N-[(**2,4-Diamino-5-pyrimidinyl)methyl]-*n*-stearylamide (9).**—5-Aminomethyl-2,4-diaminopyrimidine[17] (0.1 g, 0.72 mmole) was mixed with 1 ml of pyridine and 1 ml of $CHCl_3$. A soln of stearoyl chloride (0.22 g, 0.72 mmole) in $CHCl_3$ (1 ml) was added over a period of 10 min with cooling. The reaction mixt was stored in a refrigerator for 3 days, and the solid was collected, washed with $CHCl_3$, and dried, mp 250–265° (0.15 g). It was mixed with about 5 ml of NaOH (1 *M*) and a few drops of EtOH and stirred for about 12 hr. The solid was collected and washed with Me_2CO: ϵ 7.55 × 10^3 at λ_{max} 285 mμ (abs EtOH); λ_{min} 256 mμ; mp 168–169°. tlc, MeOH R_f 0.60. An anal. sample was prepared by recrystns from abs EtOH and 2-ethoxyethanol. *Anal.* ($C_{23}H_{43}N_5O$) C, H, N.

5-(1-Adamantyl)-4-hydroxy-2-mercaptopyrimidine (10).—A soln of ethyl formyl-(1-adamantyl)acetate[3] (0.55 g, 2.2 mmoles in 5 ml of abs EtOH) was mixed with a soln of NaOEt (0.11 g of 50% oil dispersion of NaH, 2.32 mmoles in 5 ml of abs EtOH). After stirring 0.5 hr, thiourea (0.167 g, 2.20 mmoles) was added. The resulting soln was refluxed 7 hr, and the solvent was removed *in vacuo*. The residue was mixed with H_2O (25 ml), acidified with HCl, and extd with Et_2O. The Et_2O layer was concd, filtered, dried ($MgSO_4$), and evapd to dryness to give a yellow oil. Crystn was achieved by dissolving in hot THF and decolorizing with charcoal; yield, 155 mg (27%). The anal. sample was prepared by further recrystn from THF: mp 378°; λ_{max} (abs EtOH) 217, 276 mμ (ϵ_{276} 1.75 × 10^4); λ_{min} 241 mμ; tlc, EtOH–$CHCl_3$ (1:4), R_f 0.7. *Anal.* ($C_{14}H_{18}N_2OS$) C, H, N.

5-(1-Adamantyl)-4,6-dihydroxy-2-mercaptopyrimidine (11) was prepd in the same manner as the mercaptopyrimidine **9** starting with NaH (0.17 g, 3.55 mmoles of 50% oil dispersion) in 7 ml of abs EtOH, ethyl (1-adamantyl)malonate[3] (1.00 g, 3.40 mmoles), and thiourea (0.27 g, 3.56 mmoles). After evapn of the solvent, H_2O (50 ml) was added to the residue, and the pH was adjusted to 5.0 with 5 *M* HCl to give 0.64 g of the white product (68%). The anal. sample was prepared by dissolving 80 mg in aq NaOH, extng with Et_2O, and acidifying the aq phase with HCl. The solid was collected and washed with H_2O to give 60 mg: mp 262–265°; λ_{max} (0.1 *N* NaOH) 236, 285 mμ; λ_{min} 252 mμ; tlc, THF, R_f 0.87; THF–CCl_4 (1:1), R_f 0.50. *Anal.* ($C_{14}H_{18}N_2O_2S$) C, H, N.

5-(1-Adamantyl)-4-hydroxy-2-mercapto-6-methylpyrimidine (12) was prepd in the same manner as **9** starting with ethyl aceto-(1-adamantyl)acetate[3] (1.10 g, 4.18 mmoles) in abs EtOH (5 ml) and thiourea (0.318 g, 4.18 mmoles). After 8 hr at reflux and 8 hr at room temp, a solid was collected, washed with EtOH and Et_2O, and dried (400 mg). A portion of this solid (200 mg) was dissolved in aq NaOH, and the soln was filtered and neutralized with HCl to ppt the product. Recrystn from *i*-PrOH afforded 20 mg of material: λ_{max} (abs EtOH) 277 mμ (ϵ 1.66 × 10^4); mp 315° (darkens at 290°); tlc, THF–$CHCl_3$ (1:1), R_f 0.75. *Anal.* ($C_{15}H_{20}N_2OS$) C, H, N.

