

Pteridines. VII.¹ Some 2,4-Diamino-6-phenylpteridines

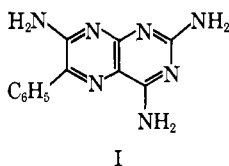
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A number of 2,4-diamino-6-phenyl-7-substituted pteridines were prepared by reaction of 2,4-diamino-7-chloro-6-phenylpteridine with nucleophilic reagents. The use of hydrazine in DMF in this reaction gave a *s*-triazolo[3,4-*h*]pteridine. Spectral data have indicated that the 6-phenyl and pteridine rings are not coplanar when the 7 substituent is as large as a methyl or NH₃⁺ group.

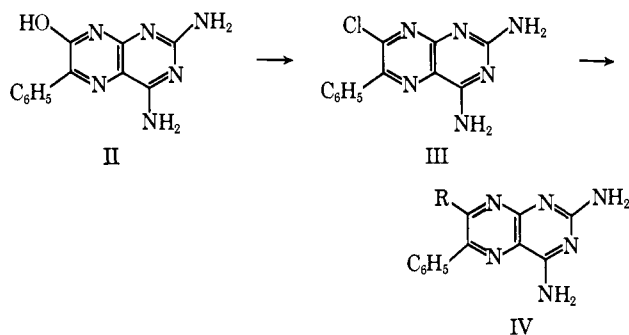
The diuretic agent triamterene (2,4,7-triamino-6-phenylpteridine) (I) contains three amino groups. In the previous paper of this series we described the preparation of compounds in which the 2- or 4-amino function was replaced by another group. In this paper we wish to report the synthesis of a number of pteridines in which the 7-amino group of triamterene has been similarly changed.



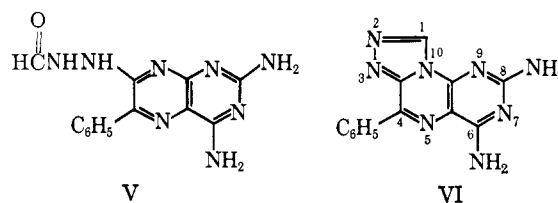
A simple approach to the preparation of pteridines in which the substituent in only one particular position is varied is to prepare an intermediate from which the required compounds may be obtained by a nucleophilic displacement. The 7-chloro derivative appeared to be a satisfactory intermediate for this purpose, since a number of hydroxyaminopteridines had been converted to the corresponding chloroaminopteridines,²⁻⁵ and replacement of the chloro group from pteridines by nucleophilic agents^{2,6} had been accomplished even from 2,4,7-trichloro⁷ and tetrachloropteridine.⁸

The required starting material for this sequence, 2,4-diamino-7-hydroxy-6-phenylpteridine (II), was readily prepared by the condensation of phenylglyoxylic acid and tetraaminopyrimidine.⁹ Treatment of this intermediate with PCl₅ in POCl₃ gave 2,4-diamino-7-chloro-6-phenylpteridine (III).

Replacement of the Cl in III with alkylamino, dialkylamino, methoxy, and mercapto was accomplished as described in the Experimental Section and Table I. The hydrazino group was introduced by reaction of III with 95% hydrazine on a steam bath for a short time. In an attempt to carry out this reaction in dimethylformamide, a product was obtained which analyzed for C₁₃H₁₀N₈ rather than the required



C₁₂H₁₂N₈. A possible source for the extra carbon was the solvent, so this suggested that the expected product (IV, R = NHNH₂) had formed, but that it had been formylated to give V which on elimination of water gave 6,8-diamino-4-phenyl-*s*-triazolo[3,4-*h*]pteridine (VI). Similar cyclizations of 2-hydrazino-



