17α-Methyl-3α-thiocyano-5α-androstan-17β-ol-2-one (X).—A solution of VIIId (1.0 g) in acetone (35 ml) was treated dropwise with standard chromic acid solution.[15] The excess reagent was destroyed by a small amount of isopropyl alcohol. The inorganic salts were removed by filtering through diatomaceous earth and the filtrate was concentrated *in vacuo*, the residue was diluted with H_2O, and a crystalline product was collected. Recrystallization from methanol–H_2O afforded the 3α-thiocyanate X (0.7 g), mp 151–153°. An additional recrystallization from methanol gave an analytical sample: mp 153–154°; $[\alpha]^{25}D$ +137.5°; λ_{max} 292 mμ (ε 60); nmr, 232.5–239.5 (3β-H), 73 (C-17 methyl), 50.5 (C-18 methyl), 49 cps (C-19 methyl).

2α-Thiocyano-5α-androstane-3β,17β-diol (XI).—To an ice-cold solution of Va (4.0 g) in THF (100 ml) was added a cold solution of lithium tri-*t*-butoxyaluminum hydride (20 g) in THF (100 ml). The reaction was stirred for 1 hr at about 5° and poured into an ice-cold 5% AcOH solution. The product was extracted with ether and the extracts were washed with H_2O, 5% $NaHCO_3$, and finally H_2O again before drying over anhydrous Na_2SO_4. Solvent removal *in vacuo* left a white solid which was recrystallized from acetone–hexane to give the diol XI (3.6 g), mp 202–205°, $[\alpha]^{25}D$ +23°.

Anal. Calcd for $C_{20}H_{31}NO_2S$: C, 68.72; H, 8.94. Found: C, 68.57; H, 9.23.

Acknowledgment.—We wish to thank Dr. F. B. Colton for his interest and comments during the course of this work.

Pteridinecarboxamide Diuretics. I. Reaction of 4,6-Diamino-5-nitrosopyrimidines with Substituted Malonamides[1]

T. S. OSDENE, ARTHUR A. SANTILLI,[2] LEE E. MCCARDLE, AND MARVIN E. ROSENTHALE

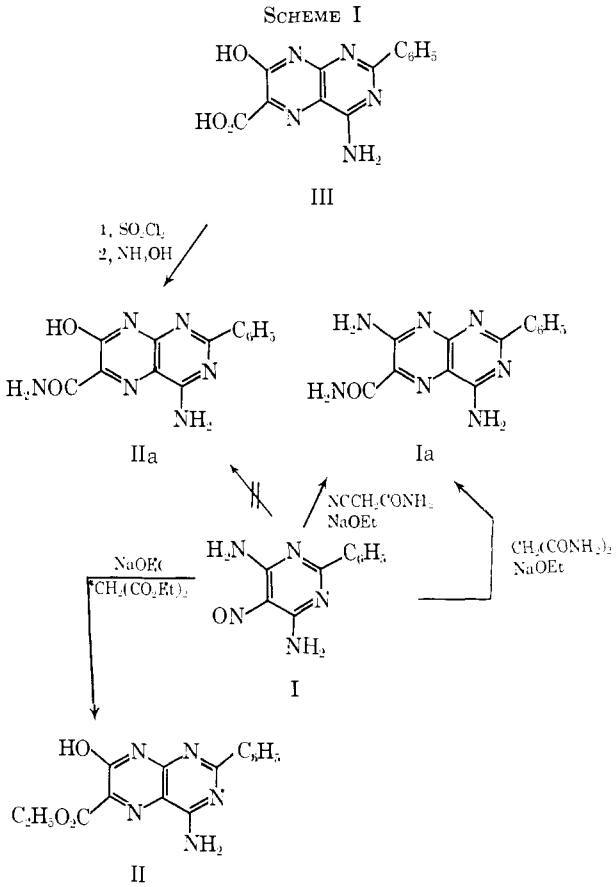
Wyeth Laboratories, Inc., Research and Development Division, Radnor, Pennsylvania

Received March 12, 1966

The reaction of 4,6-diamino-5-nitrosopyrimidines with a number of N,N′-bis-substituted malonamides in the presence of 1 equiv of sodium in ethanol afforded mixtures of 4-amino-7-substituted amino-N-substituted 6-pteridinecarboxamides and 4-amino-7-hydroxy-N-substituted 6-pteridinecarboxamides. The 7-substituted aminopteridinecarboxamides were found to be effective oral diuretics in rats, whereas the 7-hydroxypteridinecarboxamides were inactive at comparable dose levels.

