dinucleoside phosphate had produced one equivalent each of nucleoside and uridylic acid. A residue (1.3%) of each dinucleoside phosphate still remained.

Paper Chromatography.—Solvent A: isopropyl alcohol–1% aqueous ammonium sulfate (2:1). Solvent B: isopropyl alcohol–concentrated ammonium hydroxide–water (7:1:2). (See Table I.)

Paper Electrophoresis.—Electrophoresis was conducted in a Gilson Electrophorator for 1 hr., using a buffer of 0.01 *M* ammonium formate (pH 3.0) with a voltage gradient of 100 volts per cm. (See Tables II and III.)

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Pteridine Chemistry. X. Methylation Studies. III. Steric Effects of Phenyl Groups at C-6 and C-7[1]

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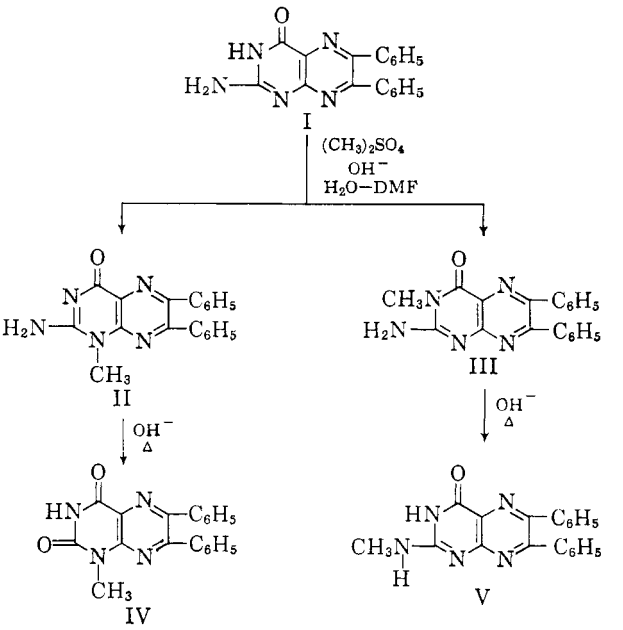
The methylation of 2-amino-3-methyl-6,7-diphenyl-4(3*H*)-pteridinone (III) with dimethyl sulfate in dimethylformamide–acetic acid occurred predominantly at N-1 and only slightly at N-8 to give the 2-imino-1,3-dimethyl derivative VII (63% yield) and the 2-imino-3,8-dimethyl derivative VIII (10% yield). Contrastingly, when the C-7 substituent was hydrogen rather than phenyl, *i.e.*, 2-amino-3-methyl-6-phenyl-4(3*H*)-pteridinone (XIIa), the relative amounts of N-1 and N-8 methylated products (XIIIa and XIVa) were reversed. However, when the C-6 substituent was hydrogen, *i.e.*, 2-amino-3-methyl-7-phenyl-4(3*H*)-pteridinone (XIIb), methylation occurred only at N-1. The varying yields of 8-methyl derivatives are ascribed to steric effects. Additional related methylations also are discussed.

The nature of the products obtained from the methylation of 2-amino-4-hydroxypteridines has been found to be dependent not only upon the conditions of the reaction[2a] but also upon the substituents located at positions 6 and 7 of the pteridine ring. Thus, 2-amino-4-hydroxypteridine-6-carboxylic acid treated with dimethyl sulfate in an aqueous alkaline solution at pH 8–11.5 gave a 30% yield of a crude mixture of the 1-methyl and 3-methyl derivatives and a 25–30% yield of the 3,8-dimethyl derivative. The isomeric 2-amino-4-hydroxypteridine-7-carboxylic acid, however, gave only the 1-methyl and 3-methyl derivatives.[1]

In order to continue the study of the effect of substituents upon this methylation reaction 2-amino-4-hydroxy-6,7-diphenylpteridine (I) was treated with dimethyl sulfate in a water–dimethylformamide[2b] solution at pH 8–11.5. There was isolated from this reaction the 1-methyl derivative II (52% yield) and the 3-methyl derivative III (10% yield). (A very small amount of the 3,8-dimethyl derivative VIII was detected by paper chromatography but was not isolated.) The comparatively high yield of the 1-methyl isomer II in this reaction is somewhat different from the results of the previous methylation studies[2a,3] where any preponderance of one isomer over the other was, in each case, in favor of the 3-methyl derivative.

The structures of the 3-methyl III and 1-methyl II derivatives were proved by well established methods.[2a,4] The 3-methyl derivative III upon treatment with 1.0 *N* sodium hydroxide rearranged to the 2-methylamino derivative V while the 1-methyl derivative II under the same conditions was hydrolyzed to the 1-methyl-2,4-pteridinedione IV. Furthermore, the 3-methyl III and 1-methyl II compounds also were synthesized unequivocally by the reactions of benzil with 3-methyl-2,5,6-triamino-4(3*H*)-pyrimidinone[4] and 1-methyl-2,5,6-triamino-4(1*H*)-pyrimidinone,[4,5] respectively.



A previous report[1] also has shown that 2-amino-3-methyl-4-pteridinones can be methylated in nonbasic solvents and that the substituents in the pyrazine ring again have some influence upon the course of the reaction. Thus the methylation of the 3-methyl derivative of 2-amino-4-hydroxypteridine-6-carboxylic acid with dimethyl sulfate in a boiling dimethylformamide–acetic acid solution gave, as the only major product, the 3,8-dimethyl derivative. In contrast, the isomeric 7-carboxylic acid derivative under the same conditions gave no detectable dimethyl derivative.[1]

In the present investigation 2-amino-3-methyl-6,7-diphenyl-4(3*H*)-pteridinone (III) when treated with

(1) Presented in part at the IIIrd International Pteridine Symposium: Stuttgart, Germany, September 12–15, 1962.