quinoxalines have previously been found to occur under mild conditions.¹⁰

This structural assignment is supported by the nmr spectrum of the compound. The spectra of 6-phenylpteridines containing a basic 7 substituent determined in trifluoroacetic acid exhibit a sharp singlet near 7.7 ppm due to the phenyl protons.¹ For example, in Table II this pattern is reported for the 7-methylamino, the 7-dimethylamino, and the 7-hydrazino analogs of IV. The spectra of certain 6-phenylpteridines lacking a basic substituent at the 7 position such as the 7-methoxy or 7-hydrogen analogs of IV also determined in trifluoroacetic acid show a complex doublet due to the phenyl protons. One peak representing three protons occupies a position near 7.6 ppm and appears as a complex triplet. The other peak representing the two *ortho* protons is more variable in its position, appearing near 8 ppm as a complex quartet. This multiplet pattern is clearly seen in the spectrum of VI. In addition, a peak appears at 8.69 ppm which although broad is not nearly as broad as the NH⁺ peaks frequently seen in this neighborhood in the spectra of aminopteridines. This peak was assigned to the hydrogen at position 1 of VI, the broadness possibly being due to its proximity to several nitrogens.

(1) Previous paper in this series: J. Weinstock, R. Y. Dunoff, B. Sutton, B. Trost, J. Kirkpatrick, F. Farina, and A. Straub, *J. Med. Chem.*, **11**, 549 (1968).

(2) C. K. Cain, E. C. Taylor, and L. J. Daniel, *J. Am. Chem. Soc.*, **71**, 892 (1949).

(3) H. Wieland, A. Tartter, and R. Purrmann, *Ann.*, **545**, 209 (1941).

(4) H. Wieland, H. Metzger, C. Schöpf, and M. Bulow, *ibid.*, **507**, 226 (1933).

(5) H. Wieland and R. Liebig, *ibid.*, **555**, 146 (1944).

(6) J. W. Daly and B. E. Christensen, *J. Am. Chem. Soc.*, **78**, 225 (1955).

(7) A. Albert, J. H. Lister, and C. Pedersen, *J. Chem. Soc.*, 4621 (1956).

(8) C. Schenker, Ph.D. Thesis, Cornell University, 1949; E. C. Taylor and W. R. Sherman, *J. Am. Chem. Soc.*, **81**, 2464 (1959).

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

(10) D. Shiho and S. Tagami, *J. Am. Chem. Soc.*, **82**, 4044 (1960).

TABLE I
 III + R₁R₂NH → IV (R = R₁R₂N)

R ₁ R ₂ N	Reaction			Recrysto solvent	Yield, %	Mp, °C	η _D (system)	Formula ^a
	Solvent	Time, hr	Temp, °C					
CH ₃ NH	BuOH	6	<i>a</i>	AcOH	43	>340	0.63 (2)	C ₁₀ H ₁₃ N ₇ ·HCl·0.25H ₂ O
<i>n</i> -C ₅ H ₁₁ NH	<i>b</i>	2	<i>a</i>	DMF	34	308-311	0.82 (2)	C ₁₁ H ₁₅ N ₇ ·HCl
						dec		
<i>n</i> -C ₆ H ₁₃ NH	<i>b</i>	5	<i>a</i>	DMF	43	198-200 ^c	0.89 (3)	C ₁₃ H ₁₉ N ₇ ·HCl ^b
C ₆ H ₅ CH ₂ NH	<i>b</i>	2.5	<i>a</i>	AcOH	47	>320	0.77 (3)	C ₁₂ H ₁₇ N ₇ ·HCl·0.25C ₁₂ H ₅ COOH
C ₄ H ₇ OCH ₂ NH ^d	<i>b</i>	2	125	EtOH	39	>300	0.28 (1)	C ₁₁ H ₁₅ N ₇ O·HCl
(CH ₃) ₂ N	DMF	5.5	100	DMF	52	>320	0.75 (2)	C ₁₁ H ₁₅ N ₇ ·HCl
C ₃ H ₁₀ N ^e	<i>b</i>	1.5	<i>a</i>	EtOH	97	267-269	0.78 (2)	C ₁₁ H ₁₅ N ₇
HOCH ₂ CH ₂ NH	EtOH	1	<i>a</i>	DMF	92	270-271	0.47 (3)	C ₁₁ H ₁₅ N ₇ O·0.33C ₁₂ H ₅ COOH
				AcOH				
CH ₃ OCH ₂ CH ₂ NH	<i>b</i>	2	100	<i>f</i>	86	218-220	0.21 (1)	C ₁₃ H ₁₆ N ₇ O

