acetate. This material was not further identified. Purified VIII from the reaction was studied with n.m.r.

The proton spectrum shows a large sharp peak at −180 c.p.s. due to nondeuterated $-O-\overset{\overset{O}{\parallel}}{C}-CH_3$, a broad doublet at −212 c.p.s. due to partially deuterated $CH_3\overset{\overset{CN}{|}}{C}$, and a broad triplet at +13 c.p.s. due to CH.

Spin decoupling at the D frequency of 9.211569 Mc. and high power sharpens both the $CH_3\overset{\overset{CN}{|}}{C}$ and CH. The CH_3 is separable into three doublets corresponding to CHD_2, CH_2D, and CH_3. These are shifted 1 c.p.s. from each other due to a small isotopic effect on the chemical shift. Their relative areas, on a molar basis, should correspond to the amounts of each present.

The CH is split by the deuterated methyls into a seven line pattern corresponding to 1/8 CH_3, 1/4 CH_2D, (1/2 CHD_2 + 3/8 CH_3), (CD_3 + 1/2 CH_2D), (1/2 CHD_2 + 3/8 CH_3), 1/4 CH_2D, and 1/3 CH_3. The integral curve gives on a normalized basis: 100 CD_3, 66.2 CHD_2, 15.8 CH_2D, ~1.1 CH_3. This corresponds well with the ratios 100 CHD_2, 47.7 CH_2D, 5.0 CH_3 in the CH_3 spectrum allowing for an apparent line shape assymetry.

The CH_3 spectrum shows no trace of a line near the center of the pattern which would be expected if there were any deuterium at the CH position.

The deuterium spectrum shows a large line due to the CD_3, CHD_2, and CH_2D and a small line near the deuterium oxide reference point. In the proton spectrum the CH_3 and CH are separated by 225 c.p.s. or 3.74 p.p.m. Multiplying 3.74 p.p.m. by the deuterium frequency of 9.211 Mc. we obtain 34.5 c.p.s. for the CD_3 to CD separation which is not near the position of the small line found. It is concluded that there is no CD in VIII and that the small line is probably deuterium oxide impurity.

Acknowledgment.—The author expresses his gratitude to Dr. J. P. Heeschen and Dr. E. B. Baker of The Dow Chemical Company who ran and interpreted the n.m.r. spectra, to Mr. R. S. Gohlke of The Dow Chemical Company who ran and interpreted the mass spectrometric analysis, and to Mr. R. A. Nyquist who helped interpret the infrared spectra. The author especially appreciates the helpful suggestions of Professor J. W. Crump of Albion College, Albion, Michigan.

Pteridines. I. Synthesis of Some 6-Alkyl-7-aminopteridines from Nitrosopyrimidines

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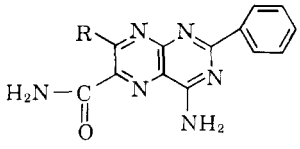
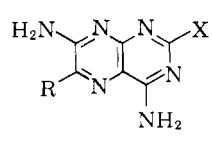
Compounds with methylenes activated by acyl groups react with 4,6-diamino-5-nitroso-2-phenylpyrimidine in the presence of sodium cyanide with incorporation of cyanide, loss of acylate, and cyclization to form 6-substituted 7-aminopteridines. The principles involved in this process were modified to permit the synthesis of six 6-alkyl-7-aminopteridines.

The diuretic activity displayed by 4,7-diamino-2-phenyl-6-pteridinecarboxamide (I) and related compounds[2] prompted us to undertake the synthesis for biological screening of a series of compounds bearing alkyl groups in the 6-position (III). Although a number of 6-aryl-7-aminopteridines (IV) have been prepared through condensation of arylacetonitriles with appropriate 4-amino-5-nitrosopyrimidines,[3] compounds of type III have not been reported. While the methylene group of an arylacetonitrile is sufficiently acidic to form an anion and react with a 4-amino-5-nitrosopyrimidine in the presence of basic catalysts, the α-methylene of a simple alkylnitrile cannot form an anion under similar conditions because it is a weaker acid than a 4-amino-5-nitrosopyrimidine. Reaction in the latter case therefore fails.

