The vinylpyrazine forms a picrate, m.p. 99–100° after recrystallization from methanol, (lit. value 99.2–100.2°).[4]

The reaction was repeated except that no silver oxide was used.

The quaternary ammonium iodide compound formed from the reaction of β-dimethylaminoethylpyrazine (0.1 mole, 15.1 g.) and 0.106 mole (15.0 g.) of methyl iodide was dissolved in 100 ml. of water. Then 4.0 g. (0.1 mole) of sodium hydroxide pellets was added and the mixture was refluxed for 1 hr. After working up the reaction by the method which was described above, there was obtained 6.4 g. (60.5%) of vinylpyrazine, b.p. 61–62° at 19 mm.

2. Attempted dehydration of 1,1-diphenyl-2-(2-methyl-6-pyrazyl)ethanol using phosphorus pentoxide. A mixture of the carbinol (0.03 mole, 8.7 g.), dissolved in 100 ml. of dry benzene, and 5 g. of phosphorus pentoxide were refluxed for 5 hr. There seemed to be no water forming, as the phosphorus pentoxide appeared to be unchanged. The reaction mixture was allowed to cool to room temperature and then it was poured over ice. The benzene layer was separated and the remaining aqueous phase was extracted with several portions of benzene. After evaporation of the benzene, there was obtained 7.8 g. (92.4%) of the recovered starting material, m.p. 143.4–144.4° alone and when mixed with an authentic sample.

3. Dehydration of 1,1-diphenyl-2-(2-methyl-6-pyrazyl)-ethanol using iodine as a catalyst. Using the dehydration of 1,1-diphenyl-2-(2-methyl-6-pyrazyl)ethanol as an example for the iodine-effected dehydration of the carbinols where a solvent was employed, the procedure used follows.

The alcohol (0.0516 mole, 15.0 g.) was dissolved in 50 ml. of dry benzene and was placed in a 100 ml. round bottom flask equipped with a Barrett trap and a condenser. To the solution 1 g. of iodine was added and the mixture was allowed to reflux for 16 hr. During the reflux there was some water formed which settled at the bottom of the Barrett trap indicating that dehydration has presumably taken place. The mixture was cooled to room temperature and was then washed with several portions of 10% aqueous solution of sodium thiosulfate to remove the residual iodine. The benzene portion was then dried over anhydrous sodium sulfate. After removing the solvent by distillation, there was obtained 12.6 g. (90%) of 1,1-diphenyl-2-(2-methyl-6-pyrazyl)ethylene, b.p. 183–184° at 1.0 mm. This olefin solidified upon standing and melted at 54.6–56.0° after recrystallization from pentane.

4. Dehydration of 3-(2-methyl-6-pyrazylmethyl)pentanol-3 using iodine as a catalyst and no solvent. Using the dehydration of this carbinol as an example for the iodine-effected dehydration without employing a solvent, the procedure used follows.

The carbinol, 3-(2-methyl-6-pyrazylmethyl)pentanol-3, (0.051 mole, 10.0 g.) was mixed with 1 g. of iodine in a 50-ml. round bottom flask equipped with an air-cooled condenser. The mixture was heated in a Woods metal bath at 185° for 1 hr. After cooling the reaction mixture to room temperature, 50 ml. of benzene were added to it. The benzene solution was then worked in the manner as described in the previous experiment to give 4.4 g. (48.9%) of 1-(2-methyl-6-pyrazyl)-2-ethylbutene-1, b.p. 69–72° at 0.7 mm.

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Pteridine Chemistry. VIII. The Cyanoethylation of Some Hydroxypteridines

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The reaction of acrylonitrile with 2-hydroxy-4-amino-6-methylpteridine (I) and some 2,4-dihydroxypteridines (VI) and the reaction of ethyl acrylate with 2-methylthio-4-hydroxy-6,7-dimethylpteridine (XIV) have been shown to give normal adducts. Some reactions dealing with the structure elucidation of these compounds are also discussed.

Previously we have described the addition of acrylonitrile to 2-amino-4-hydroxypteridines to give 8,9-dihydro-11*H*-pyrimido[2,1-*b*]pteridine-7,-11-diones[1] and to 4-hydroxy-7-methylpteridine to give 3-cyanoethyl-7-methyl-4(3*H*)pteridinone.[2] As a continuation of this work we are now describing similar reactions carried out with several other hydroxypteridines.

2-Hydroxy-4-amino-6-methylpteridine (I). Compound I was prepared in good yield by condensing 2-hydroxy-4,5,6-triaminopyrimidine sulfate[3] with methylglyoxal in an aqueous solution containing sodium sulfite and sodium bisulfite.[4] Attempted acid hydrolysis to the known 2,4-dihydroxy-6-methylpteridine[5a] by the usual procedure of refluxing in 6 *N* hydrochloric acid[5b] gave instead a dark red solid. Paper chromatography of the reaction mixture indicated the presence of the desired compound but none was isolated. The nature of the red solid was not investigated but in all probability it was similar to the dipteridylmethines which have been reported by Karrer.[6] Compound I was readily converted to 2,4-dihydroxy-6-methylpteridine[5a] by refluxing for six hours in 1 *N* sodium hydroxide.

When compound I was treated with acrylonitrile in refluxing aqueous pyridine for eight to ten hours, one product was formed as shown by paper

(1) R. B. Angier and W. V. Curran, *J. Am. Chem. Soc.*, 81, 5650 (1959).

(2) W. V. Curran and R. B. Angier, *J. Org. Chem.*, 26, 2364 (1961).

(3) A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, 70, 3112 (1948).

(4) We wish to thank Drs. J. H. Boothe and A. Green for the details of this preparation.

