Pteridinecarboxamide Diuretics. II. Reaction of 4,6-Diamino-5-nitrosopyrimidines with N-Substituted Cyanoacetamides[1]

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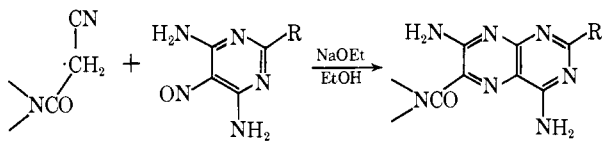
Several new 4,6-diamino-2-substituted 5-nitrosopyrimidines and N-substituted 2-cyanoacetamides were prepared and used as intermediates in the base-catalyzed preparation of a number of 4,7-diamino-2-substituted N-substituted 6-pteridinecarboxamides. Many of these pteridines were examined for diuretic activity in rats after oral administration. Increased activity was associated with certain specific structural characteristics. The more active compounds were those in which the 2 position of the pteridine nucleus bears an aromatic group, preferably phenyl or *m*-chlorophenyl, and in which the carbamoyl nitrogen bears a 2-dialkylaminoethyl or 2-(N-heterocyclic amino)ethyl group, *e.g.*, 2-diethylaminoethyl or 2-morpholinoethyl.

In the preceding paper of this series[3] the structure–diuretic activity relationship of 4-amino-2-substituted 7-substituted amino-N-substituted 6-pteridinecarboxamides prepared from 4,6-diamino-2-substituted 5-nitrosopyrimidines and N,N′-bis-substituted malonamides was discussed. In the present work a number of new 4,7-diamino-2-substituted N-substituted 6-pteridinecarboxamides were prepared by the reaction of 4,6-diamino-2-substituted 5-nitrosopyrimidines with N-substituted 2-cyanoacetamides (see Chart I and Tables I–V). The first descriptions of this type of synthesis were reported several years ago.[4] Many of the 6-pteridinecarboxamides given herein were found to be active diuretics when tested orally in rats. These compounds differ from those presented in the previous paper by having substituted in the 7 position of the pteridine nucleus an amino group rather than a hydroxy or substituted amino group. Slight modifications in structure at the 2 and 6 positions resulted in significant changes in activity and a systematic study was undertaken to determine the relationship between these structural changes and diuretic profile. Certain generalities have been observed and are presented in this report.

CHART I



(Tables I–II) (Table III) (Tables IV–V)

Chemistry.—The method used for the earlier syntheses of 4,7-diamino-6-pteridinecarboxamides[4] has now been expanded to include the preparation of 4,7-diamino-N-substituted 6-pteridinecarboxamides. The N-substituted cyanoacetamides required as intermediates were prepared generally by heating ethyl cyanoacetate with 1 equiv of a primary amine (Table I) or secondary amine (Table II) in refluxing ethanol. Various 4,6-diamino-2-substituted 5-nitrosopyrimidines (Table III) were prepared by previously described procedures.[5] Reaction of the latter compounds with N-substituted cyanoacetamides in refluxing ethanol containing catalytic amounts of sodium afforded the pteridinecarboxamides (Tables IV–V) used in this study. In those pteridines prepared from 4,6-diamino-5-nitrosopyrimidines bearing a 2-amino function, it was necessary to use a higher boiling solvent for reaction to occur. 2-Ethoxyethanol was found to be suitable for this purpose.

An examination of the infrared spectra of the pteridines thus prepared revealed the expected carbonyl and amino absorption bands. A typical example is given below.

Biological Methods.—The procedure used for evaluating the diuretic profiles of the pteridinecarboxamides in male Sprague–Dawley rats has been previously described in detail.[3] The results in Tables VI–X are expressed as the average ratios of urine volume and sodium levels in test (T) animals to those of the control urea-dosed (U) animals. All ratios (T/U) greater than unity for volume and sodium output represent statistically significant diuretic responses. This preliminary screening procedure was quite useful in that it afforded a means of rapidly evaluating the action of each drug on a quantitative basis. Further biological evaluation of the more active compounds has been carried out and is typified by other reports cited below.

Structure–Activity Relationships.—Table VI gives the relative diuretic response of a number of 4,7-diamino-2-phenyl-6-pteridinecarboxamides having various substituents (R_2) bonded to the N atom of the 6-carbamoyl group. In general, the more active pteridines are those in which R_2 contains an amino group, *e.g.*, **96**, **103**, **109**, **116**, and **118**. The most active of these are **103** and **118** where R_2 = 2-diethylaminoethyl and 2-morpholinoethyl, respectively. A more detailed account of the diuretic action of **118** in rats and dogs has recently been given.[6] The action of this drug has been compared with several other diuretic agents.[7]

Table VII shows the results of retaining an active moiety such as the 2-diethylaminoethyl group on the carbamoyl nitrogen but varying the substituent in the

(1) This work was presented in part before the Division of Medicinal Chemistry, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, p 16 P.

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(3) T. S. Osdene, A. A. Santilli, L. E. McCardle, and M. E. Rosenthale, *J. Med. Chem.*, **9**, 697 (1966).

(4) (a) T. S. Osdene and G. M. Timmis, *Chem. Ind.* (London), 405 (1954); (b) T. S. Osdene and G. M. Timmis, *J. Chem. Soc.*, 2036 (1955).

(5) O. Vogl and E. C. Taylor, *J. Am. Chem. Soc.*, **79**, 1518 (1957); E. C. Taylor, O. Vogl, and C. C. Cheng, *ibid.*, **81**, 2442 (1959), and other sources given in ref 3.

(6) M. E. Rosenthale and C. G. Van Arman, *J. Pharmacol. Exptl. Therap.*, **142**, 111 (1963).

(7) M. E. Rosenthale, *ibid.*, **147**, 399 (1965).