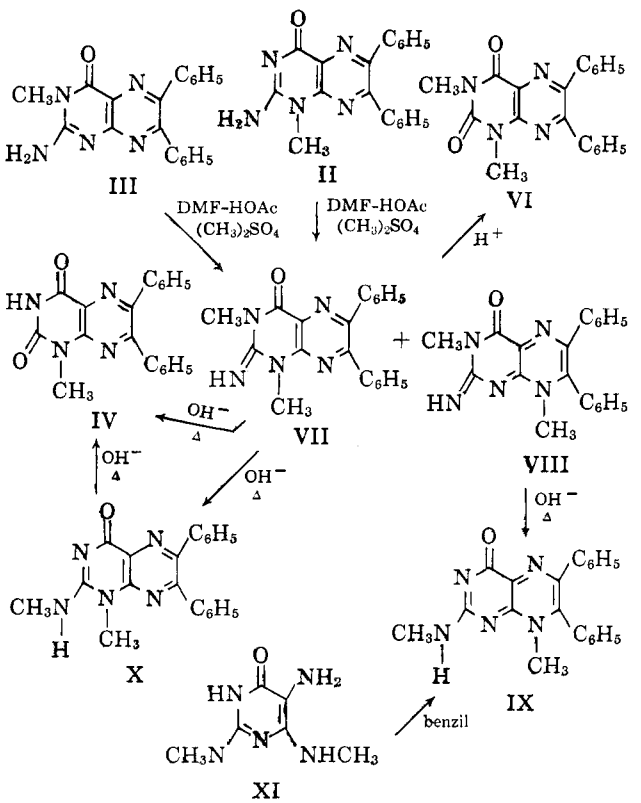
(2) (a) R. B. Angier and W. V. Curran, *J. Org. Chem.*, **27**, 892 (1962). (b) The use of dimethylformamide was necessitated by the low solubility of the 6,7-diphenyl derivative I in water.

(3) R. B. Angier and W. V. Curran, *J. Org. Chem.*, **26**, 2129 (1961).

(4) W. V. Curran and R. B. Angier, *J. Am. Chem. Soc.*, **80**, 6095 (1958).

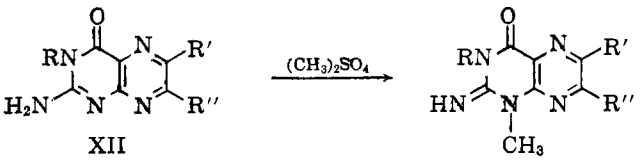
(5) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *ibid.*, **73**, 2864 (1951).

excess dimethyl sulfate in a hot dimethylformamide solution did give the 3,8-dimethyl derivative VIII in 10% yield. However, the main product was an isomeric dimethyl derivative obtained in 63% yield. This was shown to be the 2-imino-1,3-dimethyl derivative VII by the following reactions. The 1-methyl derivative II, methylated under the same conditions used for the 3-methyl derivative III, gave the same dimethyl derivative VII. Assuming no rearrangement had occurred this proved the 1,3-dimethyl structure VII. Mild alkaline treatment of VII gave the expected[1,4] isomeric 2-methylamino-1-methyl derivative X, while longer hydrolysis gave the same 1-methyl-2,4-pteridinedione IV which had been obtained by alkaline hydrolysis of the 2-amino-1-methyl derivative II. The structure of the 3,8-dimethyl derivative VIII, which was indicated by its ultraviolet absorption spectra, was proved by alkaline rearrangement to the isomeric 2-methylamino-8-methyl derivative IX which was independently synthesized from benzil and 5-amino-2,6-bis(methylamino)-4(3*H*)-pyrimidinone XI. [During the course of this study it was noted that the 2-imino-1,3-dimethyl derivative VII was hydrolyzed to 1,3-dimethyl-6,7-diphenyl-2,4(1*H*,3*H*)-pteridinedione (VI) by prolonged heating in a Methyl Cellosolve–hydrochloric acid solution.]

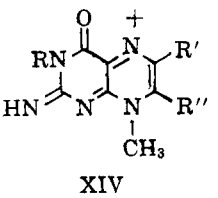


Isolation of 2-imino-1,3-dimethyl derivative VII from the methylation of III was quite unexpected since no such compound had been obtained from similar reactions with the 6- and 7-carboxylic acid derivatives of 2-amino-4-hydroxypteridine. Apparently the N-1 position in the 3-methyl-6,7-diphenyl derivative III is more subject to electrophilic attack by the alkylating agent than is the case with the corresponding 6- and 7-carboxylic acid derivatives.[1] This correlates well with the comparatively high yield of the 1-methyl isomer II obtained upon methylation of 2-amino-4-hydroxy-6,7-diphenylpteridine (I). It would also appear, however, that the presence of either a phenyl group or a carboxylic acid group in position 7 sterically hinders the methylation at N-8. In order to further elucidate this postulated steric effect the methylation studies were continued with the 6- and 7-monophenyl derivatives of 2-amino-3-methyl-4-pteridinone.