(5) (a) R. B. Angier *et al.*, *J. Am. Chem. Soc.*, 74, 408 (1952). (b) E. C. Taylor and C. K. Cain, *J. Am. Chem. Soc.*, 71, 2538 (1949).

(6) P. Karrer and R. Schwyzer, *Helv. Chim. Acta*, 33, 39 (1950), and previous papers.

chromatography.[7] Isolation and purification of this material produced a compound, $C_{10}H_{10}N_6O$, which exhibited a well defined nitrile band at 4.45 μ in the infrared spectrum. These facts indicated that the compound was 1-(2-cyanoethyl)-4-amino-6-methyl-2(1*H*)-pteridinone (III), since the reaction of acrylonitrile at the 3- position would probably have resulted in cyclization to the pyrimidopteridinone II.

Concurrently, we were also studying the methylation of 2-hydroxy-4-amino-6-methylpteridine (I). When this compound was treated with dimethyl sulfate in the presence of dilute sodium hydroxide, only one monomethyl derivative was isolated. Hydrolysis of this methylated pteridine with hot 6 *N* hydrochloric acid resulted in loss of the 4-amino function with the formation of 1,6-dimethyl-2,4-(1*H*,3*H*)-pteridinedione (V). The structure of this product was established by comparison of the ultraviolet absorption spectra with those of the known 1(and 3),6,7-trimethyl-2,4(1*H*,3*H*)-pteridinediones.[8] Therefore, the structure of the original methyl compound must be 1,6-dimethyl-4-amino-2(1*H*)-pteridinone (IV). The similarity of the ultraviolet absorption spectra of this product with those of the cyanoethylated derivative of I permits the assignment of structure III [1-(2-cyanoethyl)-4-amino-6-methyl-2(1*H*)-pteridinone] to this compound.

2,4-Dihydroxypteridines (VI). The reaction of 2,4-dihydroxy-6,7-dimethylpteridine (VI. R = R′ = CH_3) with acrylonitrile in refluxing aqueous pyridine afforded 1,3-bis(2-cyanoethyl)-2,4(1*H*,3*H*)-pteridinedione (VII. R = R′ = CH_3). The presence of two carbonyl bands in the infrared spectrum and the degradation to pyrazine derivatives, described below, provides a structure proof for this compound.

The lability of 1,3-dialkyl-2,4-pteridinediones toward nucleophilic reagents, especially hydroxide ion, has previously been reported by Albert and co-workers.[9] These workers demonstrated that refluxing 1,3-dimethyl-2,4-pteridinedione for one minute in 1 *N* sodium hydroxide gave a quantitative yield of 3-methylaminopyrazine-2-(*N*-methyl)-carboxamide. Similar treatment of the biscyanoethyl compound VII gave 3-(2-cyanoethylamino)-5,6-dimethylpyrazine-2-[*N*-(2-cyanoethyl)]carboxamide (VIII) in 49% yield. Acidification of the filtrate from compound VIII to *p*H 2 gave additional material which paper chromatography revealed to be a mixture. Heating this product for one and one-half hours on a steam bath in 1 *N* sodium hydroxide afforded a 28% yield of the diacid IX. The original mixture undoubtedly contained several products in which the nitrile groups had partially hydrolyzed.

When compound VII was treated with dilute sodium hydroxide using more vigorous conditions (150° for sixteen hours) it was converted to 3-(2-carboxyethylamino)-5,6-dimethyl-2-pyrazinoic acid (X) in low yield. Paper chromatographic examination of the filtrate from this product indicated the presence of 3-amino-5,6-dimethyl-2-pyrazinoic acid, which could have been formed by beta elimination of the 2-carboxyethyl group.[10]

Routine biological screening indicated that 1,3-bis(2-cyanoethyl)-6,7-dimethyl-2,4(1*H*,3*H*)-pteridinedione (VII) had some activity as a central nervous system depressant.[11] Therefore, several analogs were prepared. These included 1,3-bis(2-cyanoethyl)-6-methyl-2,4-(1*H*,3*H*)-pteridinedione (VII. R = CH_3, R′ = H), *N*{4-{([1,3-bis(2-cyanoethyl)-2,4-dioxo-1,2,3,4-tetrahydro-6-pteridyl]methyl)amino}benzoyl}glutamic acid (VII. R

= R′ = H), and 1,3-bis(2-cyanoethyl)-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylic acid (VII. R = COOH, R′ = H). In addition, compound VI (R = R′ = CH_3) was converted to 1,3-bis(2-carboxamidoethyl)-6,7-dimethyl-2,4(1*H*,3*H*)-pteridinedione by treatment with acrylamide and to 1,3,6,7-tetramethyl-2,4(1*H*,3*H*)-pteridinedione

