Pteridines. V.[1] Some Analogs of 4,7-Diamino-2-phenyl-6-pteridinecarboxamide[2]

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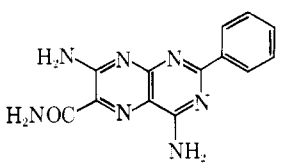
A series of 4,7-diamino-6-pteridinecarboxamides were prepared either by reaction of the appropriate 2-substituted 4,6-diamino-5-nitrosopyrimidine with the required N-substituted cyanoacetamide or by aminolysis of ethyl 4,7-diamino-2-phenyl-6-pteridinecarboxylate. The ester was prepared from ethyl cyanoacetate and 4,6-diamino-5-nitroso-2-phenylpyrimidine and was also unexpectedly obtained when the same pyrimidine was treated with diphenyl sulfoacetate, cyanoacetylurea, or cyanoacetylurethan in the presence of sodium cyanide. A series of 4-amino-7-hydroxy-2-phenyl-6-pteridinecarboxamide analogs was prepared from the corresponding ester.

Introduction to Papers V–XII of This Series.—This paper is the first of seven in which some of the medicinal chemistry related to the diuretic agent triamterene is reported. A chronology of this project was presented at the Third International Symposium on Pteridines.[2] In the previous papers new syntheses of 6-alkyl-7-aminopteridines were presented as well as the preparations of triamterene 5-oxide and the 7-phenyl isomer of triamterene. The first papers in the current group complete the discussion of chemistry and the last article presents the diuretic structure–activity relationships of the compounds reported.

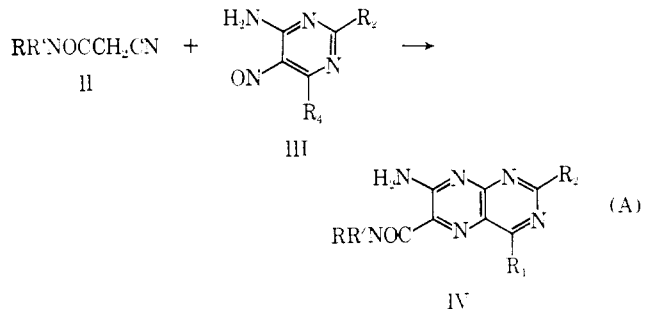
The discovery of the interesting diuretic activity of 4,7-diamino-2-phenyl-6-pteridinecarboxamide (I) in our laboratory[3] during the course of investigating the diuretic activity in a wide variety of pteridines prompted us to prepare a number of related compounds in order to explore the structure–activity relationships in this area. This paper reports a portion of this work.



I

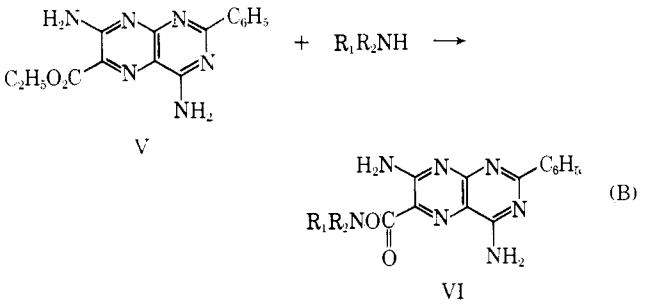
The most direct preparation of 4,7-diamino-6-pteridinecarboxamides proceeds *via* the base-catalyzed condensation of cyanoacetamides with 4-amino-5-nitrosopyrimidines.[4] This method was successfully applied to the preparation of the compounds shown in Tables I–III. Polar solvents such as dimethylformamide (DMF), capable of dissolving the sometimes poorly soluble nitrosopyrimidines, gave relatively rapid and clean reactions.

The necessary 4,6-diamino-5-nitrosopyrimidines were, in general, prepared by the thermal isomerization of the isonitrosomalononitrile salt of the appropriate amidine or guanidine.[5] The amidines were prepared by ammonolysis of the appropriate imino ether hydrochloride[6] except in the case of the *o*-chloro and *o*-methylbenzamidines. In these cases, probably because of steric hindrance, the nitrile was recovered during attempted imino ether formation. However, these nitriles reacted with hydroxylamine under basic conditions to give benzamidoximes, which were hydrogenated[7] under low pressure in the presence of Raney nickel to give the *ortho*-substituted benzamidines. The required 4-substituted 2,6-diamino-5-nitrosopyrimidines were made from 2,6-diamino-4-methylmercapto-5-nitrosopyrimidine by displacement with the appropriate amine.[2]



(A)

An alternate route for the preparation of 4,7-diamino-2-phenyl-6-pteridinecarboxamides (VI) in which the amide nitrogen is substituted consists of treating ethyl 4,7-diamino-2-phenyl-6-pteridinecarboxylate (V) with an appropriate amine. In order to verify the course of this reaction, VI ($R_1 = R_2 = CH_3$) was prepared by reaction A from 4,6-diamino-5-nitroso-2-phenylpyrimidine and N,N-dimethylcyanoacetamide and also by reaction B using V and dimethylamine in refluxing ethoxyethanol. The ester amination as carried out in



(B)

(1) Previous papers in this series: (a) I. J. Pachter and P. E. Nemeth, *J. Org. Chem.*, **28**, 1187 (1963); (b) I. J. Pachter, *ibid.*, **28**, 1191 (1963); (c) I. J. Pachter, P. E. Nemeth, and A. J. Villani, *ibid.*, **28**, 1197 (1963); (d) I. J. Pachter and P. E. Nemeth, *ibid.*, **28**, 1203 (1963).

(2) A portion of this work was presented at the Third International Symposium on Pteridines, Stuttgart, Germany, 1962, and reported in preliminary form by J. Weinstock and V. D. Wiebelhaus in "Pteridine Chemistry," W. Pfleiderer and E. C. Taylor, Ed., Pergamon Press, Oxford, 1964, p 37.

