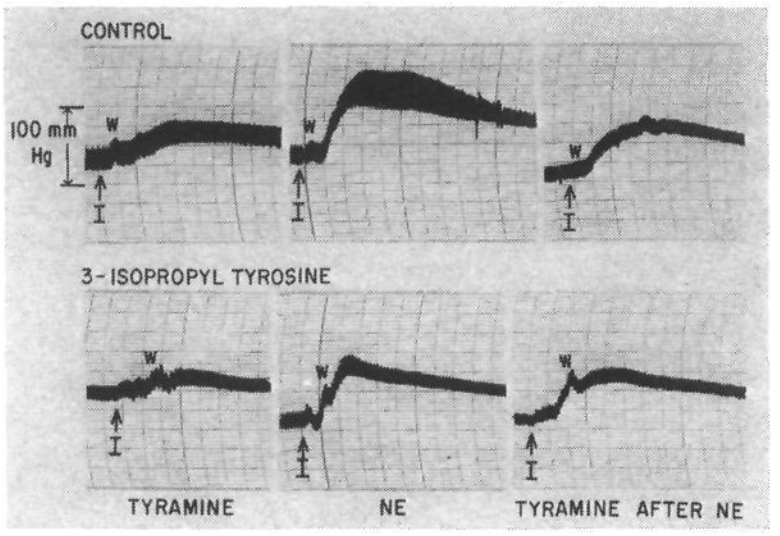

Figure 3.—Tyramine pressor response in pretreated rats. Responses shown are those of one control animal and one animal pretreated 2 hr earlier with 3-isopropyl-DL-tyrosine (monohydrate). I = point of injection; W = saline flush. Systolic blood pressure is indicated by the upper limit of the recording and diastolic blood pressure by the lower limit.

3-methoxy-, and 3-aminotyrosine were determined for the analysis of the series in terms of substituent constants. Since 3-substituted tyrosines other than 3-alkyltyrosines have been shown to be competitive inhibitors of tyrosine,[3] the more convenient method of Dixon[22] (Figure 2) was used to obtain inhibition constants for these analogs. These values are presented in Table I.

Tyramine Pressor Test.—The tyramine pressor response in rats (260–280 g female, Sprague Dawley) was determined 2 and 24 hr after the ip injection of α-methyl-*m*-tyrosine (α-MMT) and IpT (2.1 mmoles/kg) in physiological saline (2.15 mmoles/ml); control animals received saline only. Each animal was injected with atropine sulfate (0.5 mg) 15 min prior to the assay to block compensatory cholinergic reflexes.

The rats were anesthetized with Et_2O, a laparatomy was performed, and an iv catheter was inserted into a large mesenteric vein for injections. A cannula (PE-90 tubing), inserted into the abdominal aorta, was connected to a Statham pressure transducer (No P23AC), and the blood pressure was recorded on a Model 5D Grass polygraph. Transducer and tubing were filled with physiological saline containing 2 units/ml of heparin. The transducer was calibrated against an anaeroid manometer and the polygraph chart speed set at 1 mm/sec.

After the blood pressure had equilibrated, and a resting value had been recorded, a series of responses to 300 μg/kg of tyramine in 0.5 ml of saline, to several 0.2-ml doses of NE (1:25,000 in physiological saline), and finally to 300 μg/kg of tyramine were recorded.

Each injection was followed immediately by a 0.2-ml saline flush of the cannula. Pressor response was calcd as per cent change in systolic blood pressure from preinjection value to peak of response. A typical response to tyramine before and after norepinephrine is reproduced in Figure 3 and the complete results of this study are shown in Table II.

Biogenic Amine Analysis.—Biogenic amine analyses were performed 3 hr after the ip injection of MT or IpT (1 mmole/kg) and the results compared with those of saline, α-MPT, and α-MMT (1 mmole/kg) treated groups. Brain and heart from decapitated (guillotine) male Wistar rats (200 g) were placed on Dry Ice immediately after excision and stored at −15° until assayed. At that time the tissues were homogenized in acidified *n*-BuOH, serotonin was measured fluorometrically as the *o*-phthaldialdehyde condensation product according to a modification of the method of Maickel.[23] Dopamine and NE were assayed by measuring fluorescence after I_2 oxidn by modification of the method of Chang.[24] Table III lists these results.

(22) J. L. Webb, "Enzyme and Metabolic Inhibitors," Vol. I, Academic Press, New York, N. Y., 1963, p 153.

