cooled to produce a more granular precipitate which was filtered and washed thoroughly with ether. The combined filtrate was evaporated, in vacuo, and the residue dissolved in dry ether (30 mL) and dried ($MgSO_4$) again. The ether solution was filtered and HCl gas was bubbled through the filtrate. The colorless salt (3.56 g, 79%; mp 239-243 °C) was recrystallized from ethanol-hexane, mp to 242.5-244 °C; IR (KBr) ~3125 cm^{-1} (NH_3^+); ^{1}H NMR (60 MHz, $CDCl_3$/DMSO-d_6) δ 7.82 (br s, 3H, exchangeable with D_2O, NH_3^+), 7.22 (m, 4H, Ar), 2.50 (m, 2H, $C\underline{H}_2N$), 3.20-0.82 (m, 16H, AdH).

Method J: Reduction of Nitriles to Primary Amines

1-Amino-2-(2-phenyl-1-adamantyl)ethane Hydrochloride: To a solution of (2-phenyl-1-adamantyl)acetonitrile (11.9 g, 47.4 mmol) in methanol (500 mL) was added 12.3 g (94.8 mmol) of anhydrous $CoCl_2$. The mixture was stirred and cooled in ice while $NaBH_4$ (18.0 g, 0.474 mol) was added in small portions. Hydrogen evolved and a black precipitate of Co_2B was formed. Stirring was continued for 12 h after which the mixture was shaken with 6 N HCl (700 mL) to dissolve Co_2B. Neutral impurities were removed by extraction with hexane (200 mL). The acidic aqueous phase was then rendered strongly alkaline with concentrated NH_4OH (100 mL) and 10% NaOH solution (50 mL) and the amine was extracted by ether (4 x 300 mL). The ether layer was dried ($MgSO_4$) and evaporated, in vacuo. The residue was reacted with a methanolic solution of HCl. The hydrochloride (10.9 g, 83%) crystallized out upon slow dilution with anhydrous ether and was recrystallized from ethanol-ether, mp 252-254 °C (dec.); IR (KBr) 3420, 2900-3100, 1600, 1495, 1475, 1455, 1395, 753, 700 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.70 (br s, 3H, NH_3), 7.15-7.36 (m, 5H, Ph), 2.60-2.77 (m, 2H, CH_2), 2.70 (br s, 1H, H-2), 2.27-1.45 (m, 13H, Adm), 1.34-1.39 (m, 2H, $C\underline{H}_2$-Adm); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.9 (Ph,

C-i), 129.3 (Ph, C-o), 128.4 (Ph, C-m), 126.2 (Ph, C-p), 55.2 (C-2), 44.8 (C-8), 39.8 (C-10), 38.4 ($\underline{C}H_2$-Adm), 38.0 (C-9), 37.8 (C-6), 35.8 (C-3), 35.1 (C-1), 34.9 ($\underline{C}H_2N$), 30.3 (C-4), 28.9 (C-7), 28.0 (C-5); MS, m/z (rel intensity) 255 (M^+-HCl, 9), 238 (M^+-HCl-NH_3), 226 (2), 177 (2), 155 (10), 135 (11), 129 (19), 128 (14), 115 (21), 106 (30), 93 (22), 91 (100), 79 (35), 77 (25), 67 (17).

Method K: 2-Chloroacetamidine Hydrochlorides, 32; Typical example:

N-[2-(2-Phenyl-1-adamantyl)ethyl]-2-chloroacetamidine Hydrochloride: Methyl chloroacetamidate was prepared, in situ, by stirring chloroacetonitrile (396 mg, 5.25 mmol) with a solution of sodium methoxide prepared by dissolving sodium (20 mg, 0.0016 g-atom) in 10 mL of anhydrous methanol at room temperature (1.5 h). A solution of the amine hydrochloride, prepared above, (1.46 g, 5.0 mmol) in anhydrous methanol (12.5 mL) was then added and the pH was adjusted to 4 by the addition of methanolic HCl. The mixture was stirred for 12 h after which the solvent was evaporated, in vacuo, at 60 °C and the residue was triturated with 2-propanol (75 mL). Solids were filtered off and the filtrate was diluted slowly with anhydrous ether to afford the product as colorless needles (1.01 g, 87%); mp 179-181 °C (dec.); ^{1}H NMR (360 MHz, $(CD_3)_2SO$) δ 9.94, 1.17 and 9.62 (s, 3H, NH), 7.51-7.18 (m, 5H, Ph), 4.33 (s, 2H, CH_2Cl), 3.23 and 3.12 (m, 2H, CH_2N), 2.88 (s, 1H, H-2), 1.46-2.26 (m, 13H, Adm), 1.30 (m, 2H, $C\underline{H}_2$-Adm); ^{13}C NMR (90 MHz, CD_3OD) δ 163.9 (NC=NH), 145.5 (Ph, C-i), 130.6 (Ph, C-o), 129.3 (Ph, C-m), 127.1 (Ph, C-p), 56.6 (C-2), 45.3 (C-10), 40.9 (C-8), 39.7 ($\underline{C}H_2Cl$), 39.4 ($\underline{C}H_2N$), 39.2 (C-9), 39.1 (Adm-$\underline{C}H_2$), 38.9 (C-6), 37.2 (C-3), 36.0 (C-1), 31.4 (C-4), 30.5 (C-7), 29.5 (C-5); MS, m/z (rel intensity) 330 (27), and 332 (9) (M^+-HCl), 295 (M^+-HCl-Cl, 8), 281 (M^+-HCl-CH_2Cl, 4), 238 (25), 129 (9), 128 (8), 121 (11), 119 (34), 108 (31), 106 (100), 105 (35), 91 (64), 79 (21).

