in making elementary analyses. Part of the cost of this study was defrayed with a Grant from the Ministry of Education in Aid for the Miscellaneous Scientific Research, to which we express our gratitude. We are also grateful to Dr. Simon H. Wender of the University of Oklahoma for his reading of our manuscript.

HONGO, TOKYO, JAPAN

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Pteridines. X. A New Approach to the Synthesis of Pteridines[1]

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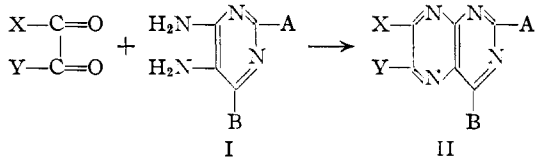
A new approach to the synthesis of pteridines is described. The method involves (a) the preliminary synthesis of a 2,4-(1H,3H)pteridinedione (lumazine) by the conventional method; (b) aminolytic cleavage of the pyrimidine portion of the lumazine to give a 3-amino-N-substituted pyrazinamide; and (c) ring reclosure of this pyrazinamide to the desired pteridine. This approach retains the advantages of the conventional synthetic procedures with regard to the ease of building up the pyrazine ring and permits a much wider variation in the structure of the pyrimidine ring. This paper records some model experiments illustrating step (c), the cyclization to pteridines of the pyrazinamides formed by cleavage of lumazines with primary amines.

The conventional methods for the synthesis of the pteridine ring system employ a condensation of a 4,5-diaminopyrimidine (I) with an α,β-dicarbonyl compound, an α-halocarbonyl compound, an α-keto alcohol or derivatives of these compounds.[2] Almost all of the known synthetic pteridines have been prepared by one of these routes. Although these methods allow considerable variation in the groups X and Y on the pyrazine ring of the resulting pteridine (II), considerably less variation has been possible in the substituents on the pyrimidine ring because of the limitations encountered in the synthesis of the requisite 4,5-diaminopyrimidines (I). Thus, substituents A and B have been restricted principally to amino or substituted amino, hydroxy or mercapto groups or to hydrogen. Only a few examples are known of pteridines substituted by alkyl groups in positions 2 and 4[3-8] or by alkyl groups on the ring nitrogen atoms in the pyrimidine ring.[9]



I II

We wish to describe preliminary results on a new approach to the synthesis of pteridines which retains the advantages of the conventional methods with regard to the ease of placing the substituents X and Y, but whose special feature is the varied manner in which the pyrimidine ring may be constructed. In brief, the method involves (a) the preliminary synthesis of a 2,4(1H,3H)pteridinedione (lumazine) by the conventional method; (b) aminolytic cleavage of the pyrimidine portion of the lumazine to give a 3-amino-N-substituted pyrazinamide; and (c) ring reclosure of this pyrazinamide to the desired pteridine. Step (a) has been reviewed extensively,[2] and step (b) has been discussed recently with respect to the action of alkylamines on 6,7-diphenyl-2,4(1H,3H)pteridinedione (6,7-diphenyllumazine) (III) to give 3-amino-N-substituted-5,6-diphenylpyrazinamides (IV, V).[10] The present paper records some model experiments illustrating step (c), the cyclization to pteridines of the pyrazinamides formed by cleavage of lumazines with primary amines. Although all of the following cyclization experiments involve 5,6-diphenylpyrazinamides derived from 6,7-diphenyllumazine (III), it will be shown in later communications that step (c) is independent of the nature of the 5- and 6-substituents, and that the synthetic method comprising steps (a), (b) and (c) is entirely general.

A few examples are known of ring closure of pyrazinamides to pteridines. Gabriel and Sonn[11] prepared 2,4(1H,3H)pteridinedione (lumazine) from pyrazine-2,3-dicarboxamide in 40% yield by use of the Hofmann reaction. Albert, *et al.*,[12] cyclized 3-aminopyrazinamide to 4(3H)pteridinone with ethyl orthoformate and acetic anhydride and also with formic acid and acetic anhydride; by the same methods, 3-aminothiopyrazinamide was cyclized to 4(3H)pteridinethione. From this Laboratory, it has been reported that the action of formic acid and acetic anhydride on 3-amino-N-benzyl-

(1) Taken in part from theses presented by John A. Carbon and Dale R. Hoff to the University of Illinois in partial fulfillment of the degree of Bachelor of Science in Chemistry.

(2) For extensive reviews, see (a) M. Gates, *Chem. Revs.*, **41**, 63 (1947); (b) J. A. Elvidge, *Ann. Rep. Prog. Chem. (London)*, **45**, 226 (1948); (c) H. N. Rydon, *ibid.*, **47**, 241 (1950); (d) A. Albert, *Rev. Pure App. Chem.*, **1**, 51 (1951); (e) A. Albert, *Quart. Revs.*, **6**, 197 (1952).

(3) H. Andersag and K. Westphal, *Ber.*, **70B**, 2035 (1937).

