Pteridines. IX.[1] Some Pteridine Isomers of Triamterene

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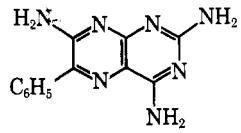
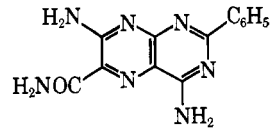
Received January 6, 1968

2-Phenyl-4,6,7-triaminopteridine and 4-phenyl-2,6,7-triaminopteridine were prepared for diuretic evaluation. Each synthesis proceeded *via* amination of a trichlorophenylpteridine.

Triamterene (2,4,7-triamino-6-phenylpteridine) (I) shares with 4,7-diamino-2-phenylpteridine-6-carboxamide (II) the biological property of causing significant diuresis in laboratory animals[2] and the structural feature of a polyaminophenylpteridine moiety. Since I is a 6-phenylpteridine and II is a 2-phenylpteridine, it



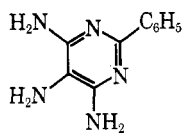
I



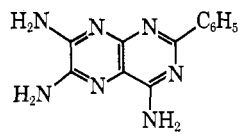
II

seemed possible that other triaminophenylpteridines might satisfy the structural requirement for significant diuretic activity. In order to test this hypothesis, we required all of the possible triamterene pteridine isomers. The synthesis of 2,4,6-triamino-7-phenylpteridine was reported in a previous paper of this series.[3] We now wish to report the synthesis of the two remaining triamterene isomers.

The ready availability of 2-phenyl-4,5,6-triaminopyrimidine (III) and the precedent of the synthesis of 2,3-diaminoquinoxaline *via* the condensation of *o*-phenylenediamine with cyanogen or its equivalent led us to explore the condensation of III with cyanogen and with diethyl iminooxalate in an attempt to prepare 2-phenyl-4,6,7-triaminopteridine (IV) by direct condensation. These attempts were unrewarding. The success achieved in our laboratory in preparing 2,4-diamino-7-chloro-6-phenylpteridine from the corresponding 7-hydroxypteridine and the



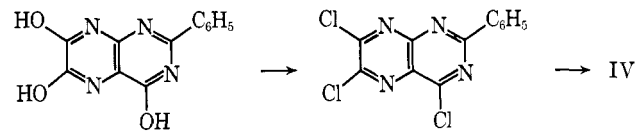
III



IV

subsequent conversion to various 7-aminopteridines[4] suggested a similar approach for this problem. Condensation of III with either oxalic acid or diethyl oxalate gave 4-amino-6,7-dihydroxy-2-phenylpteridine (V), but attempts to convert this to 4-amino-6,7-dichloro-2-phenylpteridine (VI) were unsuccessful.

As a part of our diuretic structure–activity study, we required a sample of 2,4,7-triaminopteridine which was easily prepared from 2,4,7-trihydroxypteridine *via* 2,4,7-trichloropteridine.[5] This suggested that the difficulty encountered in the conversion of V to VI could be attributed to the presence of the 4-amino group. To circumvent this, 2-phenyl-4,6,7-trihydroxypteridine (VII)[6] was prepared and converted to 2-phenyl-4,6,7-trichloropteridine (VII) by refluxing with PCl_5 in $POCl_3$. The trichloropteridine required vacuum sublimation with a consequent high loss of material before use in the next reaction. Omission of the sublimation frequently gave intractable mixtures on attempted amination, and it was apparent from the infrared spectra that considerable impurity had been removed by the sublimation. Treatment of VIII with anhydrous NH_3 at 140° gave IV. In contrast to the extreme insolubility of I in common solvents, IV could be readily recrystallized from H_2O.