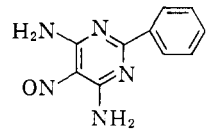


I. R = NH_2
II. R = phenyl

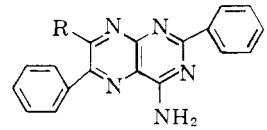


III. R = alkyl
IV. R = aryl

A solution to the problem of preparing compounds of type III came about in unexpected fashion. It was found that, although 4,6-diamino-5-nitroso-2-phenylpyrimidine (V) condenses with phenylacetaldehyde and phenylacetone in the presence of potassium acetate to give the pteridines VI and VII, the reactants condense in each case in the presence of sodium cyanide to give only the 7-aminopteridine (VIII). Compound VIII is also produced when V reacts with phenylacetonitrile in the presence of sodium cyanide.



V



VI. R = H
VII. R = CH_3
VIII. R = NH_2

In similar fashion, benzoylacetamide reacts with V in the presence of potassium acetate to produce 4-amino - 2,7 - diphenyl - 6 - pteridinecarboxamide (II). With sodium cyanide as the condensing agent, the reactants yield I.

In the synthesis of VIII from phenylacetaldehyde or phenylacetone, and in the synthesis of I from benzoylacetamide, an acyl group is lost and a nitrile incorporated at appropriate stages in the process. Kröhnke[4]

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

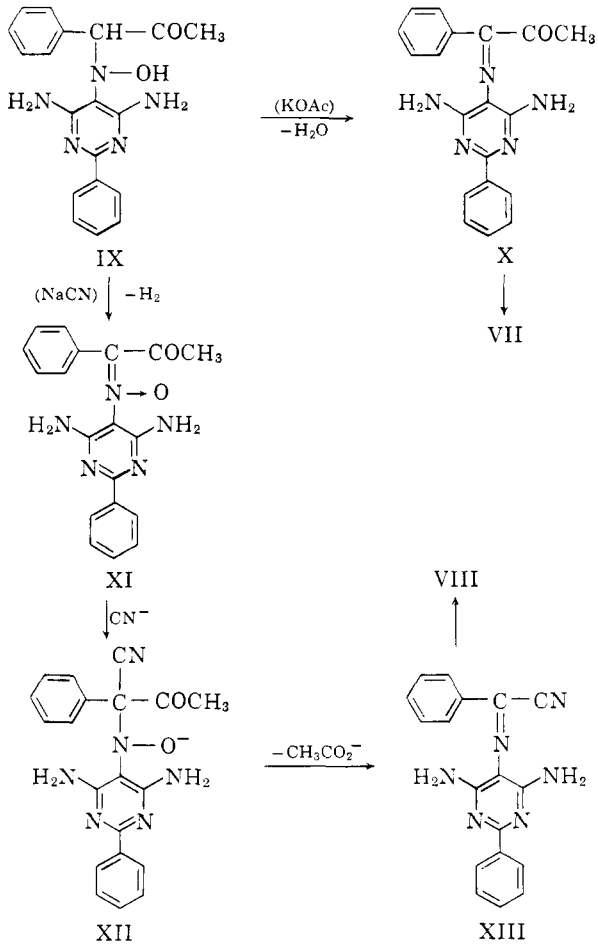
(2) (a) J. Weinstock, U. S. Patent 2,963,478 (1960); (b) E. C. Taylor, U. S. Patent 2,963,479 (1960); (c) E. C. Taylor and J. Weinstock, U. S. Patent 2,963,480 (1960); (d) J. Grannells and J. Weinstock, U. S. Patent 2,963,481 (1960); (e) T. S. Osdene and E. C. Taylor, U. S. Patent 2,975,180 (1961).

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

(4) F. Kröhnke, *Chem. Ber.*, **80**, 298 (1947).

