duced pressure. Sublimation of the residue at 150° (0.05 mm.) yielded 3.2 g. (63%) of white needles, m.p. 163–165°. Recrystallization from water yielded a hydrate which decomposed on heating above 100°.

Anal. Calcd. for $C_8H_{12}N_6$: C, 50.0; H, 6.3; N, 43.5. Found: C, 50.0; H, 6.3; N, 43.5.

PRINCETON, N. J.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, AND THE NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

Pteridines. XVII. Reactions of 2,4,6,7-Tetrachloropteridine. The Synthesis of 5,6,7,8-Tetrahydropteridine[1]

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A procedure suitable for the preparation of large quantities of 2,4,6,7-tetrahydroxypteridine (I) is given. Lithium aluminum hydride reduction of 2,4,6,7-tetrachloropteridine (II), prepared from I by chlorination, yields 2,4-dichloro-5,6,7,8-tetrahydropteridine (III), which upon catalytic reduction gives 5,6,7,8-tetrahydropteridine (XI). The structures of these reduction products are independently established. Reasons for the stability of III and XI, in contrast to the instability of 2,4-dichloropteridine (V) and pteridine (XII), and the failure of attempts to dehydrogenate XI to XII, are discussed. Catalytic reduction of 2,4,6,7-tetrachloropteridine yields a purple solid which is rapidly converted in the presence of air to 2,4-dichloro-6-hydroxy-7,8-dihydropteridine (VIII), whose structure is established by an independent synthesis and by further reduction to 6-hydroxy-7,8-dihydropteridine (X). Amination of III yields 2,4-diamino-5,6,7,8-tetrahydropteridine (XIII), which is readily oxidized through 2,4-diaminodihydropteridine (XIV) to 2,4-diaminopteridine (XV). Sodium borohydride reduction of XV in dimethylformamide solution yields XIV. Amination of II under strenuous conditions yields 2,4,6,7-tetraminopteridine (XVII) hydrochloride, which condenses with alloxan, oxalic acid and formamide to give 2,4-diamino-7,9-dihydroxypteridyl(6,7-g)pteridine (XIX), 2-amino-4,7,8-trihydroxypyrazino(2,3-g)pteridine (XX) and a formyl derivative of 2,4-diaminoimidazo(4,5-g)pteridine (XXI), respectively.

Although 2,4,6,7-tetrachloropteridine (II) has been known since 1941,[4] relatively little has been reported concerning its chemical reactivity or its use in pteridine synthesis. This compound was prepared by Schöpf[4] by the chlorination of 2,4,6,7-tetrahydroxypteridine (I) with a mixture of phosphorus pentachloride and phosphorus oxychloride. It was demonstrated that II could be partially hydrolyzed in wet ether solution or in warm 0.75 *N* sodium hydroxide to a dichlorodihydroxypteridine which was assumed to be 2,4-dichloro-6,7-dihydroxypteridine, and that it could be converted to I by heating at 140° for six and one-half hours in 25% sodium hydroxide. Schöpf further demonstrated in a preliminary experiment that partial amination of II took place under very mild conditions, although the product of the amination was not determined. More recently, Cain and Schenker[5,6] have found that all of the chlorine atoms of II may be replaced by alkylamino groups under sufficiently strenuous conditions, and the order of replacement of the chlorine atoms has been determined. No further reactions of II have been reported.

2,4,6,7-Tetrachloropteridine (II) thus appeared to be an accessible, reactive intermediate amenable to use in further pteridine syntheses, and the present communication presents the results of our further investigations with this compound. However, since relatively large amounts of II were desired, it was found necessary to re-examine the existing methods for the preparation of 2,4,6,7-tetrahydroxypteridine (I), its immediate precursor.

The first preparation of I, which may be regarded as the pteridine analog of uric acid, was reported by Wieland[7] and involved nitrous acid hydrolysis of the 2-amino group of leucopterin (2-amino-4,6,7-trihydroxypteridine). Purrmann[8] later described a direct synthesis of I by the fusion of 2,4-dihydroxy-5,6-diaminopyrimidine with oxalic acid under reduced pressure. Several minor modifications of this condensation have since been reported which utilize the pyrimidine sulfate with[4] and without[9] the addition of sodium acetate. Although these methods give satisfactory yields of I in small-scale preparations, attempts to scale up the reaction to preparative amounts have resulted, in our hands, in drastically lower yields. As a result, we have described in the Experimental section a further modification of this condensation which involves fusion of the hydrochloride salt of 2,4-dihydroxy-5,6-diaminopyrimidine with oxalic acid, and which gives consistently satisfactory yields of I in large-scale runs.

