Anal. Calcd. for $C_8H_{10}N_6S$: C, 43.23; H, 4.53; N, 37.81. Found: C, 43.45; H, 4.57; N, 37.96.

XXV and 4-Amino-6-methyl-2-methylthio-7-phenylpteridine (XXVI).—A mixture of 14.8 g. (0.08 mole) of 4,6-diamino-2-methylthio-5-nitrosopyrimidine, 16 g. (0.1 mole) of α-methylbenzoylacetonitrile, 5.0 g. (0.1 mole) of sodium cyanide and 250 ml. of 75% ethanol was heated under reflux for 16 hr. There was obtained a first crop of 4.1 g. of pteridine and, after concentration, 3.9 g. of a second crop. The first crop was recrystallized from ethanol three times to give 2.5 g. of 4-amino-6-methyl-2-methylthio-7-phenylpteridine, m.p., 268–269°.

Anal. Calcd. for $C_{14}H_{13}N_5S$: C, 59.34; H, 4.62; N, 24.72; S, 11.32. Found: C, 59.40; H, 4.70; N, 24.91; S, 11.21.

The second crop was also recrystallized three times from ethanol to yield 2.6 g. of XXV, identical with the sample prepared by the method of the preceding experiment.

4,7-Diamino-6-methylpteridine (XXVII).—A mixture of 8.2 g. of 4,6-diamino-5-nitrosopyrimidine, 15 g. of α-methylbenzoylacetonitrile, 9.0 g. of potassium acetate, and 175 ml. of ethoxyethanol was heated under reflux for 1 hr. The dark brown solution was evaporated to dryness under reduced pressure and the residue was stirred with a little water and filtered. The brown precipitate was stirred at 60° with three 85-ml. portions of 5% hydrochloric acid. The acid solutions were combined, extracted with ether, and purified with charcoal. The resulting yellow solution was made basic with sodium hydroxide, cooled in the refrigerator for 4 hr., and filtered. There was obtained 5.2 g. of buff-colored product. For further purification, the product was dissolved in 60 ml. of warm 3% hydrochloric acid and cooled to give 4.1 g. of beautiful, well formed needles of hydrochloride. The salt, on treatment with ammonia, yielded almost colorless needles of XXVII. The compound does not melt but turns black at about 330°.

Anal. Calcd. for $C_7H_8N_6$: C, 47.72; H, 4.58; N, 47.70. Found: C, 47.85; H, 4.90; N, 47.89.

The brown gummy solid which was not dissolved by the extractions with hydrochloric acid was washed with ethanol and recrystallized from glacial acetic acid with the aid of charcoal. There was obtained 1.5 g. of well formed needles of by-product. For analysis, this product was recrystallized from ethanol with charcoal treatment. It formed colorless needles, m.p., 268–269° dec.

Anal. Found: C, 64.15; H, 3.88; N, 32.05.

Reaction of XXIV with α-Methylbenzoylacetonitrile. The Cyanide-catalyzed Reaction.—To 2.8 g. of 4,6-diamino-5-nitrosopyrimidine and 6.4 g. of α-methylbenzoylacetonitrile in 250 ml. of ethanol was added 2 g. of sodium cyanide in 8 ml. of water. The mixture was heated under reflux for 3 hr., concentrated to about 50 ml., cooled, and filtered. There was obtained 2.0 g. of crystals of a compound which, upon recrystallization from acetic acid, proved to be identical with the by-product in the aforementioned sodium acetate-catalyzed reaction.

Acknowledgment.—The authors are grateful to Mrs. Doris Rolston of these laboratories for the analytical data and to Dr. Walter E. Thompson and Mr. Richard J. Warren for the spectral data.

Pteridines. II. Synthesis of 6-Substituted 7-Aminopteridines from Aldehydes

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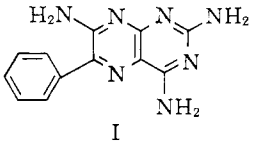
2,4,5,6-Tetraminopyrimidine and 4,5,6-triamino-2-phenylpyrimidine react with aldehydes and hydrogen cyanide to form aminonitriles which may be cyclized with sodium methoxide and oxidized with hydrogen peroxide to 6-substituted-7-aminopteridines. α,β-Unsaturated aldehydes are reduced in the process; cinnamaldehyde and phenylpropargylaldehyde yield 6-phenethyl-7-amino- and 6-styryl-7-aminopteridines, respectively.

2,4,7-Triamino-6-phenylpteridine (I) (generically named triamterene), first reported from this laboratory to be a diuretic drug by Wiebelhaus, Weinstock, and co-workers[2] has proved to be an effective diuretic agent in man.[3,4]



I

As part of an extensive program devoted to the preparation of related molecules for biological evaluation, the synthesis of 6-alkyl analogs was undertaken. The present paper reports the preparation of these and related compounds.

In the previous paper of this series,[5] the synthesis of a number of 6-alkyl-7-aminopteridines from nitrosopyrimidines was described. This synthetic method produced poor results when extended to comparatively inactive nitrosopyrimidines such as 2,4,6-triamino-5-nitrosopyrimidines, and an alternate method, more generally applicable, was sought for the work of the present investigation.

