Pteridines. VI.[1] Preparation of Some 6-Aryl-7-aminopteridines[2]

JOSEPH WEINSTOCK, ROBERTA Y. DUNOFF, BLAINE SUTTON, BARRY TROST, JOEL KIRKPATRICK, FRANK FARINA, AND ALICE S. STRAUB

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania

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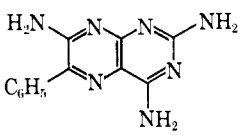
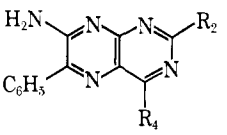
A number of 4,7-diamino-6-phenyl-, 2,7-diamino-6-phenyl-, and 2,4,7-triamino-6-arylpteridines were prepared for diuretic testing by condensation of arylacetonitriles and 4-amino-5-nitrosopyrimidines. 2,4-Diamino-6-methylmercapto-5-nitrosopyrimidine and 4,6-diamino-2-methylmercapto-5-nitrosopyrimidine were treated with amines to give replacement of the methylmercapto group by an amino group. Uv and nmr spectra suggest that the 2-cyanomethyl- and 2-carboxamidomethyl-4,7-diamino-6-phenylpteridines exist as tautomers in which the cyano and carboxamido groups are conjugated with the pteridine ring. Certain other conclusions were drawn from the spectral data.

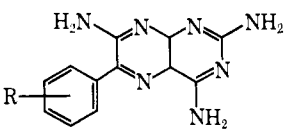
The discovery of useful diuretic activity in man of 6-phenyl-2,4,7-triaminopteridine (triamterene)[3,4] (I) prompted us to undertake the synthesis of a number of related compounds for biological evaluation. In this paper, we will report on the preparation of pteridines of the type II in which one of the pyrimidine amino groups of triamterene has been replaced by another substituent, and pteridines of the type III in which various substituents have been introduced into the phenyl group of I.



I



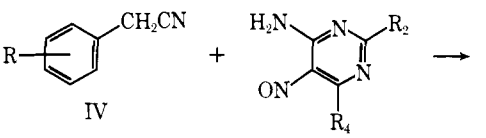
IIa, $R_2 = NH_2$
b, $R_4 = NH_2$



III

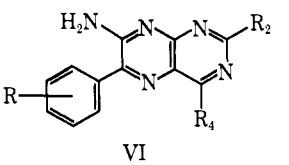
Compound I has been prepared by the base-catalyzed condensation of 5-nitroso-2,4,6-triaminopyrimidine and phenylacetonitrile.[5] This approach was useful for the preparation of many of the compounds described in this paper. Thus, most of the compounds shown in Table I were prepared by condensation of the appropriate 2-substituted 4,6-diamino-5-nitrosopyrimidine (Va) with phenylacetonitrile, and those in Table II by the same reaction using the appropriate 4-substituted 2,6-diamino-5-nitrosopyrimidine (Vb).

The condensation to form VI had been carried out previously in various alcohols or in AcOH using the sodium salt of the solvent as the basic catalyst for the reaction.[5] The reaction was found to proceed more



IV

Va, $R_4 = NH_2$
b, $R_2 = NH_2$
c, $R_2 = R_4 = NH_2$



VI

smoothly with the less soluble nitrosopyrimidines when DMF, DMSO, or a mixture of one of these solvents with an alcohol was used as solvent. Sodium methoxide was generally used as base, although in certain cases potassium *t*-butoxide proved to be better.

The choice of solvent and catalyst was in part dictated by the acidity of the phenylacetonitrile. Thus, *p*-nitrophenylacetonitrile did not condense with Vc in DMF using sodium methoxide as catalyst. Previously,[5] this condensation had been carried out in AcOH using sodium acetate as base. We found sodium acetate in DMF to be a more satisfactory system in this case. However, even this system gave no isolable product when an attempt was made to condense Vc with the substantially more acidic substance, cyanomethyl phenyl sulfone.

The 4,6-diamino-5-nitrosopyrimidines required for this work could be prepared by isomerization of either guanidine or amidine salts of isonitrosomalononitrile[6] or by nitrosation of the appropriate 4,6-diaminopyrimidine.[7] In addition, we found that primary and secondary amines react with 2-methylmercapto-4,6-diamino-5-nitrosopyrimidine (VII) in refluxing butanol to give 2-(substituted amino)-4,6-diamino-5-nitrosopyrimidines. The reaction is subject to steric hindrance in that primary carbinamines such as benzylamine react rapidly while secondary carbinamines such as isopropylamine react slowly. 1-Phenylisopropylamine, in which the amine is somewhat more sterically hindered, did not react under these conditions. Aromatic amines such as aniline required acid catalysis to promote the dis-

(1) Previous paper and introduction to this series: J. Weinstock, R. Y. Dunoff, and J. G. Williams, *J. Med. Chem.*, **11**, 542 (1968).

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

(3) This is also known as Dyrenium® and when combined with hydrochlorothiazide as Dyazide® in the U. S.

(4) V. D. Wiebelhaus, J. Weinstock, F. T. Brennan, G. Sosnowski, and T. J. Larsen, *Fed. Proc.*, **20**, 409 (1961); A. P. Crosley, Jr., L. M. Ronquillo, W. H. Strickland, and F. Alexander, *Ann. Intern. Med.*, **56**, 241 (1962); V. D. Wiebelhaus, J. Weinstock, A. R. Maass, F. T. Brennan, G. Sosnowski, and T. Larsen, *J. Pharmacol. Exptl. Therap.*, **149**, 397 (1965).

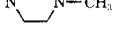
(5) R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1954).

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

(7) J. Baddiley, B. Lythgoe, D. McNeil, and A. R. Todd, *J. Chem. Soc.*, 383 (1943).