5-(1-Adamantyliminoacetamido)-2-amino-4-hydroxy-6-methylpyrimidine (12).—2-Amino-4-bromoacetamido-4-hydroxy-6-methylpyrimidine[4] (0.50 g, 1.92 mmoles) was dissolved in 5 ml of DMSO, and the yellow soln was stirred for 5 min. 1-Adamantylamine (0.4 g, 2.65 mmoles) was added, and the reaction mixt was stirred for about 18 hr and filtered. The filtrate was added to 30 ml of H_2O to ppt the product. The fluffy white solid was collected, washed with H_2O and THF, and dried (210 mg). The analytical sample was prepd by elution from a silica gel column with abs EtOH: mp 214–217°; tlc, MeOH, R_f 0.50; λ_{max} (abs EtOH) 228, 291 mμ. *Anal.* ($C_{17}H_{23}N_5O_2 \cdot H_2O$) C, H.

Derivatives of 4-Azahomoadamantane. Their Synthesis and Biological Evaluation

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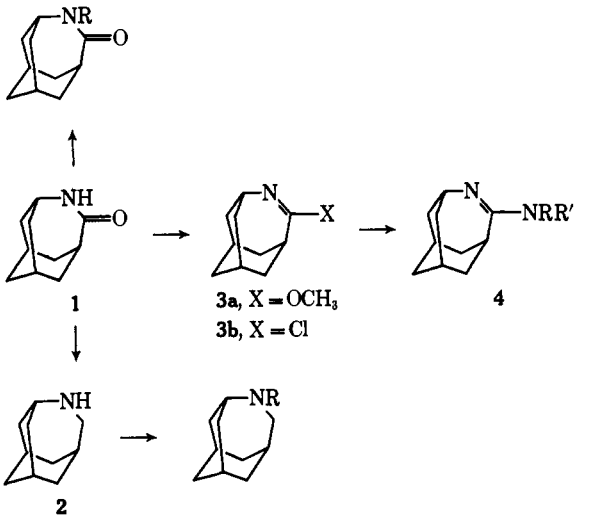
Several series of derivatives of 4-azahomoadamantane have been prepared from 4-azahomoadamantan-5-one. All compounds have been evaluated in a general pharmacological and antiviral screening. A number of the compounds exhibited blood pressure lowering and/or antiviral activities.

The introduction of the adamantane nucleus into a variety of drugs gave rise to compounds with outstanding biological properties, attributed to the lipophilic nature of the adamantane moiety.[2] The antiviral activities, especially, of several adamantane compounds are well known.[3]

In view of these facts we decided to utilize the previously described[4] 4-azahomoadamantan-5-one (**1**) as the starting material for the synthesis of potentially biologically active compounds. In this paper the synthesis of these compounds as well as the results of a preliminary pharmacological and antiviral investigation are described.

Chemistry.—The different types of derivatives of 4-azahomoadamantan-5-one (**1**) were prepared for the greater part as outlined in Scheme I.

SCHEME I



Substitution at the N atom of **1** was effected by reaction of its Na salt with an alkyl or acyl halide (method A) or by reaction of **1** with an isocyanate (method B). General procedures for methods A and B are given in the Experimental Section; the compounds obtained are shown in Table I.

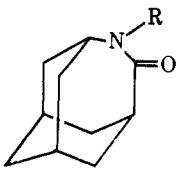
(1) Abstracted from the thesis of J. G. Korsloot, University of Groningen, Groningen, The Netherlands, 1969.

(2) (a) K. Gerzon, E. V. Krumkalns, R. L. Brindle, F. J. Marshall, and M. A. Root, *J. Med. Chem.*, **6**, 760 (1963); (b) W. Korytnyk and G. Fricke, *ibid.*, **11**, 180 (1968); (c) A. N. Voldeng, C. A. Bradley, R. D. Kee, E. L. King, and F. L. Melder, *J. Pharm. Sci.*, **57**, 1053 (1968).

(3) (a) C. E. Hoffmann, R. F. Haff, and E. M. Neumayer, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **23**, 387 (1964); (b) E. I. du Pont de Nemours, Irish Patent Application 342/64, 1963; (c) N. V. Philips, Irish Patent Application 940/65, 1964.

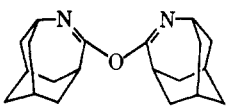
(4) J. G. Korsloot, V. G. Keizer, and J. L. M. A. Schlatmann, *Recl. Trav. Chim. Pays-Bas*, **88**, 447 (1969).