(23) R. P. Maickel, R. H. Cox, J. Saillant, and F. P. Miller, *Int. J. Neuropharmacol.*, **7**, 275 (1968).

(24) C. C. Chang, *ibid.*, **3**, 643 (1964).

Synthesis and Biological Activity of Some 5-(1-Adamantyl)pyrimidines. 2[1,2]

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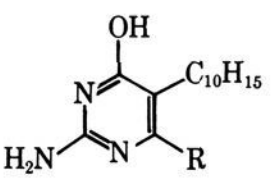
The synthesis and biological activity of eleven new pyrimidines with lipophilic substituents at the 5 position are described. Two compounds, 5-(1-adamantyl)-2,4-diaminopyrimidine (**3**) and 5-(1-adamantyl)-2,4-diamino-6-methylpyrimidine (**4**), show exceptionally high activity toward mouse mammary adenocarcinoma cells (TA3) in culture; the latter inhibits cell growth as effectively as methotrexate. An attempt is made to correlate the structure of the compounds with their activity.

A previous publication from this laboratory[3] described the synthesis and biological activity of some 5-(1-adamantyl)-2-amino-4-hydroxypyrimidines. 5-(1-Adamantyl)-2-amino-4-hydroxypyrimidine (**1a**) and the 6-Me analog **1b** were found to be moderate growth inhibitors of mouse sarcoma 180 cells in culture. In addition, **1b** was a good growth inhibitor of the cultured mouse mamary adenocarcinoma cells (TA3). Neither compound inhibited folate reductase isolated from a strain of sarcoma 180 cells grown *in vitro*, indicating that the mode of action of these compounds may not be related to the inhibition of this enzyme. In continuation of this work, seven 2,4-diaminopyrimidines (**3–9**), three 4-hydroxy-2-mercaptopyrimidines (**10–12**), and one 2-amino-4-hydroxypyrimidine (**13**) were prepared, having highly lipophilic substituents in position 5 of the pyrimidine ring.



1a, R = H
1b, R = CH_3

Synthesis.—Four basic synthetic approaches were used. The diaminopyrimidines **3** and **4** (Table I) were prepared from the corresponding 2-amino-4-hydroxy compounds[3] by replacement of OH by Cl followed by

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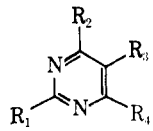
(2) The synthetic work was supported in part by Grant CA-02906 and biological testing by CA-11047 from the National Cancer Institute of the U. S. Public Health Service.

(3) J. P. Jonak, S. F. Zakrzewski, L. H. Mead, and M. T. Hakala, *J. Med. Chem.*, **13**, 1170 (1970).

TABLE I

BIOLOGICAL ACTIVITY OF 5-SUBSTITUTED PYRIMIDINES

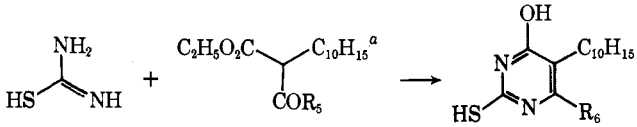


No.	R_1	R_2	R_3	R_4	Concn (M) for 50% inhibn[a]
2	NH_2	NH_2	CH_2NH_2	H	$>2 \times 10^{-4}$
3	NH_2	NH_2	$C_{10}H_{15}$[b]	H	3.1×10^{-7}
4	NH_2	NH_2	$C_{10}H_{15}$	CH_3	8.0×10^{-9}
5	NH_2	NH_2	$NHCOC_{10}H_{15}$	CH_3	1.0×10^{-6}
6	NH_2	NH_2	$CH_2NHCOC_{10}H_{15}$	H	1.8×10^{-4}
7	NH_2	NH_2	$CH_2NHCOCH_2C_{10}H_{15}$	H	3.9×10^{-6}
8	NH_2	NH_2	$CH_2NHCO(CH_2)_8CH_3$	H	1.1×10^{-5}
9	NH_2	NH_2	$CH_2NHCO(CH_2)_{16}CH_3$	H	$>10^{-5}$[c]
10	SH	OH	$C_{10}H_{15}$	H	$>10^{-4}$
11	SH	OH	$C_{10}H_{15}$	OH	$>2 \times 10^{-4}$
12	SH	OH	$C_{10}H_{15}$	CH_3	2.9×10^{-5}
13	NH_2	OH	$NHCOCH{=}NC_{10}H_{15}$	CH_3	4.3×10^{-5}