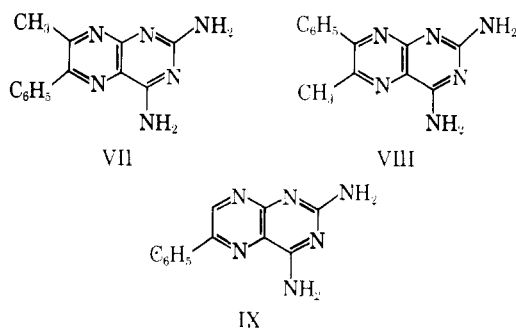
^a Reflux. ^b Excess amine. ^c Free base. ^d Furfurylamino. ^e Piperidino. ^f Dissolve in dilute HCl, precipitate with dilute NaOH at pH 8. ^g All compounds were analyzed for C, H, and N. ^h N: calcd, 26.22; found, 27.02.

 TABLE II
 NMR SPECTRAL DATA

R	δ, ppm ^a	
	6-C ₆ H ₅	Other
H	7.63 t 8.17 q	9.40 s, 7H 8.75 br, NH ⁺
CH ₃	7.64 s	2.90 s, 7-CH ₃
CH ₃ O	7.60 t, 3	4.35 s, CH ₃ O
CH ₃ NH	8.13 q, 2	8.72 br, 1, NH ⁺
	7.70 s	3.33 s, CH ₃ NH 8.7 br, NH ⁺
(CH ₃) ₂ N	7.62 s	3.22 s, (CH ₃) ₂ N
H ₂ NNH	7.65 s	8.4, HN ⁺
Triazolopteridine (VI)	7.73 t, 3	8.69 br, triazole H
	8.48 q, 2	8.9 br, NH ⁺

^a The spectra were run in F₃CCO₂H; TMS = 0; s, singlet; t, triplet; q, quintet; br, broad.

2,4-Diamino-6-phenylpteridine had been prepared unequivocally¹¹ by the condensation of diacetylated 2,4,6-triamino-5-nitrosopyrimidine and phenylacetaldehyde in ethanolic potassium acetate followed by hydrolysis of the intermediate acetylated pteridine. A similar synthesis of 2,4-diamino-7-methyl-6-phenylpteridine (VII) was attempted using phenylacetone, but no pteridine could be isolated from the reaction mixture. However, triacetylated 2,4,6-triamino-5-nitrosopyrimidine could be condensed with phenylacetone, and alkaline hydrolysis of the product gave VII. The



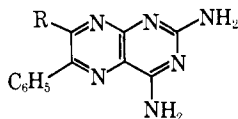
product was reported¹² to be obtained by condensation of methylphenylglyoxal with tetraaminopyrimidine hydrochloride. In our hands the condensation of methylphenylglyoxal and tetraaminopyrimidine gave a mixture of VII and its isomer 2,4-diamino-6-methyl-7-phenylpteridine (VIII) in which the former predominated. The uv spectra of the products of the two reactions were similar, but the compounds were easily differentiated by the use of nmr spectroscopy. In trifluoroacetic acid VII showed a sharp singlet at 2.90 ppm due to 7-CH₃ and a sharp singlet at 7.64 ppm due to 6-C₆H₅. However, the mixture obtained from the tetraaminopyrimidine condensation showed in addition to the above signals less intense signals at 2.85 ppm due to 6-CH₃ and at 7.67 ppm due to the 7-C₆H₅.

It is interesting to compare the nmr spectra of VII with that of 2,4-diamino-6-phenylpteridine (IX). The latter compound has a peak at 9.40 ppm resulting from the 7-H and a typical AB₂X₂ pattern for a conjugated monosubstituted phenyl with the 2-proton peak centered near 8.17 ppm and the 3-proton peak centered near 7.63 ppm. A most likely reason for the difference between the spectra of VII and IX is the steric inhibition of the coplanarity of the phenyl and pteridine rings by the methyl group of VII. In IX the phenyl and pteridine rings are coplanar. Similarly, the phenyl and pteridine rings are probably not coplanar in VIII. The difference in coplanarity of VII and IX is also seen in a comparison of their ultraviolet spectra, VII having λ_{max}^{DH} 1 254 and 348 mμ and λ_{max}^{DH} 13 262 and 372 mμ, while IX had¹¹ λ_{max}^{DH} 1 266 and 365 mμ and λ_{max}^{DH} 13 276, 302, and 389 mμ.

