trast to 2 and 6-MP both 3 and 4 showed higher activity on the single dose treatment. Compared to 3, the acetamido compounds 5–9 were less active on both dose schedules. In fact, no activity was observed for the N,N-disubstituted amides 8 and 9. Similarly, little or no activity was observed for the 9-benzylideneamino- (10, 11, and 14), 9-pyrrol-1-yl- (12, 13, and 15), and 9-pyrrolidin-1-yl- (16–18) 9*H*-purines. These results indicate that a proton on the 9-amino group is necessary for activity. Apparently these protons are involved either in enzymatic binding or removal of the 9-amino group to give the corresponding purine derivative.

Experimental Section‡

N-[6-(Methylthio)-9*H*-purin-9-yl]acetamide (5). A soln of 3 (6.0 g)[2] in DMF (120 ml) contg K_2CO_3 (4.1 g) and MeI (2.0 ml) was stirred at room temp for ~20 hr, dild with H_2O (600 ml), acidfd with dil HCl, and evapd to dryness *in vacuo*. The residue was washed with H_2O (90 ml) and recrystd from C_6H_6, and the resulting solid was dried (P_2O_5, 78°) *in vacuo*: yield, 3.4 g (53%); mp 185°. *Anal.* ($C_8H_9N_5OS$) C, H, N.

N-[6-(Benzylthio)-9*H*-purin-9-yl]acetamide (6) was prepd by a similar method from 3 (2.5 g),[2] K_2CO_3 (1.7 g), and $C_6H_5CH_2Cl$ (1.4 ml) in DMF (50 ml): yield, 2.3 g (C_6H_6, 64%); mp 200–201°. *Anal.* ($C_{14}H_{13}N_5OS$) C, H, N.

N-[6-[(Diphenylmethyl)thio]-9*H*-purin-9-yl]acetamide (7) was prepd from 3 (2.0 g),[2] K_2CO_3 (1.4 g), and $(C_6H_5)_2CHCl$ (2.0 ml) in DMF (40 ml): yield, 2.2 g (C_6H_6–hexane; 61%); mp 214–215°. *Anal.* ($C_{20}H_{17}N_5OS$) C, H, N.

N-(4-Chlorobutyl)-*N*-[6-(methylthio)-9*H*-purin-9-yl]acetamide (8). A soln of 5 (7.0 g) in DMF (140 ml) contg K_2CO_3 (4.4 g) and 1-bromo-4-chlorobutane (3.8 ml) was stirred at room temp for 18 hr, then dild with H_2O (700 ml). The resulting oily suspension was extd with Et_2O (3 × 1400-ml portions), and the combined ext was dried ($MgSO_4$) and evapd to dryness to give the product as an oil: yield, 9.8 g (99%). Elemental analyses were obtained on a sample dried at 56° *in vacuo* over P_2O_5. *Anal.* ($C_{12}H_{16}ClN_5OS$) C, H, N.

N-(4-Chlorobutyl)-*N*-[6-(diphenylmethyl)thio]-9*H*-purin-9-yl]-acetamide (9) was similarly prepd from 7 (12.0 g). The resulting oil was dried at 78° *in vacuo* over P_2O_5 to give a glass: yield, 14.5 g (97%). *Anal.* ($C_{24}H_{24}ClN_5OS$) C, H, N.

9-Benzylideneamino-6-(methylthio)-9*H*-purine (10) was prepd from 14 (5.0 g), K_2CO_3 (2.8 g) and MeI (1.3 ml) in DMF (100 ml): yield, 4.0 g (hexane, 76%): mp 200–201°. *Anal.* ($C_{13}H_{11}N_5S$) C, H, N.

9-Benzylideneamino-6-(benzylthio)-9*H*-purine (11) was prepd from 14 (3.0 g), K_2CO_3 (1.7 g), and $C_6H_5CH_2Cl$ (1.4 ml) in DMF (60 ml): yield, 3.1 g (C_6H_6, 76%); mp 208°. *Anal.* ($C_{19}H_{15}N_5S$) C, H, N.

6-(Methylthio)-9-pyrrol-1-yl-9*H*-purine (12). A mixt of 1 (1.0 g) and 2,5-dimethoxytetrahydrofuran (0.73 ml)[3] in glacial HOAc (10 ml) was refluxed for 2.5 hr and evapd to dryness *in vacuo*. The resulting residue was recrystd from hexane and dried at 78° *in vacuo* over P_2O_5: yield, 0.84 g (66%); mp 163°. *Anal.* ($C_{10}H_9N_5S$) C, H, N.