The base-catalyzed reaction of 4,6-diamino-5-nitroso-2-phenylpyrimidine (I) with cyanoacetamide yields 4,7-diamino-2-phenyl-6-pteridinecarboxamide (Ia) (see Scheme I).[3] Variation of substituents on the 2 position of the pyrimidine, as well as substitution on the amide nitrogen of the cyanoacetamide, permits the preparation of many biologically active substituted 6-pteridinecarboxamides. These have been the subject of several recent patents.[4] In each of these reactions, ring closure to the pteridine results from the elimination of 1 equiv of water between the nitroso group of the pyrimidine and the active methylene group of the cyanoacetamide and the concomitant addition of the amino group of the pyrimidine to the nitrile group of the cyanoacetamide.

SCHEME I



The reaction of I with diethyl malonate in the presence of 1 equiv of sodium in ethanol affords ethyl 4-amino-7-hydroxy-2-phenyl-6-pteridinecarboxylate (II). In this reaction, ring closure occurs with elimination of water and ethanol. Other examples of pteridine formation by reactions involving 4-amino-5-nitrosopyrimidines have been described by Pachter and co-workers.[5] A recent review has appeared on biologically active pteridines derived from 4-amino-5-nitrosopyridines.[6]

In view of what has been reported concerning these types of reactions an attempt was made to prepare 4-amino-7-hydroxy-2-phenyl-6-pteridinecarboxamide (IIa) in a single step by the reaction of I with malonamide in the presence of an equivalent amount of sodium ethoxide. It was expected that water and ammonia would be eliminated in the reaction, thus

(1) A preliminary account of this work was presented before the Division of Medicinal Chemistry, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, Abstracts, p 16.

(2) To whom inquiries regarding this article should be sent.

(3) T. S. Osdene and E. C. Taylor, U. S. Patent 2,975,180 (1961).

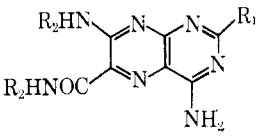
(4) J. Weinstock, U. S. Patent 2,963,478 (1960); T. S. Osdene and A. A. Santilli, U. S. Patents 3,138,595, 3,138,594, 3,138,592, and 3,122,547 (1964).

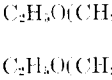
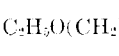
(5) I. J. Pachter and P. E. Nemeth, *J. Org. Chem.*, **28**, 1187 (1963); I. J. Pachter, P. E. Nemeth, and A. J. Villani, *ibid.*, **28**, 1197 (1963).

(6) T. S. Osdene in "Pteridine Chemistry," W. Pfleiderer and E. C. Taylor, Ed., The Macmillan Co., New York, N. Y., 1964, p 65.