2,4,6,7-Tetrachloropteridine (II) was then prepared from I by previously described procedures,[4] except that the product was best purified by vacuum sublimation rather than by recrystallization. Reduction of II in ether or tetrahydrofuran solution with lithium aluminum hydride yielded a dichlorotetrahydropteridine in almost quantitative yield. This product was assigned the structure 2,4-dichloro-5,6,7,8-tetrahydropteridine (III) on the basis of the following evidence: (1) The ultraviolet absorption spectrum of III is similar to that given by 2,4-dichloro-5,6-diaminopyrimidine, except that the position of maximum absorption is shifted to longer wave lengths by 18 mμ. A bathochromic shift of similar magnitude was observed in com-

(1) For the previous paper in this series, see E. C. Taylor, J. W. Barton and T. S. Osdene, THIS JOURNAL, **80**, 421 (1958).

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(4) C. Schöpf, R. Reichert and K. Riefstahl, *Ann.*, **548**, 82 (1941).

(5) C. K. Cain and C. Schenker, Abstracts of Papers, 117th ACS Meeting, March-April, 1950, p. 41 L.

(6) C. Schenker, Ph.D. Thesis, Cornell University, 1949.

(7) H. Wieland, H. Metzger, C. Schöpf and M. Bülow, *Ann.*, **507**, 226 (1933).

(8) R. Purrmann, *ibid.*, **546**, 98 (1940).

(9) A. Bertho and M. Bentler, *ibid.*, **570**, 127 (1950).

paring the spectra of 1,2,3,4-tetrahydroquinoxaline with *o*-phenylenediamine, of 4,6-dimethyl-5,6,7,8-tetrahydropteridine with 4-methyl-5,6-diaminopyrimidine,[10] and of 2-chloro-4,6-dimethyl-5,6,7,8-tetrahydropteridine with 2-chloro-4-methyl-5,6-diaminopyrimidine[10] (see Table I).

TABLE I

Compound	λ_{max}, mμ	Bathochromic shift, mμ
o-Phenylenediamine	292	
		18
1,2,3,4-Tetrahydroquinoxaline	310	
2,4-Dichloro-5,6-diaminopyrimidine	303	
		15
2,4-Dichloro-5,6,7,8-tetrahydropteridine	318	
4-Methyl-5,6-diaminopyrimidine	288	
		18
4,6-Dimethyl-5,6,7,8-tetrahydropteridine	306	
2-Chloro-4-methyl-5,6-diaminopyrimidine	292	
		18
2-Chloro-4,6-dimethyl-5,6,7,8-tetrahydropteridine	310	

Confirmation of the assignment of reduction to the pyrazine ring was obtained by catalytic reduction of III to 5,6,7,8-tetrahydropteridine (XI) (*vide infra*), identical with an authentic sample of 5,6,7,8-tetrahydropteridine prepared by phosphorus oxychloride cyclization of 5-amino-2-chloro-4-(N-2-hydroxyethylbenzylamino)-pyrimidine to 8-benzyl-2-chloro-5,6,7,8-tetrahydropteridine, followed by reduction with sodium in liquid ammonia.[11] The reduction of 2,4,6,7-tetrachloropteridine (II) to 2,4-dichloro-5,6,7,8-tetrahydropteridine (III) is thus consistent with the considerable evidence which has accumulated to show that a pyrazine ring is readily reduced under conditions which do not effect reduction of a pyrimidine ring.[10,12] (2) The position of the chlorine atoms in III was unequivocally established by an independent synthesis involving the condensation of 2,4-dichloro-5,6-diaminopyrimidine (IV) with glyoxal to 2,4-dichloropteridine (V), followed by lithium aluminum hydride reduction of V to III. The identity of the two products was established beyond question by comparison of ultraviolet and infrared spectra and by a mixture melting point determination.

