filtered, and the solid was washed (H_2O) 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.* ($C_{12}H_{10}N_6S$) C, H, N; S: calcd, 11.86; found, 11.08.

2,4-Diamino-7-hydrazino-6-phenylpteridine (IV, R = NH_2NH).—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.* ($C_{12}H_{12}N_8$) C, H, N.

6,8-Diamino-4-phenyl-*s*-triazolo[3,4-*h*]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.* ($C_{13}H_{10}N_8$) C, H, N. The product was not sufficiently soluble to determine a quantitative uv spectrum, but it had $\lambda_{max}^{4.5\%\ HCOOH}$ 344 mμ, $\lambda_{max}^{1\ N\ NaOH}$ 362 mμ.

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-nitrosopyrimidine[15] and 8.4 g (0.62 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.* ($C_{13}H_{12}N_8$) C, H, N.

An attempted condensation of phenylacetone with diacetylated 2,4,6-triaminonitrosopyrimidine[15] using KOAc as base or with $NaOCH_3$ 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. Ullyot, V. D. Wiebelhaus, and A. R. Maass for their interest and encouragement during the course of this work.

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

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

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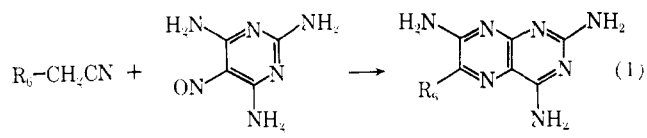
A number of 2,4,7-triamino-6-heteroarylpteridines were prepared for diuretic testing. Included among the heteroaryl groups were furans, thiophenes, pyrroles, pyrazoles, thiazoles, pyridines, and an imidazole, an oxazole, a pyrimidine, and a triazole. The uv spectra of these compounds showed a surprisingly 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)pteridine[4] which had been prepared by the base-catalyzed condensation (reaction 1, R_6 = 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.

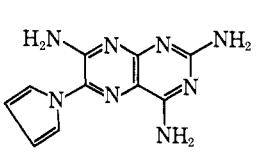
(1) J. Weinstock, R. Y. Dunoff, B. Sutton, B. Trost, J. Kirkpatrick, F. Farina, and A. S. Straub, *J. Med. Chem.*, **11**, 549 (1968).

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

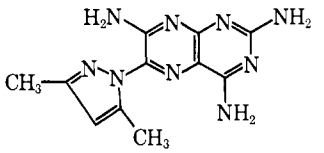
(3) I. J. Pachter, *J. Org. Chem.*, **28**, 1191 (1963).

(4) R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1951).

A similar pteridine with the 6-heteroaryl group attached to the pteridine ring through a ring nitrogen was prepared by the condensation of 3,5-dimethylpyrazole-1-acetonitrile with I to give 2,4,7-triamino-6-(3,5-dimethyl-1-pyrazolyl)pteridine (IV) in 42% yield.

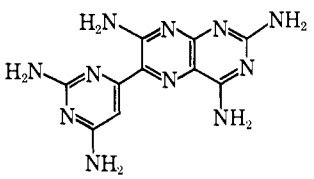


III

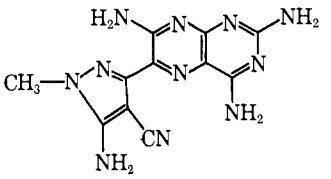


IV

The presence of an acidic hydrogen on the heteroarylacetonitrile does not always inhibit pteridine formation. 2,6-Diaminopyrimidine-4-acetonitrile condensed with I to give 2,4,7-triamino-6-(2,6-diamino-4-pyrimidyl)-pteridine (V) and 5-amino-4-cyano-3-cyanomethyl-1-methylpyrazole condensed with I to give 2,4,7-triamino-6-(5-amino-4-cyano-1-methyl-3-pyrazolyl)pteridine (VI).