TABLE I
N-SUBSTITUTED 2-CYANOACETAMIDES
$NCCH_2CONHR_2$

Compd	R	Mp or bp (mm), °C	Recrystn solvent[a]	Yield, %	Formula	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
1	CH_3[b]	100	A	60							
2	C_2H_5[c]	73	A	94							
3	*c*-C_3H_5	104	A	59	$C_6H_8N_2O$	58.05	6.50	22.57	57.94	6.40	22.36
4	*c*-C_5H_9	87	J–F	64	$C_8H_{12}N_2O$	63.13	7.95	18.41	62.97	8.10	18.36
5	*c*-C_6H_{11}[d]	132	A–C	36	$C_9H_{14}N_2O$	65.03	8.49	16.85	64.72	8.47	16.90
6	*c*-C_7H_{13}	94	A–D	58	$C_{10}H_{16}N_2O$	66.63	8.95	15.54	66.69	9.21	15.68
7	*c*-C_8H_{15}	74	A–D	51	$C_{11}H_{18}N_2O$	68.00	9.34	14.42	68.10	9.20	14.67
8	$(CH_2)_2OH$[e]	61	B	65							
9	$CHC_2H_5CH_2OH$[f]	87	B–C	92							
10	$CCH_3(CH_2OH)_2$[f]	131	A–B	74							
11	$(CH_2)_2O(CH_2)_2OH$[g]										
12	$(CH_2)_2OCH_3$	79	B	53	$C_6H_{10}N_2O_2$	50.69	7.09	19.71	50.71	7.02	19.86
13	$(CH_2)_3OCH_3$	61	B	55	$C_7H_{12}N_2O_2$	53.83	7.74	17.94	53.62	7.65	17.83
14	$(CH_2)_2OC_2H_5$	45	A–C	52	$C_7H_{12}N_2O_2$	53.83	7.74	17.94	53.70	7.73	17.82
15	$(CH_2)_3OC_2H_5$	55	B–C	76	$C_8H_{14}N_2O_2$	56.45	8.29	16.46	56.28	8.31	16.17
16	$CH_2CH(OC_2H_5)_2$	52	A–J	52	$C_9H_{16}N_2O_3$	53.98	8.06	13.99	53.74	7.98	14.30
17	$(CH_2)_3OCH(CH_3)_2$[g]	38		64	$C_9H_{16}N_2O_2$	58.67	8.75	15.21	58.64	9.07	15.28
18		55		81							
19	$(CH_2)_2SC_2H_5$[h]	52	K	55	$C_7H_{12}N_2OS$	48.81	7.02	16.26	49.10	7.11	16.04
20	$CH_2CO_2C_2H_5$[i]	99	J	36							
21	*p*-$C_2H_5OCOC_6H_4$	94	D		$C_{12}H_{12}N_2O_3$	62.06	5.21	12.06	62.30	5.64	11.99
22	$(CH_2)_2NH_2$·maleate	95	A		$C_9H_{13}N_3O_5$	44.44	5.39	17.28	44.41	5.16	17.20
23	$(CH_2)_3NHC_6H_{11}$-*c*[g]	75		36							
24	$(CH_2)_2N(CH_3)_2$	147 (1.0)		66	$C_7H_{13}N_3O$	54.17	8.44	27.08	54.21	8.73	26.90
25	$(CH_2)_3N(CH_3)_2$	128–129 (0.5)		71	$C_8H_{15}N_3O$	56.78	8.94	24.83	55.84	8.65	24.45
26	$(CH_2)_4N(CH_3)_2$	148–149 (0.35)		59	$C_9H_{17}N_3O$	58.98	9.35	22.93	59.28	9.54	22.33
27	$(CH_2)_5N(CH_3)_2$	162–164 (0.3)		46	$C_{10}H_{19}N_3O$	60.88	9.71	21.30	60.72	10.13	21.22
28	$(CH_2)_6N(CH_3)_2$[g]										
29	$(CH_2)_2N(C_2H_5)_2$	132 (0.5)		66	$C_9H_{17}N_3O$	58.98	9.35	22.93	58.87	9.39	22.79
30	$(CH_2)_3N(C_2H_5)_2$	142–143 (0.5)		59	$C_{10}H_{19}N_3O$	60.88	9.71	21.30	60.94	9.87	21.22
31	$(CH_2)_4N(C_2H_5)_2$	155–165 (0.4)		46	$C_{11}H_{21}N_3O$	62.52	10.02	19.89	62.70	10.34	19.47
32	$(CH_2)_5N(C_2H_5)_2$[g]										
33	$(CH_2)_7N(C_2H_5)_2$[g]										
34	$(CH_2)_2N(i\text{-}C_3H_7)_2$	150 (0.7)		87	$C_{11}H_{21}N_3O$	62.52	10.02	19.89	62.26	10.00	19.75
35	$(CH_2)_3N(n\text{-}C_4H_9)_2$	184 (1.0)		68	$C_{14}H_{27}N_3O$	66.36	10.74	16.59	65.74	10.35	16.68
36	$(CH_2)_2N(CH_2CH_2OH)_2$[g]										
37	$CH_2CHCH_3N(CH_3)_2$	138 (1.1)		67	$C_8H_{15}N_3O$	56.78	8.94	24.83	56.67	8.81	24.52
38	$CHCH_3(CH_2)_3N(C_2H_5)_2$[j]	156–162 (0.3)		47	$C_{12}H_{23}N_3O$	63.96	10.29	18.65	63.91	10.60	18.62
39	2-(1-Pyrrolidinyl)ethyl	109	B	72	$C_9H_{15}N_3O$	59.64	8.34	23.19	59.40	8.36	22.97
40	2-Piperidinoethyl	72	B	95	$C_{10}H_{17}N_3O$	61.51	8.78	21.52	61.80	8.97	21.49
41	3-Piperidinopropyl	48	B–C	53	$C_{11}H_{19}N_3O$	63.21	9.15	20.08	63.26	8.92	20.10
42	2-Morpholinoethyl	85	B	40	$C_9H_{15}N_3O_2$	54.80	7.67	21.31	55.05	7.83	21.27
43	3-Morpholinopropyl	65	B	44	$C_{10}H_{17}N_3O_2$	56.85	8.11	19.89	56.89	8.06	19.60
44	4-Pyridylmethyl	116	L	26	$C_9H_9N_3O$	61.70	5.18	23.99	61.74	5.11	24.04

[a] A = ethanol, B = ethyl acetate, C = petroleum ether (bp 30–60°), D = H_2O, E = 2-ethoxyethanol, F = C_6H_6, G = DMF, H = methanol, I = 1-butanol, J = cyclohexane, K = ether, L = acetone, M = acetic acid. [b] K. G. Naik and Y. N. Bhat, *Quart. J. Indian Chem. Soc.*, **4**, 547 (1927); *Chem. Abstr.*, **22**, 2353 (1928), reported mp 101°. [c] Lit.[b] mp 74°. [d] C. Whitehead and J. Traverso, *J. Am. Chem. Soc.*, **77**, 5867 (1955), reported mp 132°. [e] O. K. Behrens, J. Corse, D. E. Huff, R. G. Jones, Q. F. Soper, and C. W. Whitehead, *J. Biol. Chem.*, **175**, 771 (1948); no melting point reported. [f] Previously reported by A. A. Santilli and T. S. Osdene, *J. Org. Chem.*, **29**, 2066 (1964). [g] Sample used without purification. [h] 2-Ethylmercaptoethylamine used in the preparation of **19**, was prepared from ethylenimine and ethyl mercaptan as described by T. Wieland, E. F. Moller, and G. Dieckelmann, *Ber.*, **85**, 1035 (1952). [i] O. Diels and H. Heibtzel, *ibid.*, **38**, 304 (1905), reported mp 100–101°. [j] C. C. Price and V. Boekelheide, *J. Am. Chem. Soc.*, **68**, 1246 (1946), reported bp 165–170° (2 mm).

2 position of the pteridine nucleus. The only active member of this series is **103** (R_1 = phenyl). The other compounds were inactive at the dose levels shown.

In Table VIII are given compounds in which the same active group is retained on the carbamoyl nitrogen but the substituent R′ on the 2-phenyl group is varied. The most active compounds in this series are **103** and **155** in which R′ = H and *m*-Cl, respectively. Substitution generally diminished the activity. Compounds **145**, **148**, and **165** were inactive.

Table IX demonstrates the effect of homologation on diuretic response within an active series. The optimal methylene chain length attached to the carbamoyl nitrogen appears to be two (**103**). Activity decreased with a third methylene group (**104**) and was nonexistent for compounds containing four (**105**) or five (**106**) methylene groups in the alkyl chain. Similar results were observed with higher homologs ($n > 2$) in other active pteridines.