VII VIII

In our first approach to 2,6,7-triamino-4-phenylpteridine (IX) we planned to prepare 2-amino-6,7-dihydroxy-4-phenylpteridine and convert it to IX *via* 2-amino-6,7-dichloro-4-phenylpteridine. The readily available 2-amino-4-hydroxy-6-phenylpyrimidine[7] was nitrated under conditions just vigorous enough to avoid recovering starting material. The only product which was isolated proved to be 2-amino-4-hydroxy-5-nitro-6-(3-nitrophenyl)pyrimidine (X). 2,4-Diamino-5-nitro-6-(3-nitrophenyl)pyrimidine was prepared from X *via* 2-amino-4-chloro-5-nitro-6-(3-nitrophenyl)pyrimidine, but the presence of the nitro group on the phenyl ring discouraged us from pursuing this route further. The *meta* orientation of the nitro group in X was established by consideration of its nmr spectrum (two 2-proton complex multiplets centered at 7.90 and 8.53 ppm, the latter containing an intense spike at 8.58 ppm due to the 2-proton).

The successful synthesis of IX is outlined in Scheme I. 2,4-Dihydroxy-6-phenylpyrimidine (XI) was coupled with phenyldiazonium chloride to give 2,4-dihydroxy-6-phenyl-5-phenylazopyrimidine (XII). Refluxing XII with $POCl_3$ gave 2,4-dichloro-6-phenyl-5-phenylazopyrimidine (XIII). In order to avoid possible complications in later steps of the synthesis due to the premature presence of an amine group, it was desirable to replace selectively the 4-chlorine of XIII with an amino group. Since 2,4-dichloro-6-methyl-5-

(1) Previous paper in this series: J. Weinstock, H. Graboyes, G. Jaffe, I. J. Pachter, K. Snader, C. B. Karash, and R. Y. Dunoff, *J. Med. Chem.*, **11**, 560 (1968).

(2) V. D. Wiebelhaus, J. Weinstock, A. R. Maass, F. T. Brennan, G. Sosnowski, and T. Larsen, *J. Pharmacol. Exp. Ther.*, **149**, 397 (1965).

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

(4) J. Weinstock, I. J. Pachter, P. Nemeth, and G. Jaffe, *J. Med. Chem.*, **11**, 557 (1967).

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

(6) R. Andrisano and L. Maioli, *Gazz. Chim. Ital.*, **83**, 264 (1953).

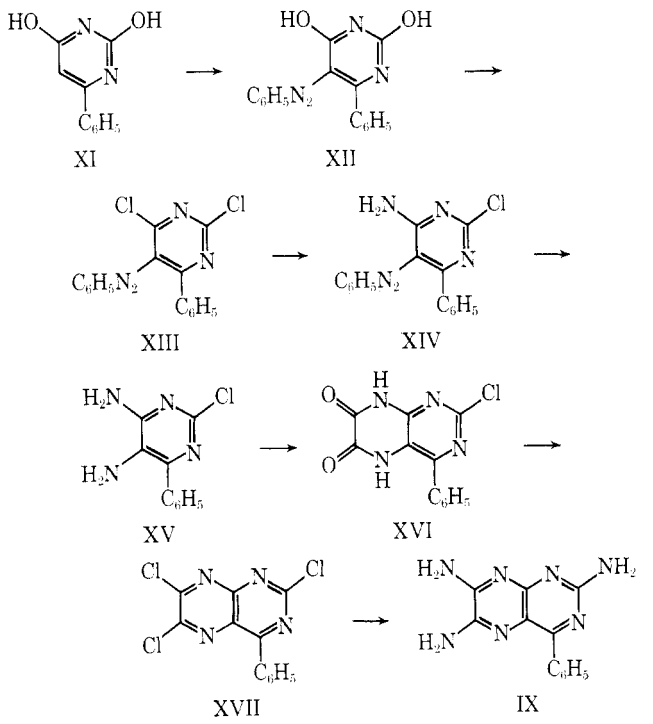
(7) T. B. Johnson and A. J. Hill, *J. Am. Chem. Soc.*, **36**, 1201 (1914).