9-(2,5-Dimethylpyrrol-1-yl)-6-(methylthio)-9*H*-purine (13) was similarly prepd from 1 (1.0 g) and 2,5-hexanedione (0.66 ml) in glacial HOAc: yield, 1.1 g (77%). *Anal.* ($C_{12}H_{13}N_5S$) C, H, N.

9-Benzylideneamino-9*H*-purine-6(1*H*)-thione (14). A suspension of 4 (10.0 g)[2] and PhCHO (10 ml) in MeOH (500 ml) contg 5 drops of concd HCl was refluxed with stirring for 2 hr. The mixt was cooled, and the solid was collected by filtration and dried *in vacuo* over P_2O_5: yield, 14.5 g (95%); mp >264°. *Anal.* ($C_{12}H_9N_5S$) C, H, N.

9-(Pyrrol-1-yl)-9*H*-purine-6(1*H*)-thione (15) was prepd similarly to that of 12 from 4 (1.0 g) and 2,5-dimethoxytetrahydrofuran (0.78 ml)[3] in glacial HOAc (15 ml). The crude product was recrystd from H_2O and dried at 110° *in vacuo* over P_2O_5: yield, 0.71 g (55%); mp >264°. *Anal.* ($C_9H_7N_5S$) C, H, N.

9-Pyrrolidin-1-yl-9*H*-purine-6(1*H*)-thione Monohydrate (16). A soln of 18 (2.2 g) and PhOH (2.2 g) in CF_3CO_2H (22 ml) was refluxed with stirring for 30 min and evapd to dryness *in vacuo*. The residue was dissolved in dil NaOH and the soln was neutralized with dil HCl. A second repptn of the solid that deposited from a NaOH soln by addn of glacial HOAc gave pure 16: yield, 0.90 g; mp >264°. *Anal.* ($C_9H_{11}N_5S \cdot H_2O$) C, H, N.

6-(Methylthio)-9-pyrrolidin-1-yl-9*H*-purine (17). A soln of 8 (2.7 g) in dioxane (100 ml) contg pyridine (3 ml) was refluxed for 44 hr and evapd to dryness *in vacuo*. The residue was washed with H_2O and recrystd from EtOH: yield, 1.5 g (64%); mp 143°. *Anal.* ($C_{10}H_{13}N_5S$) C, H, N.

6-[(Diphenylmethyl)thio]-9-pyrrolidin-1-yl-9*H*-purine (18). A soln of 9 (10.6 g) in dioxane (220 ml) contg 1 *N* NaOH (55 ml) was heated at 55–60° for 20 hr and evapd to dryness *in vacuo*. The residue was extd with $CHCl_3$ (500 ml) and the solid obtd from evapn of the ext was recrystd from EtOH: yield, 3.80 g (39%); mp 151°. *Anal.* ($C_{22}H_{21}N_5S$) C, H, N.

Acknowledgment. The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute for the microanalytical results reported and to Dr. W. R. Laster and members of the Cancer Screening Division for the screening data reported.

References

(1) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Med. Chem.*, **11**, 41 (1968).
(2) C. Temple, Jr., A. G. Laseter, and J. A. Montgomery, *J. Heterocycl. Chem.*, **5**, 711 (1968).
(3) N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.*, **6**, 867 (1952).
(4) F. I. Carroll and A. Philip, *J. Org. Chem.*, **33**, 3776 (1968).
(5) H. E. Skipper, J. A. Montgomery, J. R. Thomson, and F. M. Schabel, Jr., *Cancer Res.*, **19**, 425 (1959).
(6) H. E. Skipper, F. M. Schabel, Jr., L. B. Mellett, J. A. Montgomery, L. J. Wilkoff, H. H. Lloyd, and R. W. Brockman, *Cancer Chemother. Rep.*, **54**, 431 (1970).

‡Melting points were detd on a Kofler Heizbank apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Pyrido[2,3-*d*]pyrimidine-6-carboxamides as Potential Diuretic Agents

Arthur A. Santilli* and Dong Han Kim

Wyeth Laboratories, Inc., Research and Development Division, Radnor, Pennsylvania 19087. *Received October 20, 1971*