TABLE I



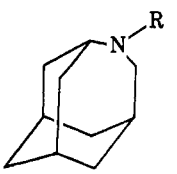
No.	R	Mp, °C	Yield, %	Method of prepn	Formula[a]	Crystn solvent
5	CH_3	184–186[b]	84	A	$C_{11}H_{18}NOCl$[c]	EtOH–Et_2O
6	$COCH_3$	70–76 dec	36	A	$C_{12}H_{17}NO_2$	
7	COC_6H_5	185–188	43	A	$C_{17}H_{19}NO_2$	MeOH
8		125–127	58	A	$C_{16}H_{18}N_2O_2$	C_6H_6–ligroin
9	$SO_2C_6H_4$-4-CH_3	164–165	18[d]	A	$C_{17}H_{21}NO_3S$	C_6H_6–ligroin
10	$CONHC_6H_3$-3,4-Cl_2	129.5–131	65	B	$C_{17}H_{18}Cl_2N_2O_2$	EtOH
11	$CONHC_6H_4$-4-NO_2	207–214 dec	38	B	$C_{17}H_{19}N_3O_4$	2-Butanone

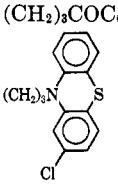
[a] All compds were analyzed for C, H, and N unless otherwise stated. [b] Hydrochloride. [c] N: calcd 6.50; found 5.87. [d] In addition, the previously described di(4-azatricyclo[4.3.1.1^{3,8}]undec-4-en-5-yl) ether[e] was obtained in 16% yield.



[e] J. G. Korsloot and V. G. Keizer, *Tetrahedron Lett.*, 3517 (1969).

TABLE II



No.	R	Salt	Mp, °C	Yield, %	Formula[a]
12	$(CH_2)_2NH_2$	2HCl	271–273	80	$C_{12}H_{24}Cl_2N_2$[b]
13	$(CH_2)_2NHC(=NH)NH_2$	2HCl	288–294 dec	79	$C_{13}H_{26}Cl_2N_4$
14	$(CH_2)_3COC_6H_4$-4-F	HCl	218–220 dec	28	$C_{20}H_{27}ClFNO$
15		HCl	*c*	54	$C_{25}H_{30}Cl_2N_2S$[d]
16	$CONHSO_2C_6H_4$-4-CH_3		211–216	55	$C_{18}H_{24}N_2O_3S$

[a] See footnote *a*, Table I. [b] Cl also analyzed. [c] Obtained as a foam. [d] Cl and S also analyzed.

Recently the reduction of **1** to the amine **2** was described.[4] The alkylation of **2** was achieved by standard methods. The compounds prepared in this way are listed in Table II.

For the preparation of amidines **4** the lactam **1** was first converted into a reactive intermediate **3** which was treated with an amine. The lactim ether **3a** was prepared from **1** with Me_2SO_4, according to the method of Benson and Cairns.[5] The imidoyl chloride **3b**, obtained as the hydrochloride from a reaction of **1** with $COCl_2$, was used without purification.

The amidines prepared are summarized in Table III. The reaction *via* the imidoyl chloride·HCl (**3b**) (Table III, method D) was used, particularly when reaction with the lactim ether **3a** (Table III, method C) failed. General procedures both for method C and method D are given in the Experimental Section. The yield in the reactions of **3a** with amines, is decreased by the acid-catalyzed conversion of **3a** to the lactam **1**. Besides the derivatives outlined in Scheme I, some fused heterocyclics (Table IV) were prepared. When **1** was melted with an isatoic anhydride at 190°,[6] fused quinazolinones **39** and **40** were obtained. Reduction of **39** with LAH in Et_2O gave the dihydroquinazoline **41**, whereas a similar reaction in THF afforded the tetrahydroquinazoline **42**. A fused pyrimidine **43** was obtained by reaction of **17** with the Na salt of malonic ester.[7]

Biology.—For the pharmacological evaluation, the compounds were investigated in a general screening program which included neurotoxicity,[8] acute lethal toxicity,[9] coronary circulation,[10] spasmolytic action,[11] po-

(5) R. E. Benson and T. L. Cairns, *J. Amer. Chem. Soc.*, **70**, 2115 (1948).

(6) E. Späth and N. Platzer, *Ber.*, **68**, 2221 (1935).

(7) R. C. Glushkov and O. Yu. Magidson, *J. Gen. Chem. USSR*, **31**, 189 (1961).

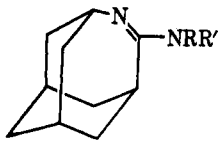
(8) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952).

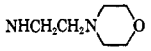
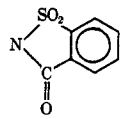
(9) LD_{50} calculated according to the method of H. J. Horn, *Biometrics*, **12**, 311 (1956).

(10) O. Langendorff, *Pflügers Arch. Gesamte. Physiol. Menschen Tiere*, **61**, 219 (1895).

(11) R. Magnus, *ibid.*, **102**, 123 (1904).