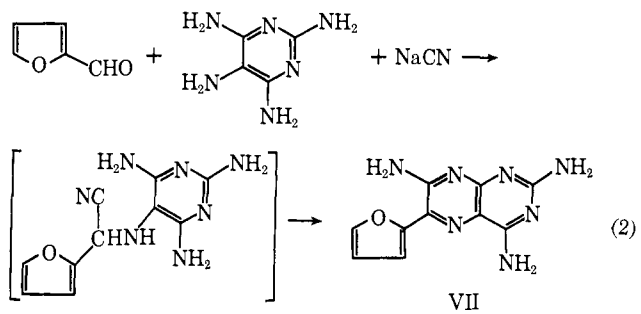
V



VI

The required heteroarylacetonitriles for many of these syntheses were previously known. Those previously unknown were prepared either by dehydration of the corresponding amide (3,5-dimethylpyrazole-1-acetonitrile and 3,5-dimethylisoxazole-4-acetonitrile) or by treatment of a chloromethyl heteroaromatic with CN^- (4-methylthienyl-2-acetonitrile, pyridyl-4-acetonitrile, and 1-benzyl-1,2,4-triazole-3-acetonitrile). 2,6-Diaminopyrimidine-4-acetonitrile was prepared from ethyl 4-uracilacetate first by reaction with NH_3–MeOH containing some sodium methoxide to give uracil-4-acetamide, followed by conversion of this intermediate to 2,6-dichloropyrimidine-4-acetonitrile with $POCl_3$ and subsequent treatment of this intermediate with NH_3–EtOH. Many of the acetonitriles were used for pteridine synthesis as obtained without extensive purification.

In many instances, heteroarylaldehydes are more readily available than the corresponding heteroarylacetonitriles. In this situation the aldehyde–cyanide pteridine synthesis[3] is useful (reaction 2). Furan-2-acetonitrile and furfural represent such a case, and synthesis of 2,4,7-triamino-6-(2-furyl)pteridine (VII) has been carried out using both routes.

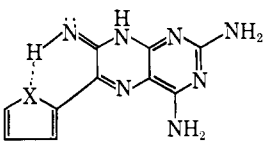


(2)

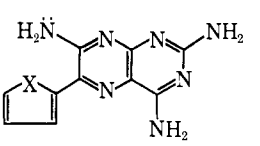
VII

The 2,4,7-triamino-6-heteroarylpteridines prepared as part of this research are listed in Table I along with their uv absorption data determined at pH 1 and pH 14. Inspection of these data shows that the compounds fall into several classes. In one class at pH 1 the long wavelength peak falls between 358 and 366 mμ and at pH 14 between 364 and 374. In this class the 6-heterocyclic ring is attached to the pteridine either β to the heteroatom or *via* a ring nitrogen. Spectrally, these compounds resemble the 6-phenyl analog which has its pH 1 and pH 14 peaks at 358 and 368 mμ.[3] In a second class at pH 1 the long wavelength peak falls between 377 and 389 mμ and at pH 14 between 386 and 400 mμ. In this class the 6-heteroaryl ring is attached to the pteridine by a carbon α to one hetero atom. A third class of compounds is characterized by pH 1 peaks between 370 and 404 mμ and pH 14 peaks between 414 and 444 mμ. In this class the 6-heteroaryl ring is attached to the pteridine by a carbon between two ring hetero atoms. 2,4,7-Triamino-6-(4-pyridyl)pteridine falls into the first class in acid solution and into the second class in basic solution.

These data may be rationalized by assuming that in the case of the 6-(β-linked) heteroaromatic pteridines, the heterocyclic nucleus is equivalent to the phenyl ring. However, in the case of the α-linked heterocyclic hydrogen, bonding of the type shown in VIII may force coplanarity of the 7-NH, C-6, and C-7 of the pteridine ring, and the hetero atom of the 6-heteroaromatic ring. This enforced coplanarity might stabi-

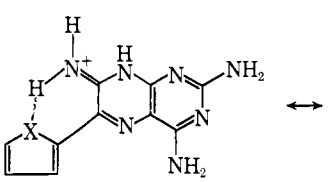


VIII

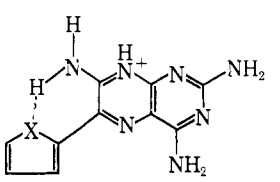


IX

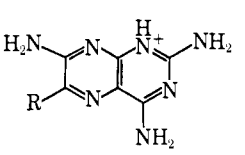
lize the 7-imino form VIII over the customarily expected 7-amino form IX. Since the spectra of these compounds at pH 1 are also abnormal, this suggests that the salts might be best represented as X rather than the customarily expected XI. Support for this