With dimethylformamide–acetic acid–dimethyl sulfate as the reaction solvent (100°) 2-amino-3-methyl-6-phenyl-4(3*H*)-pteridinone XIIa gave the 2-imino-3,8-dimethyl derivative XIVa in a 63% yield and the 2-imino-1,3-dimethyl derivative XIIIa in only a 13% yield. On the other hand, 2-amino-3-methyl-7-phenyl-4(3*H*)-pteridinone XIIb gave a 41% yield of the 2-imino-1,3-dimethyl derivative XIIIb while none of the 2-imino-3,8-dimethyl derivative was formed. (8-Methyl derivatives of these phenylpteridines possess a strong yellow-green fluorescence readily detectable on paper chromatograms.)



a series: R = CH_3; R′ = C_6H_5; R″ = H
b series: R = CH_3; R′ = H; R″ = C_6H_5
c series: R = H; R′ = C_6H_5; R″ = H
d series: R = H; R′ = H; R″ C_6H_5



Results obtained with the three phenylpteridines (III, XIIa, and XIIb) are best explained by assuming that a phenyl group in position 7 of the pteridine sterically hinders alkylation at N-8.[6] Even the production of a 10% yield of a 3,8-dimethyl derivative from the methylation of 2-amino-3-methyl-6,7-diphenyl-4-(3*H*)-pteridinone (III) compared with complete absence of any 8-methyl derivative in the methylation of the corresponding 7-phenylpteridine XIIb can be explained. Models show that in a 6,7-diphenylpteridine the two phenyl rings are not free to rotate and cannot be coplanar with the pteridine ring whereas in a 7-phenylpteridine with no substituent in position 6 the phenyl ring is free to rotate. Thus, in the latter case, approach of the alkylating agent to N-8 is more effectively hindered than in the 6,7-diphenyl series. In accordance with this postulated steric effect it was noted that the methylation of the 6-phenylpteridine XIIa proceeds at a faster rate than does the methylation of the 7-phenylpteridine XIIb.

Although the reactions were more complex and the yields were not satisfactory, similar steric effects were noted when the parent 2-amino-4-hydroxypteridines were methylated. With dimethylformamide–acetic acid–dimethyl sulfate at 100° 2-amino-4-hydroxy-7-phenylpteridine (XIId) gave the 1,3-dimethyl deriva-

(6) An alternative possibility is that these results might be explained by electron-donating or withdrawing effects of the phenyl groups. This was discounted when it was found that a consideration of the published p*K* values[7] for pyridine and its 2-, 3- and 4-phenyl derivatives would lead one to predict results exactly the opposite of those found in this investigation.

(7) A. R. Katritsky and J. M. Lagowski, "Heterocyclic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 56.

tive XIIIb in a 12% yield. This was the only isolated product and no 8-methyl derivative was detected. Considerable decomposition occurred. 2-Amino-4-hydroxy-6,7-diphenylpteridine (I) under these conditions gave a complex mixture with no predominant product. The 1-methyl derivative II was the only product isolated (10% yield), but chromatography showed the presence of the 3-methyl III and 1,3-dimethyl VII derivatives as well as a small amount of an 8-methyl derivative. On the other hand, 2-amino-4-hydroxy-6-phenylpteridine (XIIc) gave as the principal product the 8-monomethyl derivative XIVc in a 40% yield. Chromatography demonstrated the presence, in smaller amounts, of the 1-methyl and, presumably, the 3-methyl derivatives. A very small amount of the 1,3-dimethyl derivative XIIIa was also isolated. This last reaction is another example[1,8] where a neutral form of a 2-amino-4-hydroxypteridine is preferentially alkylated in the pyrazine ring at N-8. However, the other reactions demonstrate that this preferential alkylation occurs only in the absence of bulky substituents at position 7.

Experimental[9]

All of the compounds reported here as well as most of the reaction mixtures were examined by paper chromatography using the descending technique on Whatman no. 1 paper.

All evaporations were carried out under reduced pressure.

Methylation of 2-Amino-4-hydroxy-6,7-diphenylpteridine (I). A.—A mixture of 3.15 g. (10 mmoles) of 2-amino-4-hydroxy-6,7-diphenylpteridine, 50 ml. of water, 50 ml. of dimethylformamide (DMF), and 20 ml. of 1.0 *N* sodium hydroxide was stirred with a magnetic stirrer to produce almost complete solution. One milliliter (10.7 mmoles) of dimethyl sulfate (DMS) was added. Stirring was continued and at intervals the indicated materials were added as follows: 30 min., 10 ml. of 1.0 *N* NaOH and 1.0 ml. of DMS; 60 min., 5 ml. of 1.0 *N* NaOH and 0.9 ml. of DMS; 90 min., 10 ml. of 1.0 *N* NaOH and 1.0 ml. of DMS; 120 min., 10 ml. of 1.0 *N* NaOH and 1.0 ml. of DMS; 150 min., 10 ml. of 1.0 *N* NaOH and 1.0 ml. of DMS. After an additional hour of stirring the pH was *ca.* 6. The mixture was cooled and the crystalline product was collected; yield 3.0 g. (the filtrate showed the presence of a small amount of the 3,8-dimethyl derivative which was not isolated).

This product (3.0 g.) was dissolved in 170 ml. of hot DMF, which was treated with charcoal, filtered, and allowed to stand at room temperature overnight. The crystalline product was collected; yield 1.7 g. (52%); m.p. 322–325°. This was chromatographically pure 2-amino-1-methyl-6,7-diphenyl-4(1*H*)-pteridinone (II).

For analyses a portion (1.5 g.) of this product was crystallized first from 90 ml. of DMF and then from 35 ml. of 2-methoxyethanol; yield 0.50 g.; m.p. 327–329°; $\lambda_{max}^{CH_3OH}$ 268 mμ (ε 20,800), 362 mμ (ε 16,800); $\lambda_{max}^{0.1\,N\,HCl}$ 220–230 mμ (ε 24,300), 280 mμ (ε 14,100), 363 mμ (ε 14,800). The only paper chromatographic solvent system found to separate the 1-methyl II and the 3-methyl III derivatives was isopropyl alcohol–1.0 *N* NH_4OH (7:3) in which II had R_f 0.85 (deep blue) and III had R_f 0.90 (light blue).

