Pteridines. IV. Synthesis of 2,4,6-Triamino-7-phenylpteridine and Related Compounds through the Hofmann Reaction

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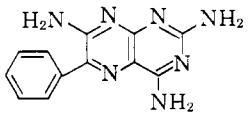
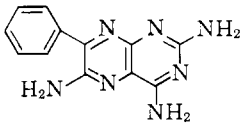
6- and 7-Pteridinecarboxamides were prepared and subjected to the Hofmann hypobromite reaction to obtain the corresponding amino compounds. A synthesis of 7-phenyl-6-pteridinecarbonitriles is described. 2,4-Diamino-6-phenylpteridine was synthesized and shown to be different from the compound previously assigned that structure.

2,4,7-Triamino-6-phenylpteridine (I) is an effective diuretic agent in man.[2] As part of a program devoted to the synthesis of compounds for comparative biological evaluation, the preparation of 2,4,6-triamino-7-phenylpteridine (II) and related substances was undertaken.



I

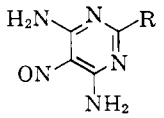


II

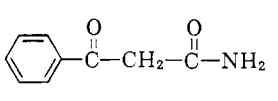
Although 2,4-diamino-6-phenyl-7(8*H*)-pteridinone[3,4] was converted into the corresponding chloro compound and thence into various 7-amino derivatives[4] of I, no useful product could be isolated when chlorination of the isomeric 2,4-diamino-7-phenyl-6(5*H*)-pteridinone[3b] was attempted under the same conditions.

As an alternate approach, the preparation of 6-pteridinecarboxamides followed by Hofmann hypobromite conversion into 6-aminopteridines appeared attractive.

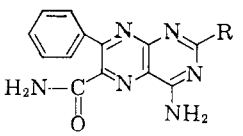
We found previously that 4,6-diamino-5-nitroso-2-phenylpyrimidine (III) reacted with benzoylacetamide (V) in the presence of potassium acetate to produce 4-amino-2,7-diphenyl-6-pteridinecarboxamide (VI).[5] When the analogous reaction was attempted with the less reactive 2,4,6-triaminopyrimidine (IV), no significant yield of product was obtained.



III. R = phenyl
IV. R = amino

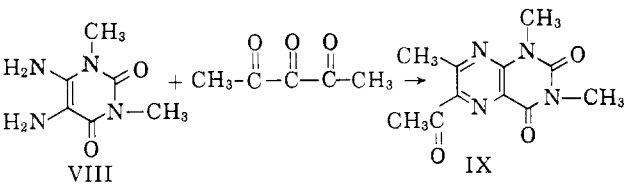


V



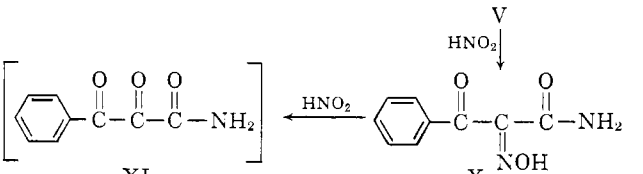
VI. R = phenyl
VII. R = amino

Sachs and Meyerheim[6] found that 5,6-diamino-1,3-dimethyl-2,4-pyrimidinedione (VIII) reacted with 2,3,-4-pentanetrione to produce a single pteridine (IX). It was hoped that substances such as VI and VII might be produced by an analogous route.

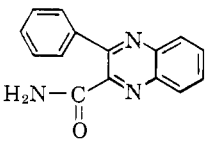


VIII IX

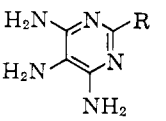
Upon treatment of benzoylacetamide with nitrous acid, the isonitroso compound X was produced. The latter reacted with excess nitrous acid to produce XI (or its solvated equivalent).[7] This product was not isolated, but was permitted to condense in solution with *o*-phenylenediamine (XII), 4,5,6-triamino-2-phenylpyrimidine (XIII) and 2,4,5,6-tetraminopyrimidine (XIV) to produce XV, VI and VII, respectively. Compound VI, prepared by this route, was identical with the product derived from III and V.