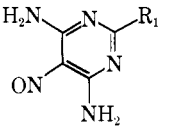
Table X shows the diuretic effect in 4,7-diamino-2-phenyl-6-pteridinecarboxamides which have the car-

TABLE II
2-CYANOACETYLAMINES AND N,N-DISUBSTITUTED 2-CYANOACETAMIDES
$NCCH_2COR_3$

Compd	R_3	Mp or bp (mm), °C	Recrystn solvent[a]	Yield, %	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
45	1-Pyrrolidinyl	71	B	67	$C_7H_{10}N_2O$	60.85	7.30	20.28	60.91	7.26	20.09
46	Piperidino[b]	87	B	76							
47	1-Hexahydroazepinyl	74	A–J	73	$C_9H_{14}N_2O$	65.03	8.49	16.85	65.19	8.60	17.10
48	Morpholino[b]	82	F–C	27							
49	Thiomorpholino	95	D	70	$C_7H_{10}N_2OS$	49.39	5.92	16.46	49.72	5.93	16.74
50	4-Methyl-1-piperazinyl	113	J	40	$C_8H_{13}N_3O$	57.46	7.84	25.13	57.59	8.08	24.96
51	4-(2-Hydroxyethyl)-1-piperazinyl	84	F	83	$C_9H_{15}N_3O_2$	54.80	7.67	21.31	55.09	7.51	21.41
52	$N(CH_3)_2$[c]	64	B	92							
53	$NCH_3(CH_2)_2N(CH_3)_2$	147 (0.7)		66	$C_8H_{15}N_3O$	56.78	8.94	24.83	56.44	8.99	24.71
54	$NCH_3C_6H_{11}$-*c*	82	A–D	99	$C_{10}H_{16}N_2O$	66.63	8.95	15.54	67.09	8.66	15.37
55	$NCH_3(CH_2)_2N(C_2H_5)_2$[d]										
56	$NC_2H_5(CH_2)_2N(CH_3)_2$	147–150 (0.7)		21	$C_9H_{17}N_3O$	58.99	9.35	22.93	58.65	9.15	23.14
57	$NC_2H_5(CH_2)_2N(C_2H_5)_2$[d]										
58	$N(i\text{-}C_3H_7)(CH_2)_2N(i\text{-}C_3H_7)_2$	86		79	$C_{14}H_{27}N_3O$	66.36	10.74	16.59	66.28	10.63	16.36

[a] See footnote *a* of Table I. [b] C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **77**, 5867 (1955), reported mp 87° for both **46** and **48**. [c] E. L. Eliel, *ibid.*, **73**, 43 (1951), reported mp 65–66°. [d] Compound used without purification.

TABLE III
4,6-DIAMINO-5-NITROSO-2-(SUBSTITUTED) PYRIMIDINES



Compd	R_1[a]	Mp, °C	Recrystn solvent[b]	Method[c]	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
59	CF_3	>360	M–D	I	$C_5H_4F_3N_5O$	29.01	1.95		28.55	2.16	
60	Morpholino[d]	236 dec	A	II	$C_8H_{12}N_6O_2$	42.85	5.39	37.48	43.03	5.41	37.20
61	*o*-$CH_3C_6H_4$	219 dec	A	I	$C_{11}H_{11}N_6O_2$	57.63	4.84	30.54	57.87	5.00	31.44
62	*m*-$CF_3C_6H_4$[a]	211	H	I	$C_{11}H_8F_3N_5O$	46.81	2.50	24.82	46.90	2.78	24.55
63	3,4-$Cl_2C_6H_3$	279 dec	E	I	$C_{10}H_7Cl_2N_5O$	42.29	2.49	24.65	42.53	4.75	24.40
64	*o*-$CH_3C_6H_4CH_2$	210	A	I	$C_{12}H_{13}N_5O$	59.25	5.39	28.79	59.51	5.41	28.80
65	*p*-$ClC_6H_4CH_2$	216	E–D	I	$C_{11}H_{10}ClN_5O$	50.10	8.32	26.56	50.02	3.88	26.67

[a] The sources for the 4,6-diamino-5-nitroso-2-(substituted) pyrimidines in which R_1 is H, *n*-C_3H_7, CH_3S, C_6H_5, *p*-$CH_3OC_6H_4$, *m*-ClC_6H_4, *p*-ClC_6H_4, and 2-thienyl were previously given in paper I of this series.[3] Other preparations: *m*-$CH_3C_6H_4$, J. Weinstock, U. S. Patent 2,963,478 (1960); *p*-$CH_3C_6H_4$, E. C. Taylor and T. S. Osdene, U. S. Patent, 2,975,180 (1961); CH_3, E. C. Taylor, O. Vogl, and C. C. Cheng, *J. Am. Chem. Soc.*, **81**, 2442 (1959); *m*-$CF_3C_6H_4$, obtained from Arapahoe Chemicals, Inc. [b] See footnote *a* of Table I. [c] See Experimental Section. [d] See ref 10.

bamoyl nitrogen disubstituted. At the doses indicated compounds **184–186** were only mildly active and all other compounds were inactive. It is interesting to note that further substitution on the carbamoyl nitrogen bearing the active 2-diethylaminoethyl moiety (**180**, **182**) eliminated the diuretic response.

In summary, the diuretic profiles of several 4,7-diamino-2-substituted N-substituted 6-pteridinecarboxamides, as determined in male Sprague–Dawley rats, show that activity is related to specific structural requirements. The more active compounds are those in which the 2 position of the pteridine nucleus bears an aromatic group, preferably phenyl or *m*-chlorophenyl, and in which the carbamoyl nitrogen bears a 2-dialkylaminoethyl or 2-(N-heterocyclic amino)ethyl group such as 2-diethylaminoethyl or 2-morpholinoethyl.

Experimental Section[8]

The examples given below illustrate procedures used for the preparation of the compounds given in Tables I–V.

The 4,6-diamino-5-nitrosopyrimidines given in Table III were prepared in general by the reaction of a suitably substituted amidine hydrochloride with the silver salt of isonitrosomalononitrile (method I) or by the direct nitrosation of the 4,6-diaminopyrimidine (method II). Illustrative examples follow.

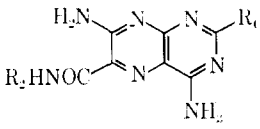
Method I.[9] 4,6-Diamino-2-trifluoromethyl-5-nitrosopyrimidine (59).—To a solution of 24.5 g of trifluoroacetamidine hydrochloride in 450 ml of absolute ethanol was added portionwise 33.6 g of finely powdered silver salt of isonitrosomalononitrile. The reaction mixture was stirred for 2 hr and the AgCl was removed by filtration. The filtrate was evaporated to dryness *in vacuo* on a rotary evaporator to give the trifluoroacetamidine salt of isonitrosomalononitrile, mp 95–96°. The material thus obtained was dissolved in 150 ml of dimethylformamide (DMF) and boiled under reflux for 10 min. An excess of water was added, resulting in the deposition of a dark green powder. Recrystallization from aqueous DMF followed by recrystallization from aqueous acetic acid gave 13.5 g of the product, mp >360°.

(8) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are corrected. Yields reported in Tables I–V are the results of single experiments. Infrared spectra were determined in KBr disks on a Perkin-Elmer Model 21 spectrophotometer.

(9) Other 5-nitrosopyrimidine intermediates prepared by this method have been previously cited in ref 3.