(3) J. Weinstock, U. S. Patent 2,963,478 (1960); T. S. Osdene and E. C. Taylor, U. S. Patent 2,975,180 (1961).

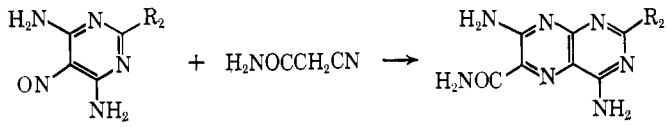
(4) T. S. Osdene and G. M. Timmis, *J. Chem. Soc.*, 2036 (1955).

(5) O. Vogl and E. C. Taylor, *J. Am. Chem. Soc.*, **79**, 1518 (1957).

(6) See A. W. Dox, "Organic Syntheses," Coll. Vol. I, 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1941, p 5, for some examples of this procedure.

(7) H. C. Carrington, *J. Chem. Soc.*, 2527 (1955).

TABLE I



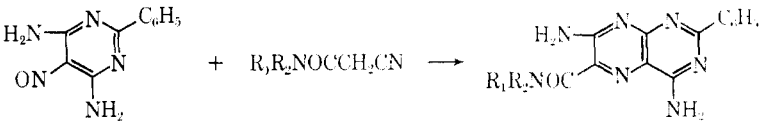
R_2	Mp, °C	Yield, %	Recrystn solvent[a]	Formula[d]	Ultraviolet spectra: Solvent[a]	λ_{max}, mμ	Log ε	Chromatography: System[a]	R_f
4-$CH_3C_6H_4$	>300	91	A	$C_{14}H_{13}N_7O$	b	240	4.358	1	0.73
						273	4.470		
						386	4.328		
3-$CH_3C_6H_4$	>310	83	A	$C_{14}H_{13}N_7O$	b	241	4.336	1	0.76
						272	4.493		
						385	4.297		
2-$CH_3C_6H_4$	>300	89	A	$C_{14}H_{13}N_7O$	b	239	4.318	1	0.85
						272	4.461		
						380	4.220		
4-ClC_6H_4	>300	75	A	$C_{13}H_{10}ClN_7O \cdot 0.5H_2O$	b	236	4.629	1	0.78
						272	4.741		
						378	4.571		
3-ClC_6H_4	>300	80	A	$C_{13}H_{10}ClN_7O$	b	239	4.420	1	0.80
						272	4.585		
						383	4.461		
2-ClC_6H_4	>300	60	A	$C_{13}H_{10}ClN_7O$	b	239	4.590	1	0.86
						272	4.731		
						380	4.458		
4-$CH_3OC_6H_4$	>300	86	A	$C_{14}H_{13}N_7O_2$[c]	b	241	4.338	1	0.61
						271	4.362		
						325	4.111		
						387	4.417		
4-Cl-3-$NH_2SO_2C_6H_3$[b]	>300	93	A	$C_{13}H_{11}ClN_8SO_3$	Insoluble			2	0.69
H	>300	23	F	$C_7H_7N_7O$	a	270	4.398	1	0.54
						374	4.068		
					c	246	4.305		
						370	3.964		
CH_3	>300	77	A	$C_8H_9N_7O \cdot 0.25H_2O$	b	233	4.134	1	0.34
						272	4.407		
						373	4.117		
$CH_2C_6H_5$	334-335	20	G	$C_{14}H_{13}N_7O \cdot 0.5H_2O$				5	0.76
NH_2	>300	72	D	$C_7H_8N_8O \cdot 0.5H_2O$	b	221	4.533		
						269	4.314		
						371	4.267		
C_6H_5NH	>300	66	A	$C_{13}H_{12}N_8O$	b	221	3.813	1	0.69
						270	3.566		
						378	3.657		
$N(CH_3)_2$	>300	87	A	$C_9H_{12}N_8$	e	242	4.686	1	0.48
						283	4.360		
						400	4.425		

[a] Recrystallization solvents: A, DMF–H_2O; B, EtOH–H_2O; C, MeOH–H_2O; D, DMF; E, EtOH; F, AcOH; G, 50% aqueous AcOH; H, precipitate from aqueous AcOH with NH_4OH; I, dissolve in EtOH, filter, evaporate to dryness, and triturate residue with Et_2O. The uv spectra were determined in the following solvents: a, 4.5% HCOOH; b, 0.1 *N* HCl; c, 1 *N* NaOH; d, 0.1 *N* NaOH; e, EtOH. For the paper chromatography systems, see the Experimental Section. [b] Prepared by Mr. Arnold Krog. The details of the preparation of the required nitrosopyrimidine will be published. [c] N: calcd, 31.50; found, 30.84. [d] All compounds were analyzed for C, H, N.

DMF at room temperature using an excess of the amine is quite clean, leading to products that are readily purified. The reaction is selective in that only primary aliphatic amines unsubstituted on the α-carbon react under these conditions. Thus, 2-amino-1-phenylpropane, N-methylpiperazine, and aniline did not react under these conditions. Further evidence of this interesting selectivity was obtained when 1,2-diaminopropane, 1,2-diamino-2-methylpropane, and 1-aminoethylpiperazine gave only single products. The structure of the compounds obtained from these amines was assigned on the assumption that the reactions involved the primary carbinamine.

The required V is best prepared by the reaction of 4,6-diamino-5-nitroso-2-phenylpyrimidine (VII) with ethyl cyanoacetate in absolute ethanol using sodium cyanide as the catalyst. This procedure gave a 75% yield of ester uncontaminated by acid. Condensation of the same reactants in absolute alcohol using sodium ethoxide as the catalyst gave the ester in 40% yield along with a 30% yield of the sodium salt of 4,7-diamino-2-phenyl-6-pteridinecarboxylic acid (VIII) (Scheme I). The corresponding methyl and isopropyl esters were also obtained in approximately 45% yield by the reaction of the appropriate alkyl cyanoacetate in the corresponding alcohol using sodium methoxide as catalyst. In each case, a substantial amount of VIII was also obtained. An attempt to prepare the isopropyl ester using sodium cyanide as the catalyst in 2-propanol was unsuccessful.