The uv and nmr spectral data for the compounds described in this paper are shown in Tables II and III. It is instructive to compare the spectral data for triamterene and all of the possible methylamino- and dimethylaminodiamino-6-phenylpteridines as reported in this and in the previous paper of this series.¹ In acid solution all of the pteridines except the 7-dimethylamino analog have their long wavelength uv peak at 358-364 mμ and all of the pteridines in basic solution have their long wavelength maxima at 367-383 mμ with the peaks of the more highly methylated pteridines appearing at higher wavelengths. The abnormal value in this uv series belongs to the protonated form of 2,4-diamino-7-dimethylamino-6-phenylpteridine. It seems likely that the presence of the highly basic dimethyl-

(11) I. J. Pachter and P. E. Nemeth, *J. Org. Chem.*, **28**, 1203 (1963).

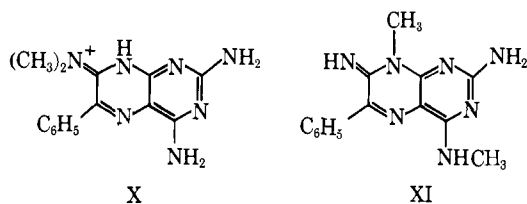
(12) C. K. Cain, U. S. Patent, 2,667,486 (1954).

TABLE III
UV SPECTRA

R	pH	λ_{\max} , m μ (log ϵ) ^a
CH ₃ NH	1	247 (4.16), 295 (3.89), 358 (4.29)
	13	236 (4.61), 266 (3.98) (sh), 367 (4.25)
<i>n</i> -C ₆ H ₁₃ NH	1	247 (4.25), 295 (4.00), 360 (4.39)
	13	279 (3.89) (sh), 372 (4.12)
<i>n</i> -C ₅ H ₁₁ NH	1	248 (4.19), 295 (3.94), 360 (4.32)
	13	234 (4.69) (sh), 274 (3.92) (sh), 368 (4.25)
HOCH ₂ CH ₂ NH	1	249 (4.21), 292 (3.91), 358 (4.33)
	13	235 (4.66), 272 (3.99) (sh), 367 (4.28)
C ₆ H ₅ CH ₂ NH	1	246 (4.21), 294 (3.97), 358 (4.33)
	13 ^b	234, 268, 367
(CH ₃) ₂ N	1	250 (4.16), 303 (3.94), 380 (4.27)
	13	243 (4.59), 292 (4.01), 383 (4.25)
C ₆ H ₁₀ N	1	309 (4.05), 386 (4.35)
	13 ^b	246, 298, 390
H ₂ NNH	1	260 (4.33), 282 (3.99) (sh), 355 (4.39)
	13	273 (4.43), 292 (4.27) (sh), 378 (4.11)
HS	1	252 (4.34), 322 (3.88), 400
	13	247 (4.49), 294 (3.89) (sh), 396 (4.22)
CH ₃ O	1	257 (4.33), 280 (3.97) (sh), 348 (4.31)
	13	265 (4.33), 286 (4.09) (sh), 363 (4.33)
Cl	1	262 (4.30), 358 (4.12)
	13	227 (4.63), 270 (4.07), 286 (3.82) (sh), 362 (4.26)
CH ₃	1	254 (4.41), 348 (4.17)
	13	262 (4.46), 372 (4.09)

^a pH 1 data obtained in 4.5% formic acid and the pH 13 data in 0.1 N NaOH. ^b Qualitative spectra, compound precipitated out of solution.

amino group in the pyrazine ring might induce protonation at N-8 rather than at N-1 to give X and its various resonance forms as the protonated species.



This is supported by the similarity of the uv spectra of X and XI, X having $\lambda_{\max}^{\text{pH } 1}$ 250, 303, and 380 m μ and XI having $\lambda_{\max}^{\text{pH } 1}$ 221, 309, and 386 m μ . The upfield position in the nmr spectra of 7-N(CH₃)₂ might be due to their position in the shielding zone of the 6-phenyl group.