The condensation of 2,4-dichloro-5,6-diaminopyrimidine (IV) with glyoxal to give 2,4-dichloropteridine mentioned above deserves separate comment. All attempts to carry out the condensation in aqueous or alcoholic solution were unsuccessful. No product was obtained when resinous hydrated polyglyoxal was used, even in non-solvolytic solvents such as acetone in the presence of drying agents. Only starting material was recovered from an attempted condensation with dry polyglyoxal at 140° in the absence of a solvent. When hydrated polyglyoxal resin was added to an anhydrous methanolic solution of IV containing sodium bicarbonate and anhydrous sodium sulfate, a compound was obtained which was probably 2,4-dimethoxypteridine (VI). Its melting point was similar to, and its ultraviolet absorption spectrum identical with, an authentic sample of VI prepared by the reaction of sodium methoxide under vigorous conditions with 2,4-dichloro-5,6,7,8-tetrahydropteridine (III), followed by oxidation of the resulting 2,4-dimethoxy-5,6,7,8-tetrahydropteridine (VII) with manganese dioxide in refluxing benzene. Reduction of VI with lithium aluminum hydride gave VII. The desired 2,4-dichloropteridine (V) was finally prepared in 7.7% yield by passing dry, gaseous monomeric glyoxal into a solution of IV in absolute acetone, evaporating the reaction mixture to dryness after twenty-four hours and purifying the remaining solid by vacuum sublimation. 2,4-Dichloropteridine proved to be extremely unstable in aqueous and alcoholic solutions, and is apparently light sensitive. The ultraviolet absorption spectrum of V in dry cyclohexane measured immediately after solution resembled closely the spectra of 2-chloro- and 4-chloropteridine,[13] but examination of the spectrum after two weeks standing in the same solvent indicated that a profound structural change had taken place, presumably under the influence of light. The nature of the change is not known.

It is significant that the condensation of 2,4-dichloro-5,6-diaminopyrimidine (IV) with biacetyl proceeds without difficulty to yield 2,4-dichloro-6,7-dimethylpteridine.[14] The decreased reactivity of the chlorine substituents in this compound, and its greatly enhanced stability in contrast with the extreme instability of V, must be attributed to the effect of the electron-donating methyl groups in relieving the electron deficiency inherent in V. These observations substantiate the arguments advanced by Albert[12] to account for the instability of pteridine itself and for its stabilization by electron-donating substituents. Further evidence illustrating this principle is presented below in connection with the properties of 5,6,7,8-tetrahydropteridine.

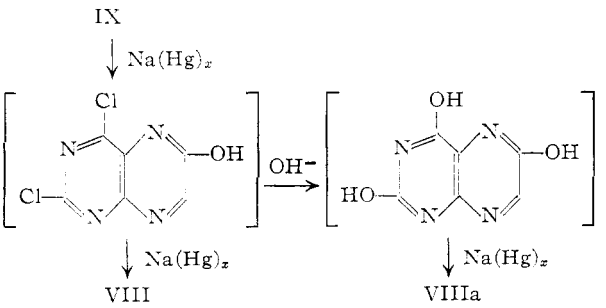
Schöpf, in his original investigation of 2,4,6,7-tetrachloropteridine (II), stated[4] that neither catalytic nor chemical reduction of II yielded crystalline products which could be characterized. We have now found that reduction of II in dry and carefully purified tetrahydrofuran, benzene, or dioxane solution with hydrogen and palladium-on-carbon or platinum catalyst, followed by flushing of the reduction mixture with nitrogen rather than air, yielded a brilliant purple solution from which a purple solid was obtained on evaporation. This purple solid was very soluble in all organic solvents, but when the resulting solutions were allowed to stand in the presence of air, the color gradually faded and a brown crystalline solid slowly separated. Recrystallization of this solid from ethanol with the aid of charcoal yielded colorless needles of 2,4-dichloro-6-hydroxy-7,8-dihydropteridine (VIII). The conversion of the purple solutions to VIII was much more rapid in wet solvents, but apparently did not take place even in wet solvents when air was excluded. When the reduction of II

(10) J. H. Lister and G. R. Ramage, *J. Chem. Soc.*, 2234 (1953).
(11) P. R. Brook and G. R. Ramage, *ibid.*, 1 (1957).
(12) A. Albert, *Quart. Revs.*, **6**, 197 (1952).
(13) S. F. Mason in "Chemistry and Biology of Pteridines," ed. by G. E. W. Wolstenholme and M. P. Cameron, J. and A. Churchill, Ltd., London, 1954, p. 74.
(14) J. W. Daly and B. E. Christensen, THIS JOURNAL, **78**, 225 (1956).

was carried out in benzene with palladium chloride-on-carbon catalyst under the usual conditions (flushing with air), a colorless solution was obtained directly from which pure VIII separated in 82% yield. The nature of this intriguing purple intermediate is under investigation.