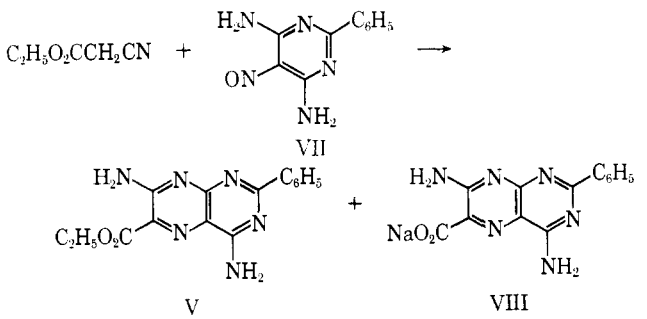
TABLE II[a]



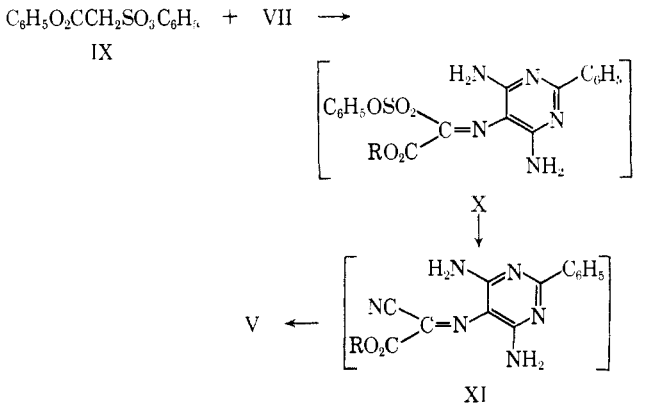
NR_1R_2	Mp, °C	Yield, %	Recrystn solvent	Formula[b]	Ultraviolet spectra: Solvent	λ_{max}, mμ	Log ε	Chromatography: System	R_f
$NHCH_3$	>300	92	A	$C_{14}H_{13}N_7O$	b	213	4.517	1	0.79
						243	4.332		
						275	4.521		
						390	4.408		
$N(CH_3)_2$	>300	67	A	$C_{15}H_{15}N_7O$	b	238	4.389	1	0.78
						266	4.461		
						364	4.322		
NHC_2H_5	336–338	85	A	$C_{15}H_{15}N_7O$	b	389	4.267		
						271	4.524		
						237	4.324		
$NHCH(CH_3)_2$	347.5–349	87	A	$C_{16}H_{17}N_7O$	b	271	4.539		
						384	4.283		
$NHCH_2CH_2OH$	308–309	94	A	$C_{15}H_{15}N_7O_2 \cdot 0.5H_2O$	b	240	4.338	1	0.76
						272	4.521		
						386	4.375		
$NH(CH_2)_3N(CH_3)_2$	275–282	70	B	$C_{18}H_{22}N_8O$	b	238	4.332	5	0.62
						272	4.520		
						385	4.279		
					d	385	4.121		
						271	4.377		
						238	4.182		
$NHCH_2C_6H_5$	314–318	88	D	$C_{20}H_{17}N_7O$	b	238	4.276	1	0.81
						273	4.459		
						388	4.210		
NHC_6H_5	>300	67	A	$C_{19}H_{15}N_7O$	a	274	4.568	3	0.84
						394	4.286		
NH_2	...	...	...	...	b	237	4.342	3	0.60
						271	4.526		
						382	4.271		
					c	236	4.305		
						258	4.386		
						352	4.221		

[a] See footnote *a*, Table I. [b] See footnote *d*, Table I.

SCHEME I



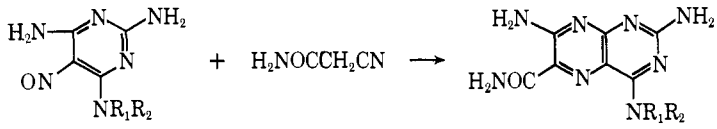
SCHEME II



The ester V was also unexpectedly obtained from the condensation of diphenyl sulfoacetate (IX) and VII in ethanol using sodium cyanide catalysis (Scheme II). A possible mechanism for this reaction might involve the condensation of IX and VII to give X, which is converted to XI by the addition of cyanide ion followed by the elimination of phenyl sulfite anion. Normal base-catalyzed cyclization of XI and transesterification of the ester at some stage would lead to V.

Another unanticipated synthesis of V occurred when VII was condensed with ethylcyanoacetylurethan in alcohol in the presence of sodium cyanide. Similarly, V was isolated from the condensation of VII with cyanoacetylurea under the same conditions (Scheme III). However, in DMF using sodium methoxide as the catalyst, reaction of VII with the urethan gave 2-phenyl-4-amino-6,8-dioxo-6,7,8,9-tetrahydropyrimido-[5,4-*g*]pteridine (XII) while the reaction of VII with cyanoacetylurea under these conditions gave the simple carboxamide I in high yield.