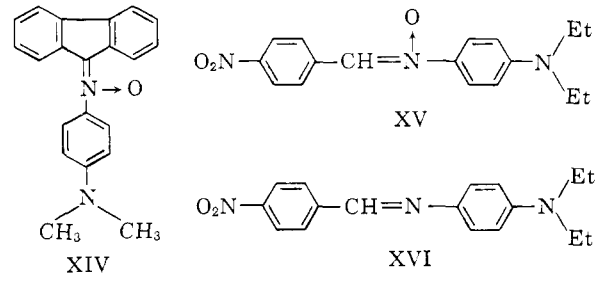
observed a related replacement of an acyl group by a nitrile some years ago.

The effect of catalyst on reaction course is noteworthy. In the acetate-catalyzed condensation of phenylacetone with V, for example, reaction proceeds through the hydroxylamine intermediate (IX). This intermediate loses water to form the anil (X) which, in turn, cyclizes to form VII.



The cyanide-catalyzed reaction also proceeds through IX, but the latter, instead of dehydrating, becomes oxidized to the nitrone (XI). This then may add cyanide (XII), lose acetate to give the anil (XIII), and cyclize to produce VIII.

That hydroxylamines related to IX may undergo oxidation rather than dehydration is well known.[4-9] For example, fluorene condenses with *p*-nitrosodimethylaniline to give only the nitrone (XIV).[6]



(5) A. Schönberg and R. Michaelis, *J. Chem. Soc.*, 627 (1937).
(6) E. Bergmann, *ibid.*, 1628 (1937).
(7) F. Barrow and F. J. Thorneycroft, *ibid.*, 769 (1939).
(8) D. C. Dittmer and J. M. Kolyer, *J. Org. Chem.*, **27**, 56 (1962).
(9) F. Kröhnke, *Ber.*, **71**, 2583 (1938).

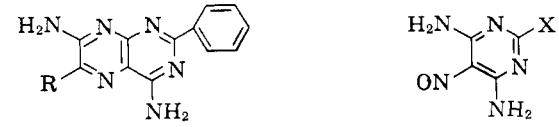
De Waal and Brink[10] have cited other instances where the nature of the product is dependent upon the condensing agent. They found that *p*-nitrobenzyl-γ-picolinium bromide reacted with *p*-nitrosodiethylaniline in the presence of sodium hydroxide at room temperature to produce the nitrone (XV), whereas the same reactants produced the anil (XVI) when the condensing agent was piperidine at 80°. Their work was complicated by the finding that the anil could be obtained, together with some *p*-nitrodiethylaniline, by heating the nitrone with *p*-nitrosodiethylaniline in the presence of piperidine. They regarded the nitrone as a possible intermediate in the formation of the anil.

It appears unlikely that nitrones are intermediates in the syntheses of II, VI, and VII for two reasons. (1) Compound II was obtained in 70% yield from V. This is higher than would have been predicted if one or more equivalents of nitrosopyrimidine had been consumed as oxidizing agent. (2) Numerous pteridine 5-oxides have been prepared in this laboratory in excellent yield through cyclization of nitrone intermediates in the presence of potassium acetate. The oxides are stable compounds and will be described in a subsequent paper.

The yield of VIII from phenylacetone is low partly because some of the nitrosopyrimidine is consumed as oxidizing agent. If one were to start with α-phenylacetoacetonitrile (XVII), the oxidation step would be omitted. Compound XVII would be expected to condense with V to form XII and ultimately to produce VIII in high yield. This is indeed the case and VIII was obtained from XVII in over 90% yield.

Compound XVII bears three activating groups on the same carbon atom. Replacement of phenyl by alkyl should give a molecule (XVIII) which is still sufficiently acidic to condense with an *o*-aminonitrosopyrimidine in the presence of alkali. If the reactions of compounds of type XVIII parallel those of XVII, 6-alkyl-7-aminopteridines (III) should result.

Four alkylnitriles were benzoylated with ethyl benzoate in the presence of sodium methoxide by the general procedure of Dorsch and McElvain.[11] Upon reaction with V in aqueous ethanol in the presence of sodium cyanide, each produced a 6-alkyl-7-aminopteridine (XIX–XXII).

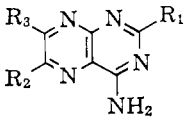


XIX. R = methyl XXI. R = cyclohexyl XXIII. X = SCH_3
XX. R = ethyl XXII. R = benzyl XXIV. X = H

Ethyl α-methylcyanoacetate used in place of α-methylbenzoylacetonitrile in reaction with V also yielded XIX. The reaction proceeded more slowly, however, and with inferior yield.