XI X XII VI; VII



XV



XIII, R = phenyl
XIV, R = amino

When it was found, in connection with subsequent work,[8] that IV could be activated for condensation reactions through diacetylation with acetic anhydride, the diacetyl compound and V were heated with ethanolic potassium acetate. A yellow pteridine formed readily. This intermediate acetylated product was hydrolyzed with cold alkali to give VII in good yield.

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

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

(3)(a) A. G. Renfrew, P. C. Piatt, and L. H. Cretcher, *J. Org. Chem.*, **17**, 467 (1952); (b) R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1954).

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

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

(6) F. Sachs and G. Meyerheim, *Ber.*, **41**, 3957 (1908).

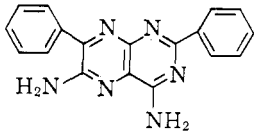
(7) F. Kröhnke, *Chem. Ber.*, **80**, 298 (1947), used a different process to make compounds related to XI.

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

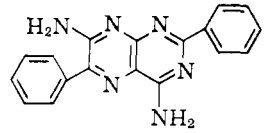
The preparation of VII by this route constitutes a proof of structure.

3-Phenyl-2-quinoxalinecarboxamide (XI) reacted with aqueous potassium hypobromite to produce the known 2-amino-3-phenylquinoxaline[9] in excellent yield.

4-Amino-2,7-diphenyl-6-pteridinecarboxamide (VI) and 2,4-diamino-7-phenyl-6-pteridinecarboxamide (VII) are much less soluble than XV in aqueous potassium hypobromite. The Hofmann reactions were therefore carried out in dimethylformamide solution and the products XVI and II were obtained.



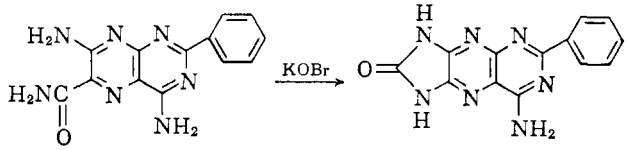
XVI



XVII

The ultraviolet spectra (Table I) of the 6-amino-7-phenylpteridines (XVI and II) were found to show absorption at much longer wave lengths than do those of the 7-amino-6-phenyl isomers (XVII and I).[3b,5,10] This is in accord with the results of previous investigations.[3b,11]

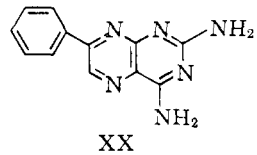
The hypobromite reaction in dimethylformamide was also used to convert 4,7-diamino-2-phenyl-6-pteridinecarboxamide (XVIII)[12] into 8-amino-2,3-dihydro-6-phenyl-1*H*-2-imidazo[4,5-*g*]pteridinone (XIX).



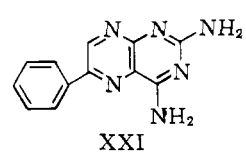
XVIII XIX

King and Spensley[13] reported that phenylglyoxal reacts with 2,4,5,6-tetraminopyrimidine (XIV) to give 2,4-diamino-7-phenylpteridine (XX), but that ω,ω-dichloroacetophenone reacts with XIV to give the isomeric compound XXI.

It was of interest to us to see whether halogen derivatives of V would react correspondingly with XIII and XIV to give products isomeric with VI and VII.



XX



XXI

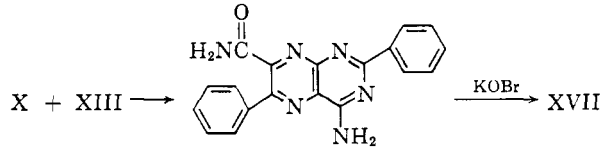
Compound V reacted with one and two moles of bromine to yield crystalline monobromo- and dibromobenzoylacetamide. Each reacted with XIII to give VI and with XIV to give VII. In the reactions of monobromobenzoylacetamide, air probably served as the oxidizing agent.

The lack of correspondence of our results with those of King and Spensley caused us to question and reinvestigate the previous work. It was reported that XX melted at 285–286°, that XXI melted at 290–291° dec., and that a mixture of the two melted at 277°. It was further reported that ω-nitroacetophenone, XIV, and sodium dithionite yielded a product, probably a mixture, m.p. 280–281°, which did not show melting point depression on admixture with either XX or XXI.