TABLE III[a]



No.	NRR'[a]	Salt	Mp, °C	Yield, %	Method of prepn	Formula[b]	Crystn solvent
17	NH_2	HNO_3	195–198 dec	44	C	$C_{10}H_{17}N_3O_3$	A[c]
18	$NHNH_2$	HCl	287–290 dec	70	Exp	$C_{10}H_{18}ClN_3$	A
19	$NHNHC_6H_5$	HCl	228 dec	50	C	$C_{16}H_{22}ClN_3$	A
20	$NHNHC_6H_4$-4-OCH_3	HCl	243 dec	29	C	$C_{17}H_{24}ClN_3O$	A
21	$NHNHCONH_2$	HCl	197.5–198.5	26	C	$C_{11}H_{19}ClN_4O$[d]	A
22	NHC≡N		239–242	76	C,[e] D[f,g]	$C_{11}H_{15}N_3$	EtOH
23	NHC(=NH)NHC_6H_5	2HCl	134–142 dec	50	*h*	$C_{17}H_{24}Cl_2N_4 \cdot EtOH$	A
24	NHC_6H_5	HCl	198–203	55	D	$C_{16}H_{21}ClN_2$	A
25	$NHCH_2CH_2N(CH_3)_2$	2HCl	270–272 dec	57	C	$C_{14}H_{27}Cl_2N_3$	A
26	$NHCH_2CH_2N(C_2H_5)_2$	2HCl	275.5–278 dec	78	C	$C_{16}H_{31}Cl_2N_3$	A
27	$NHCH_2CH_2CH_2N(CH_3)_2$	2HCl	263–265 dec	54	C	$C_{15}H_{29}Cl_2N_3$	A
28			142–144	50	C, D[i]	$C_{16}H_{27}N_3O \cdot H_2O$[j]	MeOH–H_2O
29	$NHCH_2CH_2NHC_6H_5$	HCl	218.5–220	48	C	$C_{18}H_{26}ClN_3$	A
30	$NHCH_2CH_2N(CH_3)C_6H_5$	HCl	175.5–177.5	36	C	$C_{19}H_{28}ClN_3$	A
31	$NHCH_2CH_2N(C_6H_5)CH_2C_6H_5$	HCl	249.5–251.5	41	C	$C_{25}H_{32}ClN_3$	A
32	$NHCH_2CH_2OC_6H_5$	HCl	172–173.5	40	D	$C_{18}H_{25}ClN_2O$	A
33	$NHCH_2CH_2OC_6H_4$-2-OCH_3	HCl	189–192	52	C	$C_{19}H_{27}ClN_2O_2$	A
34	$NHCH_2CH_2NHCOCH_3$	HCl	200–203	72	C	$C_{14}H_{24}ClN_3O$	A
35	$NHCH_2CH_2NHCOC_6H_4$-4-OCH_3	HCl	214–217	66	C	$C_{20}H_{28}ClN_3O_2$	A
36	$NHCH_2CH_2NHCOCH_2$-α-naphthyl	$(COOH)_2$	197.5–199	43	C	$C_{26}H_{31}N_3O_5$	EtOH
37		HCl	300–304 dec	55	D	$C_{14}H_{23}ClN_2$	A
38			210–212	33	D	$C_{17}H_{18}N_2O_3S$	CH_2Cl_2–MeOH

[a] The amidines prepd from primary amines are arbitrarily shown with the double bond endo with respect to the homoadamantane molecule. [b] See footnote *a*, Table I. [c] A = EtOH–Et_2O. [d] N calcd 21.65; found 21.14. [e] No HCl added. [f] One equiv of Na_2CO_3 added; yield 53%. [g] When **22** was prepd from **17** with BrCN, also the isomer with the CN on the ring N was obtained. [h] Prepd by reaction of **22** with $PhNH_3Cl$ in DMSO; see Experimental Section. [i] Yield 38%. [j] O also analyzed.

tentiating effect on hexobarbital narcosis,[12] anticonvulsive activity,[13] analgetic action,[14] antiinflammatory activity,[15] and effects on the blood pressure in anesthetized dogs.

Antiviral activity against the viruses, influenza A Swine, A 2 Japan, B Johannesburg, and parainfluenza 1 (Sendai) was determined according to the haemadsorption method.[16,17]

Results

The general pattern of biological activity encountered in these compounds was seen mainly in their effect on the blood pressure[18] and in their antiviral activity. The test results of those compounds that showed one of these two activities, or both, are listed in Table V. In addition to these activities, **14** has a central depressive action (a potentiating effect on hexobarbital narcosis was found at an oral dose of 8.8 mg/kg). Other activities are either absent or very weak and are not mentioned.