(4) W. C. J. Ross, *J. Chem. Soc.*, 1128 (1948).

(5) G. R. Ramage, British Patent, 619,915 (1949); *C. A.*, **43**, 9087 (1949).

(6) M. Polonovski and H. Jerome, *Compt. rend.*, **230**, 392 (1950); M. Polonovski, M. Pesson and A. Puister, *ibid.*, **230**, 2205 (1950).

(7) M. Pesson, *Bull. soc. chim. France*, **15**, Ser. 5, 963 (1948).

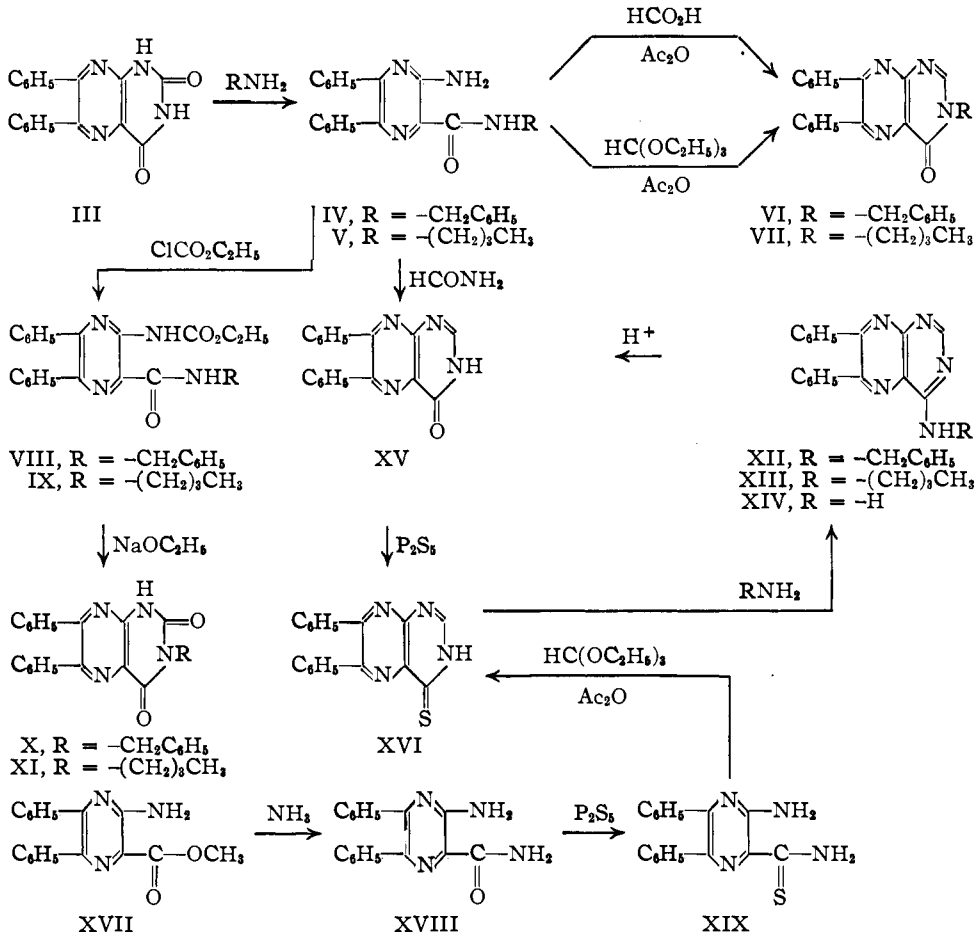
(8) H. S. Forrest, R. Hull, H. J. Rodda and A. R. Todd, *J. Chem. Soc.*, 3 (1951).

(9) (a) F. Sachs and G. Meyerheim, *Ber.*, **41**, 3957 (1908); (b) H. von Euler, K. M. Brandt and G. Neumüller, *Biochem. Z.*, **281**, 206 (1935); (c) R. Kuhn and A. H. Cook, *Ber.*, **70B**, 761 (1937); (d) M. Pesson, *Bull. soc. chim. France*, **15**, Ser. 5, 963 (1948); (e) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, THIS JOURNAL, **73**, 2864 (1948).

(10) E. C. Taylor, Jr., *ibid.*, **74**, 1651 (1952).

(11) S. Gabriel and A. Sonn, *Ber.*, **40**, 4850 (1907).

(12) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 474 (1951). NOTE ADDED IN PROOF.—A more recent article by these authors, *ibid.*, 4219 (1952), describes the cyclization of 3-amino-N-methylpyrazinamide to 3-methyl-4(3H)-pteridinone with formic acid and acetic anhydride.



5,6-diphenylpyrazinamide (IV), prepared by the action of benzylamine on III, gave 3-benzyl-6,7-diphenyl-4(3H)-pteridinone (VI).[10]

It has now been found that VI may be obtained in improved yield by cyclization with ethyl orthoformate in acetic anhydride. Similar cyclizations with 3-amino-N-(*n*-butyl)-5,6-diphenylpyrazinamide (V), prepared by cleavage of III with *n*-butylamine, gave 3-(*n*-butyl)-6,7-diphenyl-4(3H)-pteridinone (VII) in good yield.