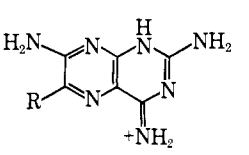
Xa



Xb



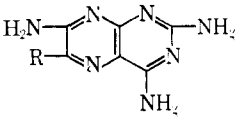
XIa



XIb

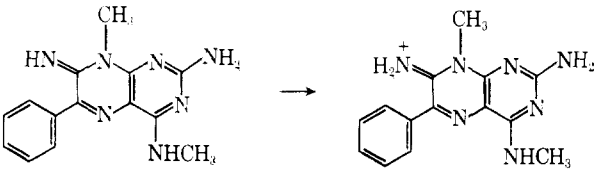
comes from the spectra of 2-amino-7-imino-8-methyl-4-methylamino-6-phenyl-7,8-dihydropteridine (XII)[1] which have $\lambda_{max}^{pH\ 1}$ 221, 309, and 386 mμ and $\lambda_{max}^{pH\ 13}$ 222 and 382 mμ which are similar to that observed for the 6-(α-linked) heteroaromatic pteridines.

TABLE I: UV ABSORPTION DATA



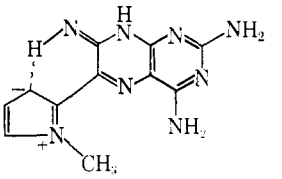
R	pH	λ_{max}, mμ (log ε)
2-Furyl	1	258 (4.25), 304 (3.94), 389 (4.33)
	14	230 (4.66), 284 (4.20), 302 (sh), 398 (4.33)
3-Furyl	1	256 (4.17), 283 (3.82), 364 (4.30)
	14	269 (4.15), 288 (sh), 372 (4.25)
2-Thienyl	1	258 (4.20), 300 (3.90), 377 (4.28)
	14	231 (4.55), 280 (4.10), 386 (4.26)
3-Thienyl	1[a]	265 (4.08), 286 (sh), 364 (4.25)
	14	276 (4.09), 301 (sh), 374 (4.22)
4-Methyl-2-thienyl	1[a]	268 (sh), 304 (3.97), 382 (4.32)
	14	282, 312 (sh), 392 (qualitative[c])
5-Chloro-2-thienyl	1[a]	266 (sh), 306 (4.00), 386 (4.33)
	14	296, 326 (sh), 400 (qualitative[b])
2-Benzothiopyl	1	259, 312, 389 (qualitative[c])
	14	298, 396 (qualitative[b])
3-Benzothienyl	1	257, 288, 298, 364 (qualitative[c])
	14	229, 262, 290 (sh), 298, 372 (qualitative[c])
1-Pyrrolyl	1	254 (4.22), 256 (sh), 280 (sh), 360 (4.303)
	14	267 (4.21), 284 (sh), 369 (4.24)
1-Methyl-2-pyrrolyl	1	256 (4.23), 309 (3.94), 385 (4.23)
	14	230 (4.67), 271 (4.12), 296 (sh), 386 (4.23)
3,5-Dimethyl-1-pyrazolyl	1	260 (4.23), 344 (4.26), 362 (sh) (4.23)
	14	266 (4.22), 332 (4.18), 364 (4.18)
5-Amino-4-cyano-1-methyl-3-pyrazolyl	1	257 (4.50), 288 (sh), 348 (3.97), 410 (4.19)
	14	250 (4.51), 264 (4.54), 296 (sh), 424 (4.28)
1-Benzyl-2-imidazolyl	1	267 (4.33), 370 (4.39)
	14	412, 440 (qualitative,[b] ill defined at lower wavelengths)
4-Thiazolyl	1	262 (4.22), 292 (4.00), 304 (sh), 379 (4.31)
	14	233 (4.62), 276 (4.17), 304 (sh), 386 (4.29)
4-Methyl-2-thiazolyl	1[a]	276 (4.10), 304 (3.97), 316 (3.96), 404 (4.37)
	14	300, 316 (sh), 374 (sh), 384 (sh), 392 (sh), 414 (qualitative[b])
3,5-Dimethyl-4-isoxazolyl	1	259 (4.23), 286 (sh) (3.79), 358 (4.35)
	14	259 (4.24), 367 (4.30)
2-Pyridyl	1	248 (sh), 260 (4.13), 294 (3.91), 305 (3.90), 380 (4.29)
	14	235 (4.50), 268 (sh), 294 (sh), 308 (sh), 386 (4.27)
3-Pyridyl	1	249 (4.27), 268 (sh), 284 (sh), 366 (4.33)
	14	230 (4.62), 260 (sh), 370 (4.29)
4-Pyridyl	1	250 (4.26), 312 (3.94), 384 (4.29)
	14	270 (4.10), 374 (4.32)
2,6-Diamino-4-pyrimidyl	1	253 (4.26), 278 (4.18), 307 (sh), 385 (4.35)
	14	238 (4.72), 290 (4.19), 352 (sh), 396 (4.29)
3-(1-Benzyl-1,2,4-triazolyl)	1	268 (4.31), 374 (4.37)
	14	300, 400, 444 (qualitative[b])
2-Thienyl(2-methylamino)	1	262 (4.17), 300 (3.84), 380 (4.26)