Numerous 6-substituted 7-pteridinones have been synthesized through condensation of α-keto acids with 4,5-diaminopyrimidines. 7-Chloropteridines have occasionally been prepared from these pteridinones.[6,7] It was hoped that such compounds might serve as intermediates in the present study.

2,4-Diamino-6-phenyl-7-pteridinone[8–10] was converted into the corresponding chloro compound and thence into various 7-amino derivatives.[10] However, this route failed at the chlorination step in a number of related cases[10,11] and was clearly not of general applicability for the preparation of 6-substituted 7-aminopteridines.

It is well known that 2,4,5,6-tetraminopyrimidine (II) condenses with carbonyl compounds preferentially

(1) Present address: Endo Laboratories, Richmond Hill 18, N. Y.

(2) V. D. Wiebelhaus, J. Weinstock, F. T. Brennan, G. Sosnowski, and T. J. Larsen, *Fed. Proc.*, **20**, 409 (1961).

(3) A. P. Crosley, Jr., L. M. Ronquillo, W. H. Strickland, and F. Alexander, *Ann. Internal Med.*, **56**, 241 (1962).

(4) R. J. Donnelly, P. Turner, and G. S. C. Sowry, *Lancet*, **1**, 245 (1962).

(5) I. J. Pachter and P. E. Nemeth, Part I, *J. Org. Chem.*, **28**, 1187 (1963).

(6) J. H. Mowat, J. H. Boothe, B. L. Hutchings, E. L. R. Stokstad, C. W. Waller, R. B. Angier, J. Semb, D. B. Cosulich, and Y. SubbaRow, *J. Am. Chem. Soc.*, **70**, 14 (1948).

(7) A. Albert and F. Reich, *J. Chem. Soc.*, 127 (1961).

(8) A. G. Renfrew, P. C. Piatt, and L. H. Cretcher, *J. Org. Chem.*, **17**, 467 (1952).

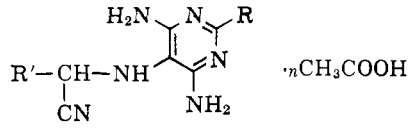
(9) R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1954).

(10) I. J. Pachter and P. E. Nemeth, to be published.

(11) Dr. J. Weinstock, private communication.

TABLE I

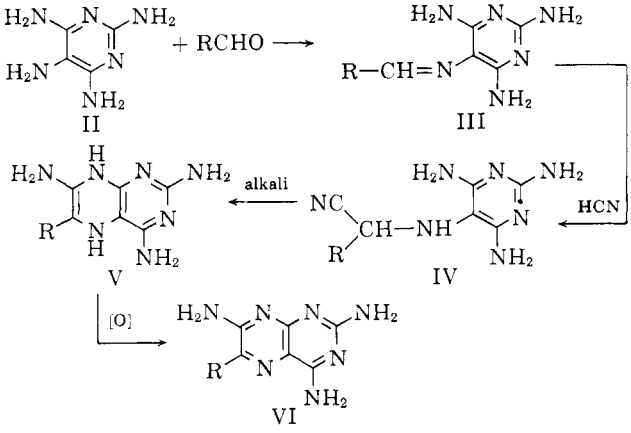
2,4,6-TRIAMINO- AND 4,6-DIAMINO-2-PHENYL-5-(α-CYANOALKYLAMINO)-PYRIMIDINES



Compound	R	R′	Yield,[a] %	n	M.p.,[f] °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	Amino	Methyl	95	1	183–184	42.60	42.60	6.15	5.97	38.65	38.92
2	Amino	Isopropyl	120[b]	2[c]	143–145	45.74	45.60	6.79	6.70	28.72	28.48
3	Amino	3-Cyclohexenyl	111[b]	2[c]	134–135	50.65	50.73	6.64	6.75	25.84	26.43
4	Amino	Benzyl	98[b]	2[c]	155–156	52.42	52.43	5.95	5.75	25.18	25.09
5	Amino	β-Phenethyl	78	2[c]	160–162	53.89	53.60	6.25	6.59	24.30	24.29
6	Amino	Phenyl	103	1	169–170	53.32	53.59	5.43	5.66	31.10	31.04
7	Amino	Styryl	77	2[c]	134–136	53.86	53.46	5.78	5.97	24.43	24.83
8	Amino	Phenethynyl	83[b]	..	[d]		[d]		[d]		[d]
9	Phenyl	Methyl	95[e]	0	212–213	61.40	60.98	5.55	5.78	33.05	33.16
10	Phenyl	Phenyl	97[e]	0	217–219	69.07	69.15	5.49	5.75	25.44	25.27
11	Phenyl	Phenyl	89[e]	0	201–203	68.34	68.31	5.10	4.75	26.57	26.64

[a] Crude yield based on assumption that products before recrystallization are monoacetate salts. [b] Cooled to −20° to ensure complete crystallization; contains extraneous salt. [c] Crystallized for analysis from methanolic acetic acid. [d] Cyclized during attempted purification. [e] Yield based on assumption that product is not a salt. [f] Melting point of analytical sample.