[a] Mouse mammary adenocarcinoma cells (TA3) (see Experimental Section for procedure). [b] 1-Adamantyl. [c] No effect at 10^{-5} M which was the limit of solubility.

aminolysis of the halogen. The diaminopyrimidines **5–9** were synthesized by reacting 5-aminomethyl-2,4-diamino- or 2,4,5-triaminopyrimidines with the corresponding acid chlorides of adamantane or fatty acids. 4-Hydroxy-2-mercaptopyrimidines **10–12** were prepared by the direct condensation of thiourea with appropriately substituted 1-adamantane derivatives (Scheme I).

SCHEME I



No.	R_5	R_6
10	H	H
11	OC_2H_5	OH
12	CH_3	CH_3

[a] $C_{10}H_{15}$ = 1-adamantyl.

Finally, **13** was prepared by *in situ* oxidation of the substituted 5-bromoacetamidopyrimidine[4] in DMSO followed by condensation with 1-adamantylamine.

Biological Data[5].—The adamantylpyrimidines were tested for their growth-inhibitory effect in cultures of mouse mammary adenocarcinoma cells (TA3). The results of these experiments are presented in the last column of Table I.

Discussion

The seven diaminopyrimidines (**3–9**) listed in Table I were inhibitory for TA3 cells in various degrees, whereas the reference compound, 5-aminomethyl-2,4-diaminopyrimidine (**2**), had no effect at a concentration of 10^{-4} M. Three observations emerge from the analysis of these data. (1) Diaminopyrimidines which have the 1-adamantyl residue bound directly to C-5 are the best inhibitors, and insertion of C and N atoms between the two moieties tends to decrease this activity. Thus, **4** is about 8×10^4 times as active as **5**, and **3** is about 2×10^3 times as active as **6**. It is interesting to note that further elongation of the chain between pyrimidine and adamantane by one C (see **6** and **7**) causes no further decrease in growth-inhibitory activity. In fact, **7** appears more than 4 times as active as **6**; however, it is not certain if this difference is statistically significant. (2) Substituents that can approximate the adamantyl structure also appear to promote growth inhibition. Compound **8** is approximately as strong an inhibitor as **7**. It has been shown that long-chain hydrocarbons in aq media tend to form spherical entities due to their hydrophobic characteristics and intramolecular van der Waals forces.[6] Examination of molecular models reveals that the side chain of **8** consisting of 9 C atoms can assume a structure which closely resembles that of the $CH_2C_{10}H_{15}$ group of **7**. Thus, the adamantyl radical, *per se*, might not be required for potentiation of activity in the compounds under consideration. The substituent would have to resemble the adamantyl group rather closely because elongation of the side chain to 17 carbons as in **9** resulted in a marked decrease of growth inhibition. (3) A Me group in the 6 position causes a marked increase in activity; **4** is 40 times as active as **3**. It is interesting to note that under the same test conditions, **4** is about as active as methotrexate which shows 50% inhibition of the TA3 cells at a concentration of 8.4×10^{-9} M. Further examination of the table reveals that **12** is more active than **10**. Work is presently in progress to test the effects of other alkyl groups at position 6.

It has been shown elsewhere that diaminopyrimidines are specific inhibitors of dihydrofolate reductase.[7] Also, it has been demonstrated[8–10] that a lipophilic substituent in position 5 and a small alkyl group in position 6 tend to increase the inhibitory activity of diaminopyrimidines toward the dihydrofolate reductase from chicken liver. Therefore, it is very likely that the mode of action of these diaminopyrimidines is related to the inhibition of the dihydrofolate reductase. However, only the direct demonstration of the inhibition of the isolated enzyme by the compounds listed in Table I will definitely establish their mode of action.

On the other hand, the mode of action of the mercaptohydroxy and aminohydroxy analogs is by no means clear; some of them (**12** and **13**) were moderate growth inhibitors while others (**10** and **11**) were inactive.

Baker, *et al.*,[8–10] demonstrated that some 2-amino-4-hydroxy-5-substituted-pyrimidines weakly inhibit dihydrofolate reductase from chicken liver. Two compounds of this general structure, which were active as growth inhibitors of cells in culture, **1a** and **1b**, were tested previously for inhibition of folate reductase isolated from sarcoma 180. No evidence for inhibition was obtained. This lack of parallel activity may be due to 2 factors. (1) Although dihydrofolate reductase activity and folate reductase activity are due to the same enzyme,[11,12] the assay conditions are different;

(4) B. R. Baker and K. Sachdev, *J. Pharm. Sci.*, **53**, 1020 (1964).