TABLE I
SPECTRAL DATA

Triaminopteridine	Ultraviolet: Solvent	Ultraviolet: λ_{max}, mμ (log ε)	Nmr[b] δ, cps (phenyl protons)	Fluorescence[c]
2-C_6H_5 (IV)	0.1 N HCl	258 (4.42), 364 (4.35)	7.70,[e] 8.15[d]	Dark blue
	0.1 N NaOH	242 (4.44), 357 (4.26)	(complex multiplet)	
4-C_6H_5 (IX)	4.5% HCOOH	263 (4.36), 400 (4.30)	7.82, 7.87	Light blue
	1 N NaOH	252 (4.24), 374 (4.22)	(complex multiplet)	
6-C_6H_5 (I)	4.5% HCOOH	254 (4.19), 288 sh (3.85), 358 (4.33)	7.73 (singlet)	Blue
	1 N NaOH	269 (4.13), 368 (4.27)		
7-C_6H_5	4.5% HCOOH[a]	262 (4.31), 404 (4.08)	7.75 (singlet)	Yellow-green
	1 N NaOH[a]	269 (4.33), 416 (4.00)		

[a] Reference 3. [b] In CF_3COOH (TMS = 0). [c] 3 H. [d] 2 H. [e] Color in EtOH, 366 mμ illumination.

SCHEME I



nitropyrimidine aminates selectively[8] to give 4-amino-2-chloro-6-methyl-5-nitropyrimidine possibly due to the hydrogen-bonding ability of the nitro group,[9] a similar *ortho* activating effect could be anticipated from the phenylazo group. The reaction of XIII with NH_3 in ether did give a single monoaminated product which, from its ultimate conversion to a 2-chloropteridine, must be 4-amino-2-chloro-6-phenyl-5-phenylazopyrimidine (XIV).

The reduction of a 5-phenylazopyrimidine to a 5-aminopyrimidine by catalytic hydrogenation is well known. In this case two complicating factors were present, namely, the low solubility of XIV in the usual solvents employed for catalytic reductions and the possibility of hydrogenolysis of the 2-chloro group. Hydrogenation of XIV with Raney nickel in DMF, however, gave the desired 4,5-diamino-2-chloro-6-phenylpyrimidine (XV) in 88% yield.

The conversion of XV to the required 2-chloro-6,7-dihydroxy-4-phenylpteridine (XVI) proved to be a low yield process. The best conditions of those tried involved refluxing XV with methyl oxalate for 20 hr in water. Shorter reaction times gave lower yields of product, and more vigorous conditions were avoided because of possible reaction of the 2-chloro group. The low reactivity of XV may be attributed to steric hindrance at the 5-amino group due to the presence of the 6-phenyl, and the electron-withdrawing base-weakening effects of both the 2-chloro and the 6-phenyl substituents. An attempt to prepare XVI by reaction of XV with oxalyl chloride gave what appears to be N,N′-(4-amino-2-chloro-6-phenyl-5-pyrimidinyl)oxamide.

The structure of XVI is best represented as 2-chloro-4-phenyl-5,6,7,8-tetrahydropteridine-6,7-dione, assigned by analogy with the dione nature of leucopterine (2-amino-3,4,5,6,7,8-hexahydropteridine-4,6,7-trione) as shown by Pfleiderer and Rukwied[10] on the basis of uv spectral comparisons with authentic N- and O-methyl analogs. In addition, the ir spectrum of XVI taken as a Nujol mull showed a broad band 3.14 μ assignable to a N–H stretching vibration as the only band in this region and a very strong band at 5.85 μ assignable to the lactam carbonyls.[11]

Reaction of XVI with PCl_5 in $POCl_3$ gave 2,6,7-trichloro-4-phenylpteridine (XVII). Again sublimation proved useful for purification of the product, but again the loss of material on sublimation was high. It was found in this case that carefully handled unsublimed XVII had, as seen in the infrared spectrum, only small quantities of impurity, mostly manifested as a small double peak at 5.97 and 6.09 μ. This unsublimed material gave reasonable yields in the next step of the synthesis.