In our hands, ω,ω-dichloroacetophenone reacted with XIV to give a product, m.p. 299–300° dec. Phenylglyoxal reacted with XIV to give a product, m.p. 300–301° dec. The infrared and ultraviolet spectra of the products were identical. Upon admixture there was no depression of melting point. Both reactions yielded XX.

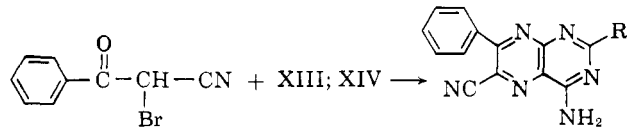
The isomeric compound (XXI) was prepared unequivocally through condensation of diacetylated 2,4,6-triamino-5-nitrosopyrimidine[8] with phenylacetaldehyde in ethanolic potassium acetate followed by hydrolysis of the intermediate acetylated product. Compound XXI melted at 340° dec. and depressed the melting point of XX upon admixture.

In the reactions of α,β-dioxohydrocinnamamide (XI), the central carbonyl is most reactive. If the isonitroso compound (X) were to react to form a pteridine, the benzoyl carbonyl would be expected to react first. This proved to be the case and XXIV was produced when X reacted with XIII. The structure of the product was proved through its conversion in a Hofmann reaction to the previously prepared compound XVII.[5]

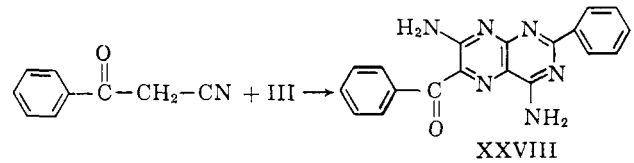


XXIV

Monobrominated α-benzoylacetonitrile (XXV) reacted with XIII and XIV to produce the corresponding 6-pteridinecarbonitriles (XXVI and XXVII). In previous work[8] it was shown that cyclization occurred predominantly through the nitrile rather than through the ketone when benzoylacetonitrile and related compounds reacted with nitrosopyrimidines such as III. 6-Pteridyl ketones (*e.g.*, XXVIII) were the products. In one reaction of III, compound XXVI was isolated as a minor by-product.[8] The formation of XXVI from III serves as proof for the structure assigned to the product of the reaction of XXV with XIII.



XXV XXVI, R = phenyl
XXVII, R = amino



XXVIII

The structure of compound XXVII was also proved when, upon hydrolysis, it yielded the amide VII.

It is tempting to suggest that the relative reactivities of the nitrile and ketone groups in the syntheses of

(9) F. Kröhnke and H. Leister, *Chem. Ber.*, **91**, 1479 (1958).
(10) I. J. Pachter, Part II, *J. Org. Chem.*, **28**, 1191 (1963).
(11) G. B. Elion, G. H. Hitchings, and P. B. Russell, *J. Am. Chem. Soc.*, **72**, 78 (1950).
(12) T. S. Osdene and E. C. Taylor, U. S. Patent 2,975,180 (1961).
(13) F. E. King and P. C. Spensley, *J. Chem. Soc.*, 2144 (1952).

XXVI and XXVIII are determined by reaction pH and that cyclization proceeds through nitrile in alkali and through ketone in near neutral or acid solution. There are most certainly other important factors involved in such reactions, for at times mixtures are produced[5] and occasionally a single product is obtained, the nature of which is at complete variance with the foregoing suggestions. For example, it has been found that when benzoylacetonitrile condenses with triazine in the presence of alkaline catalyst, ring closure to form the final product proceeds through the ketone and not through the nitrile.[14]

Kröhnke[7] reported that *o*-phenylenediamine reacts with benzoyl(*p*-dimethylaminophenylimino)acetonitrile in acetic acid to give 3-phenyl-2-quinoxazolinecarbonitrile. Although we could repeat this synthesis in excellent yield, we were unable to carry out analogous reactions with XIII or XIV to produce pteridines. Neither acid nor alkaline conditions proved useful.

The ultraviolet absorption maxima of new pteridines are recorded in Table I.