Method L: Amidinium Phosphorothioates, 34. Several examples are provided.

S-{N-[2-(2-Phenyl-1-adamantyl)ethyl]carbamidinium} methyl Hydrogen Phosphorothioate: A solution of N-2-(2-phenyl-1-adamantyl)ethyl-2-chloroacetamidine hydrochloride, (3.6 g, 9.81 mmol) in 50% aqueous ethanol (65 mL) was added to a solution of trisodium phosphorothioate (1.86 g, 10.3 mmol) in water (15 mL). The mixture was stirred for 30 min (N_2) after which it was rendered strongly acidic with methanolic HCl, concentrated, in vacuo, at room temperature to about half of its original volume and then diluted with 100 mL of water. The phosphorothioate was filtered, washed thoroughly with water, ether, carbon disulfide (to remove any sulfur), and finally with ether, and dried in a vacuum dessicator at room temperature. The yield was 3.65 g (91%); mp 158-162 °C (dec.); IR (KBr) 3400-2800 (NH_2, NH, POH), 1675, 1640 ($HNC=NH_2^+$) cm^{-1}; ^{1}H NMR (360 MHz, $(CD_3)_2SO$) δ 10.13, 10.08 (two b s, NH_2^+), 8.46 (br s, NH), 7.17-7.45 (m, 5H, Ph), 4.22 (br s, HOP/H_2O), 3.35 (d, 2H, CH_2SP, $^3J_{H,P}$ = 15.0 Hz), 3.11 and 3.00 (m, 2H, CH_2N), 2.86 (s, 1H, H-2), 1.45-2.25 (a series of complex multiplets, 13H, Adm), 1.28 (m, 2H, Adm-$C\underline{H}_2$); ^{13}C NMR (90 MHz, CD_3OD) δ 166.7 ($NHC=NH_2^+$), 145.5 (Ph, C-i), 130.7, 129.3 (Ph, C-o and C-m), 127.1 (Ph, C-p), 56.5 (C-2), 45.3 (C-8), 40.8 (C-10), 39.2 (2 overlapping signals), 39.1, 39.0 (C-9, C-6, CH_2CH_2NH) 37.2 (C-3), 36.0 (C-1), 31.4 (C-4), 30.4 (CH_2S), 30.5 (C-7), 29.5 (C-5); MS, m/z (rel intensity) 296 (M^+-SPO_3H, 10). 255 (15), 238 (8), 192 (14), 117 (30), 91 (100), 72 (71), 65 (35).

Sodium S-{N-[4-(1-adamantyl)benzyl]carboxamidinium} methyl Phosphorothioate. A solution of N-[4-(1-adamantyl)benzyl]-2-chloroacetamidinium hydrochloride (0.50 g, 1.4 mmol) in aqueous ethanol (50%, 15 mL) was mixed with one of trisodium phosphorothioate (0.25 g, 1.4 mmol in 5 mL water). After stirring for 30 min (N_2), the product was filtered, washed with little ice-cold water (1 mL), ether and was recrystallized from ethanol-ether, mp 120-121 °C. The yield was 0.4 g (75%); ^{1}H NMR (60 MHz, CD_3CO_2D) δ 7.36 (s, 4H, ArH) 4.53 (s br, CH_2N), 3.88 (d, CH_2-S-P, J_{CH_2-P} 15.4 Hz), 1.85-2.0 (m, AdH protons).

Method M: Synthesis of 2-Mercaptoacetamidine Hydrochlorides, 35

The mercaptan can be obtained from the phosphorothioate, whether the latter has been isolated, or not.