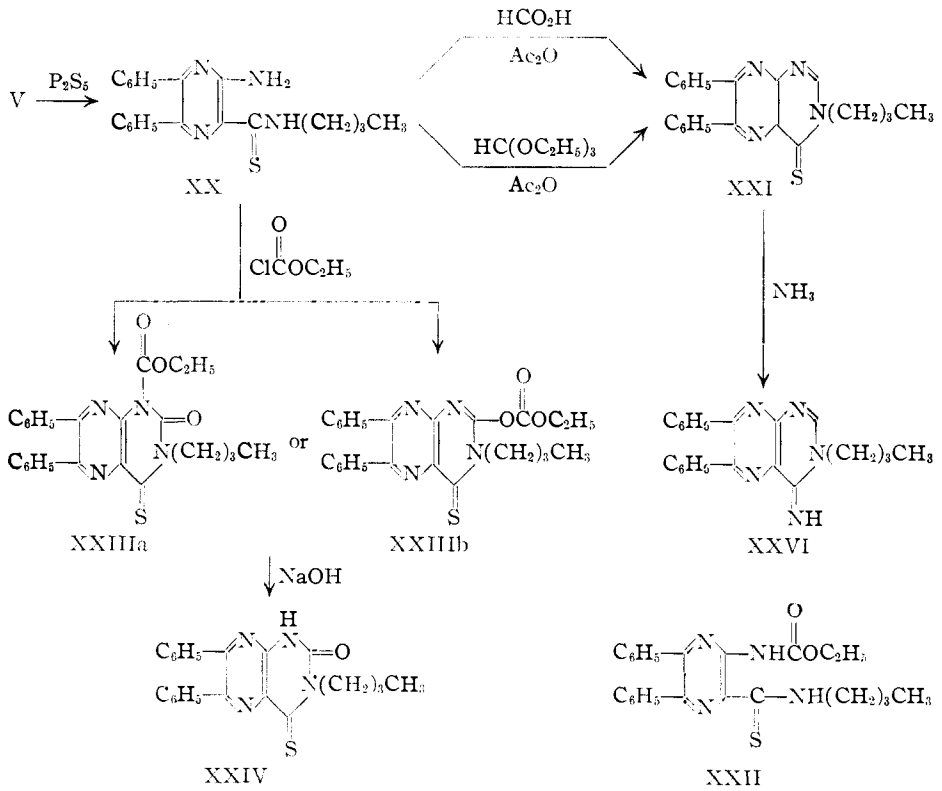
The action of ethyl chlorocarbonate on IV and V gave N-benzyl-3-carbethoxyamino-5,6-diphenylpyrazinamide (VIII) and N-(*n*-butyl)-3-carbethoxyamino-5,6-diphenylpyrazinamide (IX), respectively. These compounds were cyclized with sodium ethoxide to 3-benzyl-6,7-diphenyl-2,4(1H,3H)pteridinedione (X) and 3-(*n*-butyl)-6,7-diphenyl-2,4-(1H,3H)-pteridinedione (XI), respectively. The formation of the intermediate carbethoxyamino derivatives VIII and IX parallels the formation of 3-carbethoxyaminoquinoxaline-2-carboxamide from 3-aminoquinoxaline-2-carboxamide and ethyl chlorocarbonate.[13]

Formamide and 3-amino-N-benzyl-5,6-diphenylpyrazinamide (IV) gave 6,7-diphenyl-4(3H)-pteridinone (XV). The same product XV was also formed from V and formamide. It was noted that carefully purified formamide failed to react with either IV or V, whereas stock formamide or formamide to which a small amount of aqueous formic acid had been added reacted to give XV. Formic acid alone did not react with either IV or V. A further study of this reaction is in progress.

6,7-Diphenyl-4(3H)-pteridinone (XV) on treatment with phosphorus pentasulfide in pyridine solution gave the corresponding pteridinethione (XVI), which was also prepared by the action of ethyl orthoformate and acetic anhydride on 3-amino-5,6-diphenylthiopyrazinamide (XIX). This latter compound was prepared by direct thiation of the corresponding pyrazinamide (XVIII) in pyridine solution. The only previously recorded preparation of a thiopyrazinamide was by Albert, Brown and Cheeseman,[12] who prepared 3-amino-2-thiopyrazinamide from 3-amino-2-cyanopyrazine and hydrogen sulfide. The amide XVIII has been described previously[10]; it was prepared in this study by ammonolysis of ethyl 3-amino-5,6-diphenylpyrazinoate (XVII).