Compound VIII was shown to be 2,4-dichloro-6-hydroxy-7,8-dihydropteridine on the basis of the following evidence: (1) The infrared spectrum of VIII is strikingly similar to that given by 2,4-dichloro-5,6,7,8-tetrahydropteridine, with the exception of a strong amide carbonyl band at 1700 cm.$^{-1}$. (2) The ultraviolet spectrum of VIII in both acidic and basic solution corresponds to the spectra of a number of known 6-hydroxy-7,8-dihydropteridines[15] (see Table II). (3) Compound VIII has been synthesized independently by a route well known to yield 6-hydroxy-7,8-dihydropteridines.[16] Thus, 2,4,6,7-tetrachloropteridine (II) was hydrolyzed with 1 *N* sodium hydroxide to 2,4-dichloro-6,7-dihydroxypteridine (IX), which was reduced with sodium amalgam to give a mixture of 2,4,6-trihydroxy-7,8-dihydropteridine (VIIIa) and 2,4-dichloro-6-hydroxy-7,8-dihydropteridine (VIII). The latter compound was identical in all respects with the catalytic reduction product of II. (4) Finally, conclusive proof of the constitution of VIII was obtained by further catalytic reduction in methanol solution with hydrogen in the presence of palladium chloride-on-carbon catalyst to give 6-hydroxy-7,8-dihydropteridine[15] (X).

All attempts to convert VIII to VIIIa under the conditions of the reduction, either with alkali or with sodium amalgam, were unsuccessful, and more vigorous conditions led only to gross degradation of the pteridine ring. Since it has been shown that extreme conditions are necessary for the hydrolysis of IX to 2,4,6,7-tetrahydroxypteridine[4] and it appears[12] that amalgam reductions of 6,7-dihydroxypteridines result first in the removal of the 7-hydroxyl group, we postulate the course of the above reduction of IX to give VIII and VIIIa as



Reduction of 2,4-dichloro-5,6,7,8-tetrahydropteridine (III) with hydrogen in the presence of a palladium chloride-on-carbon catalyst yielded 5,6,7,8-tetrahydropteridine (XI) hydrochloride, from which the free base was obtained upon treatment with silver oxide or sodium hydroxide. Compound XI could be alternatively prepared by lithium aluminum hydride reduction of pteridine (XII) itself. Both samples of 5,6,7,8-tetrahydropteridine as prepared above proved to have physical properties identical with those of an authentic sample of XI kindly supplied by Dr. G. R. Ramage.[11] Compound XI readily reformed its crystalline, deliquescent monohydrochloride upon treatment with hydrogen chloride, and it could be converted to picrate and monoacetate derivatives. Brook and Ramage have also reported picrate, monoformyl, diacetate and methiodide derivatives of XI.[11]

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF 6-HYDROXY-7,8-DIHYDROPTERIDINES

7,8-Dihydropteridine	0.1 *N* NaOH λ_{max}, mμ	0.1 *N* NaOH log ε	0.1 *N* HCl λ_{max}, mμ	0.1 *N* HCl log ε
6-Hydroxy-	307	4.05	293	4.02[15]
2-Chloro-6-hydroxy-	310	4.08	295	4.03[15]
4-Chloro-6-hydroxy-	312	4.32	300	4.04[15]
2,4-Dichloro-6-hydroxy-	308	4.00	300	3.96

In contrast to pteridine, which is rapidly destroyed by acid, base and light,[12] 5,6,7,8-tetrahydropteridine (XI) is stable to boiling *N* hydrochloric acid and boiling *N* sodium hydroxide for one hour, and appears to be completely stable to light. Moreover, all attempts to oxidize XI to pteridine have been unsuccessful. A variety of different experimental conditions, reagents and techniques were employed in this attempted oxidation (see Experimental), but in no case could pteridine be detected in the reaction mixture, as judged both by ultraviolet spectroscopy and by paper chromatography. It thus appears that reduction of the pyrazine ring redresses the electron deficiency apparently responsible for the extreme instability of pteridine and thus stabilizes the tetrahydro form to such an extent that reconversion to the "aromatic" form is impossible under conditions which do not cause simultaneous destruction of the product. The same striking difference in stability was observed with 2,4-dichloropteridine and 2,4-dichloro-5,6,7,8-tetrahydropteridine.