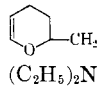
TABLE IV

4,7-DIAMINO-N-SUBSTITUTED 6-PTERIDINECARBOXAMIDES



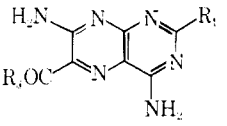
Compd	R_1	R_2	Mp, °C	Recrystn solvent[a]	Yield, %	Formula	%C calcd			%C found		
							C	H	N	C	H	N
66	H[b]	H	>360	G–D	44	$C_7H_7N_7O$	40.97	3.44	47.78	41.21	3.71	47.63
67	H	$(i\text{-Pr})_2N(CH_2)_2$	303	G–D	62	$C_{14}H_{24}N_8O$	54.20	7.28	33.71	54.22	6.88	33.97
68	CH_3	$(C_2H_5)_2N(CH_2)_2$	250	A	70	$C_{15}H_{24}N_8O$	54.20	7.28	33.71	53.49	7.65	33.80
69	CF_3	H	>360	G–D	73	$C_8H_5F_3N_7O$	35.17	2.21	35.90	35.39	2.39	35.67
70	CF_3	$(C_2H_5)_2N(CH_2)_2$	327	A	60	$C_{14}H_{19}F_3N_8O$	40.16	5.14	30.10	44.88	5.01	29.88
71	$n\text{-}C_3H_7$	H	>360	G–D	81	$C_9H_{13}N_7O$	48.57	5.29	39.65	48.43	5.11	39.46
72	$n\text{-}C_3H_7$	$(C_2H_5)_2N(CH_2)_2$	266	A–D	96	$C_{16}H_{26}N_8O \cdot 0.5H_2O$	54.07	7.65	31.53	54.50	7.48	31.71
73	$n\text{-}C_3H_7$	$(C_2H_5)_2N(CH_2)_3$	244	A–D	74	$C_{17}H_{28}N_8O \cdot 0.5H_2O$	55.26	7.91	30.75	55.35	8.04	31.04
74	CH_3S	$(C_2H_5)_2N(CH_2)_2$	300	E–D	78	$C_{14}H_{22}N_8OS$	47.98	6.33	31.98	47.48	6.59	31.80
75	CH_3S	$(C_2H_5)_2N(CH_2)_3$	305	E	55	$C_{15}H_{24}N_8OS$	49.43	6.64	30.75	49.47	6.49	30.72
76	CH_3S	$C_2H_5O(CH_2)_3$	299	E–D	89	$C_{13}H_{19}N_7O_2S$	46.28	5.68	29.06	46.30	5.22	28.89
77	$(C_2H_5)_2N(CH_2)_2NH$	$(C_2H_5)_2N(CH_2)_2$	191	A–B	4	$C_{18}H_{34}N_{10}O$	54.52	8.19	33.47	54.06	7.97	33.43
78	$(C_2H_5)_2N(CH_2)_3NH$[c]	$(C_2H_5)_2N(CH_2)_3$	119	F	54	$C_{24}H_{38}N_{10}O \cdot H_2O$	54.28	8.68	30.15	54.39	8.25	29.83
79	NH_2[b,d]	H	>360	D	32	$C_7H_8N_8O$	38.18	3.66	50.89	38.48	3.61	49.95
80	NH_2[d]	$(C_2H_5)_2N(CH_2)_2$	312	G–D	75	$C_{13}H_{24}N_8O \cdot 0.5H_2O$	47.55	6.75	38.39	47.82	7.02	38.49
81	NH_2[d]	$(C_2H_5)_2N(CH_2)_2$	317	G–D	73	$C_{14}H_{28}N_8O$	50.43	6.95	37.81	50.01	7.23	37.94
82	NH_2[d]	$(CH_3)_2N(CH_2)_3$	284	A	14	$C_{12}H_{18}N_8O \cdot 0.5H_2O$	45.85	6.41	40.11	46.13	6.43	40.22
83	NH_2[d]	2-Morpholinoethyl	294	G–D	90	$C_{13}H_{18}N_8O_2$	46.84	5.74	37.82	46.67	5.93	37.81
84	NH_2[d]	$(CH_3)_2CHO(CH_2)_3$	287	A	20	$C_{14}H_{24}N_8O_2$	48.74	6.29	34.98	48.43	6.67	34.39
85	NH_2[d]	$c\text{-}C_7H_{13}$	336	G–D	71	$C_{14}H_{20}N_8O$	53.15	6.37	35.42	53.59	6.12	35.19
86	Morpholino[d]	H	>360	G–D	39	$C_{11}H_{14}N_8O_2$	45.51	4.87	38.60	45.66	5.22	38.68
87	Morpholino[d]	$(CH_3)_2N(CH_2)_3$	241	A–D	88	$C_{15}H_{25}N_9O_2$	51.18	6.71	33.58	50.75	7.06	33.63
88	C_6H_5[e]	H	>360	G–D	85	$C_{13}H_{11}N_7O$	55.51	3.94	34.86	55.44	3.62	34.65
89	C_6H_5	CH_3	352	G–D	96	$C_{14}H_{13}N_7O$	56.94	4.44	33.20	56.94	4.53	32.60
90	C_6H_5	C_2H_5	346	E–D	99	$C_{15}H_{15}N_7O$	58.24	4.89	31.70	58.23	5.06	31.80
91	C_6H_5	$c\text{-}C_3H_5$	342	G–D	65	$C_{16}H_{15}N_7O$	59.80	4.71	30.51	60.07	4.53	30.64
92	C_6H_5	$c\text{-}C_5H_9$	344	G–D	94	$C_{18}H_{19}N_7O$	61.87	5.48	28.06	61.90	5.49	28.19
93	C_6H_5	$c\text{-}C_6H_{11}$	350	G–D	92	$C_{19}H_{21}N_7O$	62.79	5.82	26.98	62.25	5.79	26.98
94	C_6H_5	$c\text{-}C_7H_{13}$	350	A–C	95	$C_{20}H_{23}N_7O$	63.64	6.14	25.98	63.47	6.27	26.18
95	C_6H_5	$c\text{-}C_8H_{15}$	332	G–D	94	$C_{21}H_{25}N_7O$	64.43	6.44	25.05	64.37	6.25	24.73
96	C_6H_5	4-Pyridylmethyl	330	G–D	89	$C_{19}H_{16}N_8O$	61.28	4.33	30.09	60.99	4.16	30.04
97	C_6H_5[e]	$H_2N(CH_2)_2$	303	G–D	90	$C_{15}H_{16}N_8O$	55.54	4.97	34.55	55.75	5.27	34.68
98	C_6H_5	$(CH_3)_2N(CH_2)_2$	294	E–D	51	$C_{17}H_{20}N_8O$	57.94	5.72	31.80	57.95	6.18	31.65
99	C_6H_5	$(CH_3)_2N(CH_2)_3$	281	A	89	$C_{18}H_{22}N_8O$	59.00	6.05	30.58	59.17	6.29	30.80
100	C_6H_5	$(CH_3)_2N(CH_2)_4$	273	A	70	$C_{19}H_{24}N_8O$	59.98	6.36	29.46	60.17	6.40	29.37
101	C_6H_5	$(CH_3)_2N(CH_2)_5$	275	A	68	$C_{20}H_{26}N_8O$	60.89	6.64	28.41	60.78	6.64	28.64
102	C_6H_5	$(CH_3)_2N(CH_2)_6$	279	A	61	$C_{21}H_{28}N_8O$	61.74	6.91	27.43	62.00	6.62	27.29
103	C_6H_5	$(C_2H_5)_2N(CH_2)_2$	280	A	100	$C_{19}H_{24}N_8O$	59.98	6.36	29.46	60.11	6.46	29.25
104	C_6H_5	$(C_2H_5)_2N(CH_2)_3$	272	A	80	$C_{20}H_{26}N_8O$	60.89	6.64	28.41	61.09	6.93	28.55
105	C_6H_5	$(C_2H_5)_2N(CH_2)_4$	279	A	94	$C_{21}H_{28}N_8O$	61.74	6.91	27.43	61.95	6.65	27.43
106	C_6H_5	$(C_2H_5)_2N(CH_2)_5$	290	A	82	$C_{22}H_{30}N_8O$	62.53	7.16	26.52	62.71	7.20	26.54
107	C_6H_5	$(C_2H_5)_2N(CH_2)_7$	289	A–D	58	$C_{24}H_{34}N_8O$	63.97	7.61	24.87	63.71	7.41	25.10
108	C_6H_5	$(n\text{-}C_4H_9)_2N(CH_2)_3$	260	A	87	$C_{24}H_{34}N_8O$	63.97	7.61	24.87	63.17	7.58	24.63
109	C_6H_5	2-(1-Pyrrolidinyl)-ethyl	297	A–D	96	$C_{19}H_{22}N_8O$	61.30	5.86	29.61	60.18	6.08	29.50
110	C_6H_5	$[(CH_3)_2CH]_2N(CH_2)_2$	283	E	94	$C_{24}H_{28}N_8O$	61.74	6.91	27.43	61.78	7.27	26.98
111	C_6H_5	$(CH_3)_3N^+(CH_2)_3I^-$	303	D	98	$C_{19}H_{25}IN_8O$	44.89	4.96	22.04	45.26	5.03	22.19
112	C_6H_5[g]	$(C_2H_5)_3N^+(CH_2)_3I^-$	247	D	66	$C_{22}H_{31}IN_8O$	48.00	5.68	20.36	47.44	5.69	20.28
113	C_6H_5	$(CH_3)_2NCHCH_3CH_2$	286	E–D	75	$C_{18}H_{22}N_8O$	59.00	6.05	30.58	58.91	6.10	30.70
114	C_6H_5	$(C_2H_5)_2N(CH_2)_3CHCH_3$	268	E–D	58	$C_{22}H_{30}N_8O$	62.53	7.16	26.52	62.69	7.06	26.49
115	C_6H_5	$(HOCH_2CH_2)_2N(CH_2)_2$	239	A–D	75	$C_{18}H_{24}N_8O_3$	55.53	5.86	27.47	55.36	5.80	27.63
116	C_6H_5	2-Piperidinoethyl	284	G–D	83	$C_{20}H_{24}N_8O$	61.20	6.16	28.55	61.08	5.90	28.62
117	C_6H_5	3-Piperidinopropyl	271	A	67	$C_{21}H_{26}N_8O$	62.05	6.45	27.57	62.21	6.40	27.32