TABLE I

N-SUBSTITUTED 7-SUBSTITUTED AMINO-6-PTERIDINECARBOXAMIDES



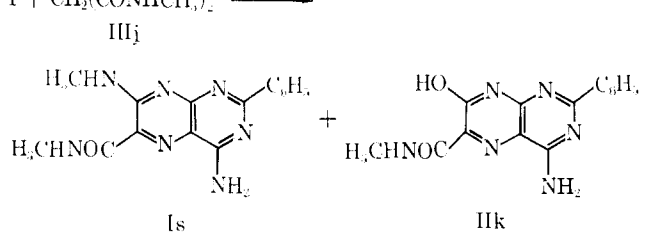
Compd I	R_1	R_2	Mp, °C	Recrystn solvent[a]	Yield, %	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
a	C_6H_5	H	>360	G	65.0	$C_{13}H_{11}N_7O$	55.49	3.94	34.86	55.58	3.82	35.21
b	H	$CH_3O(CH_2)_2$	210	A	2.7	$C_{13}H_{19}N_7O_3$	48.59	5.96	30.51	48.20	5.73	30.80
c	C_6H_5	$CH_3O(CH_2)_2$	234	A	38.0	$C_{19}H_{23}N_7O_3$	57.42	5.83	24.67	57.13	5.71	24.93
d	*m*-ClC_6H_4	$CH_3O(CH_2)_2$	195	A	33.3	$C_{19}H_{22}ClN_7O_3$	52.84	5.14	22.70	52.56	4.98	22.73
e		$CH_3O(CH_2)_2$	220	A	28.0	$C_{17}H_{21}N_7O_3S$	50.60	5.25	24.30	50.89	5.16	24.15
f	CH_3S	$CH_3O(CH_2)_2$	221	A–D	43.4	$C_{14}H_{21}N_7O_3S$	45.76	5.76	26.69	45.63	5.56	26.41
g	$(C_2H_5)_2N(CH_2)_2NH$[b]	$CH_3O(CH_2)_2$	190	A	16.6	$C_{19}H_{33}N_9O_3$	52.40	7.64	28.95	52.20	7.56	28.96
h	C_6H_5	$HO(CH_2)_2$	252	D–E	48.6	$C_{15}H_{19}N_7O_3$	55.28	5.19	26.54	55.35	5.03	26.65
i	C_6H_5	$HO(CH_2)_2O(CH_2)_2$	152–154	A–C	7.6	$C_{21}H_{27}N_7O_4$	55.13	5.95	21.43	55.38	6.12	21.70
j	C_6H_5	$C_2H_5O(CH_2)_2$	200	B	6.6	$C_{18}H_{23}N_7O_3$	55.23	7.47	25.05	55.50	7.57	25.46
k	C_6H_5	$C_2H_5O(CH_2)_2$	188	A	39.0	$C_{21}H_{27}N_7O_4$	59.28	6.40	23.05	58.90	6.57	22.84
l	C_6H_5	$C_2H_5O(CH_2)_3$	157 dec	B	29.4	$C_{23}H_{31}N_7O_4$	60.91	6.89	21.62	61.20	6.54	21.90
m	*p*-ClC_6H_4	$C_2H_5O(CH_2)_2$	218	A	14.4	$C_{21}H_{26}ClN_7O_3$	54.84	5.70	21.32	54.73	5.96	21.01
n		$C_2H_5O(CH_2)_2$	147	A	27.6	$C_{19}H_{25}N_7O_3S$	52.89	5.84	22.72	53.03	6.06	23.06
o	C_6H_5	$C_2H_5S(CH_2)_2$	195	A	14.2	$C_{21}H_{27}N_7OS_2$	55.11	5.95	21.43	55.38	5.76	21.32
p	C_6H_5	$(C_2H_5)_2N(CH_2)_2$	190	A	13.8	$C_{25}H_{37}N_9O$	62.60	7.78	26.29	62.33	7.65	25.91
q	C_6H_5		212	A	15.6	$C_{25}H_{33}N_9O_3$	59.15	6.55	24.84	58.85	6.41	24.84
r	C_6H_5		247	A	36.0	$C_{25}H_{27}N_7O_3$	63.41	5.75	20.71	63.13	5.62	20.75
s	C_6H_5	CH_3	258	A	10.7	$C_{15}H_{15}N_7O$	58.24	4.89	31.70	58.26	4.89	31.91
t	C_6H_5	C_2H_5	264	A	14.8	$C_{17}H_{19}N_7O$	60.52	5.68	29.06	60.75	5.76	28.86
u	C_6H_5	C_3H_7	293	E	30.0	$C_{19}H_{23}N_7O$	62.45	6.34	26.83	62.41	6.35	26.93
v	C_6H_5	$CH_3(CH_2)_3$	255	A	4.2	$C_{21}H_{27}N_7O$	64.10	6.92	24.92	63.90	6.77	25.05
w	C_6H_5	$CH_3(CH_2)_5$	197	A	56.0	$C_{25}H_{35}N_7O$	66.78	7.86	21.81	66.46	7.65	22.13
x	*p*-$CH_3OC_6H_4$	$CH_3O(CH_2)_2$	252	A	27.0	$C_{20}H_{25}N_7O_4$	56.20	5.89	22.94	56.37	5.78	22.83

[a] A = ethanol, B = ethyl acetate, C = petroleum ether (bp 30–60°), D = water, E = 2-ethoxyethanol, F = benzene, and G = dimethylformamide. [b] Prepared by boiling If in 2-diethylaminoethylamine for 24 hr.

affording IIa. However, none of the desired product was obtained; instead, Ia was the only product isolated from the reaction mixture. This material was identical in all respects with an authentic sample prepared from I and cyanoacetamide. A successful stepwise synthesis of IIa was achieved by the reaction of 4-amino-7-hydroxy-2-phenyl-6-pteridinecarboxylic acid (III) with thionyl chloride followed by reaction of the product with ammonium hydroxide.

The use of N,N′-bissubstituted malonamides in place of malonamide gave mixtures of 7-substituted amino- and 7-hydroxy-N-substituted 6-pteridinecarboxamides. For example, the reaction of I with N,N′-bis(methyl)-malonamide (IIIj) in the presence of 1 equiv of sodium ethoxide afforded both 4-amino-N-methyl-7-methylamino-2-phenyl-6-pteridinecarboxamide (Is) and 4-amino-7-hydroxy-N-methyl-2-phenyl-6-pteridinecarboxamide (IIk) (see Scheme II). The latter product precipitated out of the reaction solution as the sodium salt. Concentration of the filtrate by evaporation afforded (Is). The sodium salt of IIk was water soluble while Is was insoluble, thus permitting an additional means of separation. Acidification of the alkaline solution containing the sodium salt gave the hydroxypteridine IIk.