TABLE I

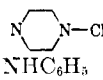
4,7-DIAMINO-6-PHENYL-2-SUBSTITUTED PTERIDINES

R₂	Mp, °C	Reaction time, min	Yield, %	Recrystn solvent[d]	Formula[e]	Ultraviolet spectra pH 1 λmax, mμ	Log ε	pH 12 λmax, mμ	Log ε	Paper chromatography[d] System	Rf
CH_3	316–317	1	63	C	$C_{13}H_{12}N_6$	261	4.196	266	4.117	4	0.73
						286	3.695	354	4.143		
						355	4.207				
CH_2CN	314–315	5	71	K	$C_{14}H_{11}N_7 \cdot 0.5H_2O$	260	4.531	250	4.408	4	0.64
						304	4.322	295	4.250		
						373	4.170	380	4.061		
CH_2CONH_2	292–293	*b*	24	K	$C_{14}H_{13}N_7O$	259	4.500	253	4.471	1	0.69
						310	4.345	286	4.342		
						382	4.041	390	4.072		
$CH_2C_6H_5$	296–299	5	18	C	$C_{19}H_{16}N_6$	261	4.253	Insoluble		2	0.84
						292 (s)	4.752				
						359	4.274				
C_6H_5	>300	10	19	I	$C_{18}H_{14}N_6$	266	4.442	Insoluble		1	0.84
						369	4.356				
NH_2[c]						254	4.19	269	4.13		
						288 (s)	3.85	368	4.27		
						358	4.33				
$NHCH_3$	235–237	*a*	58	E	$C_{13}H_{13}N_7$	253	4.215	270	4.207	2	0.71
						279 (s)	3.907	291 (s)	3.959		
						361	4.352	373	4.283		
$N(CH_3)_2$	270–271	4	50	E	$C_{14}H_{15}N_7$	246	4.270	236	4.609	4	0.75
						260 (s)	4.212	274	4.283		
						364	4.410	294 (s)	4.107		
								382	4.322		
$NHCH(CH_3)_2$	236–237	2	73	F	$C_{15}H_{17}N_7$	251	4.201	233	4.615	5	0.81
						284 (s)	3.854	264	4.196		
						362	4.346	291 (s)	3.964		
								376	4.267		
$NH(CH_2)_5CH_3$	195–198	5	40	F	$C_{18}H_{23}N_7$	250	4.233			4	0.77
						279 (s)	4.952				
						362	4.377				
$NHCH_2C_6H_5$	235–236	4	23	E	$C_{19}H_{17}N_7$	254	4.272	Insoluble		2	0.80
						283 (s)	3.913				
						362	4.401				
$NH(CH_2)_2N(CH_3)_2$	242–245	5	49	C	$C_{16}H_{20}N_8$	256	4.225	232	4.630	3	0.59
				E		282 (s)	3.836	272	4.215		
						360	4.342	374	4.283		
$NH(CH_2)_3N(CH_3)_2$	239–243	5	60	C	$C_{17}H_{22}N_8$	255	4.253	232	4.669	3	0.61
				E		284 (s)	3.876	271	4.250		
						362	4.387	375	4.316		
NHC_6H_5	320–322	1	50	K	$C_{18}H_{15}N_7$	260	4.371	Insoluble		5	0.76
						365	4.422				
	246–247	1	51	E	$C_{11}H_{10}N_7$	248	4.324	232	4.593	2	0.86
						264 (s)	4.233	272	4.314		
						367	4.435	290 (s)	4.140		
								381	4.334		
	280–283	2	63	C	$C_{17}H_{20}N_8$	261	4.305	235	4.610	2	0.82
						282(s)	3.962	273	4.310		
						362	4.391	294 (s)	4.064		
								379	4.332		
	274–276	1	68	E	$C_{16}H_{17}N_7O$	251	4.230	237	4.559	5	0.58
						364	4.371	273	4.281		
								370 (s)	4.057		
								379	4.294		

[a] Reaction carried out in ethanol for 5 hr. [b] Prepared by hydrolysis of R = CH_2CN. See Experimental Section for details. [c] Taken from I. J. Pachter, *J. Org. Chem.*, **28**, 1191 (1963). [d] Recrystallization solvent: A, dissolve substance in glacial AcOH and precipitate with NH_4OH; B, recrystallize from 50% aqueous AcOH and liberate free base with NH_4OH; C, dissolve substance in AcOH and precipitate with NH_4OH; D, dissolve substance in HCl and precipitate with NH_4OH; E, *n*-BuOH; F, EtOH; G, *i*-PrOH; H, dioxane–H_2O; I, DMF; J, 75% aqueous AcOH, liberate free base with NH_4OH; K, DMF–H_2O. For the paper chromatography systems, see Experimental Section. [e] All compounds were analyzed for C, H, N. Except as noted, analytical results were within ±0.4% of calculated values.

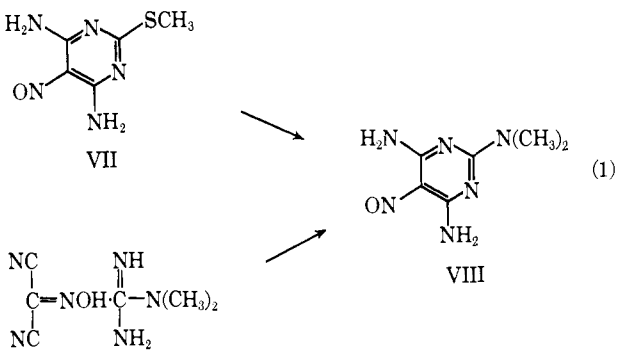
TABLE II

2,7-DIAMINO-6-PHENYL-4-SUBSTITUTED PTERIDINES

R4	Mp, °C	Reaction time, min	Yield, %	Recrystn solvent[d]	Formula[e]	Ultraviolet spectra: pH 1 λmax, mμ	pH 1 Log ε	pH 12 λmax, mμ	pH 12 Log ε	Paper chromatography[d]: System	Rf
$NHCH_3$	330	45	55	E	$C_{13}H_{13}N_7$	268	4.417	273	4.418	2	0.72
						363	4.512	374	4.473		
$NHCH(CH_3)_2$	>300	1	53	F	$C_{15}H_{17}N_7$	267	4.260	274	4.254	1	0.86
						362	4.336	375	4.290		
$NH(CH_2)_2N(Et)_2$	160	45	61	G	$C_{18}H_{24}N_8 \cdot 0.25H_2O$[f]	270	4.260	278	4.260	2	0.77
				E		360	4.352	375	4.267		
$N(CH_3)_2$	273–274	120	76	F	$C_{14}H_{15}N_7$	275	4.307	282	4.318	2	0.75
				E		362	4.360	377	4.305		
	278–279	120	50	F	$C_{17}H_{19}N_7$	281	4.314	286	4.324	5	0.74
				E		367	4.332	382	4.297		
	222	45	42	G	$C_{17}H_{20}N_8$	274	4.369	283	4.324	2	0.70
				E		363	4.418	379	4.297		
NHC_6H_5	208–209	1	80	F	$C_{18}H_{15}N_7 \cdot 0.5H_2O$	290	4.312	Insoluble		1	0.82
						372	4.439				
p-ClC_6H_5NH	300–301.5	120	61	G	$C_{18}H_{14}ClN_7$	292	4.307	Insoluble		2	0.71
				E		374	4.417				
SCH_3	252–254	60[a]	60	H	$C_{13}H_{12}N_6S \cdot 0.25H_2O$	289	4.190	281	4.225	2	0.72
						367	4.393	370	4.358		
OCH_3	275	90[b]	10	E	$C_{13}H_{12}N_6O$	285	3.873	273	4.009	2	0.72
						356	4.410	362	4.334		
$O(CH_2)_2N(CH_3)_2$	275	90[b]	10	E	$C_{16}H_{19}N_7O \cdot 0.25H_2O$[g]	286	3.927	274	4.072	2	0.73
						357	4.479	362	4.413		
$O(CH_2)_3CH_3$	221.5–222.5	120[c]	25	F	$C_{16}H_{18}N_6O$	286	3.857	228	4.694	5	0.73
						356	4.410	275	3.978		
								362	4.318		