TABLE IV (*Continued*)

Compd	R_1	R_2	Mp, °C	Recrystn solvent	Yield, %	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
118	C_6H_5	2-Morpholinoethyl	281	E–D	73	$C_{19}H_{22}N_8O_2$	57.85	5.62	28.41	58.14	5.76	28.22
119	C_6H_5	3-Morpholinopropyl	260	A	78	$C_{20}H_{24}N_8O_2$	58.81	5.92	27.44	58.81	5.92	27.38
120	C_6H_5	$HO(CH_2)_2$	324	A	81	$C_{15}H_{15}N_7O_2$	55.37	4.65	30.14	55.80	4.44	29.77
121	C_6H_5	$HOCH_2CHC_2H_5$	291	G–D	86	$C_{17}H_{19}N_7O_2$	57.77	5.42	27.75	57.91	5.49	27.73
122	C_6H_5	$(HOCH_2)_2CCH_3$	295	G–D	80	$C_{17}H_{19}N_7O_3$	55.29	5.19	26.54	55.00	5.07	26.38
123	C_6H_5	$HO(CH_2)_2O(CH_2)_2$	242	E	95	$C_{17}H_{19}N_7O_3$	55.28	5.19	26.54	54.99	5.35	26.44
124	C_6H_5	$CH_3O(CH_2)_2$	293	E	76	$C_{16}H_{17}N_7O_2$	56.63	5.05	28.90	56.32	4.91	28.61
125	C_6H_5	$CH_3O(CH_2)_3$	285	A	75	$C_{17}H_{19}N_7O_2$	57.78	5.42	27.75	58.07	5.62	27.49
126	C_6H_5	$(CH_3)_2CHO(CH_2)_3$	265	A–D	82	$C_{19}H_{23}N_7O\cdot 0.33H_2O$	61.44	6.42	26.40	61.50	6.74	26.08
127	C_6H_5	$(C_2H_5O)_2CHCH_2$	235	A	76	$C_{19}H_{23}N_7O_3$	57.42	5.83	24.67	57.42	5.70	24.43
128	C_6H_5	$C_2H_5O(CH_2)_2$	282	A	69	$C_{17}H_{19}N_7O_2$	57.78	5.42	27.75	57.99	5.76	28.01
129	C_6H_5	$C_2H_5O(CH_2)_3$	279	E–D	77	$C_{18}H_{21}N_7O_2$	58.84	5.76	26.69	59.15	5.77	26.41
130	C_6H_5		303	E–D	90	$C_{19}H_{19}N_7O_2$	60.47	5.08	25.98	60.64	5.11	25.85
131	C_6H_5	$C_2H_5S(CH_2)_2$	293	E–D	77	$C_{17}H_{19}N_7OS$	55.27	5.18	26.54	55.51	5.11	26.70
132	C_6H_5	$C_2H_5O_2CCH_2$	300	A	78	$C_{17}H_{17}N_7O_3$	55.58	4.66	26.69	55.88	4.74	26.53
133	C_6H_5	p-$C_2H_5OCOC_6H_4$	359	G–D	76	$C_{22}H_{19}N_7O_3$	61.53	4.46	22.83	61.35	4.62	22.72
134	o-$CH_3C_6H_4$	$(CH_3)_2N(CH_2)_2$	275	A	84	$C_{18}H_{22}N_8O$	59.00	6.05	30.58	58.98	6.06	30.28
135	o-$CH_3C_6H_4$	$(C_2H_5)_2N(CH_2)_2$	277	A–D	92	$C_{20}H_{26}N_8O$	60.89	6.64	28.41	61.14	6.72	28.28
136	o-$CH_3C_6H_4$	$(C_2H_5)_2N(CH_2)_3$	287	E–D	78	$C_{21}H_{28}N_8O$	61.74	6.91	27.43	61.78	6.76	27.61
137	o-$CH_3C_6H_4$	2-Morpholinoethyl	273	E–D	82	$C_{20}H_{24}N_8O_2$	58.81	5.92	27.44	58.54	5.95	27.42
138	m-$CH_3C_6H_4$	$(C_2H_5)_2N(CH_2)_2$	264	A–D	68	$C_{20}H_{26}N_8O$	60.89	6.64	28.41	60.73	6.52	28.38
139	p-$CH_3C_6H_4$	c-C_6H_{11}	>360	G–D	91	$C_{20}H_{23}N_7O$	63.64	6.14	25.98	63.64	6.40	26.01
140	p-$CH_3C_6H_4$	$(CH_3)_2N(CH_2)_3$	302	A–D	95	$C_{15}H_{24}N_8O$	59.98	6.36	29.46	59.61	6.54	29.07
141	p-$CH_3C_6H_4$	$(C_2H_5)_2N(CH_2)_2$	284	A–D	93	$C_{20}H_{26}N_8O$	60.89	6.64	28.41	60.92	6.59	28.32
142	p-$CH_3C_6H_4$	$(CH_3)_2NCHCH_3CH_2$	300	A–D	87	$C_{19}H_{24}N_8O\cdot 0.5H_2O$	58.59	6.47	28.78	58.78	6.40	29.21
143	p-$CH_3C_6H_4$	2-Morpholinoethyl	309	E–D	90	$C_{20}H_{24}N_8O_2$	58.67	5.93	27.59	58.81	5.92	27.44
144	p-$CH_3C_6H_4$	$(C_2H_5O)_2CHCH_2$	249	A	67	$C_{20}H_{25}N_7O_3$	58.37	6.12	23.83	58.34	5.97	24.02
145	m-$CF_3C_6H_4$	$(C_2H_5)_2N(CH_2)_2$	293	A	53	$C_{20}H_{23}F_3N_8O$	53.56	5.17	24.99	53.39	5.19	25.01
146	m-$CF_3C_6H_4$	$HO(CH_2)_2O(CH_2)_2$	228	A–D	57	$C_{18}H_{18}F_3N_7O_3$	49.43	4.15	22.42	49.29	4.23	22.16
147	p-$CH_3OC_6H_4$	$(CH_3)_2N(CH_2)_2$	297	A	58	$C_{18}H_{22}N_8O_2$	56.53	5.80	29.30	55.87	5.61	29.03