The singlet nature of the 6-C₆H₅ signal in the nmr spectrum which was postulated previously in the case of the 6-phenyl-7-methylpteridine to be due to steric inhibition of coplanarity of the phenyl and pteridine rings is also seen for the 7-methylamino, 7-dimethylamino, and 7-hydrazino analogs presumably for the same reason.

As noted before, the signal for the 7-H in the nmr spectrum of VII came at 9.40 as a singlet. In comparison, the 2-H of 4, 7-diamino-6-phenylpteridine¹ had its nmr signal as a singlet at 8.83 ppm. In neither case is an adjacent nitrogen strongly enough protonated to split the peak, and the upfield position of the 2-proton

indicates that it is in a more electron-rich environment, possibly due to the presence of an amino group in the same ring.

Pharmacology.—The diuretic structure-activity relationships of the compounds reported in this paper will be given in an accompanying paper.¹³

Experimental Section¹⁴

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) thin layer on silica gel G, EtOAc-AcOH-H₂O (8:1:1); (2) standing phase mineral oil applied in 20% solution in acetone, moving phase EtOH-H₂O (2:1); (3) HCOOH-H₂O-*i*-AmOH-*t*-AmOH (1:5:3:3); (4) standing phase mineral oil and castor oil (1:1) moving phase EtOH-H₂O (2:1). Melting points are uncorrected and were determined in open capillary tubes. The uv spectra were recorded with a Cary Model 14 spectrophotometer and the nmr spectra on a Varian A-60 spectrometer.

2,4-Diamino-7-chloro-6-phenylpteridine (III).—To a well-stirred mixture of 1020 ml (11.2 moles) of POCl₃ and 216 g (1.04 moles) of PCl₅ was added 60 g (0.236 mole) of 2,4-diamino-7-hydroxy-6-phenylpteridine over a 10-min period. The reaction mixture was refluxed for 3 hr and then most of the POCl₃ was removed under reduced pressure. The cooled residue was poured into a well-stirred mixture of 1.8 kg of ice and water to give a yellow solid which was collected by filtration. This was recrystallized twice from 2% HCl and once from glacial AcOH. Finally it was dissolved in HCOOH and precipitated by addition of NH₄OH. This was dried under reduced pressure to give 24 g (37%) of yellow crystals, mp 300°, *R*_f 0.55 (system 1). *Anal.* (C₁₂H₉ClN₆) C, H, N.

The hydrochloride was obtained by several recrystallizations of the crude product from EtOH as yellow crystals, mp >320°, *R*_f 0.65 (system 4) (free base liberated with Et₃NH, applied in DMSO solution). *Anal.* (C₁₂H₉N₆Cl·HCl) C, H, Cl, Cl⁻.

2,4-Diamino-7-methylamino-6-phenylpteridine Hydrochloride (IV, R = CH₃NH).—A suspension of 7.0 g (0.023 mole) of III in 1 l. of *n*-BuOH was refluxed for 6 hr while a stream of MeNH₂ was passed into the reaction mixture. On cooling 2.0 g of material separated from solution which proved to be mainly starting material. After filtration the reaction mixture was concentrated under vacuum and the residue was suspended in H₂O, and then filtered to give 3.0 g (43%) of product which was recrystallized from AcOH for analysis, mp >340° dec, *R*_f 0.63 (system 2). *Anal.* (C₁₃H₁₃N₇·HCl·0.25H₂O) C, H, Cl, N.

2,4-Diamino-7-pentylamino-6-phenylpteridine Hydrochloride (IV, R = *n*-C₅H₁₁NH).—A mixture of 5.0 g (0.0162 mole) of III and 100 ml of *n*-pentylamine was refluxed for 2 hr. The reaction mixture was taken to dryness under vacuum and the residue was suspended in 50 ml of H₂O. The gummy product was collected by filtration and washed (EtOH) to give a yellow granular product. Two recrystallizations from DMF gave yellow crystals.