(10) H. L. de Waal and C. v. d. M. Brink, *Chem. Ber.*, **89**, 636 (1956).
(11) J. B. Dorsch and S. M. McElvain, *J. Am. Chem. Soc.*, **54**, 2960 (1932).

TABLE I
ULTRAVIOLET SPECTRA

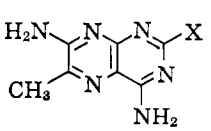


Compound	R_1	R_2	R_3	λ_{max}, mμ (log ε)	pH
II	Phenyl	Carboxamide	Phenyl	276 (4.42), 368 (4.34)	1
VI	Phenyl	Phenyl	Hydrogen	238 (4.78), 287 (4.54), 372 (4.26)	1
VII	Phenyl	Phenyl	Methyl	278 (4.45), 355 (4.23)	1
VIII	Phenyl	Phenyl	Amino	240 (4.38), 266 (4.50), 370 (4.40)	1
				266 (4.47), 270 (4.38)	13
XIX	Phenyl	Methyl	Amino	254 (4.42), 350 (4.31)	1
				243 (4.53), 346 (4.23)	13
XX	Phenyl	Ethyl	Amino	241 (4.35), 254 (4.42), 350 (4.32)	1
				243 (4.55), 346 (4.24)	13
XXI	Phenyl	Cyclohexyl	Amino	254 (4.43), 354 (4.35)	1
XXII	Phenyl	Benzyl	Amino	255 (4.44), 354 (4.35)	1
XXV	Methylthio	Methyl	Amino	255 (4.35), 347 (4.39), 363 (4.28)	1
				254 (4.58), 263 (4.37), 346 (4.25), 359 (s) (4.18)	13
XXVI	Methylthio	Methyl	Phenyl	267 (4.31), 295 (4.00), 362 (4.31)	1
XXVII	Hydrogen	Methyl	Amino	248 (4.20), 283 (3.61), 340 (4.21), 356 (s) (1.01)	1
				236 (s) (4.35), 259 (s) (4.05), 335 (4.08)	13

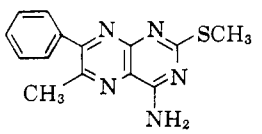
The formation of the 6-alkyl-7-aminopteridines (XIX–XXII) from substituted benzoylacetonitriles, and the formation of XIII from XVII, required in each case that acylate rather than cyanate be eliminated at an appropriate stage in synthesis. In none of these reactions involving 4,6-diamino-5-nitroso-2-phenylpyrimidine (V) was there evidence of cyclization occurring through the carbonyl group with accompanying elimination of cyanate.

This remarkable specificity did not extend to the reactions of two other nitrosopyrimidines. When 4,6-diamino-2-methylthio-5-nitrosopyrimidine (XXIII) and 4,6-diamino-5-nitrosopyrimidine (XXIV) were used in place of V in reactions with α-methylbenzoylacetonitrile, mixtures were obtained. Single products could be made to predominate, however, through appropriate choice of solvent, catalyst, and reaction temperature.

Compound XXIII reacted with α-methylbenzoylacetonitrile in ethoxyethanol in the presence of potassium acetate to form 4,7-diamino-6-methyl-2-methylthiopteridine (XXV) and 4-amino-6-methyl-2-methylthio-7-phenylpteridine (XXVI) in a molar ratio of about eleven to one. On the other hand, when sodium cyanide in aqueous ethanol was used in the reaction, the same products were formed in about a one to one ratio.



XXV. X = SCH_3
XXVII. X = H



XXVI

The reaction of compound XXIV in ethoxyethanol in the presence of potassium acetate favored formation of 4,7-diamino-6-methylpteridine (XXVII) to a pteridine by-product by a molar factor of approximately five. In an aqueous alcoholic sodium cyanide medium only the by-product, the structure of which is currently under investigation, was isolated.