148	p-$CH_3OC_6H_4$	$(C_2H_5)_2N(CH_2)_2$	283	E–D	79	$C_{20}H_{26}N_8O_2\cdot 0.5H_2O$	57.26	6.49	26.72	57.12	6.44	27.25
149	p-$CH_3OC_6H_4$	2-Morpholinoethyl	313	E–D	26	$C_{20}H_{24}N_8O_3$	56.59	5.70	26.40	56.67	5.67	26.24
150	m-ClC_6H_4	$(CH_3)_2N(CH_2)_2$	302	E–D	53	$C_{17}H_{19}ClN_8O$	52.78	4.95	28.97	52.98	4.71	28.91
151	m-ClC_6H_4	$(CH_3)_2N(CH_2)_3$	280	H	87	$C_{18}H_{21}ClN_8O$	53.93	5.28	27.95	53.77	5.03	27.92
152	m-ClC_6H_4	$(CH_3)_2N(CH_2)_4$	285	H	60	$C_{19}H_{23}ClN_8O$	55.00	5.59	27.01	55.27	5.86	27.23
153	m-ClC_6H_4	$(CH_3)_2N(CH_2)_5$	277	A–D	55	$C_{20}H_{25}ClN_8O$	56.00	5.88	26.13	56.12	6.31	26.21
154	m-ClC_6H_4	$(CH_3)_2N(CH_2)_6$	277	H	37	$C_{21}H_{27}ClN_8O$	56.94	6.14	25.30	57.11	6.48	25.24
155	m-ClC_6H_4	$(C_2H_5)_2N(CH_2)_2$	275	A	40	$C_{19}H_{23}ClN_8O$	55.00	5.59	27.01	54.72	5.35	26.89
156	p-ClC_6H_4	$(CH_3)_2N(CH_2)_2$	329	I	65	$C_{17}H_{19}ClN_8O$	52.78	4.95	28.97	52.64	5.17	28.52
157	p-ClC_6H_4	$(CH_3)_2N(CH_2)_4$	321	I	54	$C_{19}H_{23}ClN_8O$	55.00	5.59	27.01	54.72	5.55	26.39
158	p-ClC_6H_4	$(C_2H_5)_2N(CH_2)_2$	309	E–D	71	$C_{19}H_{23}ClN_8O$	52.71	5.82	25.89	52.53	5.95	25.94
159	p-ClC_6H_4	$(C_2H_5)_2N(CH_2)_3$	306	A–D	81	$C_{20}H_{25}ClN_8O$	56.00	5.88	26.13	56.02	6.29	26.00
160	p-ClC_6H_4	2-Morpholinoethyl	318	A–D	86	$C_{19}H_{21}ClN_8O_2$	53.21	4.93	26.13	52.97	4.93	26.34
161	p-ClC_6H_4	$C_2H_5O(CH_2)_2$	303	A–D	86	$C_{17}H_{18}ClN_7O_2$	52.65	4.68	25.28	52.78	4.38	25.46
162	p-ClC_6H_4	$C_2H_5O(CH_2)_3$	279	E–D	77	$C_{18}H_{21}N_7O_2$	58.84	5.76	26.69	59.15	5.77	26.41
163	p-ClC_6H_4		327	E–D	49	$C_{19}H_{18}ClN_7O_2$	55.41	4.41	23.81	55.12	4.18	23.66
164	p-ClC_6H_4	$(C_2H_5O)_2CHCH_2$	248	A	75	$C_{19}H_{22}ClN_7O_3$	52.84	5.14	22.70	52.87	5.30	22.47
165	3,4-$Cl_2C_6H_3$	$(C_2H_5)_2N(CH_2)_2$	304	A	77	$C_{19}H_{22}Cl_2N_8O$	50.78	4.94	24.94	50.11	5.19	24.96
166	3,4-$Cl_2C_6H_3$	$C_2H_5O(CH_2)_2$	285	A	79	$C_{17}H_{17}Cl_2N_7O_2$	48.35	4.06	23.22	48.58	3.97	23.33
167	2-Thienyl	$(C_2H_5)_2N(CH_2)_2$	273	A	77	$C_{17}H_{22}N_8OS$	52.83	5.74	29.00	52.98	5.50	28.98
168	2-Thienyl	2-Morpholinoethyl	274	E–D	62	$C_{17}H_{20}N_8O_2S$	50.98	5.03	27.98	51.56	5.03	28.07
169	2-Thienyl	c-$C_6H_{11}NH(CH_2)_3$	240	E–D	70	$C_{20}H_{26}N_8OS$	56.32	6.14	26.27	56.05	6.04	25.95
170	2-Thienyl		305	E–D	52	$C_{17}H_{17}N_7O_2S$	53.25	4.45	25.57	53.47	4.63	25.41
171	o-$CH_3C_6H_4CH_2$	$(C_2H_5)_2N(CH_2)_2$	262	A	73	$C_{21}H_{28}N_8O$	61.74	6.91	27.43	61.65	7.00	26.93
172	o-$CH_3C_6H_4CH_2$	$C_2H_5O(CH_2)_2$	290	E–D	61	$C_{18}H_{23}N_7O_2$	59.83	6.08	25.71	60.10	6.19	25.64
173	p-$ClC_6H_4CH_2$	$(C_2H_5)_2N(CH_2)_2$	280	G	33	$C_{20}H_{25}ClN_8O$	56.00	5.88	26.13	55.85	5.80	25.81
174	p-$ClC_6H_4CH_2$	$C_2H_5O(CH_2)_2$	311	G	80	$C_{18}H_{20}ClN_7O_2$	53.80	5.02	24.40	53.88	5.12	24.28

[a] See footnote *a* of Table I. [b] See ref 4b of text. [c] Prepared from **75** and 3-diethylaminopropylamine by procedure used for the preparation of **77**. [d] Prepared in 2-ethoxyethanol. [e] I. J. Pachter and P. E. Nemeth, *J. Org. Chem.*, **28**, 1187 (1963). [f] Prepared from 4,5-diamino-5-nitroso-2-phenylpyrimidine and **22** in ethanol using 1.2 equiv of NaOEt. [g] Prepared from **104** and ethyl iodide in refluxing ethanol.