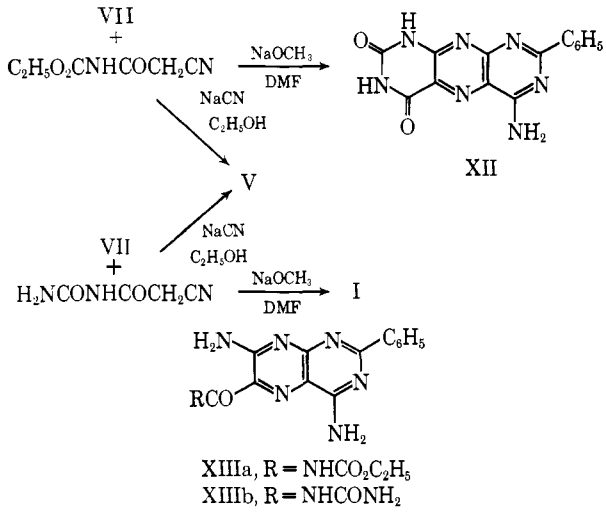
TABLE III[a,b]



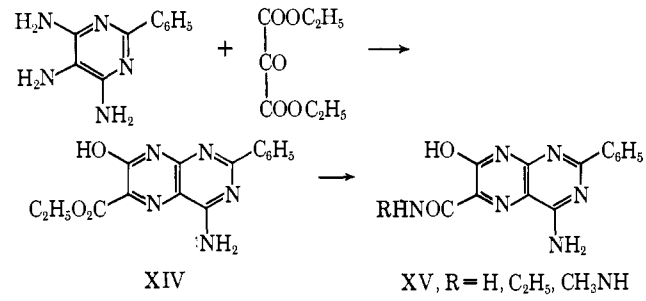
NR_1R_2	Mp, °C	Yield, %	Recrystn solvent	Formula[d]	Ultraviolet spectra: Solvent	λ_{max}, mμ	Log ε	Chromatography: System	R_f
$NHCH_3$	>300	47	H	$C_8H_{10}N_8O$	d	278	4.410	3	0.28
						393	4.167		
					a	281	4.230		
						403	4.380		
$N(CH_3)_2$	>300	62[c]	H	$C_9H_{12}N_8O$	d	234	4.548	3	0.45
						284	4.330		
						384	4.299		
					a	280	4.376		
						370	4.289		
NHC_6H_5	>300	52	E	$C_{13}H_{12}N_8O \cdot 0.5H_2O$	d	289	4.322	3	0.60
						400	4.301		
					a	289	4.395		
						385	4.369		

[a] See footnote *a*, Table I. [b] We wish to thank Mr. Barry M. Trost for assistance in preparing these compounds. [c] Reaction was run in DMSO using potassium *t*-butoxide as catalyst for 24 hr at 95°. [d] See footnote *d*, Table I.

SCHEME III



SCHEME IV



These results can be rationalized by assuming that in each case the expected product (XIIIa or XIIIb) was formed, and that in ethanol in the presence of cyanide the substituted amides undergo attack by solvent anion to give V and either urethan or urea anion. In the presence of a strong base in a nonprotonic solvent, XIIIa undergoes cyclization to give XII, and XIIIb cleaves at the urea carbonyl to give I.

The free acid of VIII was prepared in almost quantitative yield by reaction of VII with 2 moles of cyanoacetic acid in the presence of 4 moles of sodium ethoxide. This acid was decarboxylated by heating at reflux in quinoline. Similar syntheses of 6-unsubstituted pteridines have been reported previously.[4,8]

In order to obtain some representative pteridines in which the 7-amino group of I was exchanged for hydroxyl, ethyl 4-amino-7-hydroxy-2-phenyl-6-pteridinecarboxylate (XIV) was required. It was prepared by reaction of diethyl oxomalonate with 2-phenyl-4,5,6-triaminopyrimidine in refluxing alcohol (Scheme IV). Treatment of XIV with ammonia and ethylamine gave the corresponding amide and N-ethylamide. Reaction with methylhydrazine gave the corresponding β-methylhydrazide. The structure of this hydrazide was inferred from its failure to react with benzaldehyde.[9]

Pharmacology.—The structure–activity relations of a number of these compounds as diuretics is reported in an accompanying paper.[10]

Experimental Section[11]

The paper chromatography was done by the circular system using a cotton wick to bring solvent to the paper. The following systems were used: (1) BuOH–AcOH–H_2O (4:1:5); (2) DMF–HCOOH–H_2O (10:3:7); (3) BuOH–HCOOH–H_2O (5:1:5); (4) dip paper in 20% solution of castor oil–mineral oil (1:1) in acetone, allow acetone to evaporate, develop with EtOH–H_2O (2:1); (5) same as 4 using 20% mineral oil in acetone to pretreat paper; (6) BuOH–5.6 *N* NH_4OH (4:5). Melting points are uncorrected and were determined in open capillary tubes.

Many of the pyrimidines used as intermediates were prepared by known methods. Since these are summarized in a readily accessible manner,[12] individual references are not given.

(8) T. S. Osdene and G. M. Timmis, *J. Chem. Soc.*, 2038 (1955).

(9) A mixture of the α- and β-methyl isomers was obtained from the reaction of V with methylhydrazine. In that case, one isomer reacted readily with benzaldehyde, whereas the other did not react (E. C. Taylor and J. Weinstock, unpublished results).

(10) J. Weinstock, J. W. Wilson, V. D. Wiebelhaus, A. R. Maass, F. T. Brennan, and G. Sosnowski, *J. Med. Chem.*, **11**, 573 (1968), paper XII of this series.

(11) Where analyses are indicated only by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

(12) D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962.

2-Substituted 4,6-Diamino-5-nitrosopyrimidines.—A number of previously unknown pyrimidines were prepared by the thermal isomerization of the required amidine (or guanidine) salts of isonitrosomalononitrile in refluxing 5-ethyl-2-methylpyridine or α-picoline. These compounds were obtained sufficiently pure so that they could be used without further purification for the pteridine syntheses. The new compounds prepared (with their yields) in this manner as green crystals using 2-ethyl-5-methylpyridine as reaction solvent are 4,6-diamino-5-nitroso-2-(*p*-tolyl)pyrimidine (76%), mp 279–280° dec; 4,6-diamino-5-nitroso-2-(*m*-tolyl)pyrimidine (70%), mp 264–265°; 4,6-diamino-5-nitroso-2-(*o*-tolyl)pyrimidine (43%), mp 216.5–221°. Those prepared using α-picoline as isomerization solvent are 4,6-diamino-2-(*o*-chlorophenyl)-5-nitrosopyrimidine (78%), mp 233–236°; 4,6-diamino-2-(*m*-chlorophenyl)-5-nitrosopyrimidine (50%), mp 247–248°; 4,6-diamino-2-(*p*-chlorophenyl)-5-nitrosopyrimidine (45%); 4,6-diamino-2-benzyl-5-nitrosopyrimidine (37%), mp 244–246°, green-brown crystals.