More information is needed before one can speculate significantly on the manner in which the 2-substituent on nitrosopyrimidines influences the course of pteridine formation. It must first be determined whether intermediates similar to XII, which are formed from nitrosopyrimidines and compounds of type XVII and XVIII, proceed to pteridines through loss of anion followed by cyclization of whether cyclization precedes loss of anion.

The role of solvent, catalyst, and reaction temperature also remains to be clarified. Cyanide catalyst is important in causing nitrone formation (XI) rather than anil formation (X), but the experiments with XXIII and XXIV show that it clearly does not determine the course of pteridine formation once intermediates of type XII are generated.

The ultraviolet spectra of new pteridines reported in this paper are recorded in Table I.

Several of the pteridines produced potent diuretic effects in the rat. The biological data will be reported elsewhere at a later date.

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.

4,7-Diamino-2-phenyl-6-pteridinecarboxamide (I).—A mixture of 1.63 g. (0.01 mole) of benzoylacetamide, 1.0 g. (0.005 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 0.5 g. (0.01 mole) of sodium cyanide, 10 ml. of water, and 40 ml. of ethanol was heated under reflux for 3 hr. There was obtained 0.25 g. of yellow crystals, identical with an authentic sample of I.[22]

4-Amino-2,7-diphenyl-6-pteridinecarboxamide (II).—A mixture of 1.07 g. (0.005 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 1.63 g. (0.01 mole) of benzoylacetamide, 1.0 g. of potassium acetate and 50 ml. of ethanol was heated under reflux for 2 hr., during which time the nitroso compound dissolved and the product crystallized from solution in fine needles. The mixture was concentrated, cooled, and filtered to give 1.2 g. (70%) of almost colorless needles. After one recrystallization from ethanol, the compound melted at 322–324° dec.

Anal. Calcd. for $C_{19}H_{14}N_6O$: C, 66.66; H, 4.12; N, 24.55. Found: C, 66.69; H, 4.24; N, 24.67.

4-Amino-2,6-diphenylpteridine (VI).—A mixture of 6.45 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 5 g. of potassium acetate, 7.2 g. of phenylacetaldehyde, and 50 ml. of ethoxyethanol was heated under reflux for 30 min. The mixture was concentrated to half volume under reduced pressure and 10 ml. of water was added. A brown substance separated from the cooled solution. It was taken up in ethanol and the resulting solution was treated with charcoal, concentrated, and cooled. There was obtained 1.5 g. of orange crystals which, upon recrystallization from dimethylformamide, yielded 1.3 g. of orange plates, m.p., 288–289° dec.

Anal. Calcd. for $C_{18}H_{13}N_5$: C, 72.22; H, 4.38; N, 23.40. Found: C, 72.23; H, 4.53; N, 23.16.

4-Amino-7-methyl-2,6-diphenylpteridine (VII).—A mixture of 2.15 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 3.3 g. of phenylacetone, 3.0 g. of potassium acetate and 50 ml. of *n*-butyl alcohol was heated under reflux for 4 hr. The mixture was cooled in an ice bath for 1 hr. and the yellow needles were filtered, washed with water and ethanol, and dried. The product weighed 1.3 g. (41.5% yield). For analysis a sample was recrystallized from 5:1 ethanol–ethoxyethanol, m.p. 288–290° dec.

Anal. Calcd. for $C_{19}H_{15}N_5$: C, 72.82; H, 4.82; N, 22.35. Found: C, 72.38; H, 5.13; N, 22.05.

4,7-Diamino-2,6-diphenylpteridine (VIII). (A) From Phenylacetonitrile.—A mixture of 1.17 g. of phenylacetonitrile, 0.5 g. of 4,6-diamino-5-nitroso-2-phenylpteridine, 0.25 g. of sodium cyanide and 30 ml. of 90% ethanol was boiled for 10 min. The green color rapidly disappeared and the yellow pteridine separated from solution. The product was collected and recrystallized from dimethylformamide to give 0.65 g. of VIII, m.p. over 320°.

Anal. Calcd. for $C_{18}H_{14}N_6$: C, 68.78; H, 4.49; N, 26.74. Found: C, 68.43; H, 4.60; N, 26.53.