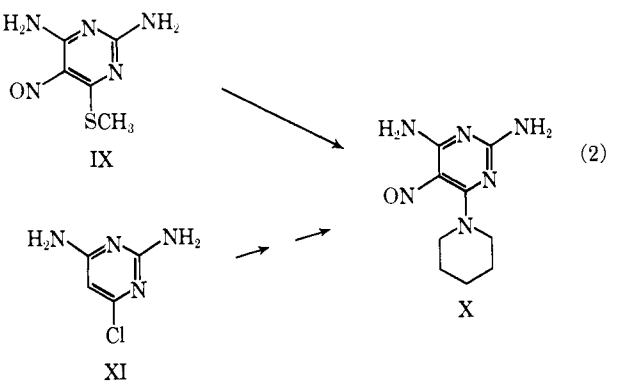
[a] Reaction carried out in 2:1 DMF–MeOH. [b] Reaction carried out in a 3:1 DMF–MeOH. [c] Reaction carried out in DMSO using potassium *t*-butoxide as catalyst. [d] See footnote *d*, Table I. [e] All compounds were analyzed for C, H, N. Except as noted, analytical results were within ±0.4% of calculated values. [f] C: calcd, 60.50; found, 61.16. [g] H: calcd, 5.94; found, 4.92.

placement. In order to establish the course of the reaction, 4,6-diamino-2-dimethylamino-5-nitrosopyrimidine (VIII) was prepared from VII and also by isomerization of the 1,1-dimethylguanidine salt of isonitrosomalononitrile[6] (eq 1).



(1)

In a similar fashion, pyrimidines Vb in which R^4 is a substituted amino group and R_2 is amino could be prepared by the reaction of the appropriate amine and 2,4-diamino-6-methylmercapto-5-nitrosopyrimidine (IX). The course of the replacement was demonstrated by establishing the identity of 2,4-diamino-5-nitroso-6-piperidinopyrimidine (X) prepared from IX and by the stepwise process of amination of 2,4-diamino-6-chloropyrimidine (XI) followed by nitrosation[8] (eq 2).



(2)

The reaction of VII with amines was found independently by other workers[9] who studied the reaction of VII and the 4-hydroxy analog of VII in water with ammonia, hydroxylamine, β-hydroxyethylamine, and some cycloalkylamines.

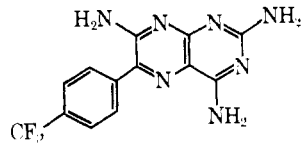
The nitrosopyrimidines prepared by displacement of methylmercaptan are shown in Table V. In most cases, the pyrimidines were used as obtained from the reaction mixtures for conversion to the pteridines.

The preparation of pteridines of the type III (shown in Table III) was generally carried out by the condensation of 2,4,6-triamino-5-nitrosopyrimidine (Vc) with the appropriately substituted phenylacetonitrile. This procedure was not applicable for the preparation of the *p*-trifluoromethyl analog XII, presumably because the anion of *p*-trifluoromethylphenylacetonitrile lost fluoride ion more rapidly than it condensed with

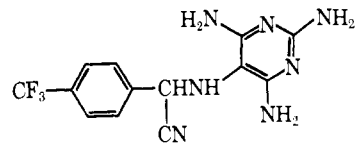
(8) B. Roth, J. M. Smith, and M. E. Hultquist, *J. Am. Chem. Soc.*, **72**, 1914 (1950); **73**, 2869 (1951).

(9) R. M. Cresswell and T. Strauss, *J. Org. Chem.*, **28**, 2563 (1963).

the nitrosopyrimidine. The desired compound was prepared from *p*-trifluoromethylbenzaldehyde, tetraaminopyrimidine, and cyanide *via* 2,4,6-triamino-5-(α-cyano-*p*-trifluoromethylbenzylamino)pyrimidine (XIII).[10]

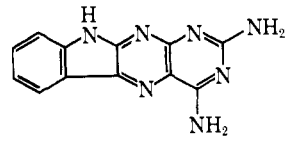


XII



XIII

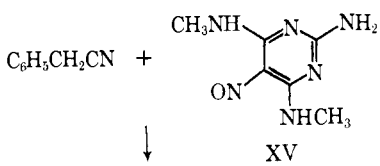
In an attempt to prepare the *o*-iodo analog of III, *o*-iodophenylacetonitrile and Vc were allowed to react in refluxing ethoxyethanol in the presence of sodium ethoxyethoxide. Two hours was required before the nitrosopyrimidine had completely reacted, and the product formed was 2,4-diaminoindolo[2,3-*g*]pteridine (XIV). This product was identical with that prepared by the reaction of tetraaminopyrimidine and isatin.[11] The condensation to form the pteridine was



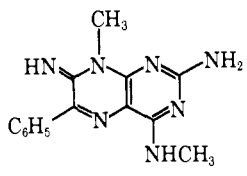
XIV

much slower than that usually observed due to the steric hindrance provided by the *o*-iodo group, and under the conditions required, the second condensation to form the indole ring occurred. Steric hindrance in the formation of pteridines by this general method had been observed previously,[5] and in general in this work low yields of products were obtained from sterically hindered phenylacetonitriles.