General Method for 7-Amino-6-pteridinecarboxamides of Tables I–III.—The 4-amino-5-nitrosopyrimidine was dissolved in a minimum quantity of refluxing DMF and cooled slightly, and a 10% excess of the cyanoacetamide and MeOH-free, freely flowing NaOMe were added. The reaction mixture was then refluxed with stirring from 2 to 15 min. The end point was reached when a small aliquot of the reaction mixture, diluted with a four- or fivefold quantity of H_2O no longer showed the characteristic color of the nitrosopyrimidine. At that point the reaction mixture was cooled, and on dilution with an equal quantity of H_2O and chilling the product separated from solution. The product was collected by filtration and washed well (H_2O). Recrystallization from the solvents indicated in the tables was followed by digestion for a 10-min period with boiling H_2O to decompose any solvates before drying at 130° for analysis.

In some cases the reaction solvent used was EtOH, and sometimes when extensive decomposition occurred in refluxing DMF, potassium *t*-butoxide in DMSO on a steam bath was employed. In some cases crude nitrosopyrimidines or cyanoacetamides were used. In general, however, better yields were obtained from purified starting material. In all cases purification was continued until paper or tlc showed the presence of only one major component, contaminated with at most, only traces of other materials. Some typical reactions are given as examples in the patent literature.[3]

Ethyl 4,7-Diamino-2-phenyl-6-pteridinecarboxylate (V). A. NaOMe Method.—To a solution of 6.45 g (0.03 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine in 400 ml of EtOH at 50° was added 3.73 g (0.033 mole) of ethyl cyanoacetate and 1.78 g (0.033 mole) of NaOMe. The reaction mixture was brought to reflux quickly and refluxed for 7 min during which time a yellow solid precipitated. The hot reaction mixture was filtered and the solid was washed with hot EtOH. Cooling of the combined filtrates gave an additional 1.29 g of solid. The first solid was extracted with 300 ml of refluxing DMF, and this was diluted with an equal volume of H_2O to give 1.63 g of a yellow solid, mp 280–283°. Concentration of the filtrate gave an additional 0.75 g of material. Ir spectral data showed that the three fractions were identical, giving a combined crude yield of 39%. A sample was recrystallized three times from DMF–H_2O to give yellow crystals: mp 288–292°; R_f 0.85 (system 1); $\lambda_{max}^{4.5\% \text{ HCOOH}}$ 272, 384 mμ (log ε 4.525, 4.300); $\lambda_{max}^{1\text{ N NaOH}}$ 250, 372 mμ (log ε 4.571, 4.236). *Anal.* ($C_{15}H_{14}N_6O_2$) C, H, N.

Extraction of the solid from the reaction mixture left 2.77 g of a yellow solid, mp >320°, which was insoluble in hot DMF. A portion of this was dissolved in H_2O to give a solution of pH 6.8. Addition of dilute HCl to pH 6 gave a yellow solid, mp 258–260°, R_f 0.59 (system 1), which was identified by its ir spectrum as 4,7-diamino-2-phenyl-6-pteridinecarboxylic acid. Thus this product represents a 30% yield of the sodium salt of this acid.

A similar reaction using 6.45 g (0.03 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 4.2 g (0.033 mole) of isopropyl cyanoacetate, and 1.78 g (0.033 mole) of $NaOCH_3$ in 400 ml of *i*-PrOH for a 1-hr reflux period gave 4.83 g (49%) of **isopropyl 4,7-diamino-2-phenyl-6-pteridinecarboxylate**, mp 285–286°, R_f 0.67 (system 4). *Anal.* ($C_{16}H_{16}N_6O_2$) C, H, N.

This reaction also gave 3.58 g (39%) of the **sodium salt of 4,7-diamino-2-phenyl-6-pteridinecarboxylic acid**, which after three recrystallizations from H_2O had mp >320°, R_f 0.62 (system 1). It was dried at 130° (0.3 mm) for analysis. *Anal.* ($C_{13}H_9N_6NaO_2 \cdot 2H_2O$) C, H, N.

A similar reaction using 72 g (0.333 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine and 36.4 g (0.363 mole) of methyl cyanoacetate dissolved in 4.4 l. of MeOH at 60°, and slowly adding a solution of 19.6 g (0.363 mole) of NaOMe in 700 ml of MeOH as catalyst followed by a 2-hr reflux period gave 46.1 g (47%) of CH$_3$OH-insoluble **methyl 4,7-diamino-2-phenyl-6-pteridinecarboxylate**, mp 283°. A sample was recrystallized twice from DMF to give yellow crystals, mp 286°, R_1 0.81 (system 1). *Anal.* ($C_{14}H_{12}N_6O_2$) C, H, N.

In addition 17.4 g of MeOH-soluble, DMF-insoluble sodium 4,7-diamino-2-phenyl-6-pteridinecarboxylate was isolated.

B. NaCN Method.—To a stirred suspension of 43 g (0.2 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine in 750 ml of absolute EtOH were added 44.6 g (0.4 mole) of ethyl cyanoacetate and 20 g (0.4 mole) of NaCN. The reaction mixture was refluxed for 10 min and cooled, and the resulting yellow solid was collected. This was washed well (H_2O) and then recrystallized from DMF–H_2O to give 46.8 g (75%) of yellow crystals, mp 288–292°, whose ir spectrum was identical with that of the sample prepared above.