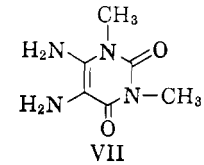
at the 5-amino group.[12] Condensation with aldehydes should, therefore, provide anils of type III which should, in turn, react with hydrogen cyanide to produce aminonitriles of type IV. If these aminonitriles, upon treatment with alkali, would undergo cyclization in preference to loss of hydrogen cyanide and regeneration of anils, a useful route to 6-substituted 7-aminodihydropteridines (V), and eventually to the desired pteridines (VI), would be at hand.



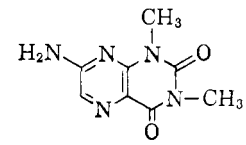
The literature contains two reports of work along these lines. Several years ago Blicke and Godt[13] successfully condensed 5,6-diamino-1,3-dimethyl-2,4-pyrimidinedione (VII) with formaldehyde and hydrogen cyanide, cyclized the intermediate with alkali and oxidized with hydrogen peroxide to obtain 7-amino-1,3-dimethyl-2,4-pteridinedione (VIII).

At about the same time, Polonovski[14] reported that 2,4,5-triamino-6-methylpyrimidine (IX) reacted with loss of ammonia during a related synthesis to produce 2-amino-7-hydroxy-4-methylpteridine (X).

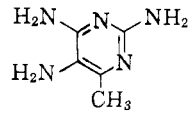
In the present work, when, 2,4,5,6-tetraminopyrimidine (II) hydrochloride[15] was suspended in methanolic



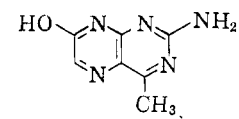
VII



VIII



IX



X

acetic acid, treated with aqueous sodium cyanide and then with various aldehydes, 2,4,6-triamino-5-(α-cyanoalkylamino)pyrimidines (IV) formed rapidly and crystallized from solution as acetate salts. Products were derived from eight aldehydes. The series included aliphatic, aromatic, α,β-unsaturated and β,γ-unsaturated aldehydes. Crude yields of the products (Table I) were generally excellent. In each case, crystallization of product began at about room temperature when proper solvent conditions were worked out.

The products crystallized originally as monoacetate salts from the acetic acid–sodium acetate-containing reaction mixtures. Although they separated in high yield from solutions containing excess aldehyde and cyanide, they dissociated considerably into simpler components upon boiling with methanol. To minimize this retrograde process, samples were prepared for analysis in several cases in the presence of excess acetic acid. In these instances the analytical products were determined to be diacetate salts (Table I). When no acetic acid was added to the methanolic recrystallization solvent, products analyzing as monoacetate salts were obtained.

It was occasionally necessary to cool a reaction mixture to −20° to effect complete crystallization; in

(12) G. B. Elion, G. H. Hitchings, and P. B. Russell, *J. Am. Chem. Soc.*, **72**, 78 (1950).

(13) F. F. Blicke and H. C. Godt, Jr., *ibid.*, **76**, 2798 (1954).

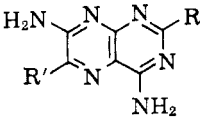
(14) M. Polonovski, *et al.*, in the "Ciba Foundation Symposium on Chemistry and Biology of Pteridines," Little, Brown and Company, Boston, Mass., 1954, p. 171.

(15) 2,4,5,6-Tetraminopyrimidine is commercially available as the sulfate salt.[16] This salt is very difficultly soluble in aqueous and alcoholic solutions and for the present work it was converted into the more readily soluble hydrochloride through treatment with barium chloride. The free base oxidizes rather readily to colored products and for this reason was not used.

(16) Aldrich Chemical Company, Milwaukee, Wis.

TABLE II

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



Compound cyclized (Table I)	R	R′	Yield,[a] %	Over-all yield,[b] %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	Amino	Methyl	41	39	>340	43.79	43.95	4.74	4.74	51.28	51.11
2	Amino	Isopropyl	28	34	343	49.30	49.38	5.98	6.28	44.72	44.61
3	Amino	3-Cyclohexenyl	33	37	>350	56.02	56.17	5.88	5.94	38.11	37.74
4	Amino	Benzyl	35	34	332	58.41	58.48	4.90	4.96	36.68	36.76
5	Amino	β-Phenethyl	54	42	296–298		[d]		[d]		[d]
7	Amino	β-Phenethyl	60	46	296–298	59.77	59.88	5.37	5.51	34.85	34.86
6	Amino	Phenyl	33[e]	34[e]	320–322		[d]		[d]		[d]
8	Amino	Styryl	45	37	345–347	60.20	60.17	4.69	4.96	35.11	34.86
..[c]	Amino	Styryl	..[c]	51[e]	345		[d]		[d]		[d]
9	Phenyl	Methyl	36	34	308–309		[d]		[d]		[d]
10	Phenyl	Benzyl	34	33	280–281		[d]		[d]		[d]
11	Phenyl	Phenyl	21[e]	19[e]	>350		[d]		[d]		[d]

[a] Yield based on crude aminonitrile (Table I). [b] Yield based on quantity of original pyrimidine prepared as described in the Experimental section. [c] Pteridine synthesized in one step in acid medium. [d] Identified through comparison with previously analyzed sample. [e] Cyclized to pteridine without use of peroxide.

such cases "yields" of crude products exceeded 100% due to co-crystallization of contaminating sodium salt.