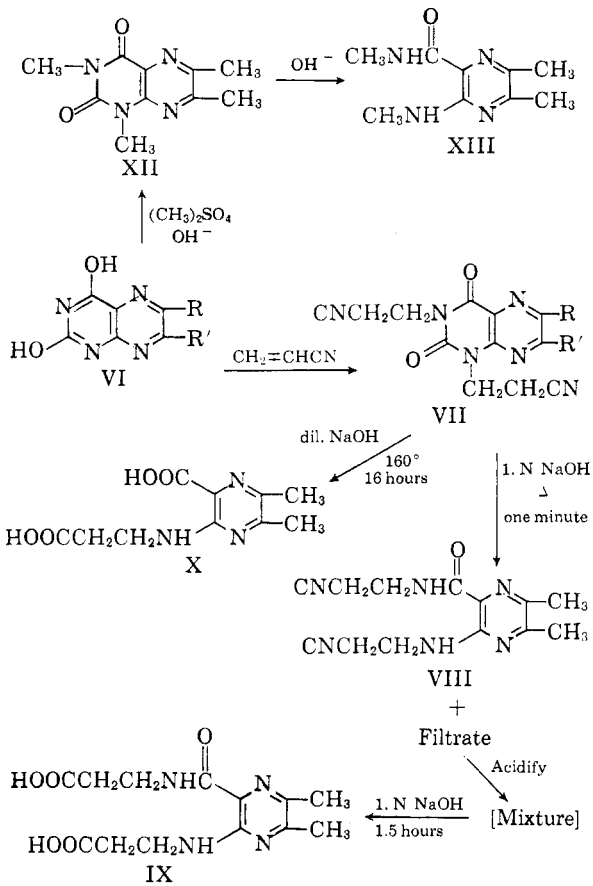
(7) The use of longer reaction periods resulted in the formation of a second product which was shown to be 1,3-bis(2-cyanoethyl)-6-methyl-2,4-pteridinedione (VI) by comparison of the R_f values in several different solvent systems with an authentic sample of this compound. This product probably was formed by slow hydrolysis of the 4-amino group of compound I or III followed by reaction with acrylonitrile.

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

(9) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956).

(10) It is also quite possible that this pyrazine could be formed from a 3-(2-cyanoethylamino) or a 3-(2-carboxamidoethylamino) compound via the same mechanism.

(11) Thanks are due to Dr. A. C. Osterberg and R. Winne for the biological screening of these compounds.

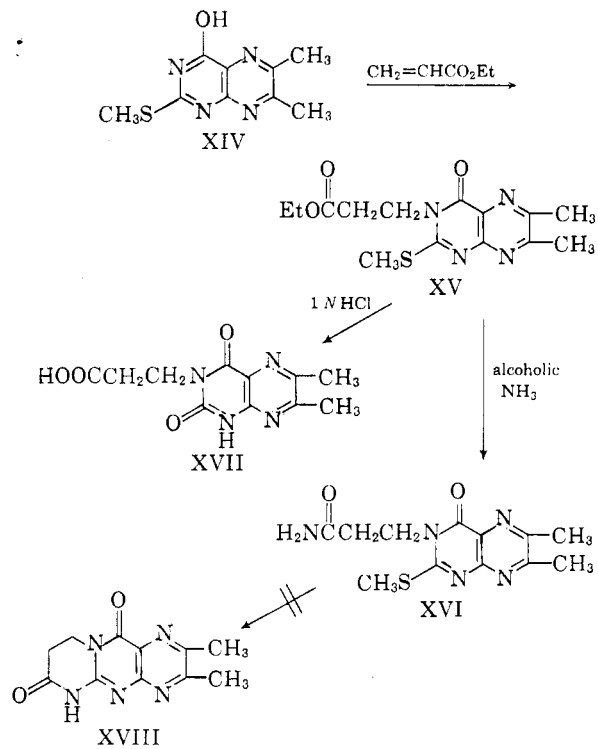


(XII) by treatment with dimethyl sulfate in a dilute alkaline solution. The latter compound was converted to 3-methylamino-5,6-dimethylpyrazine-2(*N*-methyl)carboxamide (XIII) by brief warming in 1 *N* sodium hydroxide.

2-Methylthio-4-hydroxy-6,7-dimethylpteridine (XIV). The reaction of this pteridine with acrylamide to give the pyrimido[2,1-*b*]pteridine (XVIII) has been previously described.[1] We had originally presumed that this reaction involved ring closure of the intermediate 2-methylthio-3-(2-carboxamidoethyl)-6,7-dimethyl-4(3*H*)-pteridinone (XVI). The work described below shows that this was not the path of the reaction.

When a mixture of compound XIV and ethyl acrylate in aqueous pyridine was heated to reflux for thirty-five hours, 2-methylthio-3-(2-carbethoxyethyl)-6,7-dimethyl-4(3*H*)-pteridinone (XV) was obtained in about 40% crude yield. The structure of this product was assigned on the basis of the similarity of the ultraviolet spectra with those of the known 2-methylthio-3,6,7-trimethyl-4-(3*H*)-pteridinone.[8]

The reaction of compound XV with alcoholic ammonia gave a mixture from which the corresponding amide XVI was isolated. That this reaction was complicated by concomitant hydrolysis of the 2-methylthio function and also ring closure to the pyrimidopteridine (XVIII) was shown by paper chromatography of the filtrate. However, attempts to ring close 2-methylthio-3-(2-carboxamidoethyl)-6,7-dimethyl-4(3*H*)-pteridinone (XVI) to the pyrimidopteridine (XVIII) by refluxing in aqueous pyridine were unsuccessful. Thus, it appears that in the reaction between acrylamide and compound XIV, ammonia, liberated by slow hydrolysis of excess acrylamide, could replace the 2-methylthio group of XVI after which cyclization to XVIII would occur. The fact that the 2-methylthio group of this type compound is readily replaced by amines[8] coupled with the fact that acrylamide has been shown to react with 2-amino-4-hydroxy-6,7-dimethylpteridine to give the ring-closed product XVIII[1] indicates that this would be a feasible path for the reaction.



Both XV and XVI were converted to 2-hydroxy derivatives after standing twenty-four hours in 0.1 *N* sodium hydroxide as evidenced by the change in the ultraviolet spectra. The new spectra were essentially identical to the spectra of 3,6,7-trimethyl-2,4(1*H*,3*H*)-pteridinedione.[8] The lability of the methylthio function of these compounds toward hydroxide ion is not surprising in view of the fact that they cannot enolize and hence would be expected to be susceptible to nucleophilic attack.[12] Compound XV was also converted to 3-(2-carboxyethyl)-6,7-dimethyl-2,4-(1*H*,3*H*)-pteridinedione (XVII) with hot 1 *N* hydrochloric acid. All of these reactions confirm the structures XV and XVI.