Anal. Calcd. for $C_{19}H_{15}N_5O$(329): C, 69.3; H, 4.6; N, 21.2. Found: C, 68.8; H, 5.0; N, 21.2.

The filtrate from the 1.7 g. of 1-methyl derivative II was evaporated to 10 ml., after which 40 ml. of 0.5 *N* hydrochloric acid was added. This was heated on a steam bath, then cooled to room temperature, and the product was collected; yield 0.65 g. (paper chromatography indicated this to be a mixture of starting material and the 3-methyl derivative III). The filtrate was cooled overnight to give a crystalline product; yield 0.35 g. (10%). A solution of 250 mg. of this material in 10 ml. of DMF was heated to 100° and diluted with 25 ml. of water containing 0.5 ml. of pyridine; yield of crystalline product, 200 mg.; m.p. 347–350°. Infrared spectra, mixture melting point, and paper chromatography in two systems showed this to be identical with an authentic sample of 2-amino-3-methyl-6,7-diphenyl-4(3*H*)-pteridinone (III).

B.—A mixture of 600 mg. (1.97 mmoles) of 2-amino-4-hydroxy-6,7-diphenylpteridine (I), 20 ml. of dimethylformamide (DMF), 2.0 ml. of acetic acid, and 3.0 ml. of dimethyl sulfate was heated to boiling for 10 min. An additional 1.5 ml. of dimethyl sulfate was added and the solution heated to boiling for 5 min. The solution was treated with charcoal, filtered, and evaporated to a sirup. The sirup was dissolved in 40 ml. of water, made alkaline with sodium carbonate, and cooled; yield 690 mg.

A 600-mg. portion of this product was crystallized from 7 ml. of DMF using charcoal to clarify it; yield 75 mg. A recrystallization from 4 ml. of 2-methoxyethanol gave 40 mg. of product; m.p. 325–327°. This was shown to be identical with an authentic sample of the 1-methyl derivative II (mixture melting point and infrared absorption spectra).

Paper chromatography showed that the initial crude product contained at least three other products. They were not obtained in a pure state.

2-Amino-1-methyl-6,7-diphenyl-4(1*H*)-pteridinone (II). A.—This was first prepared by the methylation of 2-amino-4-hydroxy-6,7-diphenylpteridine (I) as described previously and was shown to be identical with the product described under B (infrared absorption spectra, mixture melting point, and paper chromatography).

B.—A mixture of 155 mg. (10 mmoles) of 2,5,6-triamino-1-methyl-4(1*H*)-pyrimidinone, 230 mg. (1.1 mmoles) of benzil, 4.0 ml. of water, and 3 drops of acetic acid was heated to reflux for 1.5 hr. The mixture was cooled and the product was collected; yield 200 mg. (61%). This was crystallized from 15 ml. of DMF; yield 130 mg.; m.p. 325–328°. A sample was recrystallized from 2-methoxyethanol for infrared spectral determinations. Characterization of this compound is described under A above and under methylation of I.

2-Amino-3-methyl-6,7-diphenyl-4(3*H*)-pteridinone (III). A.—A solution containing 14.3 g. (75 mmoles) of 2,5,6-triamino-3-methyl-4(3*H*)-pyrimidinone hydrochloride, 13.8 g. (168 mmoles) of sodium acetate, and a trace of sodium hydrosulfite in 230 ml. of warm water was added to a second solution of 16.9 g. (80 mmoles) of benzil in 400 ml. of hot ethanol. The mixture was heated to reflux for 90 min. and cooled overnight; yield 21.8 g. (89%); m.p. 348–351°.

A sample (300 mg.) was recrystallized from a solution of 15 ml. of dimethylformamide and 10 ml. of water; yield 230 mg.; no change in melting point; R_f 0.30 (3% NH_4Cl) (blue), 0.57 (0.1 *N* HCl) (blue); $\lambda_{max}^{pH\,7.0\text{ and }9.2}$ 291 mμ (ε 23,000), 377 mμ (ε 12,800); $\lambda_{max}^{0.1\,N\,HCl}$ 230 mμ (ε 30,900), 280 mμ (ε 14,500), 362 mμ (ε 15,500).

Anal. Calcd. for $C_{19}H_{15}N_5O$ (329): C, 69.3; H, 4.6; N, 21.2. Found: C, 68.9; H, 4.7; N, 21.5.

B.—This compound III was also one of the products isolated from the methylation of 2-amino-4-hydroxy-6,7-diphenylpteridine (I) as described previously.

Methylation of 2-Amino-3-methyl-6,7-diphenyl-4(3*H*)-pteridinone (III).—A mixture of 14.0 g. (42.5 mmoles) of III, 500 ml. of dimethylformamide (DMF), 50 ml. of acetic acid, and 22.5 ml. (240 mmoles) of dimethyl sulfate was heated on a steam bath for 5 hr. with six 22.5-ml. portions of dimethyl sulfate being added at regular intervals. The solution was evaporated to about 125 ml. and diluted to a volume of 1 l. with warm water. This was treated with charcoal, warmed briefly on the steam bath, filtered, and cooled to 20°. Solid sodium carbonate was added slowly with stirring to pH *ca.* 9. The mixture was cooled overnight and the product collected; yield 15 g. This was slurried in 150 ml. of absolute ethanol and warmed on a steam bath. The amorphous solid dissolved and a crystalline product separated. The mixture was cooled and the product was collected; yield 9.3 g. (63%); m.p. 239–242°. Paper chromatography indicated this material to be essentially pure. However, it was recrystallized from 125 ml. of 2-methoxyethanol; yield 8.0 g. (55%) of a cream colored product subsequently shown to be 2-imino-1,3-dimethyl-6,7-diphenyl-1,2-dihydro-4(3*H*)-pteridinone (VII); m.p. 241–242°; R_f 0.65 (3% NH_4Cl), 0.70 (0.1 *N* HCl) (deep blue); $\lambda_{max}^{pH\,7.0}$ 266 mμ (ε 18,500), 290 mμ (ε 17,100) (sh), 378 mμ (ε 13,400); $\lambda_{max}^{0.1\,N\,NaOH}$ 268 mμ (ε 18,500), 290 mμ (ε 15,800) (sh 378 mμ (ε 13,300); $\lambda_{max}^{0.1\,N\,HCl}$ 232 mμ (ε 31,500), 280 mμ (ε 15,400), 363 mμ (ε 16,100).