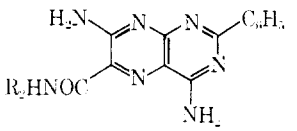
TABLE V
4,6-DIAMINO-N,N-DISUBSTITUTED 6-PTERIDINECARBOXAMIDES



Compd	R_1	R_2	Mp, °C	Recrystn solvent[a]	Yield, %	Formula	C	H	N	C	H	N
							% calcd			% found		
175	NH_2[b]	Piperidino	305	D–E	16	$C_{12}H_{16}N_8O$	49.99	5.59	38.87	49.73	6.01	38.67
176	NH_2[c]	1-Hexahydroazepinyl	305	E	71	$C_{13}H_{18}N_8O \cdot 0.33H_2O$	50.64	6.10	36.35	51.08	6.32	36.43
177	C_6H_5	$(CH_3)_2N$	320[c]	G–D	94	$C_{15}H_{15}N_7O$	58.24	4.89	31.70	58.34	5.06	30.90
178	C_6H_5	o-$C_6H_{14}NCH_3$	327	G–D	94	$C_{20}H_{23}N_7O$	63.64	6.14	25.98	63.63	5.91	26.06
179	C_6H_5	$(CH_3)_2N(CH_2)_2NCH_3$	234	A	90	$C_{18}H_{22}N_8O$	59.00	6.05	30.58	58.70	6.28	30.04
180	C_6H_5	$(C_2H_5)_2N(CH_2)_2NCH_3$	206	A	76	$C_{20}H_{26}N_8O$	60.89	6.64	28.41	60.83	6.59	28.11
181	C_6H_5	$(CH_3)_2N(CH_2)_2NC_2H_5$	218	A–D	86	$C_{19}H_{24}N_8O$	59.98	6.36	29.46	59.33	6.29	29.27
182	C_6H_5	$(C_2H_5)_2N(CH_2)_2NC_2H_5$	188	A	24	$C_{21}H_{28}N_8O$	61.74	6.91	27.43	61.97	7.02	27.63
183	C_6H_5	$(i\text{-}C_3H_7)_2N(CH_2)_2N(i\text{-}C_3H_7)$	252	A–D	33	$C_{24}H_{34}N_8O$	63.97	7.61	24.87	64.10	7.32	24.94
184	C_6H_5	1-Pyrrolidinyl	340	G–D	53	$C_{17}H_{17}N_7O$	60.88	5.11	29.24	60.94	5.52	29.03
185	C_6H_5	Piperidino	273[c]	A–D	71	$C_{18}H_{19}N_7O$	61.87	5.49	28.06	62.02	5.76	27.84
186	C_6H_5	1-Hexahydroazepinyl	266	A	84	$C_{19}H_{21}N_7O$	62.79	5.82	26.98	62.96	5.94	26.82
187	C_6H_5	Morpholino	327	G–D	91	$C_{17}H_{17}N_7O_2$	58.11	4.88	27.91	58.34	4.93	27.83
188	C_6H_5	Thiomorpholino	314	E–C	36	$C_{17}H_{17}N_7OS$	55.57	4.66	26.69	55.42	4.61	26.46
189	C_6H_5	4-Methyl-1-piperazinyl	271	A–D	83	$C_{18}H_{20}N_8O$	59.33	5.53	30.75	59.01	5.58	30.62
190	C_6H_5	4-(2-Hydroxyethyl)-1-piperazinyl	279	G–D	96	$C_{19}H_{22}N_8O_2$	57.85	5.62	28.41	58.08	5.64	28.38
191	p-ClC_6H_4	4-(2-Hydroxyethyl)-1-piperazinyl	292	G–D	89	$C_{19}H_{21}ClN_8O_2$	53.21	4.93	26.13	53.28	4.77	26.06
192	o-$CH_3C_6H_4$	$(CH_3)_2N(CH_2)_2NCH_3$	216	A	75	$C_{19}N_{24}N_8O$	59.98	6.36	29.46	60.27	6.46	29.42
193	p-$CH_3C_6H_4$	Morpholino	338	G–D	91	$C_{18}H_{19}N_7O_2$	59.16	5.29	26.84	59.06	5.36	26.78
194	Morpholino[b]	$(CH_3)_2N(CH_2)_2NCH_3$	245	E	35	$C_{16}H_{25}N_9O_2$	51.18	6.71	33.58	51.08	6.67	33.52
195	Morpholino[b]	Morpholino	334	F–C	19	$C_{15}H_{20}N_8O_3$	49.99	5.59	31.10	50.22	5.73	30.72

[a] See footnote *a* of Table I. [b] Prepared in 2-ethoxyethanol. [c] Melted with decomposition.

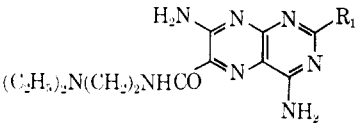
TABLE VI
EFFECT ON DIURETIC ACTIVITY OF VARYING THE SUBSTITUENTS ON THE CARBAMOYL GROUP



Compd	R_2	Dose, mg/kg, and route	T/U[a] Vol	T/U[a] Na	T/U[a] Na/K
88	H	25 *po*	1.34	1.38	5.91
90	C_2H_5	25 *po*	1.28	1.25	5.19
118	2-Morpholinoethyl	25 *po*	1.71	2.06	5.52
116	2-Piperidinoethyl	25 *po*	1.46	1.45	5.73
109	2-(1-Pyrrolidinyl)ethyl	25 *po*	1.08	1.31	3.60
103	$(CH_2)_2N(C_2H_5)_2$	25 *po*	1.59	1.66	5.91
128	$(CH_2)_2OC_2H_5$	25 *po*	1.23	1.33	4.82
127	$CH_2CH(OC_2H_5)_2$	25 *po*	1.10	1.10	5.07
130		12 *po*	0.77	0.89	3.59
132	$CH_2CO_2C_2H_5$	25 *po*	1.16	1.27	4.60
133	p-$C_2H_5OCOC_6H_4$	25 *po*	0.85	0.91	3.93
131	$CH_2CH_2SC_2H_5$	25 ip	0.72	0.88	3.61
96	4-Pyridylmethyl	25 *po*	1.46	1.40	4.86

[a] Average ratios of urine and sodium levels in test (T) animals to those of urea-dosed (U) animals. All ratios greater than unity represent statistically significant responses.

TABLE VII
EFFECT ON DIURETIC ACTIVITY OF VARYING THE SUBSTITUENTS AT THE 2 POSITION



Compd	R_1	Dose, mg/kg, and route	T/C[a] Vol	T/C[a] Na	T/C[a] Na/K
72	n-C_3H_7	25 *po*	0.77	0.87	3.61
74	CH_3S	25 ip	0.64	0.63	2.64
80	NH_2	25 *po*	0.93	0.89	3.34
103	C_6H_5	25 *po*	1.59	1.66	5.91
167	2-Thienyl	25 *po*	0.64	0.84	3.68

[a] See footnote *a*, Table VI.