Treatment of 3-amino-N-(*n*-butyl)-5,6-diphenylpyrazinamide (V) with phosphorus pentasulfide in pyridine gave the corresponding thioamide XX in good yield. Cyclization of XX either with formic acid and acetic anhydride or with ethyl orthoformate and acetic anhydride gave 3-(*n*-butyl)-6,7-diphenyl-4(3H)-pteridinethione (XXI). However, treatment of XX with ethyl chlorocarbonate did not give N-(*n*-butyl)-3-carbethoxyamino-5,6-diphenylthiopyrazinamide (XXII) as expected, but rather a compound which was shown

(13) A. H. Gowenlock, G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 517 (1948).

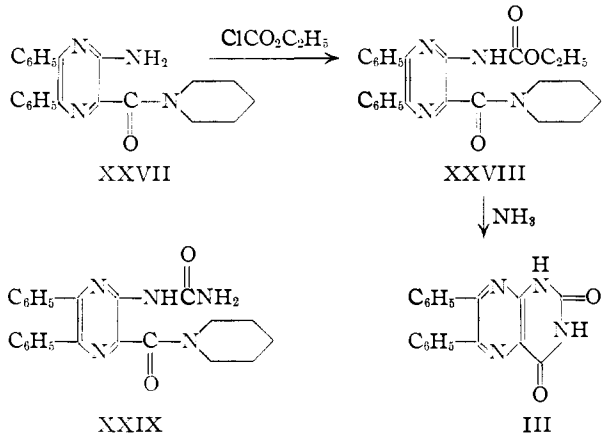


by analysis to be either XXIIIa or XXIIIb. Alcoholic sodium hydroxide converted this compound to 3-(*n*-butyl)-6,7-diphenyl-2(1H)-keto-4-(3H)-pteridinethione (XXIV).

A few preliminary experiments were carried out on the use of these pteridinethiones as intermediates in the synthesis of aminopteridines. 6,7-Diphenyl-4(3H)-pteridinethione (XVI) gave 4-benzylamino-6,7-diphenylpteridine (XII) and 4-(*n*-butylamino)-6,7-diphenylpteridine (XIII) when heated with benzylamine and *n*-butylamine, respectively. When XVI and alcoholic ammonia were heated together in a sealed tube, 4-amino-6,7-diphenylpteridine (XIV) was formed; however, when XVI was heated under reflux with alcoholic ammonia and mercuric oxide only the mercuric salt (XXV) of XVI was formed. In a similar manner, alcoholic ammonia and 3-(*n*-butyl)-6,7-diphenyl-4(3H)-pteridinethione (XXI) gave 3-(*n*-butyl)-6,7-diphenyl-4(3H)-iminopteridine (XXVI). The utilization of such replacement reactions for the introduction of amino and substituted amino groups into the pteridine ring system has been reported previously.[14,15]

A number of cyclization experiments similar to those described above were attempted unsuccessfully. 3-Amino-N-benzyl-5,6-diphenylpyrazinamide (IV) failed to react with urea, either in the absence of a solvent or in molten phenol. It has been reported that 3-aminopyrazinamide[12] and 3-aminoquinoxaline-2-carboxamide[13] also fail to react with urea. IV failed to react with potassium isocyanate under a wide variety of conditions. No reaction took place when IV was treated with carbon disulfide in pyridine[16], the expected product, 3-benzyl-6,7-diphenyl-4(3H)-keto-2(1H)-pteridinethione, was not formed and only unchanged IV was recovered.

In an attempt to prepare 3-ureido-5,6-diphenylpyrazinoic acid piperidide (XXIX) during a separate investigation, 3-amino-5,6-diphenylpyrazinoic acid piperidide (XXVII), prepared by cleavage of 6,7-diphenyllumazine (III) with piperidine,[10] was treated with ethyl chlorocarbonate to give 3-carbethoxyamino-5,6-diphenylpyrazinoic acid piperidide (XXVIII). Subsequent heating with alcoholic ammonia resulted in ring closure with loss of piperidine and alcohol to give III rather than XXIX.



Since the 3-amino-N-substituted pyrazinamides requisite for these cyclizations are readily available by the aminolysis of lumazines, the approach to pteridine synthesis represented by steps (a), (b) and (c) outlined earlier constitutes a versatile synthetic method which, in many instances, leads to products unobtainable by any other known synthetic route. Further applications of this method are being investigated.

Experimental[17]

3-Amino-N-benzyl-5,6-diphenylpyrazinamide (IV).—The preparation of this compound has been described previously.[10]

(14) E. C. Taylor, Jr., and C. K. Cain, THIS JOURNAL, **73**, 4384 (1951); **74**, 1644 (1952).

(15) E. C. Taylor, Jr., *ibid.*, **74**, 1648 (1952).

(16) A. H. Cook and E. Smith, *J. Chem. Soc.*, 2329 (1949).

(17) Microanalyses by Miss Emily Davis, Mrs. Katherine Pih, Mr. Joseph Nemeth and Mrs. Esther Fett. All melting points are corrected.