(12) We have previously described the replacement of the 2-methylthio group of this type compound by an aliphatic amine under rather mild conditions.[8]

EXPERIMENTAL

Paper chromatographic experiments were carried out on Whatman No. 1 paper using the descending technique. The spots were detected with an ultraviolet lamp provided with a filter to give primarily light of 254 mμ.

2-Hydroxy-4-amino-6-methylpteridine (I).[4] 2-Hydroxy-4,5,6-triaminopyrimidine sulfate[3] (26.0 g., 0.11 mole) was suspended in 900 ml. of water and heated until the solid had dissolved. Sodium sulfite (260 g.) was added and the solution was cooled to 30° to give a slurry. A solution of 35 ml. of 30% methylglyoxal and 40 g. of sodium bisulfite in 100 ml. of water was added to the slurry and the mixture was stirred for 18 hr. The solid was then collected, washed with water, and dried; yield 16 g. (83%).

This product was dissolved in 250 ml. of dilute sodium hydroxide, treated with Norit, and filtered. The filtrate was mixed with 250 ml. of 10 *N* sodium hydroxide and cooled. The crystalline sodium salt was collected and redissolved in 500 ml. of water which was then heated to 70° and acidified to *p*H 4; yield 9 g. (47%).

A portion (500 mg.) of this product was recrystallized from 80 ml. of water; yield 380 mg.; ultraviolet absorption spectra in 0.1 *N* sodium hydroxide, λ_{max} 255 mμ (ε 19,900), 375 mμ (ε 6700); *p*H 7.0 buffer, λ_{max} 242 mμ (ε 12,600) 282 mμ (ε 3700), 343 mμ (ε 9300); 0.1 *N* hydrochloric acid, λ_{max} 238 mμ (ε 11,200), 342 mμ (ε 8200).

Anal. Calcd. for $C_7H_7N_5O$ (177): C, 47.5; H, 4.0; N, 39.6. Found: C, 47.8; H, 4.0; N, 39.2.

2,4-Dihydroxy-6-methylpteridine (6-methyllumazine). A solution of 5.0 g. (0.028 mole) of compound I in 100 ml. of 1 *N* sodium hydroxide was refluxed for 6 hr., then treated with Norit and filtered. The filtrate was acidified to *p*H 7, seeded, and allowed to crystallize overnight at room temperature. The product was collected and dried; yield 2.75 g. (55%), R_f 0.36 (blue-green fluorescence) in isopropyl alcohol–1 *N* ammonium hydroxide (7:3) and R_f 0.64 (dull blue fluorescence which turns to blue-green on fuming with ammonia) in 3% ammonium chloride. The ultraviolet spectra and paper chromatographic behavior of this product were identical with a known sample of 6-methyllumazine.[5]

1-(2-Cyanoethyl)-4-amino-6-methyl-2(1H)-pteridinone (III). A solution of 10 g. (56.5 mmoles) of 2-hydroxy-4-amino-6-methylpteridine in 500 ml. of 50% aqueous pyridine containing 20 ml. of acrylonitrile was refluxed for 9.5 hr. Ten milliliters of acrylonitrile was added after 4 and 6 hr. of refluxing. Evaporation of the solvent gave crystals; yield 8.2 g. The crude product was recrystallized from 500 ml. of 50% aqueous ethanol; yield, 6.5 g. (50%); decomposes slowly above 250° without melting. R_f 0.82 (dull purple fluorescence) in acetone–water (4:1). Ultraviolet absorbtion spectra in 0.1 *N* NaOH, λ_{max} 245 mμ (ε 15,000), 280–284 mμ (plateau), (ε 3570), 346 mμ (ε 8500); 0.1 *N* HCl, λ_{max} 238 mμ (ε 14,000), 343 mμ (ε 8280). λ_{max}^{KBr} 4.45 μ (C≡N).

Anal. Calcd. for $C_{10}H_{10}N_6O$ (230.2): C, 52.2; H, 4.4; N, 36.5. Found: C, 52.3; H, 4.4; N, 36.6.

1,6-Dimethyl-4-amino-2(1H)-pteridinone (IV). 2-Hydroxy-4-amino-6-methylpteridine (1.77 g., 0.01 mole) was dissolved in 30 ml. of 0.5 *N* sodium hydroxide and 1.5 ml. (0.015 mole) of dimethyl sulfate added in three equal portions over a 30-min. period with vigorous stirring. After 2 hr. the *p*H had dropped to 6. The reaction mixture was chilled overnight, then filtered and washed with cold water. The wet filter cake was recrystallized as platelets from 50% aqueous alcohol; yield 1.1 g. (58%). Another recrystallization from a solution of 100 ml. of water and 50 ml. of ethanol gave 0.95 g. (50%), m.p. 285–290° with decomposition. R_f 0.69 (purple fluorescence) in butanol–5 *N* acetic acid (7:3). Ultraviolet absorption spectra in 0.1 *N* NaOH λ_{max} 246 mμ (ε 15,900), 283–288 mμ (plateau) (ε 3200), 349 mμ (ε 8700); 0.1 *N* HCl, λ_{max} 239 mμ. (ε 14,500), 348 mμ (ε 8970).

Anal. Calcd. for $C_8H_9N_5O$ (191.2): C, 50.3; H, 4.8; N, 36.6. Found: C, 50.3; H, 5.1; N, 36.6.