Experimental Section[19]

4-Azahomoadamantan-5-one (1).—Adamantanone oxime[4] (68 g, 0.41 mole) was added with stirring over a period of 60 min to polyphosphoric acid (1200 g) at 125°. The temp was maintained at 125° for a further 30 min. After cooling to 95° the mixt was poured into 25% NH_4OH (1850 ml) with stirring and cooling in ice–salt. The soln was extd with $CHCl_3$ (five 300-ml portions). The combined exts were washed with H_2O (200 ml) and dried (Na_2SO_4). The soln was treated with charcoal and filtered, and the solvent evapd *in vacuo;* yield 39 g (57%), mp 304–311° (ligroin).

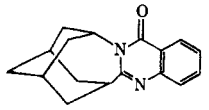
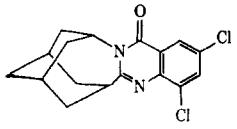
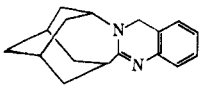
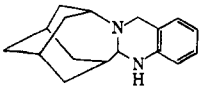
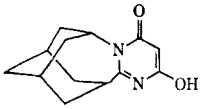
4-Azahomoadamantane·HCl (2).—Compd **1** (5.0 g, 0.03 mole) was reduced with LAH (1.3 g, 0.03 mole) in boiling THF (100 ml) (reaction time 24 hr) and worked up in the usual way. The 4-azahomoadamantane obtained was converted into the hydrochloride; yield 3.6 g (64%), mp 374–378° (EtOH–Et_2O).

5-Methoxy-4-azahomoadamant-4-ene (3a).—Compd **1** (11.0 g, 66 mmoles), dissolved in dry C_6H_6 (35 ml), was treated with

(12) D. W. Wylie, *Proc. Soc. Exp. Biol. Med.*, **98**, 716 (1958).
(13) F. M. Berger, *J. Pharmacol. Exp. Ther.*, **112**, 413 (1954).
(14) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).
(15) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
(16) W. T. Goedemans, Thesis, University of Leiden, Leiden, The Netherlands, 1967.
(17) W. T. Goedemans and A. Peters, *Arch. Gesamte Virusforsch.*, **23**, 326 (1968).
(18) It has since been shown that the blood pressure lowering effects of these compounds are caused by ganglion blockade.

(19) Melting points were measured in closed capillary tubes in an electrically heated aluminum block. Temperature was indicated by a chromel–alumel couple on a Philips G.M. 6020 tube voltmeter. Ir spectra were recorded on a Perkin-Elmer Model 337. Nmr spectra were measured on a Varian HA 100 spectrometer (Me_4Si). Mass spectra were obtained with an AEI-MS 9 mass spectrometer. Ir, nmr, and mass spectroscopic data are fully in accord with the structures proposed. Microanalyses were performed by A. Bernhardt, Microanalytisches Laboratorium, Elbach über Engelskirchen, West Germany. The compounds reported herein had analyses within ±0.4% of the theoretical values for the elements indicated unless otherwise noted.

TABLE IV

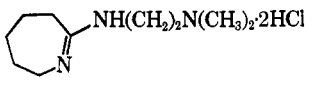
No.		Mp, °C	Yield, %	Formula[a]
39		165–167	33[b]	$C_{17}H_{18}N_2O$
40		217–220	20	$C_{17}H_{16}Cl_2N_2O$
41		148–155	60	$C_{17}H_{20}N_2 \cdot MeOH$
42		202–203.5 dec[c]	92	$C_{17}H_{23}ClN_2$[d]
43		264–269	31	$C_{13}H_{16}N_2O_2 \cdot 3H_2O$[e]

[a] See footnote *a*, Table I. [b] When prepd from the lactim ether **3a** with anthranilic acid, the yield was 25%. [c] Hydrochloride. [d] N: calcd 9.63; found 10.10. [e] O and H_2O (Karl Fischer) also analyzed.

TABLE V

	LD50[24][a]		Antiviral activity[b]				
No.	ip	o	Influenza A Swine	Influenza A2 Japan	Influenza B Johannesburg	Parainfluenza Sendai	Lowering of blood pressure[c]
1	56		+	−	−	−	−
2	147		+	−	−	−	+
6		>320	+	+	−	+	−
13	75	>1000					+
14	56	>320					+
17	75						±
18	75	>320	+	−	−	−	+
19	56						+
20	56						+
25	178	>1000					+[d]
26	178						+
27	100						±
29	56	>1000		+	+	−	−
30	56	>320					±
31		>320	+	+	+	+	−
33	56	>320	+	+	−	−	±
37	56						±
41			+	+	+	+	−

[a] mg/kg, in mice. [b] Concn used: 10^{-4} *M*; + = virus inhibition relative to the controls amounts to 20% or more; − = virus inhibition is less than 20% or completely absent. [c] Dose, 10 mg/kg; + = the lowering of the mean blood pressure caused by this compd amounts to 15% or more and lasts longer than 2 hr; ± = the lowering lasts 1–2 hr; − = the lowering lasts less than 1 hr, is less than 15% or is completely absent. [d] The analogous azacycloheptyl derivative **44** (prepd by Mr. J. R. Nienhuis according to procedure C (Exp Section), yield 76%, mp 256.5–258°) lacks this property.