In contrast to the extreme stability of 2,4-dichloro-5,6,7,8-tetrahydropteridine (III) and 5,6,7,8-tetrahydropteridine (XI), dihydro- and tetrahydropteridines containing electron-releasing substituents in the pyrimidine ring are readily reoxidized to pteridines.[12,17-19] It has already been pointed out that manganese dioxide oxidation of 2,4-dimethoxy-5,6,7,8-tetrahydropteridine (VII) yields 2,4-dimethoxypteridine (VI) in high yield. In a similar fashion, 2,4-diamino-5,6,7,8-tetrahydropteridine (XIII) is oxidized by manganese dioxide to 2,4-diaminopteridine (XV). Compound XIII, which was prepared by high pressure amination of 2,4-dichloro-5,6,7,8-tetrahydropteridine (III),

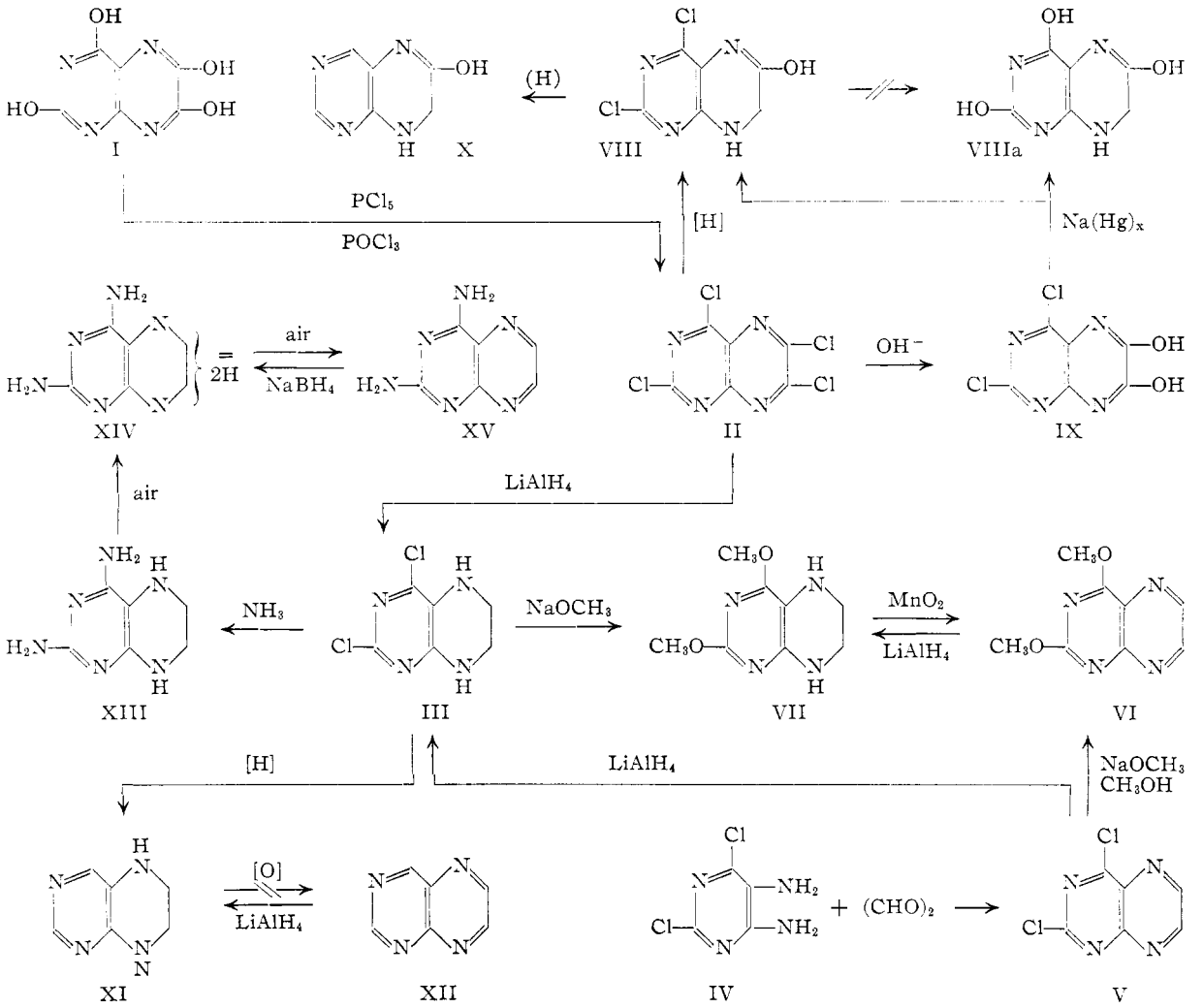
(15) W. R. Boon, W. G. M. Jones and G. R. Ramage, *J. Chem. Soc.*, 96 (1951).