(5) We are indebted to Miss Aurelie Mulhern of this department for conducting the biological tests. *In vivo* tumor assay studies on the biologically active pyrimidines are currently in progress at this Institute, and results will be reported at a later date.

(6) G. Nemethy and H. A. Scheraga, *J. Chem. Phys.*, **36**, 3382 (1962).

(7) S. F. Zakrzewski, *J. Biol. Chem.*, **238**, 1485 (1963).

(8) B. R. Baker, B. T. Ho, and D. V. Santi, *J. Pharm. Sci.*, **54**, 1415 (1965).

(9) B. R. Baker and B. T. Ho, *J. Heterocycl. Chem.*, **2**, 335 (1965).

(10) B. R. Baker and B. T. Ho, *J. Pharm. Sci.*, **55**, 470 (1966).

(11) S. F. Zakrzewski and C. A. Nichol, *J. Biol. Chem.*, **235**, 2984 (1960).

(12) S. F. Zakrzewski, M. T. Hakala, and C. A. Nichol, *Mol. Pharmacol.*, **2**, 423 (1966).

the former is usually assayed at pH 7.5, the latter at pH 5.5. This may have a profound effect on the binding of the analogs to the enzyme. (2) There are distinct differences between dihydrofolate reductases of different origin.[13] The fact that a Me group in position 6 potentiates inhibitory activity (compare **10** and **12**) and that increasing the distance of the 1-adamantyl residue from the pyrimidine ring decreases this activity (**1b** inhibits the growth of TA3 cells by 50% at 5×10^{-6} *M* whereas **13** is about 0.1 as inhibitory) may indicate that these compounds act as inhibitors of folate reductase, since the same pattern is observed with diaminopyrimidines. On the other hand, the evidence presented previously[3] that a cell line resistant to methotrexate is more sensitive to 5-(1-adamantyl)-4-hydroxypyrimidine than the parent line speaks against the involvement of dihydrofolate reductase. Inhibition studies of the compounds described here are being conducted with isolated dihydrofolate reductase from cultured sarcoma 180 cells and *Escherichia coli*.

Experimental Section

All tlc was performed on Brinkman F-254 silica gel plates on alumina. All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Uv spectra were recorded on a Cary 14 spectrophotometer. The analyses in which the results were within 0.4% of the calcd values are denoted by the symbols for those elements. Microanalyses were performed by Mr. G. I. Robertson, Florham Park, N. J. No attempt was made to optimize the yields of the reactions described below. Alumina used for column chromatography was Wolem activity grade I, neutral; silica gel (100–200 mesh) was purchased from Will Scientific.

The mouse mammary adenocarcinoma cells (TA3) were grown in stationary tube cultures in RPMI 1640 medium[14] containing 10% horse serum. An inoculum of 50,000 cells in 1 ml of medium was supplemented with 1 ml of the medium containing the compound to be tested. The tubes were incubated in an upright position for 3 days, and growth was estimated by protein assay.[15] The growth in controls varied from six-to tenfold. Every concn was tested in 5 tubes each. For compds found inhibitory, the tests were repeated at least twice, except **6** which was tested once. Variation between different tests was within ±10% for the 50% inhibitory concn.

5-(1-Adamantyl)-2-amino-4-chloropyrimidine·HCl (15).—5-(1-Adamantyl)-2-amino-4-hydroxypyrimidine[3] (0.5 g, 2.04 mmoles) was refluxed 1.25 hr with 0.5 g of PCl_5 and 5 ml of $POCl_3$. After an initial period of frothing, the solid passed into soln. After refrigeration (18 hr), the reaction mixt was poured cautiously on ice (150 ml) with vigorous stirring. The oil gradually solidified, and the yellow solid was collected, washed repeatedly with cold H_2O, and immediately dried *in vacuo* at room temp: yield, 0.60 g (98%); λ_{max} (abs EtOH) 230, 280 mμ. The identity of this compound was further established by its conversion into the 2,4-diaminopyrimidine **3**.