44

Me_2SO_4 (8.3 g, 66 mmoles), which was added dropwise and with stirring. The mixt was refluxed for 22 hr and then cooled. A soln of K_2CO_3 (10 g) in H_2O (10 ml) was added cautiously with vigorous stirring. The aq layer was sepd and extd with Et_2O (10 ml). The combined org layers were dried and concd. The residue (11.8 g) was taken up in petr ether (bp 40–60°) (50 ml), treated with charcoal, and filtered (Hyflo Supercel). The solvent was removed *in vacuo* to give 10.6 g (89%) of a colorless oil which solidified on cooling. The hydrochloride had mp 312–315° dec.

5-Chloro-4-azahomoadamant-4-ene·HCl (3b).—A soln of 1 (7.7 g, 0.046 mole) in dry, EtOH-free $CHCl_3$ (15 ml) was added dropwise in 30 min to a soln of $COCl_2$ (6.3 g, 0.063 mole) in $CHCl_3$ (20 ml). The temp was maintained at 20–25° by cooling with H_2O. After the addn the mixt was stirred for 30 min and then concd *in vacuo* to dryness, with the temp being maintained below 30°. The hydrochloride thus obtained was used without further purification.

General Procedures.—Each method is illustrated by a specific example. The relevant data regarding each compd are recorded in the tables.

Procedure A. 4-Benzoyl-4-azahomoadamantan-5-one (7).—A mixt of 1 (3.1 g, 0.019 mole) and 50% NaH dispersion (Fluka, 0.96 g, 0.020 mole) in dry dioxane (30 ml) was heated under reflux for 90 min. The solvent was removed *in vacuo*, and to the residue was added dry C_6H_6 (15 ml). Then BzCl (2.81 g, 0.020 mole) dissolved in dry C_6H_6 (20 ml) was added and the mixt was refluxed overnight. After filtration the soln was washed with H_2O and concd *in vacuo* to 30 ml, whereupon **7** (2.1 g) crystd. The mother liquor was concd to dryness and the residue was extd with hot petr ether (bp 60–80°) (15 ml). On cooling, a second crop was obtained (0.76 g). The combined fractions were recrystd from MeOH (150 ml) to give 2.2 g (43%), mp 185–188°.

Procedure B. 4-(3,4-Dichlorophenylcarbamoyl)-4-azahomoadamantan-5-one (10).—A mixt of **1** (1.65 g, 0.01 mole) and 3,4-dichlorophenyl isocyanate (1.88 g, 0.01 mole) in dry PhMe (20 ml) was refluxed with stirring for 24 hr. After being concd, the residue was crystd twice from EtOH, yielding 2.3 g (65%), mp 129.5–131°.

Procedure C. 5-[2-(2-Methoxyphenoxy)ethylamino]-4-azahomoadamant-4-ene·HCl (33).—A mixt of **3a** (1.80 g, 0.01 mole) and 2-(2-methoxyphenoxy)ethylamine·HCl (2.02 g, 0.01 mole) in MeOH (15 ml) was refluxed with stirring for 24 hr and then concd to dryness under reduced pressure. The residue was dissolved in H_2O (15 ml), washed with Et_2O (10 ml), made alk, and extd with $CHCl_3$ (three 15-ml portions). These exts were combined, treated with charcoal, and dried, and then the $CHCl_3$ was evapd. The residue was dissolved in EtOH and the soln acidified (pH 4) with ethanolic HCl. The hydrochloride crystd upon addn of Et_2O. Recrystn from EtOH–Et_2O gave 1.84 g (52%), mp 189–192°.

Procedure D. 5-(1-Pyrrolidinyl)-4-azahomoadamant-4-ene·HCl (37).—A soln of **3b** (2.2 g, 0.01 mole) in dry, EtOH-free $CHCl_3$ (15 ml) was added with stirring over a period of 30 min to a soln of pyrrolidine (2.1 g, 0.03 mole) in $CHCl_3$ (15 ml). The mixt was kept at 20° for 1 hr and then heated at 45° for another hr. The solvent was removed and H_2O (15 ml) and 2 *N* NaOH (30 ml) were added to the residue. The mixt was extd with $CHCl_3$ (3 x 15 ml). The combined exts were dried, filtered, and concd to dryness. The residue was treated with ethanolic HCl and Et_2O to give **37**; yield 1.4 g (55%), mp (EtOH–Et_2O) 300–304° dec.