Amination of XVII in anhydrous NH_3 at 140° gave 2,6,7-triamino-4-phenylpteridine (IX). This compound, like the 2-phenyl isomer, and in contrast to the 6-phenyl isomer, was appreciably soluble in ordinary solvents so that it could be purified by recrystallization from aqueous EtOH.

A comparison of the spectral properties of the four triaminophenylpteridine isomers is shown in Table I. In the nmr spectra measured in trifluoroacetic acid the 6- and 7-phenylpteridine isomers show a singlet phenyl proton peak whose unsplit nature is due to steric inhibition of coplanarity of the phenyl and pteridine

(8) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 3832 (1954).
(9) R. R. Bishop, E. A. S. Cavell, and N. B. Chapman, *ibid.*, 437 (1952).
(10) W. Pfleiderer and M. Rukwied, *Ber.*, **94**, 118 (1961).
(11) W. Pfleiderer and R. Lohrmann, *ibid.*, **95**, 738 (1962), and D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 3443 (1956), found the carbonyl band of several pteridin-6- and -7-ones to come near 5.95 μ. The dipolar field effect of the *cis*-α-carbonyl combination would be expected to shift this to a shorter wavelength.[12]
(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, pp 400–402.

rings.[13] The 4-phenylpteridine gives rise to a phenyl proton signal with only a small amount of splitting. By analogy with the above, it must be assumed that the electrons on the 5-nitrogen provide sufficient steric hindrance to prevent complete coplanarity of the phenyl and pteridine rings. In contrast, the phenyl protons from the 2-phenyl isomer appear as a complex multiplet typical of a phenyl which is interacting with an unsaturated substituent. In this case the phenyl and pteridine rings must be coplanar.

The uv spectral data show that 2- and 6-phenyl isomers have their long wavelength peaks near 365 mμ while the 7-phenyl isomer (XVIII) has its corresponding peak near 410 mμ. The 4-phenyl isomer in basic solution resembles the 2 and 6 isomers while in acid it resembles the 7-phenyl isomer. It has been noted[14] that substituents in the 2 and 6 positions of the pteridine ring exert a greater bathochromic shift than the same substituents elsewhere on the pteridine ring.

Pharmacology.—The diuretic structure–activity relationships of the compounds described in this paper will be reported in an accompanying paper.[15]

Experimental Section[16]

Paper chromatography was done by the circular system on Whatman 3 MM paper using a cotton wick to bring the solvent to the paper. Thin layer chromatography was carried out using silica gel G on glass plates. The following systems were used: (1) H_2O–concentrated NH_4OH–2-PrOH (25:5:70); (2) 6 *N* NH_4OH–isoamyl alcohol–*t*-amyl alcohol (10:5:5); (3) HCOOH–H_2O–BuOH (1:5:5); (4) thin layer chromatography (tlc), $CHCl_3$; (5) tlc, cyclohexane–EtOAc–Et_2NH (70:30:1); (6) tlc, EtOAc; (7) tlc, MeOH–cyclohexane (90:10); (8) tlc, MeOH–$CHCl_3$ (50:40); (9) HCOOH–H_2O–*i*-AmOH–*t*-AmOH (1:5:3:3); (10) pretreat paper with a mineral oil–castor oil mixture, develop with EtOH–H_2O (3:1). Melting points are uncorrected and were determined in open capillary tubes. Ir spectra were determined on a Perkin-Elmer Infracord, the uv spectra on a Cary Model 14 spectrophotometer, and the nmr data on a Varian A-60 spectrometer.

4,6,7-Trihydroxy-2-phenylpteridine (VII)[17] was prepared by the following modification of the reported procedure.[6] A mixture of 40 g (0.20 mole) of 4,5-diamino-6-hydroxy-2-phenylprimidine and 88 g (0.60 mole) of diethyl oxalate in 650 ml of ethoxyethanol was refluxed for 5.7 hr with periodic removal of the EtOH formed. Cooling and filtering gave 43 g (84%) of yellow-orange crystals, mp 364–366° dec, lit.[6] mp 370°.