TABLE I

ULTRAVIOLET SPECTRA

Compound	λ_{max}, mμ (log ε)	pH
II	262 (4.31), 404 (4.08)	1
	269 (4.33), 416 (4.00)	13
VII	254 (4.26), 354 (4.28)	1
	272 (4.39), 381 (4.08)	13
XVI	281 (4.39), 402 (4.26)	1
XIX	250 (4.21), 268 (4.24), 350 (4.34), 366 (4.26)	1
	271 (4.43), 308 (4.10), 382 (4.31), 399 (s) (4.20)	13
XX[a]	256 (s) (4.03), 280 (3.87), 357 (4.35), 366 (s) (4.33)	1
	238 (4.30), 266 (4.29), 306 (s) (3.78), 382 (4.10)	13
XXI	266 (4.50), 365 (4.13)	1
	276 (4.46), 302 (s) (4.18), 389 (4.06)	13
XXIV	290 (4.40), 370 (4.20)	1
	287 (4.42), 370 (4.12)	13
XXVI	278 (4.30), 376 (4.22)	1
XXVII	254 (4.40), 364 (4.31)	1

[a] Prepared previously by King and Spensley.[13]

Experimental

The *ultraviolet spectra* 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. In those cases where the compound crystallized from alkaline solution, no values at pH 13 are recorded.

α-Isonitrosobenzoylacetamide (X).—A solution of 2.3 g. of sodium nitrite in 4 ml. of water was added dropwise with stirring to a solution of 5.0 g. of benzoylacetamide in 16 ml. of acetic acid. The reaction mixture was kept at 10–15° during the addition and then for an additional 30-min. period, during which time the product began to crystallize. The mixture was diluted with 30 ml. of cold water, cooled at 5° for 3 hr., and filtered. The product was recrystallized from ethanol to give 5.0 g. of X, m.p. 148–149°.

Anal. Calcd. for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 55.93; H, 4.27; N, 14.40.

3-Phenyl-2-quinoxalinecarboxamide (XV).—To a solution of 5.0 g. of isonitrosobenzoylacetamide (X) in 16 ml. of acetic acid was added a solution of 6.9 g. of sodium nitrite in 15 ml. of water at such a rate that the reaction temperature did not exceed 15°. The mixture was allowed to stand at room temperature for 16 hr. and was then treated with 3.3 g. of *o*-phenylenediamine in 5 ml. of acetic acid. The resulting solution was heated on a steam bath for 10 min., made basic with aqueous ammonia, and cooled. Colorless needles crystallized. The product was collected and recrystallized from ethanol to give 2.3 g. of XV, m.p. 200–201°.

Anal. Calcd. for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.18; H, 4.13; N, 16.57.

4-Amino-2,7-diphenyl-6-pteridinecarboxamide (VI). Method A.—To a solution of 0.5 g. of α-isonitrosobenzoylacetamide (X) in 10 ml. of acetic acid was added 0.69 g. of sodium nitrite in 3 ml. of water. The solution was stirred during the addition and the temperature was kept at 10–15°. It was then allowed to stand at 25° for 16 hr. A 0.5-g. sample of 4,5,6-triamino-2-phenylpyrimidine (XIII) was added and the resulting mixture was heated on a steam bath for 15 min., diluted with 10 ml. of water, and cooled. The pale yellow needles which crystallized weighed 0.55 g. Upon recrystallization from ethanol the product melted at 325° dec. and was found to be identical with a sample of VI prepared previously.[5]

Method B.—A mixture of 4.0 g. of 4,5,6-triamino-2-phenylpyrimidine, 5.0 g. of α-bromobenzoylacetamide and 150 ml. of water was heated under reflux for 1 hr. The yellow needles which separated were collected and recrystallized from ethanol to give 2.9 g. of VI, m.p. 320–322° dec., identical with a sample prepared previously.[5]

When a similar reaction was carried out with α,α-dibromobenzoylacetamide in place of α-bromobenzoylacetamide, the same product (VI) resulted.

2,4-Diamino-7-phenyl-6-pteridinecarboxamide (VII). Method A.—To a solution of 5.0 g. of α-isonitrosobenzoylacetamide (X) in 50 ml. of acetic acid was added a solution of 7.0 g. of sodium nitrite in 15 ml. of water at such a rate that the temperature was maintained at 10 to 15°. The mixture remained in the cold bath for 2 hr. and then stood at room temperature for 2 hr. It was heated on a steam bath and 3.5 g. of 2,4,5,6-tetraminopyrimidine was added. Heating was continued for 30 min. The resulting solution was cooled and made basic with aqueous ammonia to precipitate an orange-yellow product (4.1 g.). Treatment with 5% hydrochloric acid yielded an insoluble salt which was collected and treated with aqueous ammonia. The reliberated base was recrystallized from dimethylformamide and finally boiled for 10 min. with water. The product analyzed as a hydrate of VII, m.p. 318°.