(16) The use of sodium amalgam to prepare 7,8-dihydropteridines is well substantiated. For example, reduction of leucopterin (2-amino-4,6,7-trihydroxypteridine) with sodium amalgam yields 7,8-dihydroxanthopterin (2-amino-4,6-dihydroxy-7,8-dihydropteridine) from which xanthopterin is readily prepared by oxidation (J. R. Totter, *J. Biol. Chem.*, **154**, 105 (1944) and ref. 18). Sodium amalgam also forms 7,8-dihydropteridines from 6,7-dihydroxy- (ref. 19) and 4,6,7-trihydroxypteridine (A. Albert and D. J. Brown, *J. Chem. Soc.* 74 (1953)). 6-Hydroxypteridine is converted readily to 6-hydroxy-7,8-dihydropteridine, indicating that the presence of a 7-hydroxy group is not necessary for the reduction (ref. 19).

(17) M. Gates, *Chem. Revs.*, **41**, 63 (1947).

(18) G. B. Elion, A. E. Light and G. H. Hitchings, THIS JOURNAL, **71**, 741 (1949).

(19) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 1620 (1952).



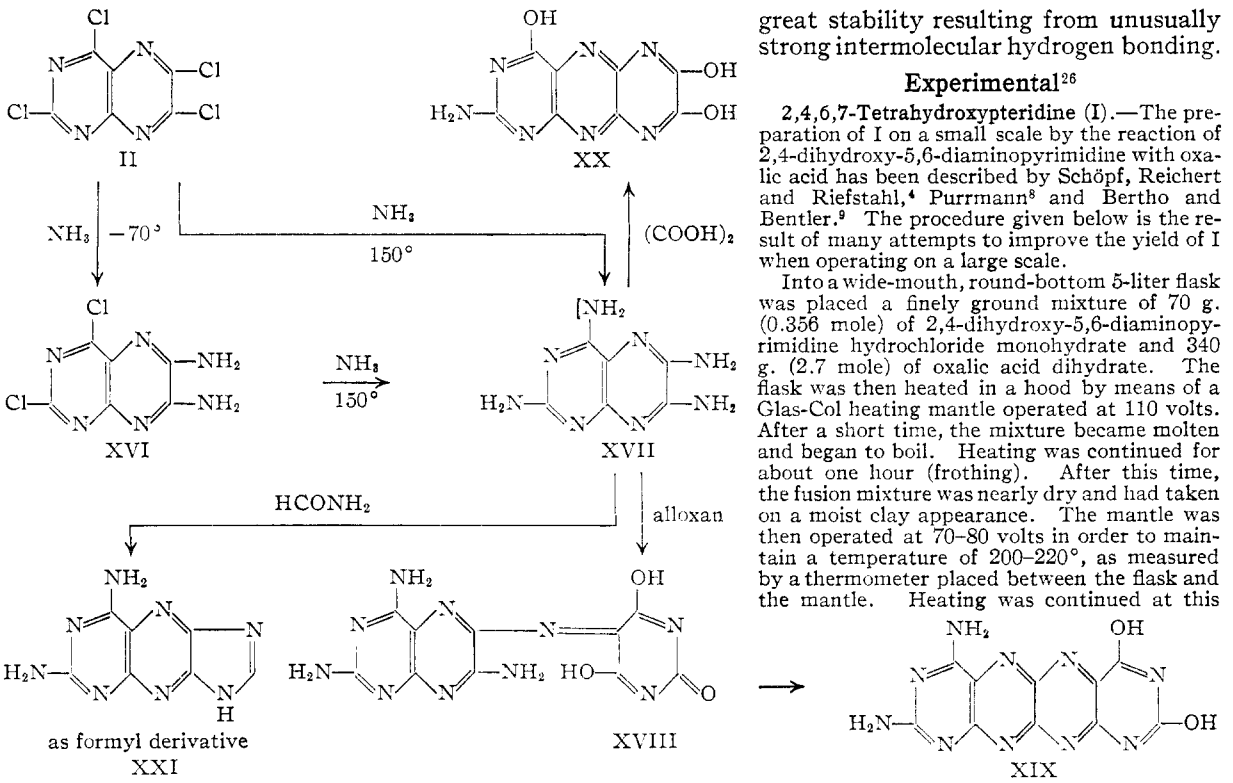
could not be isolated in a pure state due to its ready oxidation in air to a mixture of compounds. Examination of the ultraviolet absorption spectrum of this mixture showed that it contained 2,4-diaminopteridine (XV), 2,4-diaminodihydropteridine (XIV) and a third component, probably 2,4-diamino-5,6,7,8-tetrahydropteridine (XIII). Sodium borohydride reduction of XV provided XIV in a pure state. It is interesting that XIV appears to be more stable than XIII since it withstands repeated recrystallization from boiling isopropyl alcohol in the presence of air. These observations are consistent with the report that 4-hydroxy-2,6,7-trimethyl-5,6,7,8-tetrahydropteridine is readily oxidized by exposure to air to a dihydro derivative, which resists further air oxidation.[20] However, a number of 7,8-dihydro-4,6-dimethylpteridines are reported to be more readily oxidized to pteridines than the corresponding 5,6,7,8-tetrahydro derivatives.[10]