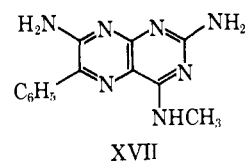
In order to study the utility of 4-amino-5-nitrosopyrimidine–phenylacetonitrile synthesis of pteridines for the preparation of 8-alkyl-7-iminopteridines, 2-amino-4,6-bismethylamino-5-nitrosopyrimidine (XV) was condensed with phenylacetonitrile in DMF using sodium methoxide as the catalyst. A pteridine was isolated in 22% yield whose elemental analysis and physical properties were consistent with those expected for XVI. The uv spectrum had its high wavelength peak at 382 mμ at pH 12 and at 386 mμ at pH 1; in comparison, the uv spectrum of 2,7-diamino-4-methylamino-6-phenylpteridine (XVII) had its corresponding peaks at 374 and 363 mμ. Thus, XVI has an extended conjugated system in comparison to XVII. The lack of a hypsochromic shift when XVI is protonated is consistent with the existence of resonance forms of the salt like XVIa, b, and c. The nmr data for these



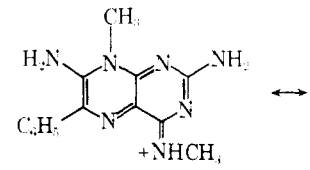
XV



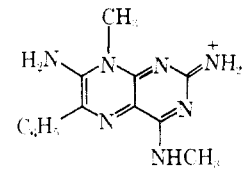
XVI



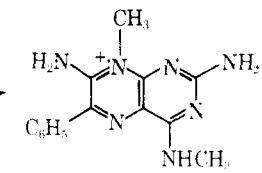
XVII



XVIa



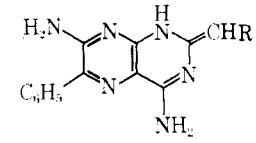
XVIb



XVIc

compounds are shown in Table IV. The spectra of both compounds show the unsplit phenyl protons at 7.69 ppm and a doublet at 3.42 ppm assignable to CH_3 on the 4-methylamino group. In addition, a singlet at 4.11 ppm in the spectrum of XVI is due to 8-CH_3. The downfield shift is consistent with the 8-methyl group being in a greater electron-deficient environment than the methyl on the 4-amino group.

Inspection of the ultraviolet data reported in Table I shows that the compounds where the 2 position was substituted by a cyanomethyl or acetamido group had absorption at much higher wavelengths (373 and 382 mμ) than the corresponding 2-methyl or 2-benzyl compounds (355 and 359 mμ). This suggested the presence of extended conjugated systems such as XVIIIa and XVIIIb. Additional evidence for these structures was found in the nmr spectra of these compounds. The spectrum of the 2-benzyl compound in F_3CCOOH showed a singlet at 4.45 ppm due to CH_2.



XVIIIa, R = CN
XVIIIb, R = $CONH_2$

The spectrum of XVIIIa and XVIIIb in F_3CCOOH showed no peak in this area; in addition, no peak appears in the region 5–7 ppm. This may be explained by rapid exchange of the proton on the double bond due to the high acidity of the solvent. Unfortunately, poor solubility precluded the use of another solvent.

Similar behavior is seen in the case of the so-called 4,6-diamino-2-cyanomethylpyrimidine.[12] In 0.1 *N* HCl it has λ_{max} 230, 294 mμ (log ε 4.60, 4.228) and

(10) I. J. Pachter, *J. Org. Chem.*, **28**, 1191 (1963).
(11) E. M. Gal, *Experientia*, **7**, 261 (1951).
(12) S. M. McElvain and B. E. Tate, *J. Am. Chem. Soc.*, **73**, 2760 (1951).

TABLE III

2,4,7-TRIAMINO-6-SUBSTITUTED PHENYLPTERIDINES (III)

R	Mp, °C	Reaction time, min	Yield, %	Recrystn solvent[e]	Formula[d]	Ultraviolet spectra: pH 1 λmax, mμ	pH 1 Log ε	pH 12 λmax, mμ	pH 12 Log ε	Paper chromatography[e]: System	R_f
p-D	>300	8	25	J	$C_{12}H_{10}DN_7$[b]	356	4.356	Insoluble		6	0.60
o-Br	>300	5	15	I	$C_{12}H_{10}BrN_7$	258	4.207	264	4.303	1	0.69
						351	4.350	362	4.922		
						275 (s)	3.866				
p-Br	>300	2	27	K	$C_{12}H_{10}BrN_7$[f]	284 (s)	3.844	273	4.130	1	0.69
						359	4.360	370	4.294		
o-F	>305	2	24	I	$C_{12}H_{10}FN_7$	259	4.241	265	4.212	1	0.63
						275 (s)	3.929	365	4.288		
						354	4.354				
m-F	>305	1	49	K	$C_{12}H_{10}FN_7$	258	4.188	270	4.146	1	0.61
						279 (s)	3.892	369	4.281		
						358	4.334				
p-F	>320	5	70	I	$C_{12}H_{10}FN_7$	257	4.217	269	4.173	1	0.62
						280 (s)	3.885	368	4.290		
						358	4.348				
p-I	>300	60[a]	29	A	$C_{12}H_{10}IN_7$[g]	247	4.270	239	4.791	1	0.68
						285 (s)	3.889	273	4.127		
						361	4.338	371	4.281		
3,4-Cl_2	>310	30	5	A	$C_{12}H_9Cl_2N_7$[h]	249	Qualitative insoluble			2	0.52
						360					
o-CH_3	>300	5	65	I	$C_{13}H_{13}N_7$	257	4.190	263	4.179	1	0.66
						274(s)	3.835	362	4.243		
						350	4.326				
m-CH_3	>300	5	65	I	$C_{13}H_{13}N_7$	254	4.212	269	4.158	1	0.68
						280 (s)	3.660	368	4.290		
						357	4.344				
p-CH_3	>300	5	72	I	$C_{13}H_{13}N_7$	280 (s)	3.895			1	0.61
						359	4.352				
p-CH_3CH_2	>300	7	55	I	$C_{14}H_{15}N_7$	257 (s)	4.255	Insoluble		2	0.61
						280 (s)	3.889				
						360	4.356				
m-CF_3	>300	2	41	K	$C_{13}H_{10}F_3N_7$	259	4.199	258	4.516	1	0.70
						358	4.387	362	4.382		
p-CF_3	See Experimental Section for procedure			K	$C_{13}H_{10}F_3N_7$	252	4.173	271	4.097	1	0.81
						284 (s)	3.881	370	4.301		
						359	4.350				
o-C_6H_5	>300	5	38	I	$C_{18}H_{15}N_7$	356	4.453	259	4.297	1	0.81
						278 (s)	4.033	366	4.279		
p-C_6H_5	>300	2	47	I	$C_{18}H_{15}N_7$	238	5.336	263	4.486	1	0.75
						241	5.386	296 (s)	4.272		
						364	4.561	362	4.310		
						262 (s)	4.394				
						283 (s)	3.013				
p-$C_6H_5CH_2O$	293–295	2	45	I	$C_{19}H_{17}N_7O$	260 (s)	4.301	Insoluble		1	0.82
						288 (s)	3.937				
						363	4.367				
p-NH_2[c]	328–330	5	31	A	$C_{12}H_{12}N_8 \cdot CH_3COOH$[i]	256	4.215	272	4.199	5	0.24
						282 (s)	4.090	288 (s)	4.090		
						360	4.330	374	4.283		
p-CH_3CONH	>320	1	27	I	$C_{14}H_{14}N_8O \cdot 0.5H_2O$[j]	256	4.378	224	4.712	2	0.42
						283 (s)	3.983	277	4.207		
						363	4.356	327	4.301		