2,4-Diamino-7-methoxy-6-phenylpteridine (IV, R = CH₃O).—A solution of 1.0 g (0.00324 mole) of 2,4-diamino-7-chloro-6-phenylpteridine hydrochloride (III) and 2.0 g (0.037 mole) of NaOCH₃ in 100 ml of MeOH was refluxed for 2.5 hr. On cooling yellow needles separated which were collected by filtration, washed with MeOH, and dried to give 0.55 g (63%) of product. Recrystallization from a mixture of DMF and MeOH gave crystals, mp 275° dec pt 248°, *R*_f 0.71 (system 1) and 0.58 (system 3). *Anal.* (C₁₃H₁₂N₆O) C, H, N.

2,4-Diamino-7-mercapto-6-phenylpteridine (IV, R = HS).—A solution of 35 g (0.63 mole) of KOH in 300 ml of absolute EtOH was saturated with anhydrous H₂S. To this was added 5.0 g (0.0162 mole) of III and 200 ml of EtOH and the mixture refluxed for 2 hr. The solution was filtered and the filtrate was concentrated to small volume. The residue was suspended in H₂O and

(13) J. Weinstock, J. W. Wilson, V. D. Wiebelhaus, A. R. Maass, F. T. Brennan, and G. Sosnowski, *J. Med. Chem.*, **11**, 573 (1968), paper XI1 of this series.

(14) We wish to thank Dr. W. E. Thompson and Mr. R. J. Warren for the spectral data, Miss M. Carroll and her staff for microanalytical data, and Mr. A. Post and Mr. E. L. Haines for chromatographic data. Where analyses are indicated only by symbols of elements, analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

filtered, and the solid was washed (H₂O) and recrystallized from DMF to give 1.5 g (34%) of an orange solid. This was recrystallized from AcOH to give a solid, mp 315° dec, *R_f* 0.53 (system 2). *Anal.* (C₁₂H₁₀N₆S) C, H, N, S: calcd, 11.86; found, 11.08.

2,4-Diamino-7-hydrazino-6-phenylpteridine (IV, R = NH₂NH₂).—A mixture of 5.0 g (0.0162 mole) of III and 30 ml of 95% hydrazine was heated at reflux for 5 min and then chilled. Filtration gave 3.0 g (69%) of an orange-yellow solid. This was recrystallized twice from DMF and once from a DMF-cyclohexane mixture to give crystals, mp 356° dec, *R_f* 0.50 (system 2). *Anal.* (C₁₂H₁₂N₈) C, H, N.

6,8-Diamino-4-phenyl-8-triazolo[3,4-*b*]pteridine (VI).—A mixture of 5.0 g (0.0162 mole) of III, 50 ml of 95% hydrazine, and 50 ml of DMF was warmed on a steam bath until the gas evolution which started when the temperature reached 75° ceased (1 hr). Concentration to 25 ml and chilling gave a solid which was collected by filtration and recrystallized from DMF to give 2.0 g (44%) of a product, mp >300° dec, *R_f* 0.40 (system 2). *Anal.* (C₁₃H₁₀N₈) C, H, N. The product was not sufficiently soluble to determine a quantitative uv spectrum, but it had $\lambda_{\max}^{4.5\% \text{ HCOOH}}$ 344 m μ , $\lambda_{\max}^{1\% \text{ NaOH}}$ 362 m μ .

2,4-Diamino-7-methyl-6-phenylpteridine (VII).—To a refluxing mixture of 8.4 g (0.03 mole) of triacetylated 2,4,6-triamino-5-

nitrosopyrimidine¹⁵ and 8.4 g (0.02 mole) of phenylacetone in 200 ml of absolute EtOH was added portionwise a solution of 6.0 g (0.061 mole) of KOAc in 80 ml of absolute EtOH. After 1.5 hr of reflux the hot solution was filtered and concentrated under reduced pressure. The residue was treated with 100 ml of 4% aqueous NaOH for 3 hr at room temperature. Neutralization of the reaction mixture with AcOH and chilling caused the separation of 5.2 g (64%) of a brown-orange solid which was recrystallized from EtOH; *R_f* 0.59 (system 3), mp 335° dec. *Anal.* (C₁₃H₁₂N₆) C, H, N.

An attempted condensation of phenylacetone with diacetylated 2,4,6-triaminonitrosopyrimidine¹⁶ using KOAc as base or with NaOCH₃ as base gave 2,4,6-triamino-5-nitrosopyrimidine as the only isolable product.