1,6-Dimethyl-2,4-(1H,3H)-pteridinedione (V). A solution of 200 mg. (1.05 mmoles) of 1,6-dimethyl-4-amino-2(1*H*)-pteridinone in 15 ml. of concd. hydrochloric acid was refluxed for 1.5 hr. The solution was evaporated to dryness *in vacuo* and again evaporated after adding 20 ml. of water. The residue was taken up in about 10 ml. of hot water, treated with Norit, and filtered. On cooling, the compound crystallized; yield 57 mg. Another 31 mg. (44% total) was obtained by concentrating the mother liquor. These two crops were combined and recrystallized from 8 ml. of water; yield 55 mg. (28%). R_f 0.74 in 3% NH_4Cl, 0.78 in 0.5% Na_2CO_3, and 0.64 in butanol–5 *N* acetic acid (7:3) (purple fluorescence in all cases). Ultraviolet absorption spectra in 0.1 *N* NaOH, λ_{max} 243 mμ (ε 18,900), 283 mμ (ε 2840), 343 mμ (ε 8800); 0.1 *N* HCl, λ_{max} 233 mμ (ε 13,500), 336 mμ (ε 8250).

Anal. Calcd. for $C_8H_8N_4O_2$ (192.2): C, 50.0; H, 4.2, N, 29.2. Found: C, 49.9; H, 4.4; N, 29.3.

1,3-Bis(2-cyanoethyl)-6-methyl-2,4-(1H,3H)-pteridinedione (VII. R = H, R′ = CH_3). 6-Methyllumazine (VI) (1.0 g., 5.6 mmoles) was dissolved in 60 ml. of 50% aqueous pyridine containing 2 ml. of acrylonitrile. The solution was refluxed for 9 hr. and acrylonitrile was added in 2-ml. portions after 2, 4, and 6 hr. After removal of the solvents *in vacuo*, the oil was dissolved in 20 ml. of water and again evaporated *in vacuo*. The oily residue was dissolved in about 25 ml. of hot water, treated with Norit, and filtered. The filtrate was chilled overnight. Several clumps of crystals formed which were broken up and chilled for several hours more before filtering: yield 0.80 g. (50%), m.p. 143–147°. Two recrystallizations from water gave 0.50 g. (31%), m.p. 148.5–150°. R_f 0.79 (purple fluorescence) in 0.5% Na_2CO_3. Ultraviolet absorption spectra in 0.1 *N* HCl, λ_{max} 236 mμ (ε 15,200), 333 mμ (ε 7730). λ_{max}^{KBr} 4.48 μ (—C≡N), 5.81, 5.97 μ (—C=O).

Anal. Calcd. for $C_{13}H_{12}N_6O_2$ (284.3): C, 55.0; H, 4.3; N, 29.6. Found: C, 55.3; H, 4.9; N, 29.6.

1,3-Bis(2-cyanoethyl)-6,7-dimethyl-2,4-(1H,3H)-pteridinedione (VII. R and R′ = CH_3). 6,7-Dimethyllumazine (VI. R and R′ = CH_3) (5.0 g., 26 mmoles) was added to 100 ml. of 50% aqueous pyridine containing 10 ml. of acrylonitrile and refluxed for 11 hr. Additional 10-ml. portions of acrylonitrile were added after 3, 6, and 9 hr. After concentrating *in vacuo*, the resulting oil was crystallized from dilute ethanol; yield 6.1 g. (78%). The crude product was recrystallized from 80 ml. of absolute alcohol (Norit); yield 5.6 g. (72%), m.p. 134–137°. R_f 0.86 (dull purple fluorescence) in 0.5% Na_2CO_3. Ultraviolet absorption spectra in 0.1 N HCl, λ_{max} 232 mμ (ε 13,300), 328 mμ (ε 9860). λ_{max}^{KB} 4.45 μ. (—C≡N), 5.79, 5.94 μ (—C=O).

Anal. Calcd. for $C_{14}H_{14}N_6O_2$ (298.3): C, 56.4; H, 4.7; N, 28.2 Found: C 56.2; H, 4.8; N, 27.9.

3-(2-Cyanoethylamino)-5,6-dimethylpyrazine-2[N-(2-cyanoethyl)]carboxamide (VIII). 1,3-Bis(2-cyanoethyl)-6,7-dimethyl-2,4-(1*H*,3*H*)-pteridinedione (9.0 g., 31.7 mmoles) was boiled for 1 min. in 135 ml. of 1*N* sodium hydroxide, then chilled immediately. After standing overnight in the cold, the 3-(2-cyanoethylamino)-5,6-dimethylpyrazine-2-[*N*-(2-cyanoethyl)]carboxamide (VIII) was filtered off; yield 3.8 g. (44%), m.p. 163–166°. For analysis a portion of this product was recrystallized from water. Ultraviolet absorption spectra in 0.1 *N* NaOH, λ_{max} 260 mμ (ε 17,900), 368 mμ (ε 8830); 0.1 *N* HCl, λ_{max} 259 mμ (ε 16,850), 371 mμ (ε 9030).

Anal. Calcd. for $C_{13}H_{16}N_6O$ (272.3): C, 57.4; H, 5.9; N, 30.9. Found: C, 57.1; H, 5.9; N, 31.1.