3-Amino-N-(*n*-butyl)-5,6-diphenylpyrazinamide (V).—A mixture of 100 ml. of dry, freshly-distilled *n*-butylamine and 15 g. of 6,7-diphenyl-2,4(1H,3H)-pteridinedione (6,7-diphenyllumazine) (III) was sealed in a glass bomb tube and heated for 12 hours at 180°. After cooling, the clear light brown reaction solution was treated with Norit and subjected to vacuum distillation to remove excess *n*-butylamine. Addition of 50 ml. of hot ethanol to the residue followed by sufficient hot water to incipient precipitation caused the separation of yellow crystals. Recrystallization from chloroform–aqueous ethanol gave bright yellow prisms melting at 146–147°; yield 8.8 g. (53.3%).

Anal. Calcd. for $C_{21}H_{22}N_4O$: C, 72.8; H, 6.4; N, 16.2. Found: C, 73.0; H, 6.3; N, 16.2.

3-Benzyl-6,7-diphenyl-4(3H)-pteridinone (VI).—A solution of 0.520 g. of 3-amino-N-benzyl-5,6-diphenylpyrazinamide (IV) in 20 ml. of ethyl orthoformate and 20 ml. of acetic anhydride was heated under reflux for five hours, and then evaporated to dryness under reduced pressure. The residue of yellow crystals was recrystallized from chloroform–petroleum ether to give 0.386 g. (72.3%) of white platelets, m.p. 248°. A mixed melting point with an authentic sample of 3-benzyl-6,7-diphenyl-4(3H)-pteridinone (VI)[10] showed no depression.

3-(*n*-Butyl)-6,7-diphenyl-4(3H)-pteridinone (VII). (a).—A suspension of 1.0 g. of 3-amino-N-(*n*-butyl)-5,6-diphenylpyrazinamide (V) in a mixture of 20 ml. of formic acid (98–100%) and 20 ml. of acetic anhydride was heated under reflux for five hours to give a clear light yellow solution. This was evaporated repeatedly to dryness under reduced pressure with 50-ml. portions of ethanol, and the residue was recrystallized from chloroform–aqueous ethanol to give 0.337 g. (32.8%) of white platelets, m.p. 194–195°.

Anal. Calcd. for $C_{22}H_{20}N_4O$: C, 74.1; H, 5.7; N, 15.7. Found: C, 74.3; H, 5.7; N, 15.7.

(b).—A mixture of 0.50 g. of 3-amino-N-(*n*-butyl)-5,6-diphenylpyrazinamide (V), 20 ml. of ethyl orthoformate and 20 ml. of acetic anhydride was heated under reflux for five hours and then worked up as usual. The yield of white platelets was 0.396 g. (77%), m.p. 194–195°. A mixed melting point with the product obtained from method (a) showed no depression.

N-Benzyl-3-carbethoxyamino-5,6-diphenylpyrazinamide (VIII).—A mixture of 1.0 g. of 3-amino-N-benzyl-5,6-diphenylpyrazinamide (IV) and 25 ml. of ethyl chloroformate was heated under reflux for 20 hours. The resulting clear yellow solution was evaporated to dryness and the residue evaporated repeatedly to dryness with 50-ml. portions of ethanol. Recrystallization of the residue from chloroform–petroleum ether gave 0.996 g. (83.7%) of colorless prisms, m.p. 129–130°.

Anal. Calcd. for $C_{27}H_{24}N_4O_3$: C, 71.7; H, 5.3; N, 12.4. Found: C, 72.2; H, 5.3; N, 12.4.

3-Benzyl-6,7-diphenyl-2,4(1H,3H)-pteridinedione (X).—A mixture of 0.574 g. of N-benzyl-3-carbethoxyamino-5,6-diphenylpyrazinamide (VIII) and ethanolic sodium ethoxide (prepared by dissolving 0.5 g. of sodium in 70 ml. of absolute ethanol) was heated under reflux for 10 hours. The resulting cloudy, light yellow solution was evaporated to dryness under reduced pressure and the yellow residue (sodium salt of X) dissolved in hot aqueous ethanol and the solution acidified with glacial acetic acid. Long colorless needles (0.211 g., 40.9%) separated upon cooling which were recrystallized from chloroform–petroleum ether; m.p. 194–195°.

Anal. Calcd. for $C_{25}H_{18}N_4O_2$: C, 73.9; H, 4.5; N, 13.8. Found: C, 74.1; H, 4.5; N, 13.7.

N-(*n*-Butyl)-3-carbethoxyamino-5,6-diphenylpyrazinamide (IX).—A mixture of 2.0 g. of 3-amino-N-(*n*-butyl)-5,6-diphenylpyrazinamide (V) and 40 ml. of ethyl chloroformate was heated under reflux for 20 hours, the clear yellow solution evaporated to dryness under reduced pressure, and the residue then evaporated repeatedly to dryness with 50-ml. portions of ethanol. Recrystallization of the residue from chloroform–petroleum ether gave 1.539 g. (63.7%) of colorless prisms, m.p. 110–111°.