(B) From Phenylacetaldehyde.—To a mixture of 2.15 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 2.4 g. of phenylacetaldehyde and 20 ml. of ethanol was added a solution of 1.0 g. of sodium cyanide in 5 ml. of water. The mixture was heated to boiling and the reactants went into solution. After standing at room temperature overnight, the 0.9 g. of yellow product that separated was washed thoroughly with water and recrystallized from dimethylformamide to yield 0.5 g. of VIII, identical with the product prepared by method A.

(C) From Phenylacetone.—Under conditions similar to those of method B 4 ml. of phenylacetone reacted with 2.15 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine to form 0.8 g. of VIII.

(D) From α-Phenylacetoacetonitrile.—To a boiling mixture of 1.1 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 1.6 g. of α-phenylacetoacetonitrile and 50 ml. of ethanol was added 0.5 g. of sodium cyanide in 5 ml. of water. The mixture was heated under reflux for 5.5 hr. Upon concentration and cooling there was obtained 1.45 g. (90.7%) of VIII, identical with an authentic sample prepared from phenylacetonitrile.

4,7-Diamino-6-methyl-2-phenylpteridine (XIX). (A) From Reaction with α-Methylbenzoylacetonitrile.—To a mixture of 21.5 g. (0.1 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine and 31.8 g. (0.2 mole) of α-methylbenzoylacetonitrile[11] in 200 ml. of ethanol was added a solution of 10 g. (0.2 mole) of sodium cyanide dissolved in 40 ml. of water. The mixture was heated for 18 hr. Upon concentration to about 60 ml. and cooling there was obtained 23 g. of crude pteridine. This was recrystallized from methanol to give 15.2 g. (60%) of pale yellow needles of XIX, m.p. 308–309° dec.

Anal. Calcd. for $C_{13}H_{12}N_6$: C, 61.89; H, 4.80; N, 33.31. Found: C, 62.05; H, 4.91; N, 33.33.

(B) From Reaction with Ethyl α-Methylcyanoacetate.—To a mixture of 2.15 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 2.6 g. of ethyl α-methylcyanoacetate and 30 ml. of ethanol was added a solution 1.0 g. of sodium cyanide in 10 ml. of water. The mixture was heated (24 hr.) until disappearance of green color. There was obtained 0.6 g. of XIX, identical with the sample obtained as described in method A.

4,7-Diamino-6-ethyl-2-phenylpteridine (XX).—To a mixture of 1.07 g. (0.005 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine and 1.7 g. (0.01 mole) of α-ethylbenzoylacetonitrile[11] in 35 ml. of ethanol was added a solution of 0.5 g. of sodium cyanide in 6 ml. of water. The mixture was heated under reflux for 8 hr. There was obtained 1.05 g. of yellow product, m.p. after recrystallization from dilute acetic acid, 276–280° dec.

Anal. Calcd. for $C_{14}H_{14}N_6$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.14; H, 5.46; N, 31.21.

α-Cyclohexylbenzoylacetonitrile.[12]—Cyclohexylacetonitrile was prepared from cyclohexylmethyl bromide by the general procedure described by Friedman and Shechter.[13] A solution of 55 g. of sodium cyanide in 400 ml. of dry dimethyl sulfoxide was heated to 60° and 177 g. of cyclohexylmethyl bromide was added at such a rate as to maintain the temperature at 60–65°. After the addition, the reaction mixture was heated to 85° for 3 hr. One liter of water was added and the oily layer was taken up in ether. The ethereal layer was dried over magnesium sulfate and distilled over phosphorus pentoxide to give 86.0 g. (70%) of cyclohexylacetonitrile, b.p. 83–86° (20 mm.), $n^{25}D$ 1.4577. Wallach[14] reported $n^{18}D$ 1.4575.

To a stirred mixture of 120 g. (0.8 mole) of ethyl benzoate and 43.2 g. (0.8 mole) of sodium methoxide heated at 80° was added 86 g. (0.88 mole) of cyclohexylacetonitrile over a period of 2 hr. The temperature of the heating bath was raised to 115–120° and heating was continued for 10 hr.