[a] 22.5% HCO_2H. [b] Sample precipitated from solution on dilution.

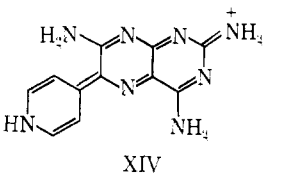


XIIa XIIb

In the case of 2,4,7-triamino-6-(1-methyl-2-pyrrolyl)-pteridine, hydrogen bonding of the type shown above would be blocked because of steric hindrance provided by the methyl on the pyrrole nitrogen. In this case, the hydrogen bonding may take place on the 3-carbon (XIII) which because of resonance is electron rich.



XIII



XIV

Another special case is 2,4,7-triamino-6-(4-pyridyl)-pteridine which shows a high long wavelength (384 mμ) peak in acid solution. This may be assumed to arise by protonation on the pyridine nitrogen giving rise to a resonance form such as XIV which has an extended conjugated system.

Pharmacology. - The diuretic structure–activity relationships of the compounds reported in this paper will be reported in an accompanying paper.[5]

Experimental Section[6]

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) HCOOH–H_2O–*i*-$C_5H_{11}OH$–*t*-$C_5H_{11}OH$ (1:5:3:3); (3) AcOH–H_2O–*n*-BuOH (1:5:4); (4) *i*-PrOH–H_2O–NH_4OH (14:1:5); (5) HCOOH–H_2O–BuOH (1:5:5); (6) standing phase, mineral oil applied at 20% solution in $AcCH_3$, moving phase, EtOH–DMF–1% NH_4OH (1:1:1); (7) standing phase mineral oil as above, moving phase, EtOH–5% HCOOH (2:1). Melting points are uncorrected and were determined in open capillary tubes. Uv spectra were recorded with a Cary Model 14 spectrophotometer using 4.5% HCO_2H for the pH 1 data and 1 *N* NaOH for the pH 14 data.

2,4,7-Triamino-6-[4-(3,5-dimethylisoxazolyl)]pteridine.—A mixture of 20 ml of $POCl_3$ and 10 g (0.0723 mole) of 3,5-dimethylisoxazole-4-acetamide was refluxed for 75 min and the volatiles were evaporated under reduced pressure. The residue was poured over an ice–water mixture and this was extracted three times with 50 ml of $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and distilled to give 8.5 g (98%) of a colorless oil, bp 125–130° (0.25 mm), whose ir spectra had a peak at 4.5 μ indicative of a nitrile and had no peak at 5.9 μ characteristic of the precursor amide. This material was assumed to be the desired 3,5-dimethylisoxazole-9-acetonitrile and used in the next reaction.

A mixture of 7.7 g (0.05 mole) of 2,4,6-triamino-5-nitrosopyrimidine and 7.2 g (0.06 mole) of the above 3,5-dimethylisoxazole-4-acetonitrile in 100 ml of DMF was heated to reflux with stirring and a slurry of 3.24 g (0.06 mole) of $NaOCH_3$ in 20 ml of DMF

(5) 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.