(8) D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.*, 869 (1961).

(9) All melting points were taken in a Mel-temp melting point apparatus using a thermometer calibrated for 3-in. immersion.

Anal. Calcd. for $C_{20}H_{17}N_5O$ (343): C, 70.0; H, 5.0; N, 20.4. Found: C, 70.3; H, 5.2; N, 20.6.

The ethanolic filtrate from the 9.3 g. of the 1,3-dimethyl derivative VII was evaporated to dryness. The residue was slurried in 40 ml. of water and sodium bicarbonate was added to pH 7.5. The mixture was cooled and the solid was collected; yield 3.6 g. This solid was dissolved in a solution of 12 ml. of water and 0.7 ml. of concentrated hydrochloric acid, which was then treated with charcoal and filtered. The filtrate was diluted first with 10 ml. of concentrated hydrochloric acid and then with 25 ml. of ethanol. This was cooled overnight, the mixture was agitated and rubbed, cooled several more hours, and the product was collected; yield 0.3 g. of product, primarily starting material, which was discarded. The filtrate was evaporated to dryness several times with the aid of ethanol, 70 ml. of ethanol was finally added, and the mixture was heated to boiling and filtered; yield 310 mg. (this was primarily the 3,8-dimethyl derivative VIII but it was less pure than the next crop). The filtrate, when cooled, gave a nicely crystalline yellow product; yield 1.4 g. (9.6%) of 2-imino-3,8-dimethyl-6,7-diphenyl-2,8-dihydro-4(3*H*)-pteridinone (VIII) as its hydrochloride; m.p. 238–240°. Since paper chromatography indicated that this contained small amounts of impurities, it was suspended in 28 ml. of 1.0 *N* hydrochloric acid which was heated to boiling, treated with charcoal, and filtered. The filtrate upon cooling deposited yellow crystals; yield 0.95 g. (6.5%); m.p. 241–243°; R_f 0.78 (3% NH_4Cl) (yellow-green becoming blue when fumed with ammonia); $\lambda_{max}^{0.1\ N\ NaOH}$ 247 mμ (ε 26,600), 283 mμ (ε 9,100) (sh), 358 mμ (ε 13,300); $\lambda_{max}^{0.1\ N\ HCl}$ 273 mμ (ε 17,500), 295 mμ (ε 16,400), 428 mμ (ε 14,400).

Anal. Calcd. for $C_{20}H_{17}N_5O \cdot HCl$ (380): C, 63.3; H, 4.8; N, 18.4; Cl, 9.4. Found: C, 63.2; H, 4.9; N, 18.3; Cl, 9.8.

Methylation of 2-Amino-1-methyl-6,7-diphenyl-4(1*H*)-pteridinone (II).—A mixture of 600 mg. (1.8 mmoles) of II, 40 ml. of dimethylformamide (DMF), 3.0 ml. of acetic acid, and 1 ml. of dimethyl sulfate was heated on a steam bath for 8 hr. Four 1-ml. portions of dimethyl sulfate were added at regular intervals. The solution was evaporated to a small volume and diluted to 90 ml. with water. This was warmed a short time, treated with charcoal, and filtered. The filtrate was brought to pH 9 with sodium carbonate and cooled; yield 500 mg.

The solid was dissolved in 10 ml. of hot ethanol, filtered from a little solid, and cooled overnight; yield of crystalline product 210 mg.; m.p. 236–240°. This was similar to the crude main product obtained from the methylation of the 3-methyl derivative III.

Recrystallization of this material from ethanol gave a product identical with 2-imino-1,3-dimethyl-6,7-diphenyl-1,2-dihydro-4(3*H*)-pteridinone (VII) originally obtained by the methylation of the 3-methyl derivative III (mixture melting point and infrared spectra).

1-Methyl-6,7-diphenyl-2,4(1*H*,3*H*)-pteridinedione (IV).[10] **A.**—A solution of 300 mg. (0.9 mmole) of 2-amino-1-methyl-6,7-diphenyl-4(1*H*)-pteridinone (II) in 10 ml. of 2-methoxyethanol and 20 ml. of 1.0 *N* sodium hydroxide was heated on a steam bath for 30 min. The hot solution was acidified with 2 ml. of acetic acid and cooled overnight; yield 240 mg. This was recrystallized first from 20 ml. of 50% 2-methoxyethanol and a second time from 3 ml. of 2-methoxy-ethanol; yield 130 mg.; m.p. 277–279° (lit.[10] 263–264) R_f 0.35 (0.1 *N* HCl) (blue); $\lambda_{max}^{0.1\ N\ NaOH}$ 267 mμ (ε 18,500), 367 mμ (ε 14,500); $\lambda_{max}^{0.1\ N\ HCl}$ 278 mμ (ε 14,900), 365 mμ (ε 13,500).

Anal. Calcd. for $C_{19}H_{14}N_4O_2$(330): C, 69.2; H, 4.2; N, 17.0. Found: C, 69.3; H, 4.4; N, 17.2.