[a] Reaction carried out in refluxing ethoxyethanol for 1 hr using sodium salt of solvent as catalyst. [b] Deuterium analysis obtained. Calcd: D, 9.09. Found: D, 8.19. Shows 90.1% purity. [c] Acetate. [d] All compounds were analyzed for C, H, N. Except as noted, analytical results were within ±0.4% of calculated values. [e] See footnote *d*, Table I. [f] C: calcd, 43.39; found, 44.19. H, calcd, 3.03; found, 3.49. [g] C: calcd, 38.01; found, 38.61. [h] N: calcd, 30.43; found, 29.65. [i] C: calcd, 51.21; found, 50.47. [j] N: calcd, 35.04; found, 35.94.

in 0.1 *N* NaOH it has λ_{max} 221, 266, 295 mμ (log ε 4.487, 3.968, 4.090). In contrast, 4,6-diamino-2-methylpyrimidine at pH 6.5 has been reported[13] to have λ_{max} 260 mμ (log ε 3.81). Here again, an extended conjugated system is indicated with XIX representing the probable structure. A similar tautomeric shift has been found in 7-acetonylxanthopterine (XXa) and erythropterine (XXb).[14] However, in these cases the vinyl proton signal appears in the nmr spectra (6.79 and 7.58 ppm, respectively) taken in F_3CCOOH,

(13) L. F. Cavalieri and A. Bendich, *J. Am. Chem. Soc.*, **72**, 2587 (1950).

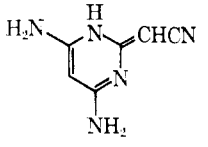
(14) W. von Philipsborn, H. Stierlin, and W. Traber, *Helv. Chim. Acta*, **46**, 2592 (1963).

TABLE IV
NMR SPECTRA

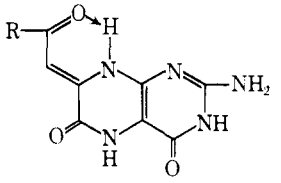
6-Phenylpteridines	6-Phenyl	NH	NCH_3	Others
	δ, ppm (J, cps)[a]			
2,4,7-Triamino	7.73 s	8.48 br		
4,7-Diamino-2-methylamino	7.73 s	8.40 br	3.31 s	
2,7-Diamino-4-methylamino	7.70 s	8.70 br	3.43 d (4)	
4,7-Diamino-2-dimethylamino	7.71 s	...	3.49 s	
2,7-Diamino-4-dimethylamino	7.72	...	3.88 s	
2,7-Diamino-4-methoxy	7.69 s	...		4.33 s (4-methoxy)
2,7-Diamino-4-butoxy	7.67 s	...		4.78 t (6) (1-CH_2 of butoxy)
				1.01 t (6) (4-methyl of butoxy)
				1.68 br m (2,3-CH_2 of butoxy)
2-Amino-8-methyl-4-methyl-amino-7-imino-7,8-dihydro	7.68 s	8.81[c] br d (~5) 8.10[d] br	3.42 d (5.5) 4.11 s	
4,7-Diamino-2-hexylamino	7.70 s	...		0.96 m (6 methyl of hexyl)
				1.45 br m (2,3,4,5-methylene of hexyl)
				3.72 br t (6) (1-methylene of hexyl)
4,7-Diamino-2-hexylamino[b]	7.70[d] m	6.93[c] s		0.87 m (6 methyl of hexyl)
	7.48[e] m	6.57[c] s		1.33 br m (2,3,4,5-methylene of hexyl)
2,7-Diamino-4-butoxy[f]	7.73[d] m	6.22 s[c]		4.53[d] t (6) (1-CH_2 of butoxy)
	7.50[e] m	5.81 s[c]		1.64 br m (2,3-CH_2 of butoxy)
				0.98 t (6) (4-methyl of butoxy)
4,7-Diamino-2-benzyl	7.77 s	8.48[c] br		4.45[d] s (benzyl methylene)
				7.46 s (benzyl phenyl)
4,7-Diamino-2-carboxamidomethyl	7.73 s	8.41[c] br		
4,7-Diamino-2-cyanomethyl	7.73	...		
4,7-Diamino	7.80 s	8.47 br		8.83 s (2-hydrogen)

[a] All spectra in F_3CCOOH unless otherwise indicated. TMS = 0. s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. [b] In DMSO-d_6. [c] 1 H. [d] 2 H. [e] 3 H. [f] In $DCCl_3$.

although the peak at 6.79 ppm of XXa disappeared when the spectrum was measured in F_3CCOOD due to rapid exchange of the vinyl proton.