(6) We wish to thank Dr. Walter E. Thompson and Mr. Richard J. Warren for the spectral data, Miss Margaret Carroll and her staff for microanalytical data, and Mr. Alex 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 ±0.4% of the theoretical values.

was added over 20 min. After an additional 30 min of reflux the reaction mixture was cooled and filtered to give a light yellow product which was recrystallized from 200 ml of 50% AcOH–H_2O. The resulting colorless acetate salt was dissolved in 100 ml of hot 10% HCl and the pH was quickly brought to pH 8 with 40% NaOH. The solution was cooled and filtered, and the solid was reslurried in 150 ml of H_2O, and then refiltered to give 8.7 g (68%) of a crystalline colorless solid, R_f 0.59 (system 1). *Anal.* ($C_{11}H_{12}N_8O \cdot 0.5H_2O$) C, H, N.

2,4,7-Triamino-6-(4-methyl-2-thienyl)pteridine.—A solution of 73.9 g (0.59 mole) of 2-formyl-4-methylthiophene[7] in 400 ml of MeOH was treated cautiously with 11.35 g (0.30 mole) of $NaBH_4$ using an ice bath to moderate the reaction. After 1 hr part of the MeOH was removed under vacuum and the remainder was diluted with H_2O and extracted (Et_2O). The ether was dried ($MgSO_4$) and distilled to give 62 g (82%) of 4-methylthiophene-2-methanol, bp 128–130° (33 mm), whose structure was indicated by its ir spectrum and used in the next reaction without further characterization.

A solution of 36.0 g (0.27 mole) of 4-methylthiophene-2-methanol in 27 ml (0.33 mole) of pyridine and 30 ml of ether was added to a solution of 22.5 ml (0.3 mole) of $SOCl_2$ in 30 ml of pentane at 5° over 1 hr. Then 150 ml of pentane and 150 ml of 10% HCl was added to the dark reaction mixture and the organic phase separated. The aqueous phase was extracted several times with pentane and the combined organic phases were washed (saturated $NaHCO_3$, saturated NaCl) and then dried ($MgSO_4$). The solvent was removed under vacuum and the residue was stirred for 1 hr at 5° and 3 hr at room temperature with a suspension of 14.7 g (0.3 mole) of NaCN in 150 ml of DMF. The suspension was filtered and the filtrate was concentrated under vacuum and diluted (H_2O). Extraction of the mixture with ether and distillation of the dried ethereal solution gave 9.2 g (22%) of 4-methylthiophene-2-acetonitrile, bp 137–141° (37 mm), which was characterized as a nitrile by its ir spectrum and used in the next reaction without further characterization.

A solution of 3.0 g (0.02 mole) of 2,4,6-triamino-5-nitrosopyrimidine in 125 ml of almost refluxing DMF was treated with 2.8 g (0.02 mole) of 4-methylthiophen-2-acetonitrile and 1.08 g (0.02 mole) of $NaOCH_3$. The reaction mixture was refluxed for 1 min, cooled, and diluted with H_2O. Filtration gave 3.2 g (58%) of product which was recrystallized by dissolving in 50% AcOH–H_2O and reprecipitating by adding NH_4OH to pH 4.5; mp >300°, R_f 0.62 (system 1). *Anal.* ($C_{11}H_{11}N_7S$) C, H, N.

4,7-Diamino-2-phenyl-6-(2-pyrrolyl)pteridine.—To a suspension of 5 g (0.0232 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine and 5 g (0.0472 mole) of pyrrole-2-acetonitrile[8] in 100 ml of EtOH was added a solution of 2.5 g (0.051 mole) of NaCN in 25 ml of water and the green mixture refluxed for 1 hr. Chilling gave a brown solid which was collected and washed well (H_2O). This was dissolved in 400 ml of refluxing 50% AcOH–H_2O, heavily charcoaled, cooled, and brought to pH 8 with concentrated NH_4OH to give a yellow solid. This was washed well (H_2O), reslurried with dilute NH_4OH, collected, and again washed (H_2O). This gave 2.4 g (34%) of yellow crystals: mp >300°; R_f 0.70 (system 3); $\lambda_{max}^{pH\ 1}$ 276 mμ (log ε 4.434), 418 mμ (log ε 4.401); $\lambda_{max}^{pH\ 6.5}$ 276 mμ (log ε 4.113), 418 mμ (log ε 4.068); $\lambda_{max}^{pH\ 11}$ 270 mμ (log ε 3.962), 418 mμ (log ε 3.951). *Anal.* ($C_{16}H_{13}N_7$) C, H, N.