C. From Diphenyl Sulfoacetate.—A suspension of 2.92 g (0.01 mole) of diphenyl sulfoacetate, 1.70 g (0.008 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, and 2.0 g (0.04 mole) of finely ground NaCN in 60 ml of EtOH was heated on a steam bath for 40 min which caused the green color of the nitrosopyrimidine to be discharged. Addition of H_2O and filtering gave 0.70 g (28%) of yellow crystals whose ir spectrum corresponded to that of an authentic sample of **ethyl 4,7-diamino-2-phenyl-6-pteridinecarboxylate.**

D. From Cyanoacetylurethan.—A stirred suspension of 2.1 g (0.01 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 3.0 g (0.02 mole) of cyanoacetylurethan, and 1.0 g (0.02 mole) of NaCN in 100 ml of EtOH was refluxed for 20 min. On cooling, a yellow product was obtained which was recrystallized from DMF–H_2O to give 1.9 g (54%) of yellow crystals, mp 288–292°. This product was identified as the ethyl ester by uv and ir spectra and paper chromatography, R_f 0.81 (system 3). *Anal.* ($C_{15}H_{14}N_6O_2$) C, H, N.

E. From Cyanoacetylurea.—A stirred suspension of 2.1 g (0.01 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 2.5 g (0.02 mole) of cyanoacetylurea, and 1.0 g (0.02 mole) of NaCN in 100 ml of EtOH was refluxed for 0.5 hr. The yellow solid which had formed was collected and recrystallized from DMF–H_2O to give 1.0 g (32%) of yellow crystals, mp 278–282° dec, identified by the ir spectrum as the ethyl ester, R_f 0.77 (system 3).

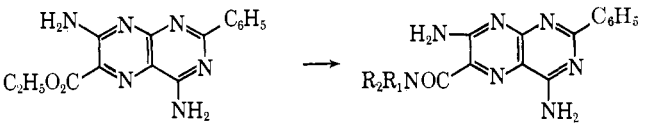
4,7-Diamino-2-phenyl-6-pteridinecarboxamide from Cyanoacetylurea.—To a solution of 21.5 g (0.10 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine in 500 ml of DMF was added 12.7 g (0.10 mole) of cyanoacetylurea and 10.8 g (0.20 mole) of NaOMe. The reaction mixture was refluxed for 2 min, cooled, diluted with H_2O, and filtered. This gave 21.7 g (77%) of an orange-yellow precipitate which was recrystallized by dissolving in aqueous 75% AcOH and precipitating with concentrated NH_4OH at pH 4.5. Boiling with water for 10 min gave yellow crystals, mp >300, R_f 0.60 (system 3). The ir spectrum was identical with that of an authentic sample prepared from cyanoacetamide. *Anal.* ($C_{13}H_{11}N_7O$) C, H, N.

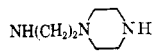
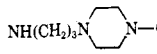
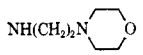
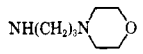
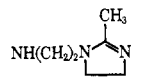
4,7-Diacetylamino-2-phenyl-6-pteridinecarboxamide.—A mixture of 5.0 g (0.0178 mole) of 4,7-diamino-2-phenyl-6-pteridinecarboxamide, 10.8 g (0.106 mole) of Ac_2O, 50 ml of DMF, and 3 drops of pyridine was refluxed for 15 min. After cooling, the yellow product was collected by filtration and washed several times with hot DMF and then with boiling H_2O. This gave 2.0 g (31%) of a yellow solid, mp >300°. *Anal.* ($C_{17}H_{15}N_7O_3$) C, H, N.

2-Phenyl-4-amino-6,8-dioxo-6,7,8,9-tetrahydropyrimido[5,4-*g*]-pteridine (XII).—To a solution of 5.1 g (0.024 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine in 200 ml of DMF was added 7.4 g (0.048 mole) of cyanoacetylurethan and 3.9 g (0.072 mole) of NaOMe. The reaction mixture was refluxed for 1 min and cooled, and the solid was collected by filtration. This was dissolved in 700 ml of boiling H_2O, and the pH was adjusted to 1 with dilute HCl. Chilling gave a solid which was collected and dissolved in dilute NaOH and precipitated at pH 4 with AcOH. It was then dissolved in 75% aqueous AcOH and the product was obtained by adjusting the pH to 6 with dilute NH_4OH, filtering, and washing well with boiling H_2O. This gave 2.1 g (28%) of crystals, mp >300, R_f 0.53 (system 4), 0.61 (system 1). *Anal.* ($C_{13}H_9N_7O_2 \cdot H_2O$) C, H, N.

General Method for N-Aminoalkyl-4,7-diamino-2-phenyl-6-pteridinecarboxamides of Table IV.—A solution of 6.2 g (0.02

TABLE IV[a]