Anal. Calcd. for $C_{13}H_{13}N_7O$: C, 52.11; H, 4.39; N, 32.76. Found: C, 52.11; H, 4.33; N, 32.68.

Method B.—A mixture of 1.2 g. of benzoylacetamide and 1.2 g. of diacetylated 2,4,6-triamino-5-nitrosopyrimidine[8] was heated under reflux for 5 min. with 30 ml. of absolute ethanol. Potassium acetate (1.0 g.) in a minimum volume of hot absolute ethanol was added and heating under reflux was continued for 30 min. The mixture was cooled and filtered and the product was stirred for 2.5 hr. with 25 ml. of 2% aqueous sodium hydroxide. During this time the pale yellow acetylated pteridine dissolved and a deeper yellow compound separated in 1.2 g. yield. Upon a single recrystallization from ethanol there was obtained 1.0 g. of the monohydrate of VII, identical with the product prepared by method A.

Method C.—A mixture of 5.6 g. of 2,4,5,6-tetraminopyrimidine, 9.6 g. of α-bromobenzoylacetamide and 250 ml. of water was heated under reflux for 6 hr. The hot solution was filtered to remove a small amount of insoluble reddish material and the filtrate was made basic with ammonia. The product (5.8 g.) separated. It was purified by converting it into a hydrochloride salt with 5% hydrochloric acid, reliberating the free base with ammonia, recrystallizing from dimethylformamide, and finally boiling with water for 10 min. The product was identical with the hydrate of VII prepared by method A.

The same product was obtained when α,α-dibromobenzoylacetamide was used in place of α-bromobenzoylacetamide in a related reaction.

2-Amino-3-phenylquinoxaline.—To a cold mixture of 1.6 g. of bromine and 15 ml. of water was added, with stirring, a cold solution of 3.4 g. of potassium hydroxide in 30 ml. of water. The resulting solution was stirred into a suspension of 2.1 g. of 3-phenyl-2-quinoxalinecarboxamide (XV) in 5 ml. of water. The resulting mixture was allowed to stand for 1 hr. at 25°. It was then heated on a steam bath for 2 hr. and cooled. There was obtained 1.9 g. of product which, upon recrystallization from 2:1 methanol–ethyl acetate, melted at 160°.

Anal. Calcd. for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99. Found: C, 76.13; H, 5.09; N, 19.00.

(14) K. R. Huffman, F. C. Schaefer, and G. A. Peters, *J. Org. Chem.*, **27**, 551 (1962).

The product was identical with a sample prepared by the method of Kröhnke and Leister[9] who reported m.p. 163°.

4,6-Diamino-2,7-diphenylpteridine (XVI).—To a cold stirred mixture of 2.8 g. of bromine and 30 ml. of water was slowly added a cold solution of 5.04 g. of potassium hydroxide in 25 ml. of water. The resulting hypobromite solution was cooled to 10° and added in one portion to 5.1 g. of 4-amino-2,7-diphenyl-6-pteridinecarboxamide (VI) in 50 ml. of dimethylformamide. The resulting solution turned dark immediately and the temperature rose spontaneously to 45°. It was allowed to stand for 1 hr. and was then heated on a steam bath for 1.5 hr. A solution 5 g. of potassium hydroxide in 25 ml. of water was added and heating was continued for another hour. Upon cooling, the brownish yellow product (4.1 g.) was collected and purified by twice dissolving it in dilute acetic acid, decolorizing with charcoal, and reprecipitating with aqueous ammonia. The yield of virtually pure product was 3.1 g. For analysis it was recrystallized once from dimethylformamide and once from ethanol to give 1.5 g. of needles of XVI, m.p. 280–281°.

Anal. Calcd. for $C_{18}H_{14}N_6$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.59; H, 4.44; N, 26.52.