Treatment of 2,4,6,7-tetrachloropteridine (II) with liquid ammonia at −70°, or with gaseous ammonia in acetone solution, gave 2,4-dichloro-6,7-diaminopteridine (XVI)[6] in high yield. Heating either II or XVI in liquid ammonia at 150° for eight hours led to the formation of 2,4,6,7-tetraminopteridine (XVII) monochloride. This compound was not characterized as its free base, since all attempts to recrystallize it produced gels. In spite of possessing four amino groups, it is a weak base; its most basic pK_a is 6.86 ± 0.03.[21] Alkaline hydrolysis of XVII yielded a triaminohydroxypteridine of undetermined structure; XVII condensed only sluggishly with α,β-dicarbonyl reagents. Thus, all attempts to carry out a condensation of XVII with biacetyl or benzil resulted only in recovery of starting material. A condensation was readily effected with glyoxal, but the resulting product was a deep green-colored substance which probably possessed an anil structure. However, a satisfactory condensation was carried out with alloxan. The initial reaction product appears to be the anil XVIII, which is cyclized irreversibly to XIX on treatment with boiling dilute alkali. The initial formation of a highly colored anil in the reaction of alloxan with 4,5-diaminopyrimidines is well known.[22] The orientation assigned the product XIX is based upon

(20) M. Polonovski and M. Pesson, "First Intern. Congr. Biochem.," Cambridge University Press, 1949, p. 231.

(21) We are indebted to Professor Adrien Albert, the Australian National University, Canberra, Australia, for carrying out this determination.

(22) E. C. Taylor, C. K. Cain and H. M. Loux, THIS JOURNAL, **76**, 1874 (1954).



the assumption that the 6-amino group is the most basic of the four amino groups in XVII. Although this assumption has no direct experimental verification, it is consistent with qualitative theoretical arguments and with the finding of Albert[19,23] that 6-aminopteridine is a much stronger base than 7-aminopteridine. Fusion of XVII with oxalic acid yielded a trihydroxyaminopyrazinopteridine (as the monohydrate), which is assigned structure XX on the assumption that the more readily hydrolyzed amino group of the initially-formed 2,4-diamino derivative would be the 4-amino group.[24] This compound can be regarded as an analog of leucopterin in which an additional pyrazine ring has been introduced into the system. Finally, cyclization of XVII with formamide yielded the formyl derivative of 2,4-diaminoimidazo(4,5-g)pteridine (XXI), which may be regarded as an analog of 2,6-diaminopurine in which a pyrazine ring has been inserted between the pyrimidine and imidazole rings of the purine system.

All these condensation products (XIX, XX and XXI) are high melting, refractory solids, insoluble in water and in most organic solvents. They all form extremely stable hydrates. These observations provide still further support for the generalization[25] that addition of amino or hydroxyl groups to nitrogen heterocyclic compounds, such as the purines and pteridines, results in a progressive decrease in solubility in water and non-polar solvents, and a marked increase in melting point. These effects seem to be due to crystal lattice bonds of great stability resulting from unusually strong intermolecular hydrogen bonding.

(23) A. Albert, D. J. Brown and H. C. S. Wood, *J. Chem. Soc.*, 3832 (1954).