Anal. Calcd. for $C_{24}H_{26}N_4O_3$: C, 68.9; H, 6.3; N, 13.4. Found: C, 68.6; H, 6.2; N, 13.2.

3-(*n*-Butyl)-6,7-diphenyl-2,4(1H,3H)-pteridinedione (XI).—A solution of 1 g. of N-(*n*-butyl)-3-carbethoxyamino-5,6-diphenylpyrazinamide (IX) in sodium ethoxide solution (prepared from 70 ml. of absolute ethanol and 1 g. of sodium) was heated under reflux for 10 hours, evaporated to dryness under reduced pressure and the bright yellow residue dissolved in aqueous ethanol. Upon acidification with glacial acetic acid, 0.80 g. (88.8%) of long white needles separated which were recrystallized from chloroform–petroleum ether; m.p. 246–247°.

Anal. Calcd. for $C_{22}H_{20}N_4O_2$: C, 70.9; H, 5.4; N, 15.0. Found: C, 70.9; H, 5.5; N, 14.8.

Reaction of 3-Amino-N-benzyl-5,6-diphenylpyrazinamide (IV) with Formamide.—A mixture of 0.597 g. of 3-amino-N-benzyl-5,6-diphenylpyrazinamide (IV) and 25 ml. of stock formamide was heated at 190° for three hours to give a deep red solution. The reaction mixture was cooled and diluted with water, and the precipitated solid was separated by filtration and recrystallized from aqueous dimethylformamide; yield 0.304 g. (64%), m.p. 280–285°. Two further recrystallizations raised the melting point to 297–298°. The product was identical with an authentic sample of 6,7-diphenyl-4(3H)-pteridinone (XV).[18]

The same product was obtained when IV was heated under reflux with pure formamide containing 2 ml. of dilute formic acid. Only starting material was obtained when pure formamide alone was employed.

Reaction of 3-Amino-N-(*n*-butyl)-5,6-diphenylpyrazinamide (V) with Formamide.—Under the same conditions as employed above, 3-amino-N-(*n*-butyl)-5,6-diphenylpyrazinamide (V) and stock formamide gave 6,7-diphenyl-4(3H)-pteridinone (XV) in 52% yield.

3-Amino-5,6-diphenylpyrazinamide (XVIII).—A mixture of 0.856 g. of methyl 3-amino-5,6-diphenylpyrazinoate (XVII)[10] in 75 ml. of methanol saturated with anhydrous ammonia at 0° was sealed in a glass bomb tube and heated for one hour at 120°. Upon cooling, the reaction mixture, containing a quantity of fine, yellow needles, was evaporated to dryness and the yellow crystalline residue recrystallized from aqueous ethanol; yield 0.700 g. (86%), m.p. 204–205°. A mixed melting point with an authentic sample of XVIII[10] showed no depression.

3-Amino-5,6-diphenylthiopyrazinamide (XIX).—A mixture of 0.529 g. of 3-amino-5,6-diphenylpyrazinamide (XVIII), 1.0 g. of phosphorus pentasulfide and 15 ml. of anhydrous pyridine was heated under reflux for one hour. The deep red reaction solution was cooled and then poured into 200 ml. of water. The resulting orange colloidal suspension was dissolved by addition of a small quantity of 10% sodium hydroxide, the solution treated with charcoal, and the filtrate acidified with glacial acetic acid. The product separated as orange needles which were recrystallized from aqueous ethanol; yield 0.304 g. (54.6%), m.p. 158–160°.

6,7-Diphenyl-4(3H)-pteridinethione (XVI). (a).—A solution of 0.286 g. of 3-amino-5,6-diphenylthiopyrazinamide (XIX) in 10 ml. of ethyl orthoformate and 10 ml. of acetic anhydride was heated under reflux for five hours. The deep red reaction solution was then evaporated to dryness under reduced pressure and the residue recrystallized from aqueous dimethylformamide to give 0.164 g. (55.4%) of bright red, shiny platelets; m.p. (dec.) 270–280°.

Anal. Calcd. for $C_{18}H_{12}N_4S$: C, 68.3; H, 3.8; N, 17.7. Found: C, 68.3; H, 3.8; N, 17.4.

(b).—A mixture of 2.975 g. of 6,7-diphenyl-4(3H)-pteridinone (XV), 4 g. of phosphorus pentasulfide and 50 ml. of anhydrous pyridine was heated under reflux for two hours, the clear deep red solution poured into 300 ml. of cold water, and sufficient 10% sodium hydroxide added to dissolve the precipitate. Treatment of the red solution with charcoal and acidification of the filtrate with glacial acetic acid caused the separation of an orange crystalline mass which was recrystallized from aqueous dimethylformamide to give the desired product (2.34 g., 75%) in the form of bright red platelets, m.p. (dec.) 270–280°.