2,4,6-Triamino-7-phenylpteridine (II).—A hypobromite solution prepared by adding a solution of 1.7 g. of potassium hydroxide in 12 ml. of water to a mixture of 0.8 g. of bromine and 8 ml. of cold water was added to a solution of 1.4 g. of 2,4-diamino-7-phenyl-6-pteridinecarboxamide (VII) in 6 ml. of dimethylformamide. The mixture was heated to 50°, allowed to stand for 2 hr., and then heated on a steam bath for 1 hr. A solution of 5 g. of potassium hydroxide in 5 ml. of water was added slowly and heating was then continued for another hour. The yellow product (0.75 g.) which separated was collected and recrystallized by dissolving in dimethylformamide, adding a little water, and cooling. The compound (II) melted at 320° dec.

Anal. Calcd. for $C_{12}H_{11}N_7$: C, 56.91; H, 4.38; N, 38.72. Found: C, 56.80; H, 4.70; N, 39.09.

8-Amino-2,3-dihydro-6-phenyl-1*H*-2-imidazo[4,5-g]pteridinone (XIX).—A solution of potassium hypobromite was prepared by adding a cold solution of 16.8 g. of potassium hydroxide in 140 ml. of water to a mixture of 8.0 g. of bromine in 90 ml. of water. It was added to a solution of 14.0 g. of 4,7-diamino-2-phenyl-6-pteridinecarboxamide (XVIII) in 70 ml. of warm dimethylformamide. The resulting mixture was heated on a steam bath for 3.5 hr. and filtered to remove 3.8 g. of unchanged XVIII. The solution was acidified with acetic acid and the product was collected, dissolved in dilute aqueous sodium hydroxide, clarified with charcoal, and reprecipitated with acetic acid. There was obtained 9.25 g. of XIX. The product, upon recrystallization from dimethylformamide formed a solvate, m.p. over 350°.

Anal. Calcd. for $C_{16}H_{16}N_8O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.93; H, 4.48; N, 32.14.

Upon boiling with water for 15 min., the unsolvated product, m.p. over 350°, was obtained.

Anal. Calcd. for $C_{13}H_9N_7O$: C, 55.91; H, 3.25; N, 35.11. Found: C, 55.77; H, 3.20; N, 34.91.

α-Bromobenzoylacetamide.—A solution of 32.0 g. (0.2 mole) of bromine in 50 ml. of chloroform was added dropwise with stirring to a solution of 32.6 g (0.2 mole) of benzoylacetamide in 450 ml. of chloroform. The reaction mixture was maintained at 10–15°. Stirring was continued for 20 min. after the bromine addition. The solvent was removed *in vacuo* and the solid residue was recrystallized from ethanol to yield 41.5 g. of colorless crystals. Upon a second recrystallization from ethyl acetate, the product melted at 124–125°.

Anal. Calcd. for $C_9H_8BrNO_2$: C, 44.65; H, 3.33; N, 5.79. Found: C, 44.94; H, 3.26; N, 5.82.

α,α-Dibromobenzoylacetamide.—A solution of 3.2 g. of bromine in 20 ml. of chloroform was added dropwise to a stirred solution of 4.85 g. of α-bromobenzoylacetamide in 100 ml. of chloroform. The mixture was kept at 15–20° during the addition. When half the bromine had been added, the product began to crystallize. After completion of the addition, the mixture was stirred for 20 min. and concentrated *in vacuo* to half volume. The product was filtered, washed with chloroform, and dried to give 5.75 g., m.p. 174°. Upon recrystallization from ethanol, needles, m.p. 178–179°, were obtained.

Anal. Calcd. for $C_9H_7Br_2NO_2$: C, 33.68; H, 2.20; N, 4.36. Found: C, 33.42; H, 2.15; N, 4.49.

2,4-Diamino-6-phenylpteridine (XXI).—A mixture of 4.8 g. of diacetylated 2,4,6-triamino-5-nitrosopyrimidine, 5.2 g. of phenylacetaldehyde, 2.0 g. of potassium acetate and 125 ml. of ethanol was heated under reflux for 2.5 hr. It was cooled to room temperature and a solution of 2.0 g. of sodium hydroxide in 75 ml. of water was added. Upon brief warming, the yellow acetylated reaction product dissolved and crystals of XXI slowly separated. After 3 hr. the compound was filtered. The filtrate was neutralized with acetic acid and concentrated *in vacuo* to obtain a second crop. The yield of crude product was 4.3 g. It was dissolved in dilute acetic acid, treated with charcoal, reprecipitated with ammonia, recrystallized from dimethylformamide, and finally boiled with water. There was obtained 3.1 g. of XXI, m.p. 340° dec.