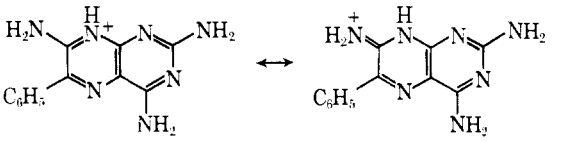
XIX



XXa, R = CH_3
XXb, R = COOH

Comparison of the uv spectra of some 7-amino and the corresponding 7-hydroxypteridines shows some interesting differences. In acid solution 2,4,7-triamino-6-(*p*-nitrophenyl)pteridine has λ_{max} 368 mμ,[5] the 6-phenyl analog λ_{max} 358 mμ,[10] and the 6-methyl analog λ_{max} 342 mμ.[10] In contrast, in acid solution 2,4-diamino-7-hydroxy-6-(*p*-nitrophenyl)pteridine has λ_{max} 394 mμ,[5] the 6-phenyl analog λ_{max} 362 mμ,[5] and the 6-methyl analog λ_{max} 332 mμ.[5] The range for the 7-amino series is 26 mμ while that for the 7-hydroxy series is 62 mμ. This suggests a more limited resonance interaction of the phenyl and pteridine rings in the amine series than in the hydroxy series in acid solution.

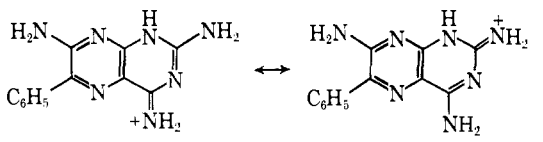
This is supported by the nmr data shown in Table IV. The spectra of all the 6-phenyl-7-aminopteridines when run in F_3CCO_2H solution show a sharp singlet near 7.70 ppm due to the aromatic protons. The spectrum of 2,4-diamino-8-methyl-7-oxo-6-phenyl-7,8-dihydropteridine shows the typical complex spectrum of a conjugated phenyl in this region with multiplets at 7.53 and 8.03 ppm. The spectra of the 6-phenyl-7-aminopteridines run in neutral solvents shown in Table IV show similar complex multiplets due to the phenyl protons even though the same compounds run in F_3CCOOH give spectra having singlets due to the phenyl protons. This might be explained by the existence of the protonated compounds as the resonance hybrid XXI in which contributions from the form



XXIa XXIb

XXIb would tend to make the hydrogen on the 7-amino group coplanar with the pteridine nucleus and thus interfere with the coplanarity of the phenyl and pteridine rings.

The nmr spectra of the 4-methylaminopteridines show a doublet near 3.43 ppm due to the N-methyl protons. The splitting indicates that the hydrogen on the 4-amino group does not exchange rapidly in trifluoroacetic acid. The peak due to the 2-methylamino proton appears as a singlet at 3.31 ppm indicating rapid exchange of the hydrogens on the 2-amino group in trifluoroacetic acid. The N-methyl protons in the 2-methylaminopteridines give rise to peaks further upfield than those in the corresponding 4-methylaminopteridines. This implies that in F_3CCOOH the 4-amino group is more electron deficient than the 2-amino group, possibly due to the greater importance of the resonance form XXIIa than XXIIb. If the tri-



XXIIa XXIIb

aminopteridines exist as diprotonated species in F_3CCOOH, then a combination of the forms shown in XXI and XXII would represent the true state of the molecule. The unsplit nature of the peak at 8.83 ppm in the spectrum of 4,7-diamino-6-phenylpteridine in F_3CCOOH due to the 2-proton suggests that any proton on N-1 due to salt formation is exchanging rapidly.[15]

Pharmacology.—The diuretic structure–activity relationships of a number of the compounds reported in this paper will be given in an accompanying paper.[16]

Experimental Section[17]

The paper chromatography was done by the circular system using a cotton wick to bring the solvent to the paper. The following systems were used: (1) HCOOH–H_2O–BuOH (1:5:4); (2) pretreat paper with mineral oil, develop with EtOH–H_2O (2:1); (3) BuOH–AcOH–H_2O (4:1:5); (4) pretreat paper with mineral oil–castor oil mixture, develop with EtOH–H_2O (3:1); (5) HCOOH–H_2O–*i*-AmOH-*t*-AmOH (1:5:3:3); (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 standard procedures. Since these are summarized in a readily accessible manner,[18] individual references are not always given. Ir spectra were taken on all the compounds, but they were used mainly for the purpose of showing the identity of samples since their complexity made interpretation difficult. Ir spectra were determined on a Perkin-Elmer Infracord, uv spectra on a Cary Model 14 spectrophotometer, and the nmr spectra on a Varian A-60 spectrometer.

General Procedure for the Preparation of Pteridines in Tables I–III.—Unless otherwise noted, the condensations to form pteridines from 4-amino-5-nitrosopyrimidines were carried out in DMF. The amount of solvent required to dissolve completely the pyrimidine was dried by slow distillation until the reported boiling point of the solvent was reached. The pyrimidine was then dissolved at the boiling point of the solvent and cooled slightly, and an excess of arylacetonitrile was added. To this hot mixture was slowly added $NaOCH_3$ (or other base as specified) in such a manner as to control the exothermic reaction which sometimes occurred. The reaction mixture was then heated the required period of time which was determined by the disappearance of the nitrosopyrimidine. The nitrosopyrimidines could be easily detected by dilution of an aliquot of the reaction mixture with H_2O and looking for the characteristic color of the nitrosopyrimidine. After completion of the reaction the less soluble pteridines were isolated by diluting the reaction mixtures with water, chilling, and collecting the product by filtration. Sometimes it was necessary to concentrate the reaction mixture or even take it to dryness under vacuum before addition of H_2O. In every case the product was washed well (H_2O) and recrystallized from the solvent indicated in the tables. In order to remove solvents such as DMF, the products were boiled with water for 15–30 min, and then dried at 130° for 18 hr. Purification was continued until paper chromatography showed the presence of only one major component with at most only trace quantities of other substances. A number of examples to illustrate the general method may be found in the patent literature.[19]

2,4,7-Amino-6-(*p*-trifluoromethylphenyl)pteridine.—A mixture of 10 g (0.071 mole) of tetraaminopyrimidine hydrochloride, 14.0 g (0.080 mole) of *p*-trifluoromethylbenzaldehyde, and 20 ml of AcOH was warmed to form a solid mass. This was taken up in 1200 ml of refluxing EtOH and the solution was treated with a rapid stream of gaseous HCN for 4 min in an efficient hood. The solution was filtered and allowed to stand at room temperature overnight. Filtration gave 13.9 g of **2,4,6-triamino-5-(α-cyano-*p*-trifluoromethylbenzylamino)pyrimidine hydrochloride,** mp 180–185°. Concentration of the filtrate to 200 ml gave 8.5 g (total yield 95%) of the same product, mp 178–183°, ir spectrum identical with that of the first fraction. The crude product was used for the next step.