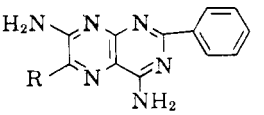
Co-crystallization of extraneous salt could be avoided through use of hydrogen cyanide gas in place of sodium cyanide and acetic acid. In one experiment with 2,4,5,6-tetraminopyrimidine hydrochloride and benzaldehyde where this was done, the hydrochloride of the product (IV) (R = phenyl) was obtained in good yield. Since it was more convenient and less hazardous to generate hydrogen cyanide *in situ*, and since contaminating salt did not affect the results in the subsequent steps, the sodium cyanide–acetic acid procedure was used generally in this work.

Each nitrile cyclized when heated briefly under reflux with methanolic sodium methoxide. Except in the instances noted in the following discussion, the resulting hot methanolic solutions were diluted with aqueous hydrogen peroxide and in each case a crystalline light yellow pteridine (VI) separated from the solution within a few minutes. In Table II two columns of yields are listed. The first column indicates the yields of pteridines based upon the crude cyano compounds consumed. The second column, more significantly, lists the overall yields of the process based upon the polyaminopyrimidine employed in the first step. Generally, the over-all yields of pteridines ranged between 30 and 50%. The convenience of the synthesis deserves emphasis. The two stages of the process require minutes to carry out and in a few cases purified pteridines were prepared from pyrimidines within two hours.

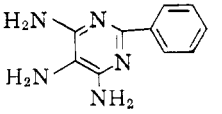
It has been assumed in this work that the 5-amino group of a 4,5,6-triaminopyrimidine system condenses with aldehyde and cyanide and that the eventual product is a 6-substituted 7-aminopteridine. Others have felt,[17] however, that "the position of the amino group is not conclusively proved" in a pteridine prepared by a synthesis of this type.

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

To prove that the products are indeed 6-substituted 7-amino compounds, we undertook the preparation of the previously and unequivocally synthesized[5] 6-methyl- and 6-benzyl-7-aminopteridines XI and XII. 4,5,6-Triamino-2-phenylpyrimidine (XIII) rapidly formed aminonitriles in excellent yield when treated with acetaldehyde and phenylacetaldehyde in the presence of generated hydrogen cyanide. The aminonitriles cyclized in alkali and were oxidized to XI and XII. In each case the identity of the product was established through comparison with an authentic sample.[5]



XI. R = methyl
XII. R = benzyl



XIII

A dihydro derivative of triamterene (I) would be of interest from a biological standpoint. A synthesis starting with benzaldehyde, but with omission of the peroxide oxidation step, was therefore carried out in the hope that such a product might be obtained. The intermediate nitrile (compound 6, Table I) formed readily and was cyclized with sodium methoxide in a small volume of methanol. A new compound (XIV) was obtained. A small quantity of 2,4,6-triamino-5-benzylidenaminopyrimidine (XV), identical with a sample[18] prepared from benzaldehyde and 2,4,5,6-tetraminopyrimidine, was found in the mother liquor.

Compound XIV gave analytical values similar to those expected for a dihydro compound. Its ultraviolet spectrum (Fig. 1) was closely related to that of I. Instances have been reported previously where dihydropteridine spectra closely resemble those of pteridines.[19]

(18) The author is grateful to Dr. J. Weinstock and Mr. J. L. Kirkpatrick for this sample.

(19) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 3877 (1952).

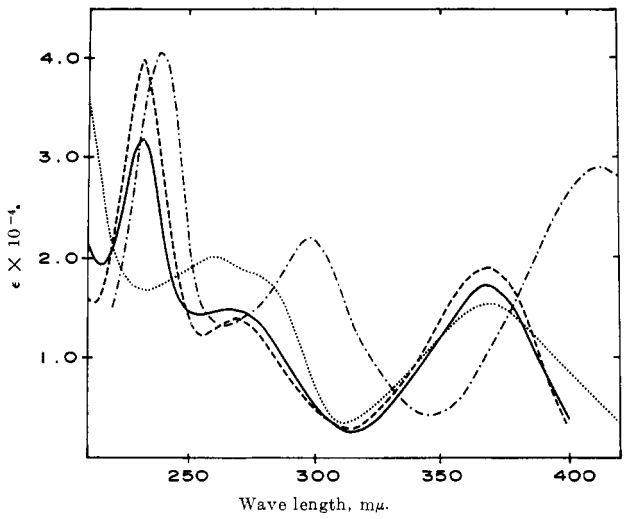
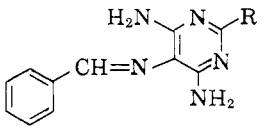
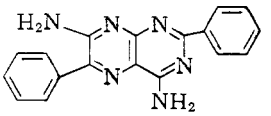


Fig. 1.—2,4,7-Triamino-6-phenylpteridine (I), – – – –; 2,4,6-triamino-5-benzylidenaminopyrimidine (XV), ...; complex XIV (of I and XV), ———; 2,4,7-triamino-6-styrylpteridine, · – · – ·. Spectra in ethanol.