B.—A 300-mg. sample (0.87 mmole) of 2-imino-1,3-dimethyl-6,7-diphenyl-1,2-dihydro-4(3*H*)-pteridinone (VII) was hydrolyzed and purified in exactly the same manner as described in preceding method A; final yield 100 mg.; m.p. 277–279°. This was shown to be identical with the product obtained before through the use of infrared spectra, mixture melting point, and paper chromatography.

2-Methylamino-4-hydroxy-6,7-diphenylpteridine (V).—A solution of 100 mg. (0.3 mmole) of 2-amino-3-methyl-6,7-diphenyl-4(3*H*)-pteridinone (III) in 5 ml. of 2-methoxyethanol and 10 ml. of 1.0 *N* sodium hydroxide was heated 2 hr. on a steam bath, then treated with charcoal, and filtered. The hot filtrate was added to a hot solution of 12 ml. of 1.0 *N* hydrochloric acid and cooled; yield was 85 mg. of crystalline product; m.p. 359–361°; R_f 0.44 (0.1 *N* HCl) (blue); $\lambda_{max}^{pH\ 9.2}$ 282 mμ (ε 22,400), 386 mμ (ε 12,500); $\lambda_{max}^{pH\ 7.0}$ 296 mμ (ε 22,400), 377 mμ (ε 11,500); $\lambda_{max}^{0.1\ N\ HCl}$ 232 mμ (ε 26,000), 283 mμ (ε 13,800), 363 mμ (ε 13,700).

Anal. Calcd. for $C_{19}H_{15}N_5O$ (329): C, 69.3; H, 4.6; N, 21.2. Found: C, 69.2; H, 4.7; N, 20.9.

2-Methylamino-1-methyl-6,7-diphenyl-4(1*H*)-pteridinone (X).—A solution of 300 mg. (0.88 mmole) of 2-imino-1,3-dimethyl-6,7-diphenyl-1,2-dihydro-4(3*H*)-pteridinone (VII) in 5 ml. of boiling 2-methoxyethanol was diluted with 10 ml. of 1.0 *N* sodium hydroxide. This was heated on a steam bath for 2 min. followed immediately by acidification with 1 ml. of concentrated hydrochloric acid. The solution was diluted with 20 ml. of hot water, then neutralized to pH 7.5 with sodium bicarbonate and cooled; yield 280 mg. This was crystallized from 10 ml. of 2-methoxyethanol; yield 200 mg. (67%); m.p. 304–306°; R_f 0.35 (3% NH_4Cl) (deep blue); $\lambda_{mnx}^{pH\ 7.0}$ 269 mμ (ε 20,200), 367 mμ (ε 16,300); $\lambda_{max}^{0.1\ N\ HCl}$ 280 mμ (ε 14,700); 365 mμ (ε 14,600).

Anal. Calcd. for $C_{20}H_{17}N_5O$ (343): C, 70.0; H, 5.0; N, 20.4. Found: C, 69.6; H, 5.2; N, 20.2.

2-Methylamino-8-methyl-6,7-diphenyl-4(8*H*)-pteridinone (IX).

A.—A solution of 100 mg. of 2-imino-3,8-dimethyl-6,7-diphenyl-2,8-dihydro-4(3*H*)-pteridinone hydrochloride (VIII·HCl) in 5 ml. of 2-methoxyethanol and 5 ml. of 1.0 *N* sodium hydroxide was heated on a steam bath for 5 min. The hot solution was acidified with 1 ml. of concentrated hydrochloric acid and a yellow crystalline product separated. The mixture was cooled and the product was collected; yield 65 mg. The infrared spectrum and paper chromatographic behavior of this product showed it to be identical with an authentic sample of IX·HCl prepared as described under B.

B.[11]—2,4-Bismethylamino-5-amino-6-hydroxypyrimidine (0.50 g., 3.0 mmoles) (XI) was dissolved in 5 ml. of hot water containing a pinch of sodium hydrosulfite. A solution of 0.75 g. (3.6 mmoles) of benzil in 10 ml. of warm ethanol was added and the mixture was heated to reflux for 2 hr. The reaction mixture was then evaporated and the residue taken up in 80 ml. of hot ethanol. Addition of 5.0 ml. of concentrated hydrochloric acid gave crystals; yield 0.70 g. (61%); m.p. 350–357° with previous browning and wetting; R_f 0.73 (yellow-green fluorescence) in 3% ammonium chloride. This material (600 mg.) was dissolved in 50 ml. of boiling water, treated with charcoal, and filtered. The filtrate was reheated to boiling and 25 ml. of concentrated hydrochloric acid was added to give crystals almost immediately; yield 330 mg.; $\lambda_{max}^{0.1\ N\ HCl}$ 285 mμ (ε 11,600) (sh); 300 mμ (ε 12,500), 430 mμ (ε 9,500); $\lambda_{max}^{0.1\ N\ NaOH}$ 252 mμ (ε 9,600), 287 mμ (ε 7,000) (sh), 375 mμ (ε 7,600); $\lambda_{max}^{pH\ 7.0}$ 289 mμ (ε 14,600), 437 mμ (ε 8,400).

Anal. Calcd. for $C_{20}H_{17}N_5O \cdot HCl$ (380): C, 63.3; H, 4.8; N, 18.4. Found: C, 63.3; H, 4.9; N, 18.5.