To 13.9 g (0.043 mole) of the above product dissolved in 500 ml of MeOH was added 4.6 g (0.086 mole) of NaOMe and the mixture refluxed for 10 min. On cooling a solid was obtained which was recrystallized from MeOH to give 6.7 g of yellow crystals, mp 325–328° dec, darkens at 280–285°. This may be a complex of the desired pteridine and **2,4,6-triamino-5-(*p*-trifluoromethylbenzylidineamine)pyrimidine** of the type previously reported.[10] A suspension of 5.3 g of this product in 200 ml of water was treated with 50 ml of 30% H_2O_2 and refluxed for 10 min. Considerable foaming occurred. On cooling 4.9 g of yellow crystals were obtained which on recrystallization from DMF–H_2O gave 2.9 g of product, mp >300°.

4,7-Diamino-6-phenyl-2-pteridineacetamide.—A solution of 2.0 g of 2-cyanomethyl-4,7-diamino-6-phenylpteridine in 25 ml of concentrated H_2SO_4 was heated on a steam bath for 1 hr. It was then diluted (H_2O) and the resulting yellow solid was collected by filtration. Two recrystallizations from aqueous DMF gave 1.05 g (51% yield) of a yellow solid, mp 259–260° dec, which analyzed as the **sulfate hydrate** of the desired product. *Anal.* ($C_{14}H_{13}N_7O$) C, H, N. The free base described in Table I was obtained by stirring the above product with 5% NaOH solution for 0.5 hr.

2-Amino-7-imino-8-methyl-4-methylamino-6-phenyl-7,8-dihydropteridine.—A solution of 6.3 g (0.035 mole) of 2-amino-4,6-bismethylamino-5-nitrosopyrimidine in 150 ml of DMF was treated with 4.2 g (0.036 mole) of phenylacetonitrile and 1.9 g (0.035 mole) of $NaOCH_3$. The reaction mixture was refluxed for 2 min, cooled, and diluted with H_2O. The resulting solid was collected and recrystallized from EtOH–H_2O to give 2.2 g (22%) of yellow crystals: mp 250–251°; R_f 0.72 (system 1); $\lambda_{max}^{0.1\ N\ NaOH}$ 222, 382 mμ (log ε 4.542, 4.286), small fine structure peaks at 252, 270, 278 mμ; $\lambda_{max}^{0.1\ N\ HCl}$ 221, 309, 386 mμ (log ε 4.511, 4.100, 4.301). *Anal.* ($C_{14}H_{15}N$) C, H, N.

2,4-Diamino-10H-indolo[3,2-*g*]pteridine.—A solution of 0.85 g (0.027 g-atom) of Na in 300 ml of ethoxyethanol was treated with 9.0 g (0.037 mole) of *o*-iodophenylacetonitrile and 5.0 g (0.032 mole) of 2,4,6-triamino-5-nitrosopyrimidine and the resulting mixture refluxed for 2 hr. Addition of H_2O and chilling gave a solid which was purified by dissolving in 75% AcOH and recovering by addition of NH_4OH. This gave 2.6 g (32%) of a yellow solid, mp >300°, R_f 0.52 (system 1). *Anal.* ($C_{12}H_9N_7 \cdot 0.5H_2O$) C, H, N. The ir spectrum of this compound was identical with that of the compound prepared by condensation of tetraaminopyrimidine with isatin.[11]

General Procedure for the Replacement of Methylmercapto by Amino Groups of Diaminomethylmercapto-5-nitrosopyrimidines.—A suspension of the required methylmercaptonitrosopyrimidine in *n*-BuOH was refluxed with 2 moles of an amine (bp >30°) until the blue or purple color of the methylmercaptonitrosopyrimidine was replaced by the color of the aminonitrosopyrimidine (generally red). For the more volatile amines, a slow stream of the amine (as the anhydrous gas) was passed through the refluxing BuOH suspension. After chilling the product was collected by filtration. If necessary the solvent was concentrated to obtain the product. In general, the products were washed well (H_2O) and used crude for pteridine synthesis. In the case of aromatic amines, it was necessary to catalyze the displacement by the addition of 0.2–0.4 mole of dry ethereal HCl. The compounds prepared are shown in Table V and some representative examples are given in detail.

2,4-Diamino-6-methylamino-5-nitrosopyrimidine.—A suspension of 15 g (0.0811 mole) of 2,4-diamino-6-methylmercapto-5-nitrosopyrimidine in 175 ml of *n*-BuOH was refluxed with stirring for 1 hr while a slow stream of $MeNH_2$ was bubbled through. After cooling at 0° the solid product was collected by filtration and washed (H_2O) to give 12.0 g (88%) of product, mp 240.5–241°, whose ir spectrum was identical with that of an authentic sample.[8]

2,4-Diamino-5-nitroso-6-piperidinopyrimidine.—A suspension of 1.85 g (0.01 mole) of 2,4-diamino-6-methylmercapto-5-nitrosopyridmidine and 1.70 g (0.02 mole) of piperidine in 40 ml of

(15) A. R. Katritzky and R. E. Reavill [*J. Chem. Soc.*, 3825 (1965)] have found NH^+–CH coupling in some aminopyridine salts.

(16) J. Weinstock, J. W. Wilson, V. D. Wiebelhaus, A. R. Maass, F. T. Brennan, and G. Sosnowski, *J. Med. Chem.*, **11**, 000 (1968), paper XII of this series.

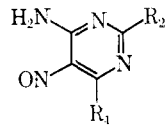
(17) We wish to thank Dr. Walter E. Thompson and Mr. Richard J. Warren for the spectral data; Miss Margaret Carroll, Mrs. Doris Ralston, and their staff for microanalytical data; and Mr. Irving Eisdorfer, Mr. Alex Post, and Mr. E. Lee Haines for chromatographic data. Where analyses are indicated only by symbols of elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

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

(19) J. Weinstock and V. D. Wiebelhaus, U. S. Patent 3,081,230 (1963).