XV. R = amino
XVII. R = phenyl



XVI

There was evidence, however, which was not consistent with a dihydropteridine structure. For one thing, the yield of XIV was considerably higher than had been obtained for any of the pteridines of Table II. Secondly, the yield of I obtained from XIV after heating with dimethylformamide or diphenyl ether did not exceed 50%. Thirdly, when XIV was warmed with dilute acid and then made basic, I was obtained together with some *benzaldehyde*. Finally the ultraviolet spectrum of XV (Fig. 1) was found to be similar to those of both I and XIV. The data suggested the possibility that XIV was a molecular complex of I and XV. The analytical requirements for such a complex would agree closely with the values found for XIV.

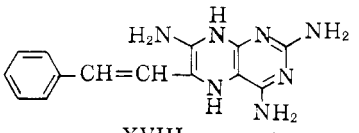
To test this possibility, methanolic solutions of I and XIV were combined in the presence of sodium methoxide. Upon concentration to small volume, XIV crystallized from solution in good yield and its nature was thus revealed.

When nitrile 11 of Table I was treated in similar fashion, a mixture of XVI[5] and XVII was obtained. In this case the compounds did not form a complex and were readily separated.

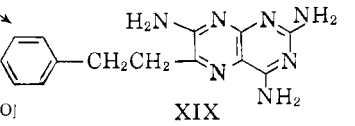
These experiments indicate that dihydro-6-aryl-7-aminopteridines lack stability and oxidize readily to the corresponding pteridines.

An attempt was made to prepare 2,4,7-triamino-6-styrylpteridine (XXIV) from cinnamaldehyde and II. The aminonitrile (compound 7, Table I) formed in the expected manner. During the methoxide-catalyzed cyclization reaction, however, a product crystallized *before* addition of hydrogen peroxide. The product was unaffected by oxidizing agents. Its ultraviolet spectrum was similar to those of 2,4,7-triamino-6-alkylpteridines and clearly was not that of the more extensively conjugated styrylpteridine. It seemed probable that an intermediate dihydropteridine (*e.g.*, XVIII) formed and then underwent isomerization to 2,4,7-triamino-6-(β-phenethyl)pteridine (XIX).

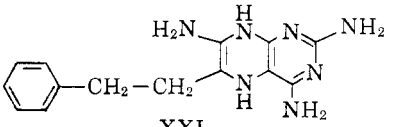
This was shown to be the case. When the nitrile XX, derived from β-phenylpropionaldehyde, was treated with methanolic sodium methoxide, a solution of XXI was obtained. Upon addition of hydrogen peroxide, the pteridine XIX crystallized and was found to be identical with the product of the cinnamaldehyde sequence.



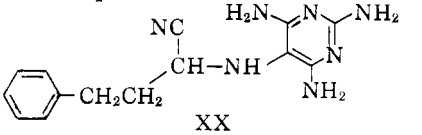
XVIII



XIX



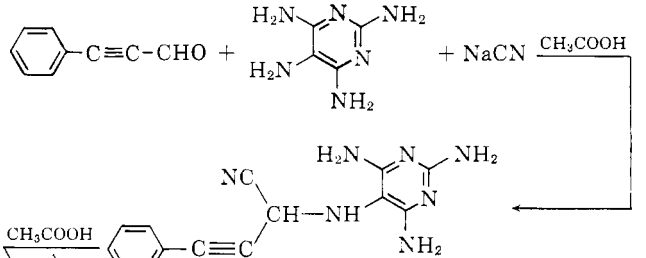
XXI



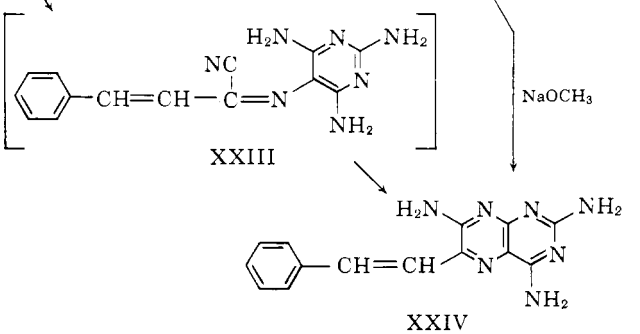
XX

If cinnamaldehyde reacts to produce a 6-phenethylpteridine, phenylpropargylaldehyde might be expected to undergo related reactions to give a 6-styrylpteridine. The intermediate nitrile XXII derived from phenylpropargylaldehyde did indeed cyclize and undergo isomerization to yield the yellow styryl compound (XXIV) when treated with methanolic sodium methoxide. The ultraviolet spectrum of the product in ethanol (Fig. 1) displayed an absorption maximum at 414 mμ, which is in keeping with the assigned structure.

When recystallization of XXII from boiling methanolic acetic acid was attempted, cyclization to the acetate salt of XXIV occurred. None of the other nitriles,



XXII



XXIII

XXIV

purified in this manner, underwent corresponding reactions. It is postulated that in the case of XXII, heating with acid causes rearrangement to the extended conjugated structure XXIII which then cyclizes readily to XXIV.