1,3-Dimethyl-6,7-diphenyl-2,4(1*H*,3*H*)-pteridinedione[12] (VI).—A solution of 500 mg. (1.45 mmoles) of 2-imino-1,3-dimethyl-6,7-diphenyl-1,2-dihydro-4(3*H*)-pteridinone (VII), 100 ml. of 2-methoxyethanol, and 2.5 ml. of concentrated hydrochloric acid was heated to reflux for 46 hr. with 2-ml. portions of concentrated hydrochloric acid being added after 4, 10, 16, and 22 hr. The solution was evaporated to dryness and the crystalline residue was slurried in 25 ml. of hot methanol and cooled; yield 440 mg. (88%); m.p. 229–231°. This was recrystallized from 6 ml. of 2-methoxyethanol; yield 380 mg. (76%); m.p. 231–232° (lit.[12] m.p. 226–227°); R_f 0.3 (0.1 *N* HCl); $\lambda_{max}^{pH\ 7.0}$ 226 mμ (ε 25,000), 276 mμ (ε 14,800), 363 mμ (ε 14,100).

Anal. Calcd. for $C_{20}H_{16}N_4O_2$ (344): C, 69.8; H, 4.7; N, 16.3. Found: C, 69.8; H, 4.7; N, 16.0.

Methylation of 2-amino-3-methyl-7-phenyl-4(3*H*)-pteridinone[13] XIIb.—A mixture of 5.0 g. (19.8 mmoles) of XIIb, 250 ml. of dimethylformamide, 25 ml. of acetic acid, and 9 ml. of dimethyl sulfate was heated on a steam bath for 4 hr. with 9-ml. portions of dimethyl sulfate being added after 30 min. and 2.5 hr. The solution was evaporated to a sirup which was dissolved in 200 ml. of water. This was heated on a steam bath for 15 min., treated with charcoal, filtered, and cooled; yield of crystalline product, 2.4 g. (fraction A).

The filtrate was adjusted to pH 3 with sodium carbonate, treated with charcoal and filtered. The filtrate was adjusted to pH 9 with sodium carbonate and cooled two days; yield 2.4 g. (fraction B).

(10) G. Henseke and H. G. Patswaldt, *Chem. Ber.*, **89**, 2909 (1956).

(11) This reaction was carried out by W. V. Curran.

(12) F. F. Blicke and H. C. Godt, Jr., *J. Am. Chem. Soc.*, **76**, 2798 (1954).

(13) R. B. Angier, *J. Org. Chem.*, **28**, 1398 (1963).

Fraction A was dissolved in 60 ml. of hot water, treated with charcoal, and filtered. The hot solution was acidified with 6 ml. of concentrated hydrochloric acid and cooled to give a crystalline product; yield 1.9 g. (fraction C). Paper chromatography indicated this to be essentially pure 1,3-dimethyl derivative XIIIb.

Fraction B was suspended in 40 ml. of boiling water and acidified to pH 2 with concentrated hydrochloric acid. This was filtered hot and the solid was discarded. The filtrate was clarified with charcoal, acidified with 5 ml. of concentrated hydrochloric acid, and cooled; yield 0.75 g. This purification was repeated; yield 0.6 g. (fraction D).

Fractions C and D were combined to give 2.5 g. (41%) of XIIIb as a hydrochloride.

For analyses a portion (140 mg.) of this product was dissolved in 30 ml. of hot water containing a drop of concentrated hydrochloric acid. This was heated to 85° and neutralized with a solution of sodium acetate and cooled; yield, 90 mg. of 2-imino-1,3-dimethyl-7-phenyl-1,2-dihydro-4(3*H*)-pteridinone XIIIb; m.p. 290–292°; R_f 0.53 (3% NH_4Cl) (purple); $\lambda_{max}^{pH\ 7.0}$ 214 mμ (ε 22,200), 235 mμ (ε 22,900), 262 mμ (ε 15,000), 367 mμ (ε 16,000); $\lambda_{max}^{0.1\ N\ HCl}$ 229 mμ (ε 25,800), 348 mμ (ε 23,200).

Anal. Calcd. for $C_{14}H_{13}N_5O$ (267): C, 62.9; H, 4.9; N, 26.2. Found: C, 62.7; H, 4.7; N, 26.1.

At no time did chromatography indicate the presence of any 8-methyl derivatives.

Methylation of 2-Amino-4-hydroxy-7-phenylpteridine[13] (XIId).—A mixture of 2.4 g. (10 mmoles) of XIId, 125 ml. of dimethylformamide, 12 ml. of acetic acid, and 4.5 ml. of dimethyl sulfate was heated on a steam bath for 5 hr. with 4.5-ml. portions of dimethyl sulfate being added after 2 and 3.5 hr. heating. The dark solution was evaporated to a sirup which was dissolved in 100 ml. of water and heated 10 min. on a steam bath. This was treated with charcoal, filtered, cooled, and adjusted to pH 3 with sodium carbonate. The material (a few mg.) which separated was removed by filtration. The filtrate was adjusted to pH 9 with sodium carbonate and cooled overnight; yield 1.3 g. of dark material. Although paper chromatography indicated the presence of the 1,3-dimethyl derivative XIIIb, this crop was not successfully purified.

The filtrate, upon further cooling, deposited 320 mg. of product. This filtrate was extracted with three 60-ml. portions of chloroform which were dried over magnesium sulfate and evaporated to a sirup. This was slurried in 20 ml. of hot ethanol and cooled; yield of crystalline product, 180 mg.

These last two fractions were combined (500 mg.), suspended in 15 ml. of hot water, and treated with 6 drops of concentrated hydrochloric acid. This was heated to boiling, clarified with charcoal, treated with 1.6 ml. of concentrated hydrochloric acid, and cooled; yield, 380 mg. (12.5%) of the hydrochloride of 2-imino-1,3-dimethyl-7-phenyl-1,2-dihydro-4(3*H*)-pteridinone XIIIb. It was shown to be identical with the product obtained by the methylation of XIIb described previously. This was the only pure product isolated from this reaction and no 8-methyl derivative was detected.