Previously we reported 4,7-diamino-*N*-(2-morpholinoethyl)-2-phenyl-6-pteridinecarboxamide (3)[1a] and related amides[1b] to have significant diuretic activity in rats. Further interest in the structural requirements for activity led us to prepare the 5-deaza isostere 4,7-diamino-*N*-(2-morpholinoethyl)-2-phenylpyrido[2,3-*d*]pyrimidine-6-carboxamide (6a) and related amides (6b–d). (See Scheme I and Table I.) The previously undescribed synthetic route to these compounds parallels the one used for preparing 3 except that the 4,6-diamino-5-pyrimidinecarboxaldehydes (5a–b) were used instead of 4,6-diamino-5-nitrosopyrimidines such as 1. Treatment of 4,6-dichloro-2-phenyl-5-pyrimidinecarboxaldehyde (4a)[2] with NH_4OH afforded 4,6-diamino-2-phenyl-5-pyrimidinecarboxaldehyde (5a). This intermediate, when allowed to react with 2-cyano-*N*-(2-morpholinoethyl)-acetamide (2) in refluxing EtOH containing an equivalent of NaOEt, afforded 6a. Similarly, the pyrido[2,3-*d*]pyrimidine-6-carboxamides 6b–d were prepared from 5a–b and the corresponding 2-cyano-*N*-(substituted)acetamides. When 5b was treated with *N,N'*-bis(2-methoxethyl)malonamide under the same conditions, 4-amino-7-hydroxy-*N*-(2-methoxyethyl)-2-phenylpyrido[2,3-*d*]pyrimidine-6-carboxamide (7) was formed.

Interestingly, neither 6a nor the other pyrido[2,3-*d*]-pyrimidines described in this report were active in the standard rat diuretic screen[3] used in our laboratories. Replacement of N at the 5 position with CH in compounds such as 3, therefore, must offer sufficient steric and/or

Scheme I

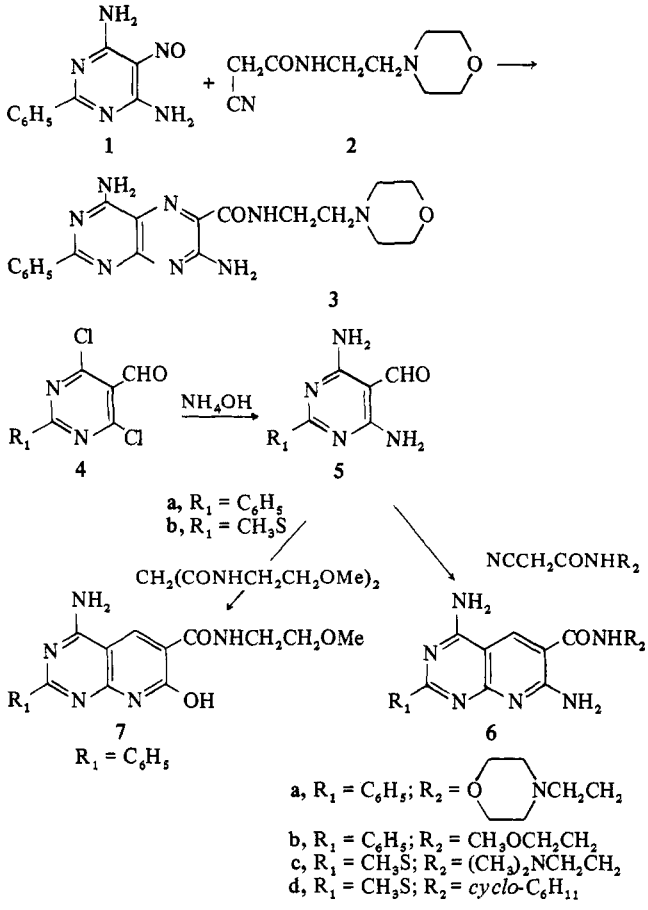


Table I. Substituted Pyrido[2,3-*d*]pyrimidine-6-carboxamides

No.	R_1	R_2	Recrystn solvent[a]	Mp, °C	Yield, %	Formula
6a	C_6H_5	$(CH_2)_2N$⟨O⟩	A	299–300	50	$C_{20}H_{23}N_7O_2$
b	C_6H_5	$(CH_2)_2OCH_3$	B	258–261	10	$C_{17}H_{18}N_6O_2$
c	CH_3S	$(CH_2)_2N(CH_3)_2$	B	297–300	29	$C_{13}H_{19}N_7OS$
d	CH_3S	*cyclo*-C_6H_{11}	A	>360	30	$C_{15}H_{20}N_6OS$

[a] A = aq DMF, B = EtOH.

electronic difference to nullify the diuretic effect previously observed.

Experimental Section†

4,6-Diamino-2-phenyl-5-pyrimidinecarboxaldehyde (5a). To 50 ml of concd NH_4OH in a pressure flask was added 15 g of 4,6-dichloro-2-phenyl-5-pyrimidinecarboxaldehyde.[2] The mixt was heated on a steam bath for 1 hr and a sufficient quantity of EtOH was added to solubilize it. Heating was cont for an addl hour. The reaction mixt was cooled in ice and the cryst product deposited amounted to 9.5 g. A portion was recrystd from EtOH for analysis, mp 217–218°. *Anal.* $C_{11}H_{10}N_4O$.