N-[2-(2-Phenyl-1-adamantyl)ethyl]-2-mercaptoacetamidine Hydrochloride: A solution of S-{N-[2-(2-phenyl-1-adamantyl)ethyl]carboxamidinium} methyl hydrogen phosphorothioate (3.65 g, 8.94 mmol) in ethanol (50 mL) containing 6 N HCl (100 mL), was refluxed under a blanket of N_2 (20 min). The mixture was cooled, concentrated, in vacuo, to about one-half of its original volume and diluted with cold water (100 mL). The mercaptan separated as a gummy solid which was filtered, washed with water and finally with ether, dried in vacuum (~1 Torr) at 25 °C to give shiny flakes (3.03 g, 92%); mp 88-95 °C (dec.); IR (KBr) 3200 (br, NH), 2478 (SH), 1677, 1636 ($NHC=NH_2^+$) cm^{-1}; ^{1}H NMR (360 MHz, CD_3OD) δ 7.48-7.18 (m, 5H, Ph), 3.35 (s, 2H, CH_2S), 3.23-3.14 (M, 2H, CH_2N), 2.93 (br s, 1H, H-2), 2.34 (m, 1H, H-4), 2.15-1.46 (m, 12H, remaining Adm H's), 1.36 (m, 2H, $C\underline{H}_2$-Adm); ^{13}C NMR (90 MHz, CD_3OD) δ 168.2 ($NHC=NH_2^+$), 145.5 (Ph, C-i), 130.7, 129.3 (Ph, C-o

and C-m), 127.1 (Ph, C-p), 56.5 (C-2), 45.3 (C-8), 40.9 (C-10), 39.2 (two overlapping signals: $\underline{C}H_2$-Adm, C-9), 39.09 (CH_2N), 39.00 (C-6), 37.2 (C-3), 36.0 (C-1), 31.5 (C-4), 30.5 (C-7), 29.5 (C-5), 25.0 (CH_2SH); MS, m/z (rel intensity) 297 (10), 296 (51), 295 (23), 255 (15), 238 (31), 131 (31), 115 (28), 91 (77), 85 (43), 72 (92), 69 (100), 58 (28).

N-[2-(1-Phenyl-2-adamantyl)ethyl]-2-mercaptoacetamidinium Hydrochloride: An aqueous solution of trisodium phosphorothioate (2.43 g, 13.5 mmol in 38 mL) was added to a suspension of N-[2-(1-phenyl-2-adamantyl)ethyl]-2-chloroacetamidine hydrochloride (4.72 g, 12.8 mmol) in 50% ethanol (72 mL). The mixture was allowed to stir at ambient temperature for 30 min under a stream of nitrogen. To the homogeneous solution was added 6 N HCl (61.5 mL) and the mixture was heated at 85-90 °C (20 min). Upon cooling, the colorless solid (3.98 g, 85%, mp 182-186 °C, dec.) was filtered, washed thoroughly with water, recrystallized from ethanol-ether to give a powder (2.80 g), mp 191-193 °C (dec.); IR (KBr) 1679 ($C{=}NH_2^+$), 1643 cm^{-1} (C=N); ^1H NMR (60 MHz, DMSO-d_6) δ 9.75, 9.38, 8.61 (three br s, 3H, exchangeable with D_2O, 3 NH's), 7.30 (s, 5H, Ph), 3.89 (br s, 1H, exchangeable with D_2O, SH), 3.31 (br s, 2H, $C\underline{H}_2S$), 2.96 (br s, 2H, $C\underline{H}_2N$), 2.26-0.50 (m, 16H, AdH).

Method N: Synthesis of Bunte Salts, 37

S-{N-[2-(1-Phenyl-2-adamantyl)ethyl]carboxamidiniummethyl} Thiosulfate. To a solution of N-2-(1-phenyl-2-adamantyl)ethyl-2-chloroacetamidine hydrochloride (1.0 g, 2.72 mmol) in 50% methanol (12 mL) was added an aqueous solution of sodium thiosulfate (0.43 g, 2.72 mmol) in water (2.7 mL). The mixture was heated at 80-85 °C for 30 min. The solid was filtered, washed thoroughly with water and dried (0.99 g, 89%). Repeated recrystallization from ethanol-ether furnished a white powder, mp 155-157 °C (dec.); IR (KBr) 1662 cm^{-1} ($C{=}NH_2$), 1625 cm^{-1} (C=N), 1216 cm^{-1} (SO_2); ^1H NMR (60 MHz, DMSO) δ 8.86 (br s, 2H, NH_2), 7.30 (s, 5H ArH), 3.77 (s, 2H, CH_2S), 3.00 (m, 2H), 2.37-1.27 (m, 16H).