SCHEME II

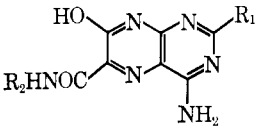


Other novel 7-substituted amino-6-pteridinecarboxamides (Table I) and 7-hydroxy-6-pteridinecarboxamides (Table II) were formed by variation of the substituent in the 2 position of the pyrimidine as well as substitution on the malonamide molecule (Table III). The former pteridines proved to be effective oral diuretics in rats, whereas the latter ones failed to elicit diuretic responses in the test animals at the doses reported here.

Biological Methods.—Male Sprague–Dawley rats, 14–17 weeks old, weighing 170–200 g were used for oral diuretic assays. Animals were deprived of food and water for about 16 hr and were then administered an oral physiological saline load of 25 ml/kg containing

TABLE II

7-HYDROXY-N-SUBSTITUTED 6-PTERIDINECARBOXAMIDES

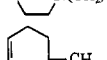


Compd II	R_1	R_2	Mp, °C	Recrystn solvent[a]	Yield, %	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
a	C_6H_5	H	340° dec.	D-G	18.1	$C_{13}H_{10}N_6O_2$	55.31	3.57	29.78	55.54	3.66	29.34
b	C_6H_5	$CH_3O(CH_2)_2$	316° dec.	E	27.1	$C_{16}H_{16}N_6O_3$	56.46	4.74	24.70	56.26	4.52	24.34
c		$CH_3O(CH_2)_2$	290	A	31.7	$C_{14}H_{14}N_6O_3S$	48.54	4.07	24.27	48.19	4.80	24.60
d	CH_3S	$CH_3O(CH_2)_2$	279	E	12.9	$C_{11}H_{14}N_6O_3S$	42.57	4.55	27.08	42.70	4.69	26.76
e	C_3H_7	$C_2H_5O(CH_2)_2$	253	A	4.0	$C_{14}H_{20}N_6O_3$	52.49	6.29	26.24	52.42	6.29	26.13
f	C_6H_5	$C_2H_5O(CH_2)_3$	248	A		$C_{18}H_{20}N_6O_3$	58.69	5.47	22.81	58.87	5.63	22.49
g	p-ClC_6H_4	$C_2H_5O(CH_2)_2$	310	A	18.9	$C_{17}H_{17}ClN_6O_3$	52.51	4.41	21.62	52.21	4.52	21.53
h		$C_2H_5O(CH_2)_2$	292	A	18.5	$C_{15}H_{16}N_6O_3S$	49.99	4.48	23.32	49.83	4.41	23.20
i	C_6H_5	$C_2H_5S(CH_2)_2$	276	A	11.7	$C_{17}H_{18}N_6O_2S$	55.12	4.90	22.69	55.56	4.89	22.71
j	C_6H_5		278–279	E	50.0	$C_{19}H_{21}N_7O_3$	57.71	5.35	24.80	57.52	5.02	24.37
k	C_6H_5	CH_3	320	E	16.8	$C_{14}H_{12}N_6O_2$	56.75	4.08	28.37	56.51	4.20	28.18
l	C_6H_5	C_2H_5	>360	E	12.0	$C_{15}H_{14}N_6O_2$	58.05	4.55	27.08	57.95	4.55	27.30
m	C_6H_5	C_3H_7	301	E	15.4	$C_{16}H_{16}N_6O_2$	59.25	4.97	25.91	59.11	5.00	25.76
n	C_6H_5	$CH_3(CH_2)_3$	296	E	33.3	$C_{17}H_{18}N_6O_2$	60.34	5.36	24.84	60.09	5.14	24.76
o	C_6H_5	$CH_3(CH_2)_5$	258–260	A	13.6	$C_{19}H_{22}N_6O_2$	62.28	6.05	22.94	62.35	5.97	22.63

[a] See footnote *a* of Table I.