2,4,7-Triamino-6-(2-furyl)pteridine. Aldehyde–Cyanide Method.[9]—A mixture of 10.7 g (0.05 mole) of tetraaminopyrimidine dihydrochloride, 75 ml of MeOH, and 30 ml of AcOH was heated to 50° and a solution of 5.0 g (0.10 mole) of NaCN in 22 ml of H_2O was added followed by 7.35 g (0.0765 mole) of furfural in 20 ml of MeOH. The warm solution was immediately filtered to remove the salts formed and the solution was allowed to stand at room temperature for 1 hr. Chilling gave a yellow crystalline material which was dried before proceeding to the next step. This product was added to a solution of 15 g of $NaOCH_3$ in 240 ml of MeOH and the solution was refluxed for 10 min. The reaction mixture was diluted with 240 ml of H_2O and 30 ml of 30% H_2O_2 was added. After standing at room temperature overnight, the reaction mixture was chilled and filtered to give 5.7 g (47%) of a yellow product. Several recrystallizations from 50% aqueous AcOH followed by treatment with NH_4OH gave 2.6 of yellow crystals whose ir spectrum was identical with that of product listed in Table II; R_f 0.41 (system 1) and 0.27 (system 2).

2-Cyanomethyl-4-methylthiazole.—To a solution of 8.8 g of NaCN in 125 ml of redistilled DMSO was added at below 20° with efficient stirring 20 g (0.135 mole) of 2-chloromethyl-4-methylthiazole.[10] The reaction mixture was then warmed on a steam bath to 40° at which time an exothermic reaction started. The temperature was kept at 45–50° by cooling during the exothermic phase, following which the temperature was raised to 60° briefly. After cooling, the reaction mixture was poured into 500 ml of water and extracted three times with 200 ml of ether. The combined ethereal extracts were washed (H_2O), dried ($MgSO_4$), and distilled to give 9.0 g (54%) of a yellow oil, bp 82–84° (0.6 mm). A portion was redistilled for analysis (bp 82–83° at 0.45 mm). *Anal.* ($C_6H_6N_2S$) C, H, N.

3,5-Dimethylisoxazole-4-acetamide.—To 100 ml of saturated ammoniacal MeOH containing 0.65 g of $NaOCH_3$ was added 18.3 g (0.1 mole) of ethyl 3,5-dimethylisoxazole-4-acetate[11] and the mixture was allowed to stand at room temperature for 64 hr. Concentration of the reaction mixture gave an almost colorless solid, mp 112–115°. This was dissolved in 20 ml of EtOH, treated with charcoal, diluted with 100 ml of Et_2O, and chilled to give 10.7 g (77%) of colorless crystals, mp 114–115°. *Anal.* ($C_7H_{10}N_2O_2 \cdot {}^1/_8H_2O$) C, H, N.

3,5-Dimethylpyrazole-1-acetamide.—A suspension of 5.28 g (0.22 mole) of NaH in 100 ml of toluene was treated with a solution of 19.2 g (0.20 mole) of 3,5-dimethylpyrazole in 100 ml of hot toluene. After 1 hr of reflux, the solution was cooled, 42 g (0.25 mole) of ethyl bromoacetate was added, the mixture refluxed for 17 hr. The hot mixture was filtered and the insoluble solid was washed with dry $PhCH_3$. The combined filtrates were distilled to give 27 g (74%) of ethyl 3,5-dimethylpyrazole-1-acetate, bp 128–136° (0.3 mm), as a colorless oil. A mixture of 21.3 g (0.117 mole) of this ester and 110 ml of 14 *N* NH_4OH was shaken vigorously for 10 min and the crystals which formed were collected by filtration and washed (H_2O) to give 14 g (80%) of product. A sample for analysis was recrystallized from H_2O to give crystals, mp 190–191°, lit.[12] mp 192.5–193°. *Anal.* ($C_7H_{11}N_3O$) C, H, N.