NR_1R_2	Mp, °C	Yield, %	Recrystn solvent	Formula[e]	Ultraviolet spectra Solvent	λ_{max}, mμ	Log ε	Chromatography System	R_f
$N(CH_3)_2$[b]	>300								
$NHCH_2CH_2NH_2$	265–270	89	B	$C_{15}H_{16}N_8O$	a	271	4.525	3	0.44
						385	4.250		
					c	250	4.568		
						385	4.236		
$NHCH_2CHCH_3$	280–283	47	B	$C_{16}H_{18}N_8O$[c]	a	272	4.560	3	0.40
NH_2						385	4.318		
					c	250	4.597		
						385	4.290		
$NHCH_2C(CH_3)_2$	>300	73	B	$C_{17}H_{20}N_8O$	a	272	4.551	4	0.75
NH_2						385	4.281		
					c	250	4.583		
						385	4.255		
$NH(CH_2)_2N(CH_3)_2$	264–266	54	E	$C_{17}H_{22}N_8O$	a	271	4.521		0.48
						386	4.262		
$NH(CH_2)_2N(C_2H_5)_2$	262–265	86	B	$C_{19}H_{24}N_8O$	a	272	4.528	3	0.57
						385	4.270		
$NHCH_2CHOHCH_2N(C_2H_5)_2$	260–262	41	E	$C_{20}H_{26}N_8O_2$	a	272	4.524	3	0.43
						386	4.258		
					c	251	4.529		
						387	4.193		
	248–252	63	C	$C_{19}H_{23}N_9O$	a	272	4.508	3	0.30
						386	4.274		
					c	251	4.587		
						386	4.248		
	249–253	49	B	$C_{21}H_{27}N_9O$	a	271	4.467	3	0.30
						386	4.233		
					c	250	4.502		
						385	4.201		
	277–279	47	B	$C_{19}H_{22}N_8O_2$	a	272	4.535	3	0.50
						385	4.303		
					c	249	4.582		
						385	4.255		
	248–250	75	B	$C_{20}H_{24}N_8O_2$	a	272	4.533	3	0.44
						386	4.292		
					c	251	4.574		
						385	4.241		
	120	47	I	$C_{19}H_{21}N_9O \cdot 0.5H_2O$[d]	a	272	4.502	3	0.52
						386	4.238		
					c	250	4.558		
						386	4.212		

[a] See footnote *a*, Table I. [b] Prepared by bubbling Me_2NH into a refluxing mixture of ester in 2-ethoxyethanol for 2 hr. See Table II for characterization. [c] C: calcd, 56.79; found, 56.29. [d] N: calcd, 31.48; found, 32.11. [e] See Table I, footnote *d*.

mole) of ethyl 4,7-diamino-2-phenyl-6-pteridinecarboxylate in 200 ml of warm DMF was treated with 0.04–0.20 mole of the amine depending on the availability of the amine. The reaction mixture was allowed to stand at room temperature 18–66 hr and either water was added to precipitate the product or the solvents were removed under vacuum to obtain the product free of the reaction solvent. The latter was required with the more soluble members of the series. Recrystallization was accomplished using the solvents indicated in the table to give the products in the yields indicated.

2-Phenyl-4,5,6-triaminopyrimidine.—To a refluxing suspension of 10.7 g (0.05 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine in 500 ml of EtOH was added 3.75 g (0.075 mole) of 85% hydrazine hydrate and 2 tablespoons of Raney nickel. The mixture was boiled 5 min (during which time the green color of the nitroso compound was discharged) and filtered hot, and the filtrate was concentrated to give 8.73 g (87%) of a brown solid, mp 186–189°. Recrystallization of a small portion gave yellow crystals, mp 186–190°, lit.[13] mp 186–189°. The crude product was sufficiently pure to use for further reactions.

Ethyl 4-Amino-7-hydroxy-2-phenyl-6-pteridinecarboxylate (XIV).—A solution of 4.12 g (0.12 mole) of 2-phenyl-4,5,6-triaminopyrimidine and 3.9 g (0.0225 mole) of diethyl oxomalonate in 100 ml of EtOH was refluxed for 2 hr. Cooling and filtration gave 4.8 g (77%) of yellow crystals, mp 215–230°. Two recrystallizations from aqueous DMF gave yellow crystals: mp 234°; R_f 0.93 (system 1); $\lambda_{max}^{4.5\%\ HCOOH}$ 283, 378 mμ (log ε 4.307, 4.041); $\lambda_{max}^{1\ N\ NaOH}$ 268, 310, 380 mμ (log ε 4.338, 4.152, 4.021). *Anal.* ($C_{15}H_{13}N_5O_3$) C, H, N.

4-Amino-7-hydroxy-2-phenyl-6-pteridinecarboxamide (XV, R = H).—A stream of anhydrous NH_3 was passed for 1 hr through a refluxing stirred suspension of 5 g (0.016 mole) of ethyl 4-amino-7-hydroxy-2-phenyl-6-pteridinecarboxylate in 200 ml of EtOH. During the course of the reaction a clear solution was obtained from which a precipitate slowly appeared. The mixture was cooled and the solid was collected. This was recrystallized from aqueous DMF to give 0.91 g (20%) of crystals: mp >300°; R_f 0.53 (system 4); $\lambda_{max}^{4.5\%\ HCOOH}$ 285, 378 mμ (log ε 4.534, 4.204); $\lambda_{max}^{1\ N\ NaOH}$ 282, 418 mμ (log ε 4.660, 4.230). *Anal.* ($C_{13}H_{10}N_6O_2$) C, H, N.

4-Amino-N-ethyl-7-hydroxy-2-phenyl-6-pteridinecarboxamide (XV, R = C_2H_5).—A mixture of 4.0 g (0.0128 mole) of ethyl 4-amino-7-hydroxy-2-phenyl-6-pteridinecarboxylate and 40 ml of 70% aqueous $EtNH_2$ in 150 ml of EtOH was refluxed for 2.5 hr. On cooling, a solid was obtained which was collected and dissolved in hot H_2O. The solution was filtered, the pH was adjusted to 4.5 with AcOH, and the yellow-orange product which separated was collected. Recrystallization of this from aqueous DMF gave a yellow product, mp 295–299° dec, R_f 0.67 (system 4). *Anal.* ($C_{15}H_{14}N_6O_2$) C, H, N.

4-Amino-N-(2-diethylaminoethyl)-7-hydroxy-2-phenyl-6-pteridinecarboxamide.—A solution of 3.4 g (0.011 mole) of ethyl 4-amino-7-hydroxy-2-phenyl-6-pteridinecarboxylate and 3 ml of diethylaminoethylamine in 50 ml of DMF was allowed to stand for 18 hr at room temperature. The solution was filtered and the solvent was removed under reduced pressure to give 4.4 g of a gold solid, mp 98–180°. This was dissolved in 500 ml of refluxing

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

ethyl acetate and filtered, and the solution was concentrated to 150 ml. Chilling gave a product which was recrystallized twice from benzene to give 1.7 g (40%) of crystals, mp 239–241°, R_f 0.67 (system 6). *Anal.* ($C_{19}H_{23}N_7O_2 \cdot 0.25H_2O$) C, H, N.