TABLE III

N,N′-BISSUBSTITUTED MALONAMIDES, $CH_2(CONHR)_2$

Compd III	R	Mp, °C	Recrystn solvent[a]	Yield, %	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
a	$CH_3O(CH_2)_2$	91–92	F	38.0	$C_9H_{18}N_2O_4$	49.53	8.31	12.84	49.71	8.31	12.61
b	$HO(CH_2)_2$[b]	128–130	A								
c	$HO(CH_2)_2O(CH_2)_2$[c]			79.1							
d	$C_2H_5O(CH_2)_2$	117	B	22.4	$C_{11}H_{22}N_2O_4$	53.64	9.00	11.37	53.37	8.95	11.24
e	$C_2H_5O(CH_2)_3$	80	B	51.0	$C_{13}H_{26}N_2O_4$	56.91	9.55	10.21	56.93	9.36	10.20
f	$C_2H_5S(CH_2)_2$	120	F	31.0	$C_{11}H_{22}N_2O_2S_2$	47.45	7.97	10.06	47.83	7.93	9.90
g	$(C_2H_5)_2N(CH_2)_2$[d]			50.0							
h	 [e]	123–125	B	15.5							
i		100	B	36.6	$C_{15}H_{22}N_2O_4$	61.20	7.53	9.52	61.09	7.52	9.59
j	CH_3[f]	129–130	B	40.0							
k	C_2H_5[g]	148	F	23.0							
l	C_3H_7[h]	139	F	37.6							
m	$CH_3(CH_2)_3$[i]	131	F	71.9							
n	$CH_3(CH_2)_5$	129	B	81.4	$C_{15}H_{30}N_2O_2$	66.62	11.18	10.36	66.46	11.16	10.23

[a] See footnote *a* of Table I. [b] W. H. Rauscher and W. H. Clark, *J. Am. Chem. Soc.*, **70**, 438 (1948), reported mp 127–127.5°. [c] Attempts to recrystallize this material were unsuccessful. [d] Burroughs Wellcome and Co. (U. S. A.) Inc., British Patent 701,209 (1953), reported bp 160° (2 mm). [e] R. W. Bost and L. V. Mullen, Jr., *J. Am. Chem. Soc.*, **73**, 1967 (1951), reported mp 120.5°. [f] M. Freund, *Ber.*, **17**, 133 (1884), reported mp 128°. [g] J. V. Backes, R. W. West, and M. A. Whiteley, *J. Chem. Soc.*, 359 (1921), reported mp 149°. [h] Lit.[g] mp 139°. [i] Lit.[g] mp 132.5°.

the compound being tested. This dose of test compound was given to 8 rats (T). An osmotic diuretic urea solution was given concurrently to a separate group of 8 rats (U) at a dose of 960 mg/kg. The animals were placed in metabolism cages, 2 rats/cage, and urine was collected for 5 hr. Volume was measured and sodium and potassium were determined.[7] The results in Tables IV–VII are expressed as the average ratios of urine volume and sodium levels in test animals (T) to those in urea-dosed animals (U).[8] All ratios greater than unity for volume and sodium output represent statistically significant diuretic responses.

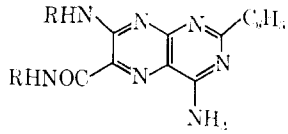
Structure–Activity Relationships.—Table IV gives the diuretic activity of a number of 4,7-diamino-6-pteridinecarboxamides having various substituents on the N atoms of the 6-carbamoyl and the 7-amino

(7) Baird Atomic Model KY-1 flame photometer adapted for automatic flow-type analysis.

(8) W. L. Lipschitz, Z. Hadidian, and A. Kerpcsar, *J. Pharmacol. Exptl. Therap.*, **79**, 97 (1943).

TABLE IV

EFFECT ON DIURETIC ACTIVITY OF VARYING THE SUBSTITUTENTS AT THE 6 AND 7 POSITIONS

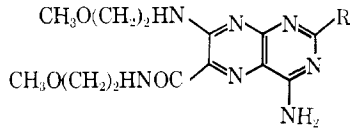


Compd	R	Dose, mg/kg	T, U[a] Vol	T, U[a] Na	Na/K
Ia	H	12 oral	1.31	1.36	4.71
It	C_2H_5	12 oral	1.28	1.42	5.92
Ic	$CH_3O(CH_2)_2$	12 oral	1.82	2.14	5.12
Ik	$C_2H_5O(CH_2)_2$	12 oral	1.50	1.56	5.46
Il	$C_2H_5O(CH_2)_3$	12 oral	0.98	1.12	4.35
Iq		12 oral	1.03	0.99	4.19
Ip	$(C_2H_5)_2N(CH_2)_2$	25 oral	0.58	0.74	3.73
Io	$C_2H_5S(CH_2)_2$	25 ip	1.03	1.11	3.30

[a] Ratios of volume and sodium levels in test (T) animals to those in urea-dosed (U) animals.