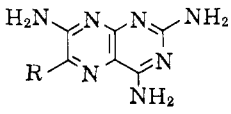
It was subsequently found that ten-minute reflux of a mixture of phenylpropargylaldehyde, 2,4,5,6-tetraminopyrimidine hydrochloride, methanolic acetic acid, and aqueous sodium cyanide produced the acetate salt of XXIV in 51% yield.

Further experiments along these lines are in progress and will be reported subsequently.

The ultraviolet maxima of the 2,4,7-triamino-6-substituted pteridines are recorded in Table III.

TABLE III

ULTRAVIOLET SPECTRA (AQUEOUS SOLUTIONS)



R	λ_{max}, mμ (log ε)	pH
Methyl	255 (4.16), 278 (s) (3.65), 342 (4.29)	1
	257 (4.16), 350 (4.15)	13
Isopropyl	253 (4.18), 278 (s) (3.75), 342 (4.32)	1
	258 (4.18), 280 (s) (3.76), 351 (4.18)	13
Cyclohexenyl	253 (4.20), 279 (s) (3.76), 344 (4.33)	1
	258 (4.21), 282 (s) (3.76), 349 (4.20)	13
Benzyl	257 (4.23), 276 (s) (3.89), 344 (4.30)	1
	260 (4.24), 282 (s) (3.88), 356 (4.19)	13
β-Phenethyl	241 (4.26), 252 (s) (4.21), 280 (s) (3.76), 342 (4.29)	1
	258 (4.20), 281 (s) (4.78), 354 (4.16)	13
Phenyl	254 (s) (4.19), 288 (s) (3.85), 358 (4.33)	1
	269 (4.13), 368 (4.27)	13
Styryl	269 (4.33), 309 (4.22), 397 (4.43)	1
	297 (4.30), 409 (4.42)	13

The new compounds were tested for biological effects. The results will be discussed elsewhere at a later date.

Experimental

The *ultraviolet spectra* of Table III at pH 1 were determined in 4.5% aqueous formic acid. The spectra at pH 13 were determined by taking a 5- to 10-ml. aliquot of compound in 4.5% formic acid and bringing the volume to 100 ml. with 1 *N* aqueous sodium hydroxide.

The *aldehydes* were obtained from commercial sources and were redistilled before use.

2,4,5,6-Tetraminopyrimidine Hydrochloride.—A 300-g. sample of 2,4,5,6-tetraminopyrimidine sulfate[16] was dissolved in a boiling mixture of 1500 ml. of water and 400 ml. of concentrated hydrochloric acid. The solution was treated with an equivalent amount of barium chloride in aqueous solution. Toward the end of the addition, the barium chloride was added dropwise until no further barium sulfate separated. The resulting mixture was filtered and concentrated to small volume under reduced pressure. Filtration and drying yield 252 g. of hydrochloride. *Chlorine analyses by ionic titration and organic combustion* showed that the product was an equal mixture of dihydrochloride and trihydrochloride. This material was used in the experiments described in this paper and yields are calculated based on this composition of the hydrochloride.

Formation of Aminonitriles.—The condensations of 2,4,5,6-tetraminopyrimidine hydrochloride and 4,5,6-triamino-2-phenylpyrimidine with aldehydes and hydrogen cyanide generally were carried out in similar fashion. Solvent conditions for proper crystallization of the rather labile reaction products were sometimes of critical importance and varied from case to case. Several reaction procedures are exemplified below and may be used, together with the data of Table IV, to construct procedures for the other products listed in Table I which are not specifically exemplified in this section.

2,4,6-Triamino-5-(α-cyanoethylamino)pyrimidine Acetate (Compound 1).—A suspension of 9 g. of 2,4,5,6-tetraminopyridine hydrochloride in 50 ml. of methanol and 20 ml. of acetic acdi was heated to 50° and treated first with a solution of 5 g. of sodium cyanide in 20 ml. of water and then with a solution of 3 g. of acetaldehyde in 10 ml. of methanol. The solids dissolved and the resulting solution warmed spontaneously. Prisms soon began to crystallize. The mixture was allowed to stand at room temperature for 15 min. and then in the refrigerator for 2 hr. Upon filtration, there was obtained 11.6 g. of product.

2,4,6-Triamino-5-(α-cyanoisobutylamino)pyrimidine Acetate (Compound 2).—A mixture of 9 g. of 2,4,5,6-tetraminopyrimidine hydrochloride, 25 ml. of acetic acid and 40 ml. of methanol was heated to 50°. There was added 5 g. of sodium cyanide dissolved in 17 ml. of water followed by 5.5 g. of isobutyraldehyde in 10 ml. of methanol. The hot solution was filtered by suction to remove about 1 g. of insoluble solid and the filtrate was allowed to stand at room temperature for 1 hr. and then cooled to −20° overnight. Upon filtration there was obtained 13.4 g. of almost colorless needles.