4,6,7-Trichloro-2-phenylpteridine (VIII).—A mixture of 26.5 g (0.104 mole) of 4,6,7-trihydroxy-2-phenylpteridine, 104 g (0.50 mole) of PCl_5, and 300 ml of $POCl_3$ was refluxed for 5 hr. After careful removal of most of the $POCl_3$ under vacuum on a steam bath, the residue was extracted with about 500 ml of dry Et_2O. The Et_2O solution was treated with charcoal, filtered, concentrated, and chilled to give 25.3 g of crystals, mp 189° (78% yield of crude material). Attempts to use this material as isolated for further reactions usually gave impure products, so this was purified by sublimation at 187–189° (0.5 mm). A pale yellow solid was obtained in about 25% recovery, mp 193–195°. *Anal.* ($C_{12}H_5Cl_3N_4$) C, H, N.

4,6,7-Triamino-2-phenylpteridine (IV).—A mixture of 1.8 g (0.0058 mole) of 4,6,7-trichloro-2-phenylpteridine and 100 ml of anhydrous NH_3 was heated at 140° for 6 hr. The solid residue obtained after evaporation of the NH_3 was taken up in EtOH and filtered, and the filtrate was taken to dryness under vacuum. The residue thus obtained was dissolved in dilute HCl, filtered, and reprecipitated at pH 8 with concentrated NH_4OH. This gave a tan solid which was recrystallized from H_2O to give 1.1 g (73%) of buff crystals: mp 285–287° dec; $\lambda_{max}^{0.1\ N\ HCl}$ 258 mμ (log ε 4.42), 364 (4.35); $\lambda_{max}^{0.1\ N\ NaOH}$ 242 mμ (log ε 4.44), 357 (4.26). *Anal.* ($C_{12}H_{11}N_7$) C, H, N.

4-Amino-6,7-dihydroxy-2-phenylpteridine (V). A.[18]—A mixture of 2.01 g (0.01 mole) of 2-phenyl-4,5,6-triaminopyrimidine[19] and 6.32 g (0.07 mole) of oxalic acid was heated at 170° at 25 mm for 2 hr. Since a large fraction of the oxalic acid had sublimed out of the reaction mixture, the reaction was interrupted and the oxalic acid was washed back into the reaction mixture using 4 ml of DMF. After heating for 3 hr more at 170°, a yellow solid was obtained which was dissolved in 2 *N* NaOH, decolorized with charcoal, and precipitated by adjusting the pH to 6.5 with 12 *N* HCl. This gave 2.15 g (84%) of a yellow solid, mp >300°. After two similar recrystallizations *via* base and acid, the resulting pale yellow product was recrystallized by dissolving in refluxing DMF and bringing out with H_2O; R_f 0.43 (system 1), 0.07 (system 2); $\lambda_{max}^{0.1\ N\ NaOH}$ 342 mμ (log ε 4.54), 331 (sh) (4.29), 342 (4.35). *Anal.* ($C_{12}H_9N_5O_2$) C, N; H: calcd, 3.55; found, 4.01.

B.[20]—A mixture of 14.7 g (0.072 mole) of 4,5,6-triamino-2-phenylpyrimidine and 23.6 g (0.200 mole) of dimethyl oxalate in 200 ml of ethylene glycol was refluxed for 1.5 hr. Cooling gave a yellow solid which was collected by filtration and washed in turn (H_2O, MeOH) to give 14.5 g (79%) of product. This was purified by two recrystallizations from base–acid as above to give 11.6 g (62%) of product whose uv spectra was identical with that prepared above; R_f 0.48 (system 1).