TABLE V

EFFECT ON DIURETIC ACTIVITY OF VARYING THE SUBSTITUTENTS AT THE 2 POSITION



Compd	R	Dose, mg/kg	T, U[a] Vol	T, U[a] Na	Na/K
Ic	C_6H_5	12 oral	1.82	2.14	5.12
Id	*m*-ClC_6H_4	12 oral	1.72	1.89	4.10
Ie		12 oral	1.73	1.74	5.52
Ix	*p*-$CH_3OC_6H_4$	25 ip	1.35	1.37	4.49
Ib	H	25 oral	1.07	0.99	3.59
If	CH_3S	25 oral	1.0	0.95	4.84
Ig	$(C_2H_5)_2N(CH_2)_2NH$	25 oral	0.59	0.63	4.10

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

groups. The greatest degree of activity was found in compound Ic,[9] where the substituent in these two positions was 2-methoxyethyl. Replacement with a 2-aminoalkyl moiety as in Ip and Iq substantially decreased the diuretic response. Increasing the length of the methylene chain also decreased it: *i.e.*, Ic > Ik > Il.

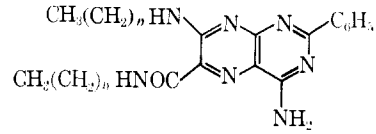
Table V shows the result of retaining the active 2-methoxyethyl group in the 6 and 7 positions of the pteridine nucleus and varying the group substituted in the 2 position. Although this series exhibited a wide range of diuretic response, the most active members were those compounds having an aromatic moiety in the 2 position (Ic, Id, Ie, and Ix); all other members were only mildly diuretic. Compound Ig was found to be highly toxic.

Table VI illustrates the characteristic pattern of diuretic response within a homologous series. The pteridines bearing a methyl and ethyl group at the 6 and 7 positions of the nucleus (Is and It) were the most active members. Diuretic activity diminished with the higher homologs.

(9) M. E. Rosenthale and T. S. Osdene, *The Pharmacologist*, **7**, 164 (1965), recently presented a more detailed account of the diuretic activity of this compound.

TABLE VI

EFFECT ON DIURETIC ACTIVITY OF EXTENDING THE METHYLENE CHAIN LENGTH WITHIN A HOMOLOGOUS SERIES

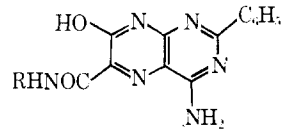


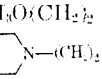
Compd	*n*	Dose, mg/kg	T, U[a] Vol	T, U[a] Na	Na/K
Is	0	12 oral	1.47	1.40	4.07
It	1	12 oral	1.28	1.42	5.92
Im	2	12 oral	1.23	1.11	3.30
Iv	3	12 oral	1.39	1.14	4.07
Iw	5	12 oral	0.84	0.82	3.15

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

TABLE VII

EFFECT ON DIURETIC ACTIVITY OF VARYING THE SUBSTITUENT ON THE CARBAMOYL NITROGEN IN THE 7-HYDROXY SERIES



Compd	R	Dose, mg/kg	T, U[a] Vol	T, U[a] Na	Na/K
IIk	CH_3	12 oral	0.87	0.89	4.56
IIl	C_2H_5	25 oral	0.96	0.90	3.88
IIb	$CH_3O(CH_2)_2$	25 ip	1.06	0.90	3.71
IIj		25 ip	0.91	0.91	3.31
IIi	$C_2H_5S(CH_2)_2$	25 ip	0.74	0.82	2.59

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

Table VII shows the result of varying the type of group attached to the carbamoyl nitrogen in the 7-hydroxy series. None of these compounds elicited a diuretic response in test animals at dose levels more than double those of the active pteridines listed in Tables IV–VI.

In summary, the presence of a 2-aryl group in the 7-substituted amino-6-pteridinecarboxamides appears to be a requisite for good oral diuretic response. Compound Ic, in which the 2-aryl group is unsubstituted phenyl and the side chain at the 6 and 7 positions of the pteridinecarboxamide is 2-methoxyethyl, was the most active compound tested. Increasing the length of the alkyl portion of the side chain reduced the diuretic response. The 7-hydroxy-6-pteridinecarboxamides were inactive as diuretics at comparable dose levels.