5-(1-Adamantyl)-2,4-diaminopyrimidine (3).—5-(1-Adamantyl)-2-amino-4-chloropyrimidine·HCl (**15**) (0.65 g, 2.17 mmoles) was mixed with abs EtOH (40 ml), and the mixt was satd with NH_3 at 0°. The reaction mixt was then heated in a bomb at 160° for about 18 hr. The solid obtained after filtration, evapn, and treatment with aq NaOH weighed 0.43 g. A portion of this solid (0.28 g) was loaded on an alumina column and eluted with abs EtOH to give ultimately 0.10 g of material with the desired spectral properties: tlc, MeOH, R_f 0.50. The analytical sample was prepd by further recrystns from *i*-PrOH: mp 270°; λ_{max} (abs EtOH) 287 mμ (ϵ 7.12×10^3). *Anal.* ($C_{14}H_{20}N_4$) C, H, N.

5-(1-Adamantyl)-2-amino-4-chloro-6-methylpyrimidine·HCl (16) was prepd by analogy with the corresponding chloropyrimidine **15**, starting with 0.87 g (3.36 mmoles) of 5-(1-adamantyl)-2-amino-4-hydroxy-6-methylpyrimidine,[3] 8.7 ml of $POCl_3$, and 0.87 g of PCl_5. A quant yield was obtained (1.09 g): mp 256–262°; λ_{max} (abs EtOH) 238, 291 mμ; λ_{min} 264 mμ. The identity of this material is confirmed by conversion into the diaminopyrimidine **4**.

5-(1-Adamantyl)-2,4-diamino-6-methylpyrimidine (4) was prepared by the amination of the corresponding 4-chloropyrimidine·HCl (2.0 g, 6.4 mmoles) (**16**) in the manner described for the prepn of the diaminopyrimidine **3**. A yellow–white residue remained after the solvent was removed *in vacuo*. This material was triturated with a soln of abs EtOH–0.1 *N* NaOH (1:1) (2 × 5 ml) and then washed with H_2O (2 × 5 ml) and cold Me_2CO (2 × 5 ml) to give a white solid (1.42 g). The crude product was eluted from a silica gel column and then an alumina column with abs EtOH. The fractions contg the product were run through a fine filter, and the vol was reduced from 500 to 20 ml on a hot plate. The product was collected on cooling (300 mg, 18.2%): mp 274–75°; tlc, MeOH, R_f 0.40; dried at 150° for 24 hr over P_2O_5 *in vacuo*, λ_{max} (0.1 *N* HCl), 218, 278 mμ; λ_{max} (abs EtOH) 228, 292 mμ (ϵ_{292} 7.77×10^3); λ_{min} 262 mμ. *Anal.* ($C_{15}H_{22}N_4 \cdot 0.5H_2O$) C, H, N.

5-*N*-(1-Adamantoyl)amino-2,4-diamino-6-methylpyrimidine (5).—A soln of 6-methyl-2,4,5-triaminopyrimidine sulfate (0.30 g, 1.26 mmoles) in 10 ml of 1 *N* NaOH was stirred vigorously with a soln of 1-adamantylcarboxylic acid chloride[16] (0.250 g, 1.26 mmoles) in 5 ml of C_6H_6 for 24 hr. The solid product was collected by filtration (55 mg) and recrystd from *i*-PrOH. The product was collected and washed several times with Et_2O: tlc, abs EtOH, R_f 0.58; mp 294–296°; λ_{max} (0.1 *M* HCl) 274 mμ (ϵ 5.90×10^3). *Anal.* ($C_{16}H_{23}N_5O \cdot 0.5H_2O$), C, H, N.

5-[*N*-(1-Adamantoyl)]aminomethyl-2,4-diaminopyrimidine (6).—5-Aminomethyl-2,4-diaminopyrimidine·2HCl[17] (0.2 g, 0.94 mmole) was dissolved in 5 ml of 1 *N* NaOH. A soln of 1-adamantylcarboxylic acid chloride[16] (0.22 g, 1.11 mmoles) in 5 ml of C_6H_6 was added with vigorous stirring. A white solid formed almost immediately. After vigorous stirring (18 hr), the solid was collected (0.27 g): tlc; MeOH, R_f 0.58. The analytical sample was prepd by recrystn from 95% EtOH (charcoal): mp 295–300°; λ_{max} (0.1 *M* HCl) 270 mμ (ϵ 5.15×10^3); λ_{min} 256 mμ. *Anal.* ($C_{16}H_{23}N_5O$) C, H, N.