A mixture of 13.7 g (0.0895 mole) of this amide and 135 ml of $POCl_3$ was refluxed for 1.5 hr. The volatiles were removed from the resulting solution under vacuum and the resulting dark yellow syrup was poured over crushed ice. The pH of the cold solution was brought to 10 with 2.5 *N* NaOH and extracted four times with 100 ml of ether. The combined ethereal extract was washed (H_2O) and dried ($MgSO_4$). Evaporation of the solvent gave 12.2 g of a residue which on recrystallization from an ether–petroleum ether (bp 30–60°) mixture gave 10.0 g (82%) of 3,5-dimethylpyrazole-1-acetonitrile, mp 36–39°, which was used as obtained for the pteridine synthesis.

Uracil-4-acetamide.—Ethyl 4-uracilacetate[13] (68 g, 0.34 mole) was suspended in 300 ml of MeOH, 950 ml of saturated CH_3OH–NH_3 containing 2.0 g of $NaOCH_3$ was added, and the mixture was allowed to stand overnight. Filtration gave 51 g (89%) of a solid which was purified by dissolving in dilute alkali and reprecipitating by addition of dilute acid. This gave 22 g (38%) of crystals, mp 284–285° dec. *Anal.* ($C_6H_7N_3O_3$) C, H, N.

2,6-Dichloropyrimidine-4-acetonitrile.—A stirred mixture of $POCl_3$ (200 ml), 14.7 g (0.12 mole) of N,N-dimethylaniline, and 10 g (0.059 mole) of uracil-4-acetamide was taken to dryness under vacuum after 1.25 hr of reflux, and the residue was quenched in ice and water. The mixture was immediately extracted ($CHCl_3$) and the organic portion was dried ($MgSO_4$). Evaporation of the dried solution gave 13 g of a dark crystalline solid which on distillation through a small wrapped column gave 9 g of product. This was recrystallized three times from benzene to give 3.5 g (39%) of crystals, mp 113–115.5°. *Anal.* Calcd for $C_6H_3Cl_2N_3$: C, 38.30; H, 1.60; N, 22.35. Found: C, 38.86; H, 1.97; N, 21.60.

A mixture of 13.6 g (0.0725 mole) of 2,6-dichloropyrimidine-4-acetonitrile and 650 g of 10% NH_3–EtOH was heated in a pressure

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TABLE II

$R_6CH_2CN + I \rightarrow II$

R_6	Reaction: Solvent	Reaction: Time, min	Recrystn solvent	Yield, %	Mp, °C	R_f (system)	Formula[a]	Lit. ref for R_6CH_2CN
2-Furyl	DMF	1	*a*	31	>320	0.36 (1)	$C_{10}H_9N_7O$	*c*
3-Furyl	DMF	30	50% AcOH, *b*	44	>310	0.48 (1)	$C_{10}H_9N_7O$	*f*
2-Thienyl(2-methylamino)	EtOH	240	EtOH–H_2O	47	235–239	0.73 (1)	$C_{11}H_{11}N_7S$	*g*
3-Thienyl	DMF	5	DMF	45	335–343	0.31 (2)	$C_{10}H_9N_7S$[t]	*h*
5-Chloro-2-thienyl	EtOEtOH	300	DMF	41	>310	0.61 (1)	$C_{10}H_8ClN_7S$	*i*
2-Thianaphthenyl	DMF	5	DMF, *a*	20	>320	0.53 (2)	$C_{14}H_{11}N_7S$	*j*
3-Thianaphthenyl	DMF	25	80% HCOOH, *b*	55	>300	0.77 (3)	$C_{14}H_{11}N_7S$	*k*
1-Pyrrolyl	DMF	60	Dil HCl, *b*, 50% AcOH	14	>330	0.49 (4)	$C_{10}H_{10}N_8$	*l*
1-Methyl-2-pyrrolyl	DMF	30	50% AcOH, *b*	39	>330	0.51 (1)	$C_{11}H_{12}N_8$	*m*
1-(3,5-Dimethylpyrazolyl)	DMF	20	50% AcOH, *b*	42	>300	0.70 (3)	$C_{10}H_{13}N_9 \cdot 0.75H_2O$	*n*
3-(5-Amino-4-cyano-1-methylpyrazolyl)	DMF	20	12 *N* H_2SO_4, *b*	20	>300	0.31 (7)	$C_{11}H_{11}N_{10} \cdot 2H_2O$	*o*
2-(1-Benzylimidazolyl)	DMF	30	50% AcOH, *b*	63		0.69 (1)	$C_{16}H_{15}N_9 \cdot 0.25H_2O$	*p*
4-Thiazolyl	DMF	60	50% AcOH, *b*	50	311 dec	0.47 (1)	$C_9H_8N_8S$	*q*
4-Methyl-2-thiazolyl	DMF	60	50% AcOH, *b*	75	>330	0.54 (1)	$C_{10}H_{10}N_8S$	*n*
2-Pyridyl	DMF	0.5	*c*	68	>300	0.51 (1)	$C_{11}H_{10}N_8$	*e*
3-Pyridyl	DMF	3	DMF–H_2O	18	317–321 dec	0.36 (5)	$C_{11}H_{10}N_8$	*s*
4-Pyridyl	DMF	3	*d*	48	>300	0.43 (3)	$C_{11}H_{10}N_8$	*l*
4-(2,6-Diaminopyrimidyl)	DMF	25	DMF	52	>300	0.36 (6)	$C_{10}H_{11}N_{11}$	*u*
3-(1-Benzyl-1,2,4-triazolyl)	DMF	10	50% AcOH, *b*	52		0.79 (1)	$C_{15}H_{14}N_{10}$	*v*