Experimental Section[10]

4,6-Diamino-2-methylthio-5-nitrosopyrimidine and 4,6-diamino-2-*p*-methoxyphenyl-5-nitrosopyrimidine were prepared as described by Taylor, *et al.*[11] 2-Phenyl-, 2-*p*-chlorophenyl-, and 2-thienyl-4,6-diamino-5-nitrosopyrimidines were obtained commercially.[12] The direct nitrosation of 4,6-diaminopyrimidine hydrochloride afforded 4,6-diamino-5-nitrosopyrimidine.[13]

***m*-Chlorobenzamidine Hydrochloride.**—Anhydrous ethanol (32.3 g) was added to *m*-chlorobenzonitrile (96.3 g) in anhydrous

(10) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are corrected. Yields reported in Tables I–III are the results of single experiments and should not be construed as maximal.

(11) E. C. Taylor, O. Vogl, and C. C. Cheng, *J. Am. Chem. Soc.*, **81**, 2442 (1959).

(12) Supplied by Arapahoe Chemicals, Inc., Boulder, Colo.

(13) R. M. Evans, P. G. Jones, P. J. Palmer, and F. F. Stephens, *J. Chem. Soc.*, 4106 (1956).

ether (100 ml), producing a clear solution. The solution was protected from atmospheric moisture while HCl gas (25.9 g) was passed into it. The reaction mixture was allowed to stand at ambient temperature for 16 hr. The resulting precipitate, after being dried for 4 hr over KOH, amounted to 76 g. The solid was treated with 200 g of 10% ethanolic ammonia solution. The reaction mixture was stirred at room temperarure for 5 days and filtered, and the solvent was removed *in vacuo*. The oily residue, crude *m*-chlorobenzamidine hydrochloride, was used directly in the next step.

***m*-Chlorobenzamidine Salt of Isonitrosomalononitrile.**—To a stirred solution of 64 g of *m*-chlorobenzamidine hydrochloride in 1 l. of absolute ethanol was added a slurry of 68 g of the silver salt of isonitrosomalononitrile in 50 ml of absolute methanol. The reaction mixture was stirred for 1 hr and filtered, and the solvent was removed by rotary evaporation *in vacuo*. The residue was dried for 16 hr over P_2O_5, affording the product (77 g), mp 227°.

Anal. Calcd for $C_{10}H_7ClN_5O$: C, 48.30; H, 2.84; Cl, 14.26; N, 28.17. Found: C, 48.08; H, 2.97; Cl, 14.1; N, 28.25.

Butyramidine Salt of Isonitrosomalononitrile.—In identical fashion, 61.2 g of butyramidine hydrochloride[14] and 122 g of the silver salt of isonitrosomalononitrile in 300 ml of methanol afforded 92 g of product, mp 85–86°. An analytical sample (mp 86.5–87.5°) was obtained by recrystallization from ethyl acetate–petroleum ether (bp 30–60°).

Anal. Calcd for $C_7H_{10}N_5O$: C, 46.65; H, 5.59; N, 38.87. Found: C, 46.47; H, 6.07; N, 38.54.

4,6-Diamino-2-*m*-chlorophenyl-5-nitrosopyrimidine.—A mixture of 74 g of the *m*-chlorobenzamidine salt of isonitrosomalononitrile in 50 ml of 5-ethyl-2-methylpyridine was heated under reflux for 4–5 min. The reaction mixture was quickly cooled in ice and filtered under suction. Ethanol was added, followed by petroleum ether, resulting in the deposition of 50 g of a green solid, mp 240°. The solid was recrystallized from aqueous 2-ethoxyethanol and dried (KOH) for 6 hr, yielding 34 g of product. An analytical sample (mp 241°) was obtained by recrystallization from 2-ethoxyethanol–petroleum ether.

Anal. Calcd for $C_{10}H_8ClN_5O$: C, 48.11; H, 3.23; Cl, 14.20; N, 28.05. Found: C, 48.35; H, 3.25; Cl, 14.3; N, 28.34.

4-6-Diamino-5-nitroso-2-propylpyrimidine.—In similar fashion, heating 54 g of the butyramidine salt of isonitrosomalononitrile in 275 ml of boiling 5-ethyl-2-methylpyridine for 15 min afforded 26 g of product, mp 224–225° dec. An analytical sample (mp 227–228° dec) was obtained from ethanol.

Anal. Calcd for $C_7H_{11}N_5O$: C, 46.45; H, 6.11; N, 38.69. Found: C, 46.74; H, 6.08; N, 38.86.

The substituted malonamides (Table III) were prepared in general by heating under reflux at least 2 equiv of the amine with 1 equiv of diethyl malonate in ethanol. Where the amines were gases such as methyl and ethylamine, a large excess of the amine was used.