TABLE V

4-AMINO-5-NITROSOPYRIMIDINES PREPARED FROM IV OR VI



R_2	R_1	Reaction time, hr	Yield, %	Mp, °C	Paper chromatography System	Paper chromatography R_f
$NHCH_3$	NH_2	1	52	288–290	2	0.66
$N(CH_3)_2$	NH_2	1				
$NHCH(CH_3)_2$	NH_2	2.5	44	204–208		
NHC_6H_{13}	NH_2	0.5	49	168–172		
$NHCH_2C_6H_5$	NH_2	0.75	30	230–235	2	0.80
NHC_6H_5	NH_2	2[a]	77	222–225		
	NH_2	1	45	193–195	2	0.82
	NH_2	1	38	224–230	2	0.75
	NH_2	2	48	...		
$NH(CH_2)_2N(CH_3)_2$	NH_2	0.33	65	...		
$NH(CH_2)_3N(CH_3)_2$	NH_2	0.33	76	...		
NH_2	$NHCH_3$	2	88	240–241		
NH_2	$N(CH_3)_2$	1.25	93	252–253		
NH_2	$NHCH(CH_3)_2$	5	81	193–194	1	0.80
NH_2	NHC_6H_5	1[a]	94	245–246	1	0.53
NH_2		1.5	67	212–214		

[a] Catalyzed by HCl.

n-BuOH was refluxed for 90 min. On chilling and filtering 1.50 g (67%) of red crystals, mp 212–214°, was obtained. This material had an ir spectrum identical with that of an authentic sample.[8]

2,4-Diamino-6-anilino-5-nitrosopyrimidine.—A mixture of 15 g (0.0811 mole) of 2,4-diamino-6-methylmercapto-5-nitrosopyrimidine, 10 g (0.107 mole) of aniline, 7 ml of 10% ethereal HCl, and 175 ml of *n*-BuOH was refluxed with good stirring for 1 hr. Chilling, filtration, and washing the product well with H_2O gave 17.6 g (94%) of crystals, mp 240.5–241°. Recrystallization twice from EtOH gave crystals, mp 245–246°.

2,4-Diamino-6-dimethylaminoethoxypyrimidine.—A mixture of 27 g (0.3 mole) of 2-dimethylaminoethanol and 5.8 g (0.25 g-atom) of Na in 500 ml of dry xylene was stirred under reflux for 3 hr at which time the sodium had completely dissolved. The mixture was cooled and 29 g (0.2 mole) of 2,4-diamino-6-chloropyrimidine was added and the mixture refluxed with stirring for 6 hr. The hot solution was filtered and the filtrate was chilled to give a solid. Recrystallization from *i*-PrOH gave 29 g (74%) of white crystals, mp 152.5–154°. *Anal.* ($C_8H_{15}N_5O$) C, H, N.

2,4-Diamino-6-ethoxyethoxypyrimidine.—In a similar manner sodium β-ethoxyethoxide in an excess of the alcohol was treated with 2,4-diamino-6-chloropyrimidine to give a 64% yield of product, mp 129–130°, after recrystallization from EtOH. *Anal.* ($C_8H_{14}N_4O_2$) C, H, N.

2,4-Diamino-6-(4-methylpiperazino)pyrimidine.—A mixture of 20 g (0.145 mole) of 2,4-diamino-6-chloropyrimidine and 75 ml of N-methylpiperazine was stirred at reflux for 5 hr. The excess N-methylpiperazine was distilled *in vacuo*, and the residual oil was triturated with ether. The resulting solid was recrystallized twice from *i*-PrOH to give 20 g (67%) of white crystals, mp 215° dec. *Anal.* ($C_9H_{16}N_6$) C, H, N.

2,4-Diamino-6-methylmercapto-5-nitrosopyrimidine.—A suspension of 7.8 g (0.05 mole) of 2,4-diamino-6-mercaptopyrimidine in a mixture of 8 ml of glacial AcOH and 120 ml of H_2O was heated to 40° until a solution resulted. Heating was discontinued as a solution of 5.0 g (0.07 mole) of $NaNO_2$ in a minimum volume of H_2O was added dropwise until the reaction mixture gave a persistent positive reaction to starch–iodide test paper. The mixture was then stirred for 15 min, cooled, and filtered to give a solid which was washed (H_2O) until the washings were colorless. This gave 9.2 g (100%) of a deep purple solid which was used without further purification as an intermediate.

In a similar fashion **2,4-diamino-6-(2-ethoxyethoxy)-5-nitrosopyrimidine** was obtained in 92% yield as deep red crystals, mp 202° dec, after recrystallization from EtOH. *Anal.* ($C_8H_{13}N_5O_3$) C, H, N.

Similarly, 2,4-diamino-6-(2-dimethylaminoethoxy)-5-nitrosopyrimidine, red crystals, mp 235° dec, was obtained in 80% yield; 2,4-diamino-6-(2-diethylaminoethylamino)-5-nitrosopyrimidine, pink crystals, mp 200° dec, was obtained in 35% yield; 2,4-diamino-6-(4-methylpiperazino)-5-nitrosopyrimidine, blue crystals, mp 245° dec, was obtained in 97% yield; and 2,4-diamino-6-(*p*-chloroanilino)-5-nitrosopyrimidine, brick red crystals, mp 265–267° dec, was obtained in 93% yield. These compounds were used for pteridine synthesis without further purification or characterization.

4,6-Diamino-2-cyanomethyl-5-nitrosopyrimidine.—A suspension of 2.98 g (0.02 mole) of 4,6-diamino-2-cyanomethylpyrimidine[12] in a solution of 1.38 g (0.02 mole) of $NaNO_2$ in 75 ml of H_2O was chilled in an ice bath and 5 ml of AcOH was added dropwise. This gave a clear red solution which when allowed to warm to room temperature deposited a red solid, mp >310°. Recrystallization of this product from DMF–H_2O gave 2.5 g (70%) of a red solid, mp >300°. Paper chromatography using mineral oil–castor oil (1:1) pretreated paper and developing with EtOH–H_2O (2:1) showed the presence of a major component at R_f 0.66 (red-purple under uv light) and a minor component at R_f 0.20 (purple under uv light). This material was used without further purification for pteridine synthesis.

2-Amino-4,6-bismethylamino-5-nitrosopyrimidine.—A solution of 52.2 g (0.34 mole) of 2-amino-4,6-bismethylaminopyrimidine[20] in 1 l. of 10% aqueous AcOH was treated at room temperature with a solution of 29.8 g (0.43 mole) of $NaNO_2$ in 50 ml of H_2O. After 15 min the pH was adjusted to 7 with 10% NaOH and the solution chilled. This gave 46.6 g (76%) of a red solid, mp 254–255°. Two recrystallizations from H_2O gave a red solid, mp 264–266°, which was used without further purification for pteridine synthesis.

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