3-(2-Carboxyethylamino)-5,6-dimethylpyrazine-2[N-(2-carboxyethyl)]carboxamide (IX). The filtrate from compound VIII was acidified to *p*H 2 with concentrated hydrochloric acid to give an oil which crystallized on chilling; yield 2.5 g. The mother liquor deposited an additional 0.75 g. on standing. Paper chromatography revealed that both crops were mixtures containing similar products. They were therefore combined, dissolved in 50 ml. of 1 *N* sodium hydroxide, and heated for 1.5 hr. on a steam bath. Acidification of the

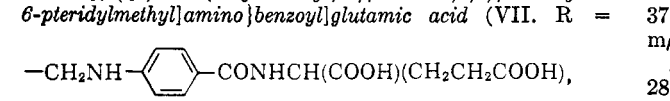
solution with concd. hydrochloric acid gave an oil which crystallized immediately. After chilling overnight the crystals of the biscarboxyethylamide (IX) were collected and dried; yield 2.7 g. (27.6%) based on VII; m.p. 172–175°. For analysis a portion of this product was recrystallized from water and then from ethyl acetate. The melting point was raised to 174–175°. R_f 0.51 (blue fluorescence) in isopropyl alcohol–1 *N* NH_4OH (7:3). Ultraviolet absorption spectra in 0.1 *N* NaOH, λ_{max} 262 mμ (ε 19,100), 374 mμ (ε 8200); in 0.1 *N* HCl, λ_{max} 257 mμ (ε 17,000), 376 mμ (ε 9300); in methanol, λ_{max} 260 mμ (ε 19,200), 369 mμ (ε 8400).

Anal. Calcd. for $C_{18}H_{18}O_6N_4$ (310.31): C, 50.3; H, 5.9; N, 18.1. Found: C, 50.0; H, 5.9; N, 18.3.

3-(2-Carboxyethylamino)-5,6-dimethyl-2-pyrazinoic acid (X). 1,3-Bis(2-cyanoethyl)-6,7-dimethyl-2,4-(1*H*,3*H*)-pteridinedione (VII. R and R′ = CH_3) (2.0 g., 6.7 mmoles) was added to 75 ml. of water containing 2.0 g. of sodium hydroxide and heated for 16 hr. in a bomb at 150°. The solution obtained was treated with Norit and filtered. The filtrate was acidified to *p*H 2–2.5 with cond. hydrochloric acid to give 0.70 g., m.p. 170–172° (gas evolution) with previous softening. The crude product was taken up in boiling ethyl acetate and filtered from a small amount of insoluble material. The filtrate was concentrated to about 40 ml. and 25 ml. of petroleum ether added to induce crystallization; yield 0.50 g. (31%), m.p. 177–179° (gas evolution). R_f 0.41 (dull blue fluorescence) in isopropyl alcohol–1 *N* NH_4OH (7–3). Ultraviolet absorption spectra in 0.1 *N* NaOH, λ_{max} 260 mμ (ε 15,350), 363 mμ (ε 6660); 0.1 *N* HCl, λ_{max} 263 mμ (ε 16,650), 386 mμ (ε 6550).

Anal. Calcd. for $C_{10}H_{13}N_3O_4$ (239.2): C, 50.2; H, 5.5; N, 17.6. Found: C, 50.0; H, 5.6; N, 17.9.

N-[4-{[1,3-Bis(2-cyanoethyl)-2,4-dioxo-1,2,3,4-tetrahydro-6-pteridylmethyl]amino}benzoyl]glutamic acid (VII. R =



(R′ = H)

A solution of 4.0 g. (9.1 mmoles) of 2-hydroxy-2-deaminopteroylglutamic acid,[5] 40 ml. of water, 35 ml. of pyridine, and 4 ml. of acrylonitrile was refluxed for 15 hr. with 2-ml. portions of acrylonitrile being added every 3 hr. The solution was evaporated to dryness under reduced pressure. The residue was dissolved in 30 ml. of hot water, treated with Norit, and filtered. When the filtrate was acidified with 3 ml. of acetic acid, an oil separated which solidified while standing at 5° overnight. The solid was collected, washed with water, and dried; yield 4.2 g. (84%). A solution of this material in 12 ml. of hot acetic acid was treated with Norit, filtered, cooled to room temperature, and diluted with water to a volume of 35 ml. A yellow microcrystalline product slowly separated. The mixture was diluted further with water to a total volume of 70 ml. and cooled overnight. The product was collected, washed with water, and dried; yield 3.2 g. (65%); R_f 0.95 (absortion) in 0.5% Na_2CO_3 and 3% NH_4Cl: 0.60 (absorption) in butanol–5 *N* acetic acid (7:3). Ultraviolet absorption spectra in 0.1 *N* hydrochloric acid. λ_{max} 234 mμ (ε 19,700), 296 mμ (ε 15,900), 340 mμ (shoulder) (ε 7400).

Anal. Calcd. for $C_{25}H_{24}N_8O_7$ (548): C, 54.7; H, 4.4; N, 20.4. Found: C, 54.4; H, 4.9; N, 20.2.

1,3-Bis(2-cyanoethyl)-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylic acid (VII. R = COOH, R′ = H). A solution of 3.9 g. (18.7 mmoles) of 2,4-dihydroxypteridine-6-carboxylic acid,[5,13] 55 ml. of water, 30 ml. of pyridine, and 6 ml. of acrylonitrile was heated on a steam bath for 11 hr. with 3-ml. portions of acrylonitrile being added at 3 hr. intervals. The solution was evaporated to dryness under reduced pressure and the residue was dissolved in 25 ml. of hot water which was treated with Norit and filtered. The filtrate was acidified with 2 ml. of acetic acid and cooled; yield of crystalline product 4.6 g. (74%). Recrystallization of this product from 150 ml. of water, using Norit, gave a white crystalline product; yield 3.2 g. (52%); R_f 0.60 (absorption) in isopropyl alcohol–1 *N* NH_4OH (7:3). Ultraviolet absorption spectra in 0.1 *N* hydrochloric acid, λ_{max} 243 mμ (ε 13,200), 263 mμ (ε 10,400), 328 mμ (ε 8200).