The thick mixture was cooled and diluted with ice and water at 0°. Ether was added and the mixture was stirred while sulfuric acid was added until the pH was brought to between 2 and 3. The mixture was extracted with several portions of ether and the combined ethereal extracts were washed with 5% sodium bicarbonate solution to remove benzoic acid. The ethereal solution was dried over magnesium sulfate and distilled. There was obtained 41 g. of pale yellow oil, b.p., 180–190°(1 mm.). The product solidified and, upon recrystallization from ether–hexane mixture, melted at 45–46°.

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54. Found: C, 79.53; H, 7.63.

4,7-Diamino-6-cyclohexyl-2-phenylpteridine (XXI).—A mixture of 7.4 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 15 g. of α-cyclohexylbenzoylacetonitrile, 3.5 g. of sodium cyanide, 60 ml. of water and 180 ml. of ethanol was heated under reflux for 20 hr. The green color remained and an additional 7 g. of α-cyclohexylacetonitrile was added and reflux maintained for an additional 16 hr. Upon cooling there was obtained 5.5 g. of yellow solid. Concentration yielded an additional 0.95 g. The two crops were combined and recrystallized from dilute acetic acid to give 5.4 g. of XXI, m.p. 338–340°.

Anal. Calcd. for $C_{18}H_{20}N_6$: C, 67.48; H, 6.29; N, 26.23. Found: C, 67.56; H, 6.49; N, 26.26.

α-Benzylbenzoylacetonitrile.[12]—This compound was prepared from hydrocinnamonitrile and ethyl benzoate by the same procedure used for the preparation of α-cyclohexylbenzoylacetonitrile. From 164 g. of hydrocinnamonitrile there was obtained 63 g. of product, b.p., 186–202° (0.5 mm.), m.p., upon recrystallization from methanol, 79–80°.

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.81; H, 5.65.

4,7-Diamino-6-benzyl-2-phenylpteridine (XXII).—To a mixture of 12.9 g. (0.06 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 27.0 g. (0.12 mole) of α-benzylbenzoylacetonitrile and 225 ml. of ethanol was added a solution of 6 g. (0.12 mole) of sodium cyanide in 75 ml. of water. The resulting mixture was heated under reflux for 20 hr. The solvent was removed under reduced pressure and the residue was washed thoroughly with water and recrystallized from ethanol to yield 4.8 g. of XXII, m.p., 280–281° dec.

Anal. Calcd. for $C_{19}H_{16}N_6$: C, 69.49; H, 4.91; N, 25.59. Found: C, 69.27; H, 5.21; N, 26.53.

4,7-Diamino-6-methyl-2-methylthiopteridine (XXV).—A mixture of 1.85 g. of 4,6-diamino-2-methylthio-5-nitrosopyrimidine, 3.2 ml. of α-methylbenzoylacetonitrile, 3.0 g. of potassium acetate and 50 ml. of ethoxyethanol was heated under reflux for 2 hr. The brown solution was concentrated to 30 ml. and cooled. A yellow solid (1.0 g.) separated and was filtered. When the filtrate stood for 1 hr., 0.2 g. of a second compound separated which proved to be identical with XXVI described in the following experiment. The filtrate was then concentrated to about 15 ml. and diluted with 5 ml. of water. Upon standing overnight, an additional 0.8 g. of the first compound separated. The combined first and third crops (1.8 g.), upon recrystallization from ethanol, melted at 308–310° dec.

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(12) We thank Mr. A. J. Villani of this laboratory for the preparation of this compound.

(13) L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 877 (1960).

(14) O. Wallach, *Ann.*, **359**, 311 (1908).

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.

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

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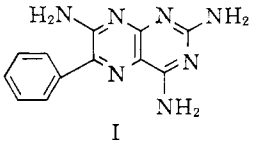
2,4,5,6-Tetraminopyrimidine and 4,5,6-triamino-2-phenylpyrimidine react with aldehydes and hydrogen cyanide to form aminonitriles which may be cyclized with sodium methoxide and oxidized with hydrogen peroxide to 6-substituted-7-aminopteridines. α,β-Unsaturated aldehydes are reduced in the process; cinnamaldehyde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

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(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.