2,4-Diamino-5-nitro-6-(3-nitrophenyl)pyrimidine.[21]—A mixture of 10 g (0.043 mole) of 2-amino-4-hydroxy-5-nitro-6-(3-nitrophenyl)pyrimidine and 40 ml of $POCl_3$ was refluxed for 3 hr. The reaction mixture was poured onto ice and resulting solid was collected, washed with H_2O, and air dried to give 6.1 g (57%) of 2-amino-4-chloro-5-nitro-6-(3-nitrophenyl)pyrimidine, mp 73–78°, which was used without further purification in the next step. This product was suspended in 200 ml of *n*-BuOH and saturated with NH_3 at 0°. The mixture was then refluxed for 2.5 hr while passing a slow stream of NH_3 into the reaction mixture. The reaction mixture was filtered, decolorized with charcoal, and chilled overnight to give a yellow solid. Several recrystallizations of this from EtOH–H_2O gave 2.4 g (36%) of yellow crystals, mp 244–246°, R_f 0.63 (system 9). *Anal.* ($C_{10}H_8N_6O_4$) C, H, N.

2-Amino-4-hydroxy-5-nitro-6-(3-nitrophenyl)pyrimidine (X).[21]—A solution of 5.0 g (0.027 mole) of 2-amino-4-hydroxy-6-phenylpyrimidine[7] in a mixture of 15 ml of concentrated H_2SO_4 and 15 ml of 90% HNO_3 was prepared at 10° and allowed to stand at room temperature for 15 min. Pouring over ice gave 3.7 g (50%) of a solid which was recrystallized for analysis from dioxane–H_2O. This gave yellow crystals, mp 320–323° dec, R_f 0.65 (system 2). *Anal.* ($C_{10}H_7N_5O_5$) C, H, N.

2,4-Dihydroxy-6-phenyl-5-phenylazopyrimidine (XII).—To a stirred suspension of 28.2 g (0.15 mole) of 2,4-dihydroxy-6-phenylpyrimidine[22] in 2 l. of H_2O was added 40% NaOH until a solution formed. To this, cooled between 0 and 5° by the addition of ice, was added a solution of phenyldiazonium chloride prepared from 14 g (0.15 mole) of aniline and 10.4 g (0.15 mole) of $NaNO_2$ in 60 ml of 6 *N* HCl. The reaction mixture was then stirred at room temperature for 2 hr maintaining the pH at 8–9 by addition of 10% NaOH as required. The pH was then adjusted to 2 with concentrated HCl and a light orange solid collected, mp 215–221°. Recrystallization from about 3 l. of 50% EtOH–H_2O gave 36.5 g (83%) of product: mp 233–234°; R_f 0.76 (system 10); λ_{max}^{EtOH} 340 mμ (log ε 4.21), 269 (3.97). *Anal.* ($C_{16}H_{12}N_4O_2$) C, H, N.

2,4-Dichloro-6-phenyl-5-phenylazopyrimidine (XIII).—A suspension of 29.2 g (0.10 mole) of 2,4-dihydroxy-6-phenyl-5-phenyl-

(13) See J. Weinstock, I. J. Pachter, P. Nemeth, and G. Jaffe, *J. Med. Chem.*, **11**, 557 (1968), for a discussion of the 6-phenyl case.

(14) S. F. Mason, *J. Chem. Soc.*, 2336 (1955).

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

(16) We wish to thank Miss Margaret Carroll and her staff for microanalytical data, Dr. Walter Thompson and Mr. Richard J. Warren for spectral data, and Mr. Alex Post and Mr. E. L. Haines for chromatographic data. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the calculated values.

(17) We wish to thank Dr. J. W. Wilson for carrying out this preparation.

(18) We wish to thank Mrs. J. G. Williams for carrying out this reaction.

(19) R. M. Evans, P. G. Jones, P. J. Palmer, and F. F. Stephens, *J. Chem. Soc.*, 4106 (1956).

(20) We wish to thank Mrs. C. B. Karash for carrying out this preparation.

(21) We wish to thank Mr. J. Kirkpatrick for carrying out this preparation.