Method O: Disulfides (36) from Bunte Salts (37)

Di-N-{[2-(1-Phenyl-2-adamantyl)ethyl]carboxamidinium}methyl Disulfide Dihydrochloride. From a Bunte salt, **37**: a mixture of S-N-2-(1-phenyl-2-adamantyl)ethyl carboxamidinium methyl thiosulfate (0.80 g, 2.0 mmol), thiourea (0.152 g, 2.0 mmol), 2-propanol (16 mL) and 1 N HCl (40 mL) was heated at 95-100 °C for 10 h. After concentration in vacuo, the aqueous layer was decanted from a gummy residue. The product was extracted with hot toluene to remove sulfur which is known to accompany the product. Recrystallization of the residue from 2-butanol-acetone-ether yielded a colorless product (0.47 g, 65%), mp 201-203 °C (dec.). Repeated recrystallization from the same solvent mixture raised the mp to 205.5-207.5 °C (dec.); IR (KBr) 1677 cm^{-1} ($C{=}NH_2$), 1640 cm^{-1} (C=N); ^1H NMR (60 MHz, DMSO-d_6) δ 9.87, 9.45, 8.77 (three br s, 6H), 7.29 (s, 10H), 3.83 (s, 4H), 3.03 (br s, 4H), 2.29-1.40 (m, 16H).

Method P: Disulfides (36) from Phosphorothioates (34)

From a phosphorothioate, **34**: A solution of trisodium phosphorothioate (0.18 g, 1 mmol) in H_2O (4 mL) was added to a solution of N-[2-(1-phenyl-2-adamantyl)ethyl]-2-chloroacetamidine hydrochloride (0.37 g, 1 mmol) in 50% ethanol (5 mL). The mixture was stirred at ambient temperature (30 min). After the addition of 6 N HCl (5 mL), the reaction was heated at 90 °C (20 min). Upon cooling, a gummy precipitate was obtained; solvents were removed, in vacuo, and attempts to crystallize the gummy residue were unsuccessful. To this gum was added 30% H_2O_2 (2 mL), methanol (1 mL) and 6 N HCl (2 mL). After stirring at room temperature (1.5 h), concentration in vacuo, and repeated trituration with ether provided a light grey powder (0.15 g, 42%) identical to the disulfide sulfide prepared in **Method O.**

Method Q:

4-(1-Adamantyl)benzamide. A mixture of 4-(1-adamantyl)benzoic acid[21] (2.0 g, 0.0078 mol) phosphorus pentachloride (1.62 g, 0.0078 mol) in carbon tetrachloride (40 ml) was refluxed for 1 h. Solvents were evapoarated, in vacuo, and the residue dissolved in carbon tetrachloride (20 ml) and reevaporated. This procedure was repeated twice to remove volatile phosphorus halides. The residue was taken up in anhydrous benzene and added dropwise to stirred ammonium hydroxide (28%, 50 ml) at 0 °C. This mixture was stirred (8 h), extracted with ether (3 x 100 ml), the ether phase washed with water and dried (Na_2SO_4). The product was recrystallized from ethanol to yield 1.5 g (75%) of amide, mp 200-202 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 1.78-2.07 (m, AdH), 5.90 (br s, $CONH_2$), 7.42, 7.77 (m, AA'BB', ArH).

Method R:

4-(1-Adamantyl)phenylacetonitrile. A solution of 4-(1-adamantyl)toluene (5.0 g, 0.022 mol), N-bromosuccinimide (3.5 g, 0.0196 mol) in CCl_4 (75 mL), benzoyl peroxide (0.45 g), was heated on a steam bath (45 min).

The solution was cooled, succinimide filtered off and evaporated to give the crude bromide (6.4 g, mp 40-60 °C). The product was dissolved in ethanol (100 mL) and treated with KCN (1.7 g, 0.026 mol) in 20 mL of water. After boiling for 4.0 h, solvents were removed and the residue diluted with ice. The nitrile was purified by chromatography over silica gel using 0-25% benzene in petroleum ether as eluent; mp 114-116 °C; ^{1}H NMR ($CDCl_3$) δ 1.77-1.92 (m), 2.10 (br s), (adamantane protons), 3.70 (s, CH_2CN), 7.32 (br s, ArH's); IR (Nujol) 2225 cm^{-1} (C≡N); MS, m/z (rel intensity) 253 (M^+ + 2, 252 (M^+ + 1, 15), 251 (M^+, 74), 240 (25), 195 (34), 194 (100), 183 (16), 167 (37), 155 (42), 154 (38), 135 (35), 94 (85).

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