Method II. 4,6-Diamino-2-morpholino-5-nitrosopyrimidine (60).[10]—4,6-Diamino-2-morpholinopyrimidine (39 g) was dissolved in a mixture of 12 g of glacial acetic acid and 250 ml of water. To this solution was added dropwise, with stirring and cooling, a solution of 14 g of $NaNO_2$ in 100 ml of water. Acetic acid (12 g) was added. The red nitrosopyrimidine crystallized out of the solution after a few minutes. After 30 min the material amounted to 53 g, mp 235–236° dec. Recrystallization from ethanol gave the analytical sample, mp 236° dec.

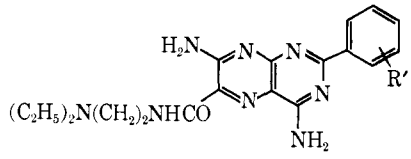
2-Cyano-N-(2-diethylaminoethyl)acetamide (29).—A solution of 65.6 g of ethyl cyanoacetate and 58 g of 2-diethylaminoethylamine in 100 ml of absolute ethanol was boiled under reflux for 3 hr. The solvent was removed on a rotary evaporator *in vacuo* and the residual oil was distilled through a Vigreux column. The fraction distilling at 132° (0.3 mm) amounted to 60 g (66%); λ_{max}^{film} 4.45 (C≡N), 5.99 (C=O), 6.46 μ (amide II).

The Maleate Salt of 2-Cyano-N-(2-aminoethyl)acetamide (22).—To 48 g of ethylenediamine was added dropwise and with stirring 22.6 g of ethyl cyanoacetate over the course of 50 min. The reaction mixture was allowed to stand for 2 days and concentrated *in vacuo* to small bulk on a rotary evaporator. To the residue was added 80 ml of ethanol and 25 g of maleic acid.

(10) R. M. Cresswell and T. Strauss, *J. Org. Chem.*, **28**, 2563 (1963), prepared **60** by the reaction of 4,6-diamino-2-methylthio-5-nitrosopyrimidine with morpholine and reported mp 237–238° dec.

TABLE VIII

EFFECT ON DIURETIC ACTIVITY OF VARYING THE SUBSTITUENT ON THE 2-PHENYL GROUP

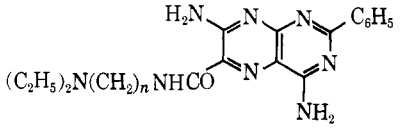


Compd	R	Dose, mg/kg, and route	T/U[a] Vol	T/U[a] Na	Na/K
103	H	25 *po*	1.59	1.66	5.91
135	*o*-CH_3	25 *po*	1.22	1.30	3.77
138	*m*-CH_3	12 *po*	1.29	1.35	5.22
141	*p*-CH_3	25 *po*	1.42	1.32	4.93
145	*m*-CF_3	25 ip	0.33	0.36	2.77
148	*p*-CH_3O	25 *po*	0.72	0.80	2.75
155	*m*-Cl	25 *po*	1.57	1.85	7.36
158	*p*-Cl	25 *po*	0.96	1.03	2.81
165	3,4-Cl_2	25 *po*	0.71	0.82	3.31

[a] See footnote *a*, Table VI.

TABLE IX

EFFECT ON DIURETIC ACTIVITY OF INCREASING THE LENGTH OF THE METHYLENE CHAIN ATTACHED TO THE CARBAMOYL NITROGEN



Compd	*n*	Dose, mg/kg, and route	T/U[a] Vol	T/U[a] Na	Na/K
103	2	25 *po*	1.59	1.66	5.91
104	3	25 *po*	1.43	1.13	5.24
105	4	25 ip	0.76	0.96	3.18
106	5	25 *po*	0.69	0.79	3.24

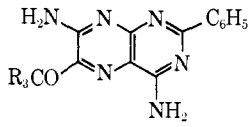
[a] See footnote *a*, Table VI.

After the heat of reaction subsided, the reaction vessel was cooled in ice to afford 49 g of a crystalline product, mp 155–160°. The infrared spectrum of this material indicated it to be the maleate salt of ethylenediamine. On further cooling of the filtrate the desired product (**22**) was obtained. Recrystallization from ethanol afforded 29 g of pure product: λ_{max}^{KBr} 4.45 (C≡N), 3.05 μ (NH stretch).

In preparing the pteridinecarboxamides given in Tables IV and V a catalytic amount of sodium (0.01 g-atom) in 500 ml of refluxing ethanol was used, followed by the addition of 0.03 mole of a suitably substituted diaminonitrosopyrimidine (Table III) and 0.032 mole of a cyanoacetamide (Tables I and II). A striking change in the color of the reaction solution from blue or green (nitroso compound) to yellow-brown (pteridine) generally occurred within a few minutes and marked the completion of the reaction. The method is illustrated by example **103**. In a number of examples where the 2 substituent of the diaminonitrosopyrimidine was an amino function the reaction was carried out in boiling 2-ethoxyethanol.

TABLE X

EFFECT ON DIURETIC ACTIVITY OF N,N-DISUBSTITUTION ON THE CARBAMOYL NITROGEN



Compd	R_3	Dose, mg/kg *po*	T/U[a] Vol	T/U[a] Na	Na/K
184	1-Pyrrolidinyl	25	1.08	1.12	4.59
185	Piperidino	25	0.92	1.06	2.91
186	1-Hexahydroazepinyl	25	0.95	1.01	4.60
187	Morpholino	25	0.97	0.98	5.06
180	$N(CH_3)(CH_2)_2N(C_2H_5)_2$	25	0.76	0.86	4.37
182	$N(C_2H_5)(CH_2)_2N(C_2H_5)_2$	25	0.72	0.87	3.52

[a] See footnote *a*, Table VI.

4,7-Diamino-N-(2-diethylaminoethyl)-2-phenyl-6-pteridinecarboxamide (103).—To a stirred solution of 0.2 g of sodium in 500 ml of absolute ethanol was added 6.5 g of 4,6-diamino-5-nitroso-2-phenylpyrimidine. The mixture was heated to boiling and 6 g of **29** was added. The mixture was allowed to reflux an additional 10 min and was then cooled and concentrated *in vacuo* on a rotary evaporator, yielding 11.4 g (100%) of product, mp 279–281°. Recrystallization from ethanol (300 ml) afforded 9.7 g of pure product: mp 280°; λ_{max}^{KBr} 3.01, 3.15 (sh) (NH stretch), 6.04 (C=O), 6.18 (aromatic + NH deformation), 6.48 μ (aromatic + amide II).

4,7-Diamino-N-(2-diethylaminoethyl)-2-(2-diethylaminoethylamino)-6-pteridinecarboxamide (77).—A solution of 2 g of 4,7-diamino-N-(2-diethylaminoethylamino)-2-methylthio-6-pteridinecarboxamide (**74**) in 10 ml of 2-diethylaminoethylamine was boiled under reflux for 24 hr. The excess amine was removed *in vacuo* on a rotary evaporator. Recrystallization of the residue from ethanol–ethyl acetate gave 0.1 g of product (**77**), mp 191°, λ_{max}^{KBr} 6.04 μ (C=O).

[3-4,7-Diamino-2-phenyl-6-pteridinecarboxamido)propyl]trimethylammonium Iodide Salt (111).—To a solution of 2 g of 4,7-diamino-N-(3-dimethylaminopropyl)-2-phenyl-6-pteridinecarboxamide (**99**) in 50 ml of ethanol was added 1.4 g of methyl iodide. The reaction mixture was heated under reflux with stirring for 15 min and cooled in ice. The precipitate which was deposited amounted to 2.8 g. Recrystallization from boiling water gave the product, mp 303°.

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