Anal. Calcd. for $C_{12}H_{10}N_6$: C, 60.49; H, 4.23; N, 35.28. Found: C, 60.41; H, 4.45; N, 35.02.

4-Amino-2,6-diphenyl-7-pteridinecarboxamide (XXIV) and 4,7-Diamino-2,6-diphenylpteridine (XVII).—A mixture of 2.0 g. of α-isonitrosobenzoylacetamide (X) and 2.1 g. of 4,5,6-triamino-2-phenylpyrimidine (XIII) was heated under reflux with 100 ml. of water for 24 hr. There was obtained 1.4 g. of yellow pteridine. Upon standing for a day, a second crop of 0.7 g. was obtained. The two fractions had different infrared spectra. Upon recrystallization of each from dimethylformamide, however, each yielded the same compound (XXIV), m.p. 308–309°.

Anal. Calcd. for $C_{19}H_{14}N_6O$: C, 66.66; H, 4.12; N, 24.55. Found: C, 66.68; H, 4.08; N, 24.82.

When a sample of XXIV was treated with potassium hypobromite in a reaction analogous to that used for the conversion of VI into XVI, the previously described[5] 4,7-diamino-2,6-diphenylpteridine (XVII) was produced.

4-Amino-2,7-diphenyl-6-pteridinecarbonitrile (XXVI).—A solution of 6.0 g. of bromine in 25 ml. of chloroform was added dropwise to a stirred solution of 5.45 g. of benzoylacetonitrile in 25 ml. of chloroform. Stirring was continued for 45 min. after the addition while a stream of air was blown over the surface of the solution. The residual liquid was diluted with 50 ml. of methanol and 4.1 g. of 4,5,6-triamino-2-phenylpyrimidine (XII) was added. From the resulting solution, the reaction product was permitted to crystallize over a period of 1 hr. The yellow needles were collected and recrystallized from dimethylformamide to give 3.0 g. of XXVI, m.p. 306–307°.

Anal. Calcd. for $C_{19}H_{12}N_6$: C, 70.36; H, 3.73; N, 25.91. Found: C, 70.75; H, 3.82; N, 26.04.

The product was identical by infrared spectral comparison and mixed melting point with a sample of XXVI derived[8] from 4,6-diamino-5-nitroso-2-phenylpyrimidine (III).

2,4-Diamino-7-phenyl-6-pteridinecarbonitrile (XXVII).—To a solution of 3.7 g. of benzoylacetonitrile in 30 ml. of chloroform maintained at 10 to 15° was added a solution of 4.0 g. of bromine in 20 ml. of chloroform. After the addition, the solution was stirred at room temperature for 30 min. The solvent was removed under reduced pressure and the residual oil was dissolved in 25 ml. of ethanol. The ethanolic solution was added to a hot solution made by heating to boiling 3.2 g. of 2,4,5,6-tetraminopyrimidine dihydrochloride, 6.0 g. of potassium acetate, and 20 ml. of water. Upon admixture a brown solution resulted. The product formed rapidly and separated. The mixture was permitted to stand at room temperature for 2 hr. The yellow product (2.8 g.) was collected and dissolved in dimethylformamide. The resulting solution was diluted with ethanol and 2.15 g. of needles of XXVII, m.p. 328–330° dec., crystallized.

Anal. Calcd. for $C_{13}H_9N_7$: C, 59.31; H, 3.45; N, 37.25. Found: C, 59.13; H, 3.59; N, 37.55.

Hydrolysis of 2,4-Diamino-7-phenyl-6-pteridinecarbonitrile (XXVII). Synthesis of VII.—A 0.25-g. sample of 2,4-diamino-7-phenyl-6-pteridinecarbonitrile (XXVII) was heated on a steam bath for 15 min. with 2 ml. of concentrated sulfuric acid. The resulting yellow solution was cooled and poured into 25 ml. of cold water. Pale yellow plates of the sulfate salt crystallized immediately. The mixture was made strongly basic with aqueous ammonia. The salt dissolved and a new product (VII) crystallized in 0.25 g. yield. The product was identical with a previously prepared sample.

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