Acknowledgment.—The authors wish to thank Drs. J. W. Wilson, G. E. Ulyot, V. D. Wiebelhaus, and A. R. Maass for their interest and encouragement during the course of this work.

(15) I. J. Pachter, P. E. Nemetz, and A. J. Villani, *J. Org. Chem.*, **28**, 1197 (1963).

Pteridines. VIII. Some 2,4,7-Triamino-6-heteroarylpteridines

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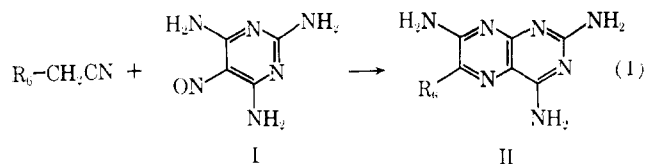
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A number of 2,4,7-triamino-6-heteroarylpteridines were prepared for diuretic testing. Included among the heteroaryl groups were furans, thiophenes, pyrroles, pyrazoles, thiazoles, pyridines, and an imidazole, an oxazole, a pyrimidine, and a triazole. The uv spectra of these compounds showed a surprisingly regular pattern.

The discovery of the interesting diuretic activity of triamterene (2,4,7-triamino-6-phenylpteridine) prompted us to prepare related pteridines in order to study structure-activity relationships. In previous papers we have described the preparation of pteridines in which the amines were replaced either by a substituted amine or by another group,^{1,2} pteridines in which the 6-phenyl is replaced by a substituted aryl,¹ and pteridines in which the 6-phenyl is replaced by a 6-alkyl.³ In this paper we wish to describe the preparation of a series of 2,4,7-triamino-6-heteroarylpteridines.

At the time this work was carried out the only reported member of this series was 2,4,7-triamino-6-(2-thienyl)pteridine⁴ which had been prepared by the base-catalyzed condensation (reaction 1, R₆ = 2-thienyl) of 2-thienylacetonitrile with 2,4,6-triamino-5-nitrosopyrimidine (I). This general scheme proved useful for the preparation of the compounds reported in this paper, although it failed in several instances. One such failure involved the attempted preparation of 2,4,7-triamino-6-(2-pyrrolyl)pteridine. No characterizable material was isolated from the black reaction mixture resulting from reaction of I with pyrrole-2-acetonitrile under a variety of conditions. Since I is a relatively unreactive nitrosopyrimidine in this type



of pteridine synthesis, 4,6-diamino-5-nitroso-2-phenylpyrimidine was used as a prototype pyrimidine in attempted reactions with pyrrole-2-acetonitrile. It was found that using NaCN as the catalyst in EtOH as the solvent 4,7-diamino-2-phenyl-6-(2-pyrrolyl)pteridine could be formed in 34% yield. However, attempts to use these conditions for the synthesis of the 2-amino analog failed because of the insolubility of I in ethanol and the instability of the nitrile to the basic reaction conditions. The use of NaCN in DMF also was not successful.

When 1-methylpyrrole-2-acetonitrile was condensed with I, no unusual difficulty was encountered and the desired 2,4,7-triamino-6-(1-methyl-2-pyrrolyl)pteridine was obtained in 39% yield. Possibly the key to the failure with the unmethylated pyrrole lies in its ability to form a reactive anion easily by the removal of the hydrogen on the ring nitrogen. A similar failure was also encountered with 2-methylpyrrole-4-acetonitrile which was not useful for preparing pteridines by this reaction in our hands. The ability of the pyrrole ring to activate the hydrogens of pyrroleacetonitriles was also demonstrated by the formation of 2,4,7-triamino-6-(1-pyrrolyl)pteridine (III) from I and pyrrole-1-acetonitrile.

(1) J. Weinstock, R. Y. Dunoff, B. Sutton, B. Trost, J. Kirkpatrick, F. Farina, and A. S. Straub, *J. Med. Chem.*, **11**, 549 (1968).

(2) J. Weinstock, I. J. Pachter, P. E. Nemetz, and G. Jaffe, *ibid.*, **11**, 557 (1968).

(3) I. J. Pachter, *J. Org. Chem.*, **28**, 1191 (1963).

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