†Melting points were detd in capillary tubes (Thomas-Hoover mp apparatus) and are uncor. Where analyses are indicated only by empirical formulas, analytical results for C, H, N, and S (where applicable) were within ±0.4% of theory. Ir spectra were obtd in KBr discs using a Perkin-Elmer (Model 21) spectrophotometer and are compatible with the assigned structures. The NHC=O bands for **6a–d** and **7** ranged from 6.06 to 6.14 μ.

4,6-Diamino-2-methylthio-5-pyrimidinecarboxaldehyde (5b) was prepd in the same fashion as **5a**. From 15 g of 4,6-dichloro-2-methylthio-5-pyrimidinecarboxaldehyde[4] and 80 ml of concd NH_4OH was obtd 10 g of **5b**. The analytical sample, mp 228–230°, was obtd by recrystn from MeOH. *Anal.* $C_6H_8N_4OS$.

The following procedure typifies the method used for preparing **6b–d**.

4,7-Diamino-*N*-(2-morpholinoethyl)-2-phenylpyrido[2,3-*d*]-pyrimidine-6-carboxamide (6a). To 0.69 g of Na in 100 ml of EtOH was added 6.1 g of **4a** and 5.9 g of 2-cyano-*N*-(2-morpholinoethyl)acetamide. The reaction mixt was heated under reflux for 20 min, during which time a yellow ppt was deposited. The mixt was then cooled in ice and filtered under suction. The product amounted to 5.9 g. The analytical sample was obtd by recrystn of a portion from aq DMF.

4-Amino-7-hydroxy-*N*-(2-methoxyethyl)-2-phenylpyrido-[2,3-*d*]pyrimidine-6-carboxamide (7). To a soln contg 0.7 g of Na in 60 ml of abs EtOH was added 6.1 g of **5a** and 5.9 g of *N,N'* bis(2-methoxyethyl)malonamide. The reaction mixt was heated under reflux with stirring for 3 hr and then cooled in ice. The yellow ppt which formed was collected on a filter and recrystd from aq DMF; yield 2 g, mp >360°. *Anal.* $C_{17}H_{17}N_5O_3$.

Acknowledgments. The authors are indebted to Mr. Bruce Hofmann and staff for the analytical results and to Dr. Marvin E. Rosenthale for the diuretic assays.

References

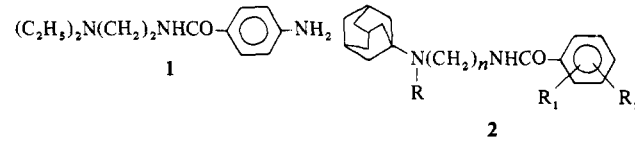
(1) (a) T. S. Osdene, A. A. Santilli, L. E. McCardle, and M. E. Rosenthale, *J. Med. Chem.*, **10**, 165 (1967); (b) *ibid.*, **9**, 697 (1966).
(2) H. Bredereck, G. Simchen, and A. A. Santos, *Chem. Ber.*, **100**, 1344 (1967).
(3) W. L. Lipschitz, Z. Hadidian, and A. Kerpcsar, *J. Pharm. Exp. Ther.*, 79, 97 (1943).
(4) A. A. Santilli, D. H. Kim, and S. V. Wanser, *J. Heterocycl. Chem.*, 8, 445 (1971).

Synthesis and Antiarrhythmic Activity of Some *N*-(Adamantylaminoalkyl)benzamides[1]

V. L. Narayanan* and F. J. Sweeney

The Squibb Institute for Medical Research, New Brunswick, New Jersey 08903. *Received October 15, 1971*

The publication by Yung, *et al.*,[2] concerning the synthesis of novel analogs of procaine amide (**1**) prompts us to report our efforts in this direction. Recently several reports have appeared describing the synthesis and biological activity of a variety of adamantane derivatives.[3] Our paper describes the synthesis and antiarrhythmic activity of a series of *N*-(adamantylaminoalkyl)benzamides (**2**).



2
R = H, C_2H_5
n = 2, 3
R_1 = H, Cl, CH_3
R_2 = NH_2, NO_2

Chemistry. Routes to the preparation of the key intermediates *N*-(1-adamantyl)-*N*-ethylethylenediamine (**6**) and *N*-(1-adamantyl)-1,3-propanediamine (**8**), required for the final synthesis of the *N*-(adamantylaminoalkyl)benzamides (**2**) are outlined below.

Refluxing a suspension of 1-acetamidoadamantane[4] (**3**) with an excess of LAH in Et_2O afforded an 80% yield of *N*-ethyl-1-adamantylamine (**4**). Treatment of **4** with a large excess of aziridine gave only starting material. However, the reaction of **4** with aziridine tosylate gave a mixture of