(22) J. H. Burckhalter and H. C. Scarborough, *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 545 (1955). We obtained better yields in the conversion of 4-hydroxy-2-mercapto-6-phenylpyrimidine to 2,4-dihydroxy-6-phenylpyrimidine by hydrolysis in gently refluxing 48% HBr for 24 hr with efficient stirring. The product has λ_{max}^{EtOH} 284 mμ (log ε 4.09).

azopyrimidine in 500 ml of $POCl_3$ was refluxed for 4 hr with stirring. The solvent was removed under vacuum and the residue was extracted with Et_2O. Evaporation of the Et_2O under vacuum gave a residue which was triturated with an ice–water mixture. Filtration gave 21.5 g (65%) of a solid, mp 110–112°, R_f 0.49 (system 4). A small sample recrystallized from hexane had mp 114–115°. *Anal.* ($C_{16}H_{10}Cl_2N_4$) H, N; C: calcd, 58.38; found, 59.03.

4-Amino-2-chloro-6-phenyl-5-phenylazopyrimidine (XIV).—A stream of anhydrous NH_3 was passed into a solution of 10.8 g (0.033 mole) of 2,4-dichloro-6-phenyl-5-phenylazopyrimidine in 500 ml of ether for 1 hr at 0–5°, and the solution was stirred at 0–5° for 1 hr and at room temperature for 1 hr. The precipitate which formed was collected, washed (H_2O), and recrystallized from EtOH to give 7.4 g (72%) of product, mp 239–241°, R_f 0.50 (system 5). *Anal.* ($C_{16}H_{12}ClN_5$) C, H, N.

4,5-Diamino-2-chloro-6-phenylpyrimidine (XV).—A solution of 14.0 g (0.045 mole) of 4-amino-2-chloro-6-phenyl-5-phenylazopyrimidine in 200 ml of DMF containing suspended Raney nickel catalyst was shaken in an H_2 atmosphere at 3.5 kg/cm² pressure until the theoretical quantity of H_2 was taken up (about 1 hr). The catalyst was removed by filtration and the solvent was removed under vacuum. Trituration of the residue with Et_2O gave 8.2 g (88%) of product, mp 193–198°. A sample recrystallized from EtOH–H_2O had mp 205–207°, R_f 0.65 (system 6), 0.82 (system 7). *Anal.* ($C_{10}H_9ClN_4$) C, H, N.

2-Chloro-6,7-dihydroxy-4-phenylpteridine (XVI).—A mixture of 56 g (0.26 mole) of 4,5-diamino-2-chloro-6-phenylpyrimidine and 100 g (0.84 mole) of methyl oxalate in 1 l. of H_2O was refluxed for 20 hr with stirring. Cooling and filtration gave 23.7 g (33%) of product, mp >300°. In other experiments similar to the above, refluxing for 2.5 hr gave a 14.5% yield, for 6 hr a 25% yield, and for 20 hr a 37% yield. A reaction using the same pyrimidine and diethyl oxalate in ethoxyethanol for a 48-hr reflux period gave a 31% yield of the same product. The product was recrystallized by dissolving in dilute NH_4OH and reprecipitating by addition of AcOH to pH 4. This gave a cream-colored solid, mp >300°, R_f 0.80 (system 3). *Anal.* ($C_{12}H_7ClN_4O_2$) C, H, N.

N,N′-(4-Amino-2-chloro-6-phenyl-5-pyrimidinyl)oxamide.—To a stirred solution of 1.1 g (0.005 mole) of 4,5-diamino-2-chloro-6-phenylpyrimidine in 60 ml of $CHCl_3$ was added slowly a solution of 1.26 g (0.01 mole) of oxalyl chloride in 5 ml of $CHCl_3$. Material separated out immediately. The reaction mixture was refluxed with stirring for 2 hr and cooled, and the precipitate was collected. This was washed well with ether and then recrystallized from a DMF–H_2O mixture to give a product, mp >300°, whose ir spectrum differed from 2-chloro-6,7-dihydroxy-4-phenylpteridine; R_f 0.68 (system 8). *Anal.* ($C_{22}H_{16}Cl_2N_8O_2$) C, H; N: 22.63; found, 21.92.