4-(2-Aminoethyl)-4-azahomoadamantane·2HCl (12).—A mixt of **2** (2.9 g, 19 mmoles), chloroacetonitrile (2.4 g, 32 mmoles), and Na_2CO_3 (1.6 g, 15 mmoles) in dry C_6H_6 (35 ml) was stirred at room temp for 23 hr and thereafter refluxed for 40 hr. After filtration, the soln was concd to dryness. The residue (3.5 g) was dissolved in dry Et_2O (10 ml) and reduced with LAH (1.5 g). The mixt was worked up as usual. The amine was converted into **12**; yield 4.3 g (80%), mp 271–273°.

4-(2-Guanidinoethyl)-4-azahomoadamantane·2HCl (13).—Compd **13** was prepared by reaction of **12** with H_2NCN in MeOH.[20]

4-[3-(4-Fluorobenzoyl)propyl]-4-azahomoadamantane·HCl (14).—A mixt of **2** (0.75 g, 5 mmoles), Na_2CO_3 (1.7 g, 16 mmoles), 4-chloro-4′-fluorobutyrophenone (1.5 g, 7 mmoles), and a few cryst of KI in dry PhMe (10 ml) was stirred and refluxed for 60 hr. A further 3.5 g of the butyrophenone was added in portions of 0.5 g every 8 hr. The mixt was allowed to cool to room temp. H_2O (25 ml) was added and the layers were sepd. The org layer was concd to dryness. The residue was dissolved in EtOH

(20) Philips' Gloeilampenfabrieken, Dutch Patent Application 64,04604; *Chem. Abstr.*, **64**, 11180*a* (1966).

and treated with charcoal. The hydrochloride **14** was prepd and recrystd from EtOH–Et_2O to give 0.49 g (28%), mp 218–220° dec.

4-[3-(2-Chlorophenothiazin-10-yl)propyl]-4-azahomoadamantane·HCl (15) was prepd from **2** analogously to the method of Grogan, *et al.*[21]

4-*p*-Tolylsulfonylcarbamoyl-4-azahomoadamantane (16) was prepd from **2** according to the method described by Gerzon, *et al.*[2a]

5-Hydrazino-4-azahomoadamant-4-ene·HCl (18).—A mixt of **3a** (2.7 g, 0.015 mole) and hydrazine hydrate (1.0 g, 0.02 mole) was stirred at room temp for 48 hr. Then CH_2Cl_2 (25 ml) was added, and the resulting soln was dried and evapd *in vacuo*. The residue was treated with ethanolic HCl and Et_2O to yield **18**, 2.26 g (70%), mp 287–290° dec.

1-(4-Azahomoadamant-5-ylidene)-3-phenylguanidine·2HCl (23).—A mixt of **22** (2.2 g, 11.6 mmoles) and $PhNH_2$·HCl (1.5 g, 11.6 mmoles) in DMSO (25 ml) was heated on a steam bath for 17 hr and then concd to dryness. The residue was dissolved in a mixt of H_2O (50 ml) and 2 *N* HCl (6 ml). The soln was washed with Et_2O (3 × 15 ml). The aq layer was filtered (Hyflo Supercel), made alk, and extd with Et_2O (4 × 30 ml). These exts were combined, dried, and concd. The residue was treated with ethanolic HCl and Et_2O to give **23**, yield 2.32 g (50%), mp 134–142° dec. According to the nmr spectrum and the elemental analysis the compd contained 1 mole of EtOH.

4-Azahomoadamantano[5,4-*b*]quinazolin-4′(3′*H*)-one (39).—The lactam **1** (3.50 g, 21 mmoles) and isatoic anhydride (3.55 g, 22 mmoles) were mixed thoroughly and then heated in a metal bath to approx 160°. After melting, the mixt was kept at this temp for 10 min and then the temp was raised to 190° over a period of 5 min. After the evolution of CO_2 had ceased, the residue was cooled and dissolved in concd HCl (60 ml). This soln was treated with charcoal and filtered (Hyflo Supercel). The filtrate was made alk with 50% NaOH. The first few milliliters caused the sepn of some tarry material, which was discarded. Further addn of NaOH gave a white ppt which was filtered, washed with H_2O, and dried. Recrystn from EtOH–H_2O (1:1) yielded 1.89 g (33%), mp 165–167°.