2,4,6-Triamino-5-(α-cyanobenzylamino)pyrimidine Hydrochloride. Formation with Gaseous Hydrogen Cyanide.—A mixture of 5 g. of 2,4,5,6-tetraminopyrimidine monohydrochloride (obtained from the aforedescribed mixed hydrochlorides by treatment with aqueous ammonia), 6 g. of benzaldehyde and 10 ml. of acetic acid was heated until solution was achieved. A 75-ml. portion of hot ethanol was added and the mixture was heated to the boiling point. Heating was discontinued and a stream of hydrogen cyanide gas was passed into the solution for 10 min. The temperature fell to 65° and the product began to crystallize. The flask was stoppered and allowed to stand for 5 hr. Filtration yielded 6.0 g. of pure product, m.p. 197° dec.

The mother liquor was concentrated under reduced pressure and, on standing, yielded an additional 1.1 g. of product for a total yield of 7.1 g. of the hydrochloride. For analysis, a sample was recrystallized from ethanol.

Anal. Calcd. for $C_{12}H_{14}ClN_7$: C, 49.40; H, 4.84; N, 33.61. Found: C, 49.22; H, 4.72; N, 33.75.

4,6-Diamino-5-(α-cyanobenzylamino)-2-phenylpyrimidine (Compound 6).—A solution of 10 g. of 4,5,6-triamino-2-phenylpyrimidine in 75 ml. of methanol and 25 ml. of acetic acid was treated at room temperature with 5 g. of sodium cyanide in 25 ml. of water and 10 g. of benzaldehyde in 20 ml. of methanol. The solution became warm and within a minute began to deposit large crystals. The mixture was allowed to stand at room temperature overnight and was then filtered. The product was washed well with methanol and dried. It weighed 14.0 g. and melted at 201–203°. The melting point was unchanged upon recrystallization from dimethylformamide and methanol.

Formation of Pteridines.—The cyclization of aminonitriles was carried out in each case in methanolic sodium methoxide. The cyclization reaction time varied from 2 min. for compound 7 (Table I) to 20 min. for the difficultly soluble compound 10. Except in the cyclizations of compounds 6 and 11, it was found advantageous to add hydrogen peroxide to produce fully aromatic pteridines in best yield. The following examples are illustrative.

4,7-Diamino-6-methyl-2-phenylpteridine (XI).—To a solution of 5.0 g. of sodium methoxide in 80 ml. of methanol was added 5 g. of 4,6-diamino-5-(α-cyanoethylamino)-2-phenylpyrimidine. The mixture was heated under reflux for 10 min. during which time complete solution was obtained. The hot solution was diluted with 80 ml. of water and 10 ml. of 30% hydrogen peroxide. Upon standing, the product crystallized from solution. After 5 hr. at room temperature the mixture was filtered and 2.5 g. of crystals was obtained. Recrystallization from methanol yielded 1.8 g. of pure product, identical with a sample prepared by another procedure.[5]

2,4,7-Triamino-6-phenylpteridine (I), 2,4,6-Triamino-5-benzylidenaminopyrimidine (XV), and Their Complex (XIV).—A 5-g. sample of 2,4,6-triamino-5-(α-cyanobenzylamino)pyrimidine acetate and 2.5 g. of sodium methoxide were added to 40 ml. of methanol and the mixture was heated to boiling. The nitrile reacted and dissolved. After 10 min. of boiling, the solution was allowed to stand for 8 hr. There was obtained 3.6 g. of yellow elongated plates. The product, upon recrystallization from methanol yielded 3.0 g. of a complex of I and XV, m.p. 288–292°.

TABLE IV

CONDITIONS FOR AMINONITRILE PREPARATIONS

Compound	Aldehyde, g.	2,4,5,6-Tetraminopyrimidine hydrochloride, g.	Methanol, ml.	Acetic acid, ml.	Sodium cyanide, g.	Water, ml.	Remarks
1	Acetaldehyde, 3	9	50 + 10	20	5	20	[b]
2	Isobutyraldehyde, 5.5	9	40 + 10	25	5	17	[a]
3	3-Cyclohexene-1-aldehyde, 9.5	9	40 + 10	25	5	17	[a]
4	Phenylacetaldehyde, 10	9	75 + 20	25	5	25	[b]
5	β-Phenylpropionaldehyde, 9.5	9	40 + 10	35	5	22	[b]
6	Benzaldehyde, 9	9	75 + 20	30	5	22	[b]
7	Cinnamaldehyde, 10	9	75 + 20	60	5	25	[a]
8	Phenylpropargylaldehyde, 10	9	45 + 10	45	5	20	[a]
		4,5,6-Triamino-2-phenylpyrimidine, g.					
9	Acetaldehyde, 3	10	50 + 10	23	5	25	[b]
10	Phenylacetaldehyde, 10	8.4	75 + 20	25	5	25	[c]
11	Benzaldehyde, 10	10	75 + 10	25	5	25	[c]

[a] Cooled overnight at −20°. [b] Cooled for 1 to 5 hr. at 7°. [c] Crystallized completely at room temperature.

Anal. Calcd. for $C_{23}H_{23}N_{13}$: C, 57.36; H, 4.82; N, 37.82. Found: C, 57.08; H, 4.86; N, 38.01.