4-Benzylamino-6,7-diphenylpteridine (XII).—A mixture of 0.50 g. of 6,7-diphenyl-4(3H)-pteridinethione (XVI), 1 ml. of benzylamine, 1 g. of mercuric oxide and 30 ml. of ethanol was heated under reflux for five hours. The reaction mixture was then filtered, the black residue washed with 10 ml. of hot ethanol, and the combined filtrates heated to boiling and diluted with water until crystallization commenced. Cooling gave 0.61 g. (99%) of light yellow platelets which were recrystallized from aqueous acetone; m.p. 178–179°

(18) E. C. Taylor, Jr., THIS JOURNAL, **74**, 2380 (1952).

Anal. Calcd. for $C_{25}H_{19}N_5$: C, 77.1; H, 4.9; N, 18.0. Found: C, 77.1; H, 4.7; N, 17.9.

4-(*n*-Butylamino)-6,7-diphenylpteridine (XIII).—A mixture of 0.951 g. of 6,7-diphenyl-4(3H)-pteridinethione (XVI), 1.5 ml. of *n*-butylamine, 1 g. of mercuric oxide and 20 ml. of absolute ethanol was heated under reflux for 2.5 hours. The original deep red color changed gradually during the heating to a light yellow. The reaction mixture was filtered, the filtrate evaporated to a small volume, and a few milliliters of hot water added cautiously. Cooling caused the separation of bright yellow plates which were recrystallized from aqueous ethanol; yield 0.870 g. (74.3%), m.p. 150–151°.

Anal. Calcd. for $C_{22}H_{21}N_5$: C, 74.3; H, 6.0; N, 19.7. Found: C, 74.4; H, 5.9; N, 19.6.

4-Amino-6,7-diphenylpteridine (XIV).—A mixture of 2.0 g. of 6,7-diphenyl-4(3H)-pteridinethione (XVI) and 50 ml. of absolute ethanol saturated with ammonia was sealed in a glass bomb tube and heated at 130° for 10 hours. After cooling, the bomb contents were evaporated to dryness and the residue was recrystallized from aqueous acetone to give 1.59 g. (84%) of light yellow needles, m.p. 175°.

Anal. Calcd. for $C_{18}H_{13}N_5$: C, 72.2; H, 4.4; N, 23.4. Found: C, 72.2; H, 4.4; N, 23.3.

In an attempt to obtain 4-amino-6,7-diphenylpteridine under less strenuous conditions, anhydrous ammonia was passed into a refluxing solution of 0.924 g. of 6,7-diphenyl-4(3H)-pteridinethione in 5 ml. of chloroform and 20 ml. of absolute ethanol containing 0.8 g. of mercuric oxide. After two hours, the reaction mixture was filtered and the filtrate evaporated to a small volume. Cooling gave light yellow crystals which were recrystallized from chloroform–absolute ethanol; yield 0.414 g. (33%), m.p. 268–271°. Analysis showed this compound to be the mercuric salt (XXV) of XVI.

Anal. Calcd. for $C_{36}H_{22}N_8S_2Hg$: C, 52.0; H, 2.7; N, 13.5. Found: C, 51.7; H, 3.0; N, 13.3.

Acid Hydrolysis of 4-Benzylamino-6,7-diphenylpteridine (XII) to 6,7-Diphenyl-4(3H)-pteridinone (XV).—A solution of 0.20 g. of 4-benzylamino-6,7-diphenylpteridine (XII) in 10 ml. of 6 N hydrochloric acid was heated under reflux for one-half hour. Neutralization of the cooled reaction mixture with ammonium hydroxide gave a white solid which was collected and recrystallized from aqueous dimethylformamide; yield 0.14 g. (93%), m.p. 297–298°. A mixed melting point with an authentic sample of 6,7-diphenyl-4-(3H)-pteridinone[18] (XV) showed no depression. Similar results were obtained upon hydrolysis of 4-(*n*-butylamino)-6,7-diphenylpteridine (XIII); XV was formed in 88% yield.

3-Amino-N-(*n*-butyl)-5,6-diphenylthiopyrazinamide (XX).—A mixture of 1.75 g. of 3-amino-N-(*n*-butyl)-5,6-diphenylpyrazinamide (V), 2.0 g. of phosphorus pentasulfide and 25 ml. of anhydrous pyridine was heated under reflux for one hour, cooled, and poured into 150 ml. of water. The orange-yellow solid which separated was collected by filtration, washed generously with water, and recrystallized from absolute ethanol to give 1.54 g. (83.4%) of bright yellow needles, m.p. 168–169°.

Anal. Calcd. for $C_{21}H_{22}N_4S$: C, 69.6; H, 6.1; N, 15.5. Found: C, 69.6; H, 6.0; N, 15.5.