Anal. Calcd. for $C_{13}H_{10}N_6O_4$ (314): C, 49.7; H, 3.2; N, 26.7. Found: C, 49.3; H, 3.4; N, 26.6.

1,3,6,7-Tetramethyl-2,4(1H,3H)pteridinedione (XII). 6,7-Dimethyllumazine (VI. R and R′ = CH_3) (1.9 g., 10 mmoles) was slurried in 20 ml. of water using a magnetic stirrer and 4 ml. of dimethyl sulfate was added in four portions over a 45-min. period. Simultaneously, over a 1-hr. period, a solution of 1.6 g. (40 mmoles) of sodium hydroxide in 20 ml. of water was added dropwise. Stirring was continued for an additional hour during which time crystals appeared and the *p*H dropped to 4.0. The solution was chilled for several days before collecting the product; yield 1.0 g. (49%), m.p. 164–166.5° [14], ultraviolet absorption spectra in methanol, λ_{max} 237 mμ (ε 14,500), 333 mμ (ε 8900). These data are in good agreement with those reported by W. Pfleiderer[15] for 1,3-dimethyl-2,4-pteridinedione and also with the data reported above for 1,3-bis(2-cyanoethyl)-6,7-dimethyl-2,4(1*H*,3*H*)-pteridinedione.

3-Methylamino-5,6-dimethylpyrazine-2(N-methyl)carboxamide (XIII). 1,3,6,7-tetramethyl-2,4-pteridinedione (0.80 g., 3.9 mmoles) in 8 ml. of 1 *N* sodium hydroxide was boiled for 1 min. to give an oil which crystallized on cooling; yield 0.59 g. (84%), m.p. 95–97.5°. For analysis a small portion was recrystallized from low boiling petroleum ether (m.p. raised to 96–98°); R_f 0.61 (blue) in 0.5% Na_2CO_3; ultraviolet spectra in 0.1 *N* NaOH, λ_{max} 262 mμ (ε 16,200), 375 mμ (ε 7700); 0.1 *N* HCl, λ_{max} 255 mμ (ε 15,800), 378 mμ (ε 9200).

Anal. Calcd. for $C_9H_{14}N_4O$ (194): C, 55.7; H, 7.3; N, 28.9. Found: C, 55.8; H, 7.4; N, 28.7.

1,3-Bis(2-carboxamidoethyl)-6,7-dimethyl-2,4(1H,3H)-pteridinedione. 6,7-Dimethyllumazine (VI. R and R′ = CH_3) (3.0 g.; 15.6 mmoles) was added to 100 ml. of a 50% aqueous pyridine solution containing 6.0 g. of acrylamide and refluxed for 11 hr. Six-gram portions of acrylamide were added after 3, 6, and 9 hr. of refluxing. The reaction mixture was then evaporated to a syrup under reduced pressure, dissolved in 100 ml. of water, and again evaporated. After this procedure had been repeated using 100-ml. and then 200-ml. portions of water the resulting oily liquid was dissolved in 50 ml. of hot water, treated with Norit, and filtered. The filtrate deposited crystals on standing overnight at room temperature. The product was collected and dried; yield 0.60 g., m.p. 255–257° dec.

The filtrate was evaporated under reduced pressure to an oily solid. This was boiled in 100 ml. of 75% ethanol, filtered to remove some gummy solid, and seeded with the first crop, then allowed to crystallize overnight at room temperature. The crystals were collected and dried: yield 0.80 g., m.p. 256–262° dec. Similar treatment of the filtrate using smaller amounts of aqueous ethanol gave two additional crops of 0.80 g., m.p. 258–262° dec. and 0.60 g., m.p. 260–262° dec. All four crops were combined, boiled in 110 ml. of 80% ethanol, treated with Norit, and filtered to remove a small amount of insoluble material. After the solution had been chilled overnight, the crystalline product was collected and dried; yield 1.95 g. (38%), m.p. 265–267° dec.; R_f 0.81 (dark purple) with a small amount of lower R_f spot in 0.5% Na_2CO_3; ultraviolet absorption spectra in 0.1 *N* HCl, λ_{max} 237 mμ (ε 15,800), 332 mμ (ε 9500). The spectra were essentially the same in *p*H 7 buffer solution.

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(14) F. F. Blicke and H. C. Godt, Jr., *J. Am. Chem. Soc.*, **76**, 2800 (1954), give m.p. 158–159°.

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Anal. Calcd. for $C_{14}H_{18}N_6O_4$ (334): C, 50.3; H, 5.4; N, 25.1. Found: C, 50.5; H, 5.7; N, 25.1.

2-Methylthio-3-(2-carbethoxyethyl)-6,7-dimethyl-4(3H)-pteridinone (XV). A solution of 1 g. (4.5 mmoles) of 2-methylthio-4-hydroxy-6,7-dimethylpteridine[1] (XIV) in 60 ml. of 50% aqueous pyridine containing 2 ml. of ethyl acrylate was heated to reflux for 33 hr. Two-milliliter portions of ethyl acrylate were added at 6-hr. intervals until a total of 10 ml. had been added. The solvents were removed *in vacuo* and the resulting oil taken up in absolute alcohol, treated with Norit, and filtered. An oil came out of the dark solution which crystallized on standing; yield 0.55 g. (38%). After two recrystallizations from isopropyl alcohol the yield was 0.30 g. (20.6%), m.p. 156–159°. R_f 0.87 (dark purple absorption) in butanol–5 *N* acetic acid (7–3). Ultraviolet absorption spectra in 0.1 *N* NaOH, λ_{max} 249 mμ (ε 13,100), 288 mμ (ε 12,300), 335 mμ (ε 7720); 0.1 *N* HCl, λ_{max} 246 mμ (ε 13,200), 287 mμ (ε 14,630), 335 mμ (ε 7900).