4,6,7-Trichloro-4-phenylpteridine (XVIII).—A mixture of 10.2 g (0.036 mole) of 2-chloro-6,7-dihydroxy-4-phenylpteridine, 39 g (0.19 mole) of PCl_5, and 120 ml of $POCl_3$ was refluxed with stirring for 4 hr. The volatiles were then removed under vacuum and the residue was extracted with four 250-ml portions of Et_2O. The combined extracts were washed quickly with ice water and dried ($MgSO_4$). Evaporation of the Et_2O gave a solid, mp 143–146°. Sublimation of this at 155–160° under vacuum gave 2.2 g (19.5%) of bright yellow crystals, mp 154–156°. *Anal.* ($C_{12}H_5Cl_3N_4$) C, H, N.

In another experiment starting with 3.4 g (0.012 mole) of dihydroxypteridine, the dried etheral extracts were concentrated to small volume on a steam bath (10 ml) and filtration gave 1.4 g (37%) of crystals, mp 153–155°.

2,6,7-Triamino-4-phenylpteridine (IX).—A mixture of 3.3 g (0.011 mole) of 2,6,7-trichloro-4-phenylpteridine and 100 ml of anhydrous NH_3 was allowed to stand in an autoclave at room temperature for several days and then heated at 140° for 6 hr. After evaporation of the NH_3 the residue was taken up in EtOH and allowed to stand at −10° for 3 weeks. Filtration gave a solid which was recrystallized twice from about 200 ml of 60% EtOH–H_2O to give 1.2 g (42%) of product: mp >300°; R_f 0.63, 0.64, 0.70 (system 3). A sample recrystallized from H_2O had mp 298–304° dec; $\lambda_{max}^{1\ N\ NaOH}$ 252 mμ (log ε 4.24), 374 (4.22); $\lambda_{max}^{4.5\%\ HCOOH}$ 263 mμ (log ε 4.36), 400 (4.30); *Anal.* ($C_{12}H_{11}N_7 \cdot 0.25H_2O$) C, H, N.

Acknowledgment.—We wish to thank Mr. Arnold Litt and Mrs. Joyce Carevic for experimental assistance and Dr. J. W. Wilson for his interest and encouragement during the course of this work.

Pteridines. X.[1] Some Pyrimidopyrimidine Isomers of Triamterene

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Received January 6, 1968

2,4,7-Triamino-5-phenylpyrimido[4,5-*d*]pyrimidine was prepared by the condensation of guanidine with 2,6-diamino-5-cyano-4-phenylpyrimidine. Similar reactions gave 5-alkyl analogs of this compound. An attempt to use 4-amino-5-cyano-2,6-dimethylpyrimidine in this reaction gave 2,4,7-triamino-5-methylpyrimido[4,5-*d*]-pyrimidine in contrast to the diphenyl analog which gave the expected product. 2,4,5-Triamino-7-phenylpyrimido[4,5-*d*]pyrimidine was prepared by the fusion of guanidine carbonate with 4-amino-5-cyano-6-methylmercapto-2-phenylpyrimidine. 2,4,8-Triamino-6-phenylpyrimido[5,4-*d*]pyrimidine was prepared by condensation of methyl 2,4,5-triaminopyrimidine-6-carboxylate with benzamidine to form 2,4-diamino-8-hydroxy-6-phenylpyrimido[5,4-*d*]pyrimidine followed by deoxychlorination and amination.

Several of the pteridine isomers of triamterene (2,4,7-triamine-6-phenylpteridine) are interesting diuretic agents.[3] This suggested that other similarly substituted polyaza heterocyclic compounds might also have useful diuretic properties. Our interest was first directed to the pyrimido[4,5-*d*]pyrimidine ring system by the report[4] that certain 2,5- and 2,4,7-polyaminopyrimido[4,5-*d*]pyrimidines showed interesting diuretic activity in dogs when given orally at low doses, and we hoped that a phenyl triamino analog would have superior activity.

The previously used method[4–6] for the preparation of 4-aminopyrimido[4,5-*d*]pyrimidines is the reaction of the appropriately substituted 4-amino-5-cyanopyrimidine with the proper amidine or guanidine. This method was adapted for the synthesis of 2,4,7-triamino-

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