Methylation of 2-Amino-3-methyl-6-phenyl-4(3*H*)-pteridinone[13] (XIIa).—A solution of 3.1 g. (12.2 mmoles) of XIIa, 120 ml. of dimethylformamide, 12 ml. of acetic acid, and 6 ml. of dimethyl sulfate was heated on a steam bath for 1 hr. The solution was evaporated to a sirup which was dissolved in 85 ml. of water and heated 10 min. on a steam bath. This was brought to pH 3 with sodium bicarbonate, cooled, treated with charcoal, and filtered to remove cloudiness. The filtrate was adjusted to pH 10 with sodium carbonate and cooled well. The product was collected and dried; yield 2.8 g. (86%).

A suspension of this material in 65 ml. of absolute ethanol was heated to boiling, then cooled several hours. The crystalline product was collected; yield 430 mg. (13%); m.p. 249–251° (slight residue). Chromatography indicated that this was fairly pure 1,3-dimethyl derivative XIIIa. It was recrystallized from 9 ml. of 2-methoxyethanol; pale yellow platelets; yield, 320 mg. (10%) of 2-imino-1,3-dimethyl-6-phenyl-1,2-dihydro-4(3*H*)-pteridinone (XIIIa); m.p. 251–253°; R_f 0.70 (0.1 *N* HCl) (purple); $\lambda_{max}^{pH\ 7.0}$ 288 mμ (ε 18,700), 370 mμ (ε 8000); $\lambda_{max}^{0.1\ N\ HCl}$ 279 mμ (ε 20,800), 351 mμ (ε 9800).

Anal. Calcd. for $C_{14}H_{13}N_5O$ (267): C, 62.9; H, 4.9; N, 26.2. Found: C, 63.1 H, 5.0; N, 26.4.

The ethanol filtrate from the 430 mg. of XIIIa above was cooled overnight and the resulting hazy solution was filtered. The filtrate was treated with 2.0 ml. of concentrated hydrochloric acid to give, immediately, a yellow crystalline product. The mixture was cooled several hours and the product was collected; yield 2.4 g. (63%). Chromatography showed this to be fairly pure 3,8-dimethyl derivative XIVa.

For analyses a sample (270 mg.) of XIVa was dissolved in 10 ml. of water containing a drop of concentrated hydrochloric acid. The hot solution was treated with charcoal, filtered, and acidified, while hot, with 2 ml. of concentrated hydrochloric acid. The product crystallized in diamond shaped crystals; yield 210 mg.; R_f 0.65 (0.1 *N* HCl) (yellow-green becoming blue when fumed with ammonia), 0.60 (3% NH_4Cl); $\lambda_{max}^{0.1\ N\ NaOH}$ 242 mμ (ε 17,400), 292 mμ (ε 8800), 360 mμ (ε 17,900); $\lambda_{max}^{0.1\ N\ HCl}$ 275 mμ (ε 18,200), 305 mμ (ε 25,600), 425 mμ (ε 12,200).

Anal. Calcd. for $C_{14}H_{13}N_5O \cdot HCl$ (304): C, 55.3; H, 4.6; N, 23.0; Cl, 11.7. Found: C, 55.5; H, 5.1; N, 22.8; Cl, 11.8.

Slow evaporation of the filtrate from the 2.4 g. of XIVa while being dried by suction on the filter, gave 120 mg. of a crystalline product different from XIIIa or XIVa. This appears to be an 8-methyl derivative but its exact structure is unknown.

Methylation of 2-Amino-4-hydroxy-6-phenylpteridine[13] (XIIc).—A mixture of 1.4 g. (5.8 mmoles) of XIIc, 80 ml. of dimethylformamide, 7.0 ml. of acetic acid, and 2.5 ml. of dimethyl sulfate was heated on a steam bath for 4 hr. with 2.5-ml. portions of dimethyl sulfate being added after 1 hr. and 2.5 hr. The solution was evaporated to a sirup and diluted to a volume of 125 ml. with water. This was heated 10 min., treated with charcoal, filtered, and brought to pH 8 with sodium carbonate; yield of solid, 1.2 g. (Extraction of the filtrate with chloroform gave 60 mg. of material which was identical with the 1,3-dimethyl derivative XIIIc.)

This solid (1.2 g.) was extracted twice with 20-ml. portions of warm chloroform and the extracts were discarded. The remaining solid (0.95 g.) was dissolved in 40 ml. of hot 0.1 *N* hydrochloric acid, treated with charcoal, and filtered. The hot filtrate was diluted with 10 ml. of concentrated hydrochloric acid and cooled; yield of crystalline product 0.7 g. (41%); chromatography indicated the presence of some impurities but ultraviolet absorption spectra indicated a purity of 90–95% 2-amino-8-methyl-6-phenyl-4(8*H*)-pteridinone (XIVc) as its hydrochloride. This was crystallized two more times in the manner described before; yield 0.30 g. (19%); R_f 0.55 (0.1 *N* HCl) (yellow-green), 0.35 (3% NH_4Cl) (yellow-green); $\lambda_{max}^{0.1\ N\ NaOH}$ 248 mμ (ε 15,600), 285 mμ (plateau) (ε 5800), 367 mμ (ε 18,300); $\lambda_{max}^{pH\ 7.0-9.2}$ 289 mμ (ε 29,600), 430 mμ (ε 11,000); $\lambda_{max}^{0.1\ N\ HCl}$ 270 mμ (plateau) (ε 12,400), 304 mμ (ε 28,000), 425 mμ (ε 12,000).

Anal. Calcd. for $C_{13}H_{11}N_5O \cdot HCl \cdot {}^1/_2H_2O$ (299): C, 52.2; H, 4.4; N, 23.4; Cl, 11.9. Found: C, 52.3; H, 4.2; N, 23.6; Cl, 12.0.

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