Anal. Calcd. for $C_{14}H_{18}N_4O_3S$ (322.3): C, 52.2; H, 5.6; N, 17.4; S, 10.0. Found: C, 52.2; H, 6.1; N, 17.0; S, 9.9.

2-Methylthio-3-(2-carboxamidoethyl)-6,7-dimethyl-4(3H)-pteridinone (XVI). Seven hundred and fifty milligrams (2.3 mmoles) of compound XV was dissolved in 75 ml. of methanol, cooled to −3°, and anhydrous ammonia passed in for 20 min. (final temperature 14°). The solution was chilled overnight (protected with Drierite) then allowed to stand at room temperature for several hours during which time some crystals appeared. In order to ensure complete reaction the mixture was heated to reflux for 1 hr. and then evaporated to about 20 ml. and cooled; yield 0.35 g. (52%), m.p. 261–264°. Recrystallization of the product from 20 ml. of water containing 4 ml. of ethanol gave 0.26 g. (39%), m.p. 265–267°. R_f 0.61 (absorption) in 3% NH_4Cl; 0.57 (dark purple fluorescence) in butanol–5 *N* acetic acid (7:3). Ultraviolet absorption spectra in 0.1 *N* NaOH, λ_{max} 245 mμ (ε 10,900), 288 mμ (ε 11,200), 333 mμ (ε 6950); 0.1 *N* HCl, λ_{max} 247 mμ (ε 13,800), 287 mμ (ε 14,900), 335 mμ (ε 8210).

Anal. Calcd. for $C_{12}H_{15}O_2N_5S$ (293.3): C, 49.1; H, 5.2 N, 23.9; S, 10.9. Found: C, 49.0; H, 5.2; N, 23.8; S, 10.8.

3-(2-Carboxyethyl)6,7-dimethyl-2,4-(1H,3H)-pteridinedione (XVII). 2-Methylthio-3-(2-carbethoxyethyl)-6,7-dimethyl-4(3*H*)-pteridinone (XV) (100 mg., 0.31 mmole) was heated on a steam bath for 2.5 hr. in 5 ml. of 1.0 *N* hydrochloric acid. The hot solution was treated with Norit, filtered, and chilled, yield 50 mg. (60%); m.p. 287–293° dec. R_f 0.88 (blue fluorescence) in 0.5% Na_2CO_3. Ultraviolet absorption spectra in 0.1 *N* NaOH, λ_{max} 247 mμ (ε 17,500), 271 mμ (ε 11,350), 361 mμ (ε 7540); 0.1 *N* HCl, λ_{max} 232 mμ (ε 12,500), 330 mμ (ε 10,300).

Anal. Calcd. for $C_{11}H_{12}N_4O_4$ (264.2): C, 50.0; H, 4.6; N, 21.1. Found: C, 50.3; H, 4.8; N, 21.3.

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Some Pyrido[1,2-*a*]pyrimidones

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The facile reaction of ethyl α-ethoxyethylidenecyanoacetate with 2-aminopyridine and its 3- and 4-methyl derivatives to yield the corresponding 4*H*-pyrido[1,2-*a*]pyrimidones is ascribed to hyperconjugation. The ultraviolet spectra of several 4*H*-pyrido[1,2-*a*]pyrimidones are reported and display a band with λ_{max} at *ca.* 245 mμ ascribed to the —C=C—C=O chromophore of the pyrimidine moiety. This observation is extended to the spectra of 5*H*-thiazolo[3,2-*a*]pyrimidine-5-one and *s*-triazolo[2,3-*a*]pyrimidine-7-one. The condensation of ethyl acetaminomalonate with 2-aminopyridine and its 4-methyl derivative is reported.

The thermal facile cyclization of ethyl 2-pyridylaminocrotonate[1] as compared with the α-substituted β-2-pyridylaminoacrylate,[2] which could only be cyclized by distillation under reduced pressure, prompted the synthesis of similarly substituted crotonic esters to determine whether this effect may be attributed to the unsaturated α-substituent or to hyperconjugation.[3]

Refluxing ethyl orthoacetate with ethyl cyanoacetate in acetic anhydride solution gave ethyl α-ethoxyethylidenecyanoacetate in moderate yield. Reaction of the latter ester with 2-aminopyridine and its 3- and 4-methyl derivatives at 150° gave by condensation followed by smooth cyclization 2-methyl, 2,9-, and 2,8-dimethyl-3-cyano-4*H*-pyrido[1,2-*a*]pyrimidine-4-one in excellent yield. The effect of hyperconjugation on ease of cyclization is thus clearly evidenced.

The ultraviolet spectra in absolute ethanol are reported in Figure 1. It is to be remarked that the absorption spectrum of 3-cyano-2,8-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidine-4-one exhibits the normal three bands characteristic of 4*H*-pyrido[1,2-*a*]pyrimidine-4-one bearing an unsaturated 3-substituent (Fig. 1).

The previously observed rearrangement[2] of ethyl 4-methyl-2-pyridylaminomethylenecyanoacetate to ethyl *N*-(4-methyl-2-imino-1,2-dihydropyridyl)methylenecyanoacetate led by cyclization to the isomeric 3-cyano-8-methyl-2*H*-pyrido[1,2-*a*]pyrimidine-2-one, which displayed an anomalous ultraviolet spectrum. Such a rearrangement is partly dependent on the thermal lability of the —C—N= bond. The effect of electron release due

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