From the alkaline methanolic filtrate a small quantity of a second yellow compound was obtained. It crystallized from ethanol in long solvated needles which, on drying *in vacuo*, melted at 159–161° and proved to be identical with a sample of 2,4,6-triamino-5-benzylidenaminopyrimidine (XV) prepared from 2,4,5,6-tetraminopyrimidine and benzaldehyde.[18]

Anal. Calcd. for $C_{11}H_{12}N_6$: C, 57.88; H, 5.30; N, 36.82. Found: C, 57.79; H, 5.29; N, 36.92.

The complex (3 g.) was heated to boiling with 100 ml. of 1.5 *N* hydrochloric acid for 3 min. The mixture generated a strong odor of benzaldehyde and a pale yellow hydrochloride formed. The mixture was cooled, the hydrochloride collected, and dissolved in 250 ml. of hot water containing a few drops of hydrochloric acid. Addition of ammonia to the hot solution resulted in the crystallization of 1.3 g. of pure I, m.p. 320–322°.

4,7-Diamino-2,6-diphenylpteridine (XVI)[5] and 4,6-Diamino-5-benzylidenamino-2-phenylpyrimidine (XVII).—To a solution of 14 g. of sodium methoxide in 400 ml. of methanol was added 14 g. of 4,6-diamino-5-(α-cyanobenzylamino)-2-phenylpyrimidine. The mixture was boiled and stirred. Within 5 min., complete solution was achieved. Shortly thereafter the product began to crystallize. The mixture was stirred vigorously, concentrated to 150 ml. over a period of 30 min., cooled, and filtered. There was obtained 11.1 g. of yellow-orange solid.

The crude product was finely powdered and boiled, with stirring, with 400 ml. of methanol. It was then filtered and the hot methanolic filtrate was concentrated to yield 5.1 g. of XVII, which after one further crystallization from methanol, gave yellow-orange flat long prisms, m.p. 211–212°. The product was identical with a sample prepared from benzaldehyde and 4,5,6-triamino-2-phenylpyrimidine.

Anal. Calcd. for $C_{17}H_{15}N_5$: C, 70.57; H, 5.23. Found: C, 70.54; H, 4.89.

The methanol-insoluble fraction weighed 4.6 g. Upon recrystallization from dimethylformamide there was obtained 2.9 g. of XVI, m.p. over 350°, identical by infrared spectral comparison with a previously prepared sample.[5]

2,4,7-Triamino-6-β-phenethylpteridine (XIX). Method A.—A 9.3-g. sample of finely divided 2,4,6-triamino-5-(α-cyanocinnamylamino)pyrimidine acetate was added to a solution of 9 g. of sodium methoxide in 200 ml. of methanol. The mixture was stirred and boiled for 2 min. The starting material rapidly dissolved and a yellow solid separated. It was collected, washed with methanol and dried to give 6.3 g. of product. Upon recrystallization from a large volume of ethanol with charcoal treatment, there was obtained 4.55 g. of light yellow plates, m.p. 296–298° dec.

Method B.—A 2.5-g. sample of 2,4,6-triamino-5-(α-cyano-γ-phenylpropylamino)pyrimidine acetate was added to a solution of 2.5 g. of sodium methoxide in 35 ml. of methanol. The mixture was heated to boiling for 3 min. and was then diluted with 30 ml. of water and 4 ml. of 30% hydrogen peroxide. Within a minute, pale yellow crystals of pteridine began to separate from solution. After 1 hr. the product was collected by filtration, washed with methanol, and dried to give 1.1 g. of XIX, identical by infrared spectral comparison with the product of method A. There was no depression of melting point on admixture of the samples.

2,4,7-Triamino-6-styrylpteridine (XXIV). Method A.—To a solution of 6 g. of sodium methoxide in 125 ml. of methanol was added 6 g. of 2,4,6-triamino-5-(α-cyano-γ-phenylpropargylamino) pyrimidine. The mixture was boiled for 3 min., cooled, and filtered. A yellow insoluble pteridine was obtained in 2.2 g. yield. It formed large solvated prisms from dimethylformamide. Upon recrystallization from ethanol it melted at 345–347° dec.

Method B.—A mixture of 2.5 g. of 2,4,5,6-tetraminopyrimidine hydrochloride, 12 ml. of methanol, and 12 ml. of acetic acid was diluted successively with solutions of 1.5 g. of sodium cyanide in 6 ml. of water and 2.5 g. of phenylpropargylaldehyde in 3 ml. of methanol. The resulting mixture was boiled and stirred for 10 min. An orange solution formed from which a bright yellow solid crystallized. The mixture was cooled to room temperature and filtered. The product was washed with methanol, then thoroughly with water, then with methanol again, and dried. It weighed 1.9 g. and was identical by infrared spectrum with an acetate salt prepared from the product of method A. The acetate of XXIV was dissolved in boiling 5% acetic acid and the solution was filtered to remove traces of insoluble brown material and then diluted with excess aqueous ammonia and boiled for 2 min. The light yellow prisms that crystallized from the hot aqueous solution weighed 1.35 g. and were identical with the product of method A.

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