N,N′-Bis(2-methoxyethyl)malonamide (IIIa).—A mixture of 75 g of 2-methoxyethylamine and 80 g of diethyl malonate was boiled under reflux for 5 hr and the reaction solution concentrated on a rotary evaporator, yielding a residual oil which solidified on cooling. Recrystallization of the product from benzene gave IIIa, mp 91–92°.

The pteridines shown in Tables I and II were prepared by the reaction of a 4,6-diamino-5-nitroso-2-substituted pyrimidine with a suitably substituted malonamide. The following examples will serve to describe the general method employed for the preparation of these compounds.

4-Amino-N-methyl-7-methylamino-2-phenyl-6-pteridinecarboxamide (Is).—To a solution containing 0.7 g of sodium in 500 ml of absolute ethanol was added 6.45 g of 4,6-diamino-5-nitroso-2-phenylpyrimidine (I), followed by 4.3 g of N,N′-bis(methyl)malonamide (IIIj). The reaction mixture was heated under reflux for 5 min and then cooled in ice, yielding a precipitate (3.3 g), mp >360°. This material was set aside for separate treatment as described below for the preparation of IIk. The mother liquor was concentrated *in vacuo*. Ethanol (5 ml) was added to the residue, giving Is as a yellow crystalline product (1.0 g), mp 253°. The analytical sample (mp 258°) was obtained by recrystallization from ethanol.

4-Amino-7-hydroxy-N-methyl-2-phenyl-6-pteridinecarboxamide (IIk).—The 3.3 g of material, mp >360°, obtained as described above was dissolved in 400 ml of water. The water solution was treated with charcoal and filtered, and the filtrate was acidified with 10 ml of glacial acetic acid. A yellow precipitate (mp 315°) was deposited and recrystallized from 2-ethoxyethanol, affording IIk (1.5 g), mp 320°.

4,7-Diamino-2-phenyl-6-pteridinecarboxamide (Ia).—To a solution of 0.2 g of sodium in 250 ml of absolute ethanol was added 4.3 g of I followed by 2.0 g of malonamide. The reaction mixture was stirred and heated under reflux for 0.5 hr, yielding Ia as a precipitate (3.0 g), mp >360°. Recrystallization from aqueous dimethylformamide afforded a product with an infrared spectrum identical with Ia prepared from I and cyanoacetamide as previously described.[3]

4-Amino-7-hydroxy-2-phenyl-6-pteridinecarboxylic Acid (III).—To a solution of 0.8 g of sodium in 500 ml of absolute ethanol was added 6.45 g of I followed by 5.6 g of diethyl malonate. The mixture was stirred and heated under reflux for 20 min, during which time a precipitate was deposited. The reaction mixture was cooled in ice and the product was removed by filtration, dissolved in boiling water, and acidified with acetic acid. The resulting precipitate was recrystallized from aqueous dimethylformamide, affording III as a monohydrate, mp 276° dec.

Anal. Calcd for $C_{13}H_9N_5O_3 \cdot H_2O$: C, 54.73; H, 3.89; N, 24.55. Found: C, 54.37; H, 4.03; N, 23.94.

Ethyl 4-amino-7-hydroxy-2-phenyl-6-pteridinecarboxylate (II) was prepared in identical fashion but 1 equiv of sodium was used. From 4.3 g of I and 3.5 g of diethyl malonate in 100 ml of absolute ethanol containing 0.5 g of sodium was obtained 5 g of II. The analytical sample (mp 255°) was obtained by recrystallization from aqueous dimethylformamide.

Anal. Calcd for $C_{15}H_{13}N_5O_3$: C, 57.87; H, 4.21; N, 22.50. Found: C, 58.02; H, 3.85; N, 22.76.

4-Amino-7-hydroxy-2-phenyl-6-pteridinecarboxamide (IIa).—A mixture of 1 g of dried III and 35 ml of $SOCl_2$ was boiled under reflux for 2 hr. The $SOCl_2$ was removed *in vacuo* on a rotary evaporator and the residue was treated with 20 ml of 3 *N* NH_4OH. The mixture was heated on a steam bath and filtered, and the filtrate was acidified with 3 *N* acetic acid. The precipitate thus obtained was recrystallized from aqueous dimethylformamide, affording IIa (0.18 g), mp 340° dec.

Anal. Calcd for $C_{13}H_{10}N_6O_2$: C, 55.31; H, 3.57; N, 29.78. Found: C, 55.54; H, 3.66; N, 29.34.

Acknowledgment.—The authors wish to thank Dr. Gordon Ellis and staff for the microanalytical determinations.

(14) Supplied by Winthrop Laboratories, New York, N. Y.