3-(*n*-Butyl)-6,7-diphenyl-4(3H)-pteridinethione (XXI). (a).—A mixture of 0.635 g. of 3-amino-N-(*n*-butyl)-5,6-diphenylthiopyrazinamide (XX), 0.7 g. of freshly fused sodium acetate, 10 ml. of 98–100% formic acid and 10 ml. of acetic anhydride was heated under reflux for five hours. The resulting clear red solution was evaporated to dryness under reduced pressure, the residue taken up in 50 ml. of ethanol and the solution again evaporated to dryness. The resulting orange solid was recrystallized from chloroform–ethanol to give 0.441 g. (67.6%) of orange needles; m.p. 193–195°.

Anal. Calcd. for $C_{22}H_{20}N_4S$: C, 70.9; H, 5.4; N, 15.0. Found: C, 71.0; H, 5.4; N, 15.0.

(b).—A solution of 1.53 g. of 3-amino-N-(*n*-butyl)-5,6-diphenylthiopyrazinamide (XX) in 10 ml. of ethyl orthoformate and 10 ml. of acetic anhydride was heated under reflux for three hours, and then evaporated to dryness under reduced pressure. The orange-red residue was recrystallized from chloroform–ethanol to give 0.962 g. (61.2%). A mixed melting point with the product obtained by method (a) above showed no depression.

3-(*n*-Butyl)-6,7-diphenyl-2(1H)-keto-4(3H)-pteridinethione (XXIV).—A solution of 1.139 g. of 3-amino-N-(*n*-butyl)-5,6-diphenylthiopyrazinamide (XX) in 30 ml. of ethyl chloroformate was heated under reflux for 20 hours, the excess ethyl chloroformate removed by evaporation under reduced pressure and the residue evaporated to dryness three times with 50-ml. portions of absolute ethanol. The residual red solid was recrystallized from chloroform–ethanol to give a microcrystalline orange solid (1.11 g., 77%) melting at 173–174°. Analysis showed this product to be a carbethoxy derivative (XXIIIa or XXIIIb) of XXIV.

Anal. Calcd. for $C_{25}H_{24}N_4O_3S$: C, 65.2; H, 5.2; N, 12.2. Found: C, 65.4; H, 5.1; N, 12.4.

Heating of the above carbethoxy derivative (XXIIIa or XXIIIb) for 15 minutes in a solution of 5 ml. of 10% sodium hydroxide in 20 ml. of ethanol, evaporating to dryness and recrystallizing from aqueous ethanol gave 3-(*n*-butyl)-6,7-diphenyl-2(1H)-keto-4(3H)-pteridinethione (XXIV) as an orange-red solid in 73% yield, m.p. 205–209°.

Anal. Calcd. for $C_{22}H_{20}N_4OS$: C, 68.0; H, 5.2; N, 14.4. Found: C, 68.3; H, 5.2; N, 14.5.

3-(*n*-Butyl)-4(3H)-imino-6,7-diphenylpteridine (XXVI).—A solution of 0.179 g. of 3-(*n*-butyl)-6,7-diphenyl-4(3H)-pteridinethione (XXI) in 1.5 ml. of chloroform and 10 ml. of absolute ethanol containing 0.2 g. of mercuric oxide was heated under reflux for six hours, while a continuous stream of anhydrous ammonia was passed through the solution. Filtration of the hot reaction mixture gave a light yellow filtrate which, upon evaporation to a small volume, deposited yellow platelets; yield 0.119 g. (69.8%), m.p. 149–151°.

Anal. Calcd. for $C_{22}H_{21}N_5$: C, 74.3; H, 6.0; N, 19.7. Found: C, 74.5; H, 6.1; N, 19.9.

3-Carbethoxyamino-5,6-diphenylpyrazinoic Acid Piperidide (XXVIII).—A solution of 1.50 g. of 3-amino-5,6-diphenylpyrazinoic acid piperidide (XXVII)[10] in 50 ml. of ethyl chloroformate was heated under reflux for five hours, then evaporated to dryness under reduced pressure and the residue evaporated twice to dryness with 50-ml. portions of absolute ethanol. Recrystallization of the residue first from aqueous acetone and then from methylene chloride–petroleum ether gave 1.42 g. (79%) of yellow platelets, m.p. 174–175°.

Anal. Calcd. for $C_{25}H_{26}N_4O_3$: C, 69.8; H, 6.1; N, 13.0. Found: C, 69.9; H, 6.2; N, 13.1.

6,7-Diphenyllumazine (III).—A solution of 0.50 g. of 3-carbethoxyamino-5,6-diphenylpyrazinoic acid piperidide (XXVIII) in 40 ml. of ethanol was saturated with anhydrous ammonia and then heated in a sealed glass bomb tube at 155° for six hours. After cooling, the bomb contents were evaporated to dryness, the residue dissolved in dilute ammonium hydroxide and the solution acidified with glacial acetic acid to give 0.330 g. (90%) of a colorless microcrystalline solid, m.p. 320–325°. The product was identical with an authentic sample of 6,7-diphenyllumazine, as shown by melting point and mixed melting point[19] determinations and also by a determination of the ultraviolet absorption spectrum of the product.[20]

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