(21) C. H. Grogan, R. Kelly, and L. M. Rice, *J. Med. Chem.*, **9**, 654 (1966).

6′,8′-Dichloro-4-azahomoadamantano[5,4-*b*]quinazolin-4′(3′*H*)-one (40).—A mixt of **1** (3.0 g, 18 mmoles) and 3,5-dichloroisatoic anhydride[22] (4.5 g, 19 mmoles) was heated at 165° for 10 min. Then the temp was raised to 190°, and the mixt was kept at this temp for 45 min. After cooling, the residue was successively extd with 100, 25, and 25 ml of boiling EtOH. On cooling the combined exts yielded a ppt which was recrystd from EtOH; yield 1.17 g (20%), mp 217–220°.

4-Azahomoadamantano[5,4-*b*]-3′,4′-dihydroquinazoline (41).—Compd **39** (3.7 g, 0.014 mole), dissolved in dry Et_2O (275 ml), was added slowly to a soln of LAH (1.4 g, 0.037 mole) in dry Et_2O (75 ml). After being refluxed for 7 hr the mixt was worked up in the usual way; yield, after recrystn from MeOH (50 ml), 2.38 g (60%), mp 148–155°. The product contained 1 mole of MeOH.

4-Azahomoadamantano[5,4-*b*]-1′,2′,3′,4′-tetrahydroquinazoline·HCl (42).—Compd **39** (5.9 g, 0.022 mole) was reduced with LAH (3.0 g, 0.080 mole) in boiling THF (50 ml) (reaction time 64 hr), and the reaction mixt was worked up as usual. The base [yield 5.2 g (92%), mp 132.5–135°] was converted into **42**, mp 202–203.5° dec.

4′-Hydroxy-4-azahomoadamantano[4,5-*a*]pyrimidin-6′(1′*H*)-one (43).—To a soln of Na (0.5 g, 0.022 g-atom) in EtOH (15 ml) were added diethyl malonate (1.8 g, 0.011 mole) and **17**·HCl (2.01 g, 0.010 mole). The mixt was stirred and refluxed for 5 hr. After evapn of the solvent, H_2O (10 ml) was added, and the soln was acidified (pH 4) with 2 *N* HCl. The resulting ppt was filtered off and washed with H_2O. After recrystn from H_2O, 0.9 g (31%) of **43**, contg 3 moles of H_2O, was obtained, mp 264–269°.

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(22) R. Dorsch, *J. Prakt. Chem.*, **33**, 45 (1886).

2-Alkylthioadenosines, Specific Coronary Vasodilators

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2-Methylthio-, 2-ethylthio-, 2-*n*-propylthio-, and 2-isopropylthioadenosines were synthesized in almost quantitative yield from 2-chloroadenosine by nucleophilic displacement of Cl by the appropriate sodium alkylmercaptide in anhyd DMF. 2-Methylthioadenosine was also synthesized in 45% overall yield from 2-methylthioadenine by the chloromercuri procedure; 2-ethylthioadenosine was obtained similarly from 2-ethylthioadenine, and from 2-ethylthio-6-chloropurine by fusion with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose. 2-*n*-Propylthioadenosine and 2-isopropylthioadenosine were also synthesized by the fusion method from 2-*n*-propylthio-6-chloropurine and 2-isopropylthio-6-chloropurine, respectively. The four 2-alkylthioadenosines had coronary vasodilator activity in the dog of prolonged duration. The coronary vasodilator potency of the compounds increased with increasing length of the alkyl chain; the isopropylthio derivative was slightly less potent than 2-*n*-propylthioadenosine. Doses of the 2-alkylthioadenosines which caused coronary vasodilatation had no depressant effect on heart rate and contractility.

The effects of adenosine on the mammalian cardiovascular system, which were first described by Drury and Szent-Györgi in 1929, include a transient increase in coronary blood flow, a transient decrease in systemic blood pressure, sinus brachycardia, and arterioventricular block.[1] The dose of adenosine which slows the heart rate is greater than the dose which causes a threshold increase in coronary blood flow, but even low doses of adenosine may have a depressant effect on the heart.[2] The use of adenosine in cardiovascular therapy has been precluded both by the transitory nature of its vasodilator effects and by its toxic actions on the heart. It would seem feasible however that certain analogs of adenosine may be found which have the coronary vasodilatory activity of adenosine, but which have greater duration of action *in vivo* and which lack the cardiac depressant action of the parent compound. Clarke,

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(2) H. Schöndorf, W. Rummel, and K. Pfleger, *Experentia*, **25**, 44 (1969).