[a] Dissolve in dilute AcOH, precipitate with concentrated NH_4OH. [b] Liberate free base with NH_4OH. [c] Dissolve in 75% AcOH, precipitate with concentrated NH_4OH at pH 6. [d] Dissolve in hot 50% AcOH, precipitate with concentrated NH_4OH at pH 5. [e] O. Moldenhauer, G. Trautmann, and R. Pfluger, *Ann.*, **583**, 61 (1953). [f] E. Sherman and E. D. Amstutz, *J. Am. Chem. Soc.*, **72**, 2195 (1950). [g] K. Pettersson, *Acta Chem. Scand.*, **4**, 395 (1950). [h] E. Campaigne and W. C. McCarthy, *J. Am. Chem. Soc.*, **76**, 4466 (1954). [i] T. L. Cairns and B. C. McKusick, *J. Org. Chem.*, **15**, 790 (1950). [j] F. F. Blicke and D. G. Sheets, *J. Am. Chem. Soc.*, **71**, 2856 (1949). [k] A. H. Schlesinger and D. T. Mowry, *ibid.*, **73**, 2614 (1951). [l] W. Herz, D. S. Raden, and D. R. K. Murty, *J. Org. Chem.*, **21**, 896 (1956). [m] W. Herz and J. L. Rogers, *J. Am. Chem. Soc.*, **73**, 4921 (1951). [n] See Experimental Section. [o] E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.*, **81**, 2456 (1959). [p] R. G. Jones, *ibid.*, **71**, 383 (1949). [q] A. Burger and G. E. Ullyot, *J. Org. Chem.*, **12**, 342 (1947). [r] T. Itai and H. Ogura, *J. Pharm. Soc. Japan*, **75**, 296 (1955). [s] Commercially available. [t] N: calcd, 37.81; found, 37.14. [u] All compounds were analyzed for C, H, N and except as noted results were within ±0.4% of calculated values.

vessel for 6 hr at 130°. The recovered reaction mixture was filtered and the filtrate was concentrated to dryness to give 8 g (74%) of 2,6-diaminopyrimidine-4-acetonitrile, mp 290–295°, which was used without further purification for pteridine synthesis.

1-Benzyl-3-cyanomethyl-1,2,4-triazole (Crude).—A solution of 4.9 g (0.1 mole) of NaCN in 25 ml of DMSO was treated with 9.76 g (0.04 mole) of 1-benzyl-3-chloromethyl-1,2,4-triazole hydrochloride[14] dissolved in 25 ml of warm DMSO and the mixture was stirred at 50° for 30 min. The reaction mixture was poured into 500 ml of cold H_2O and extracted three times with 100 ml of $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated under vacuum to give about 3.5 g of a pale yellow oil in whose ir spectra a peak appeared at 4.4 μ indicating the presence of a nitrile group. This product was assumed to be crude 1-benzyl-3-cyanomethyl-1,2,4-triazole and used for pteridine synthesis.

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