***N*-[2,4-Diamino-5-pyrimidinyl)methyl]-1-adamantaneacetamide (7).**—1-Adamantylacetyl chloride[18] (440 mg, 2.07 mmoles) was added to a mixt of 5-aminomethyl-2,4-diaminopyrimidine[17] (209 mg, 1.40 mmoles) and 2 ml of MeCN. The suspension was stirred at room temp for 90 hr. The solid was collected and dried 12 hr *in vacuo* (610 mg): tlc, MeOH, R_f 0.0. A portion of this solid (300 mg) was boiled for 15 min in 75 ml of 0.1 *N* HCl and filtered. The filtrate was taken to pH 10 with NaOH, then back to pH 7. The hot soln was then cooled to 0°; the pptd solid was collected, washed with 10 ml of H_2O, and dried for 2 hr at 135° over P_2O_5 *in vacuo* to give 110 mg: λ_{max} (abs EtOH) 235 (s), 286 mμ, (ϵ_{286} 3.98×10^3); λ_{min} 258 mμ; mp 178–80°; tlc, MeOH, R_f 0.55. A portion of this material (100 mg) was mixed with 20 ml of 1 *N* NaOH, wetted with 10 drops of EtOH, and allowed to stir about 12 hr at room temp. The desired product (50 mg) was collected, washed with 5 ml of H_2O and 2 ml of Me_2CO, and dried *in vacuo* over P_2O_5 at 135°: λ_{max} (abs EtOH) 234, 286 mμ (ϵ_{256} 7.5×10^3); tlc, MeOH, R_f 0.55; mp 212–214°. *Anal.* ($C_{17}H_{22}N_5O$) C, H, N.

***N*-[(2,4-Diamino-5-pyrimidinyl)methyl]-*n*-decanylamide (8).**—Decanoyl chloride (0.275 g, 1.44 mmoles) was condensed with 5-aminomethyl-2,4-diaminopyrimidine[17] (0.200 g, 1.44 mmoles) in MeCN (2 ml). The solid product was collected after 68 hr. The free base was generated by neutralization with aq NaOH and extd from the aq soln with $CHCl_3$. The $CHCl_3$ exts were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo* (0.14 g, 33%). The anal. sample was recrystd from abs EtOH: mp 189–191°; tlc, abs EtOH, R_f 0.70; λ_{max} (abs EtOH) 235, 287 mμ (ϵ_{287} 7.36×10^3); λ_{min} 257 mμ. *Anal.* ($C_{15}H_{27}N_5O$) C, H, N.

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(14) G. E. Moore, R. E. Gerner, and H. A. Franklin, *J. Amer. Med. Ass.*, **199**, 519 (1967).
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(16) L. F. Fieser, M. Z. Nazer, S. Archer, D. A. Berberian, and R. G. Slighter, *J. Med. Chem.*, **10**, 517 (1967).
(17) H. Tieckelmann, R. Guthrie, and J. G. Nairn, *J. Org. Chem.*, **25**, 1257 (1960).
(18) W. H. W. Lunn, W. D. Pedmore, and S. S. Szinai, *J. Chem. Soc. C*, 1657 (1968).

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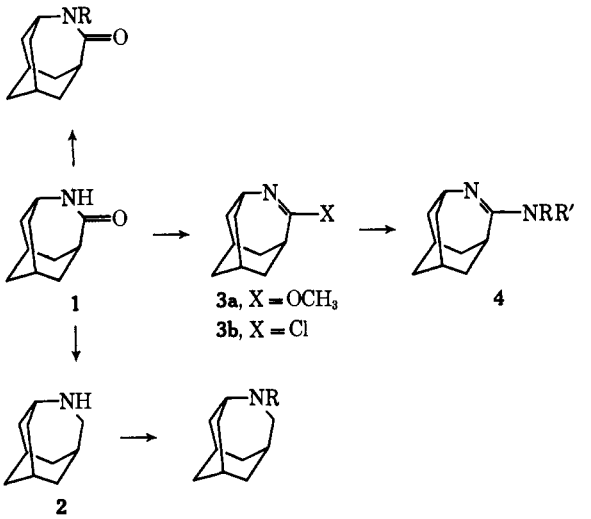
Several series of derivatives of 4-azahomoadamantane have been prepared from 4-azahomoadamantan-5-one. All compounds have been evaluated in a general pharmacological and antiviral screening. A number of the compounds exhibited blood pressure lowering and/or antiviral activities.

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.

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