1-(4-Amino-7-hydroxy-2-phenyl-6-pteridinoyl)-2-methylhydrazine (XV, R = CH_3NH).—To a stirred solution of 9.3 g (0.03 mole) of ethyl 4-amino-7-hydroxy-2-phenyl-6-pteridinecarboxylate in 125 ml of DMF at 0–5° was added 20 g (0.42 mole) of methylhydrazine dropwise. After 9 hr the reaction temperature was allowed to come to room temperature with continued stirring for 14 more hr. Addition of 125 ml of water and adjustment of the pH to 3 with concentrated HCl gave a yellow product. Recrystallization from aqueous DMF gave yellow crystals: mp 282° dec; R_f 0.77 (system 1); $\lambda_{max}^{1.5\%\ HCO_2H}$ 242, 287, 392 mμ (log ε 4.262, 4.315, 3.987). *Anal.* ($C_{14}H_{13}N_7O_2$) C, H, N.

4,7-Diamino-2-phenyl-6-pteridinecarboxylic Acid. A.—A mixture of 6.45 g (0.03 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 2.8 g (0.033 mole) of cyanoacetic acid, and 3.56 g (0.066 mole) of $NaOCH_3$ in 250 ml of DMF was refluxed for 10 min. This gave a yellow solid which was collected by filtration and slurried in aqueous EtOH, and AcOH was added to bring the pH to 4.5. The resulting solid was collected by filtration and washed well with EtOH and then ether to give 4.7 g (56%) of buff crystals. This was dissolved in 7 l. of 15% NH_4OH and filtered through Celite, and the filtrate was brought to pH 5.5 with AcOH. The product was collected and recrystallized several times from H_2O using charcoal to decolorize the solution. This gave yellow needles, mp 256° dec, $\lambda_{max}^{0.1\ N\ HCl}$ 239, 272, 383 mμ (log ε 4.318, 4.494, 4.255); R_f 0.60 (system 1). *Anal.* ($C_{13}H_{10}N_6O_2$) C, N; H: calcd, 3.57; found, 4.06.

B.—To a solution of 9.3 g (0.4 g-atom) of Na in 400 ml of redistilled ethoxyethanol was added a mixture of 17 g (0.2 mole) of cyanoacetic acid and 21.5 g (0.1 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine. The mixture was refluxed for 2 min, cooled, and filtered to give the sodium salt of the product. This was dissolved in 500 ml of H_2O and acidified (AcOH) to give 28.1 g (98%) of a white solid, mp 263° dec. The ir spectrum of this product was identical with that of the product obtained above.

4,7-Diamino-2-phenylpteridine.[14]—A suspension of 10 g (0.053 mole) of 4,7-diamino-2-phenyl-6-pteridinecarboxylic acid in 250 ml of redistilled quinoline was refluxed for 5 hr, cooled, and diluted with 600 ml of hexane. Filtration gave a light brown solid which was stirred in 2 l. of 0.7 *N* NH_4OH, collected by filtration, and washed (H_2O). Recrystallization of this from 50% aqueous EtOH gave 4.5 g (53%) of yellow crystals, mp 299–302°. A second recrystallization from the same solvent gave 4.0 g of yellow crystals: mp 303° (soften at 295°); R_f 0.61 (system 3); $\lambda_{max}^{0.1\ N\ HCl}$ 352 mμ (log ε 4.29), 258 (4.45), 236 (4.37); $\lambda_{max}^{0.1\ N\ NaOH}$ 348 mμ (log ε 4.20), 244 (4.57). *Anal.* ($C_{12}H_{10}N_6$) C, H, N.

o-Toluamidoxime.—A solution of Na (15.8 g, 0.687 g-atom) in 224 ml of EtOH was added to a solution of 46.9 g (0.4 mole) of *o*-tolunitrile in 154 ml of EtOH, and to this was added a solution of 44 g (0.634 mole) of $NH_2OH \cdot HCl$ in 88 ml of H_2O. The mixture was stirred under reflux for 9 hr, and then the solvents were removed under reduced pressure. The residue was treated with 10% NaOH to bring the pH to 13, and the solid was collected by filtration to give 29.7 g of product, mp 115–135°. An additional 1.75 g of product, mp 135–146°, was obtained by acidification of the filtrate to pH 5 with glacial AcOH after first extracting with ether. Recrystallization of the combined products from H_2O gave 21.8 g (36%) of crystals, mp 147–148.5°, lit.[15] mp 149.5°.

o-Chlorobenzamidoxime was obtained in a similar fashion in 60% yield as a solid, mp 115–118°, lit.[16] mp 117°.

o-Chlorobenzamidine.—A solution of 8.54 g (0.05 mole) of *o*-chlorobenzamidoxime in EtOH was shaken under 3 atm of H_2 in the presence of Raney nickel for 7 hr at 65°. Removal of the catalyst and evaporation of the solvent under reduced pressure gave a yellow oil. A picrate prepared from a small portion of this had mp 214–215°, lit.[17] mp 217°, and a benzenesulfonate had mp 163–165°, lit.[15] 167°. The oil was dissolved in a minimum amount of EtOH and the pH was brought to 3.5 with *i*-PrOH–HCl. Addition of Et_2O gave 6.12 g (64%) of the hydrochloride, mp 258–260°.

o-Toluamidine.—In a similar fashion reduction of 15.1 g (0.1 mole) of *o*-toluamidoxime gave 11.38 g (67%) of *o*-tolumidine hydrochloride, mp 252–253°.

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(14) We wish to thank Mrs. J. Carevic and Mr. H. Shah for assistance in preparing this compound.

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(16) A. Werner and C. Block, *ibid.*, **32**, 1979 (1899).

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