(24) E. C. Taylor and C. K. Cain, THIS JOURNAL, **71**, 2538 (1949).

(25) A. Albert in "Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," The Chemical Society, London, Special Publication No. 3, 1955, p. 124.

Experimental[26]

2,4,6,7-Tetrahydroxypteridine (I).—The preparation of I on a small scale by the reaction of 2,4-dihydroxy-5,6-diaminopyrimidine with oxalic acid has been described by Schöpf, Reichert and Riefstahl,[4] Purrmann[8] and Bertho and Bentler.[9] The procedure given below is the result of many attempts to improve the yield of I when operating on a large scale.

Into a wide-mouth, round-bottom 5-liter flask was placed a finely ground mixture of 70 g. (0.356 mole) of 2,4-dihydroxy-5,6-diaminopyrimidine hydrochloride monohydrate and 340 g. (2.7 mole) of oxalic acid dihydrate. The flask was then heated in a hood by means of a Glas-Col heating mantle operated at 110 volts. After a short time, the mixture became molten and began to boil. Heating was continued for about one hour (frothing). After this time, the fusion mixture was nearly dry and had taken on a moist clay appearance. The mantle was then operated at 70–80 volts in order to maintain a temperature of 200–220°, as measured by a thermometer placed between the flask and the mantle. Heating was continued at this temperature until the crude product was completely dry and no longer evolved moisture (15–45 minutes). The flask was then cooled, its contents dissolved in 2 l. of boiling 1 *N* sodium hydroxide, charcoal added and the solution filtered. The yellow filtrate was quickly adjusted to *p*H 3 with concentrated hydrochloric acid, and the tan microcrystalline solid was collected by filtration, washed with water followed by acetone and dried *in vacuo;* yield, 38.3 g. (55%); $\lambda_{max}^{0.1\ N\ NaOH}$ 236, (279, 283, 286; fine structure) 347 mμ; log ε 4.27, 3.90, 3.90, 3.90, 4.03.[27]

2,4,6,7-Tetrachloropteridine (II) was prepared essentially as previously described.[4] It should be pointed out, however, that 2,4,6,7-tetrachloropteridine reacts rapidly with warm water, and considerable care must be taken in destroying excess phosphorus oxychloride and phosphorus pentachloride with ice so that the temperature of the reaction mixture does not rise above 5°. The crude product was dried in a vacuum desiccator over phosphorus pentoxide and purified by sublimation at 140° (0.1 mm.); yield 33% (on a 0.2-mole scale), m.p. 161–162°; $\lambda_{max}^{tetrahydrofuran}$ 236, 327, 338 mμ; log ε 4.21, 4.04, 3.99.

2,4-Dichloropteridine (V).—A solution of 0.30 g. of 2,4-dichloro-5,6-diaminopyrimidine[28] in 25 ml. of dry reagent-grade acetone was prepared in a thoroughly dried 100-ml. three-necked flask. The flask was equipped with a gas-inlet tube reaching below the surface of the solution and with a reflux condenser protected with a drying tube. Glyoxal monomer,[29] prepared from 2 g. of polyglyoxal, was passed into the solution by means of a stream of dry nitrogen. The reaction mixture was allowed to stand in the dark at room temperature for 24 hours, the acetone was then removed under reduced pressure and the resinous residue sublimed at 130° (0.4 mm.) to yield dense yellow crystals of 2,4-dichloropteridine. Yields were variable, but a typical run gave 0.026 g. (7.7%). The melting point of the product was variable and not characteristic, decomposition with

(26) We are indebted for the microanalyses to Mr. Joseph Nemeth, Mrs. Esther Fett and Mrs. Lucy Chang of the University of Illinois, and Dr. Joseph F. Alicino of Metuchen, N. J. All melting points are corrected unless otherwise noted.

(27) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 4219 (1952).

(28) P. Bitterli and H. Erlenmeyer, *Helv. Chim. Acta*, **34**, 835 (1951).

(29) C. Harries and P. Temme, *Ber.*, **40**, 165 (1907).

melting taking place about 150°. The material was purified for analysis by vacuum sublimation. $\lambda_{max}^{cyclohexane}$ 250(s), 258-(s), 269, 289(s), 295(s), 301, 306, 313, 318, 327 mμ; log ε 3.58, 3.45, 3.29, 3.55, 3.65, 3.85, 3.84, 4.03, 3.84, 4.01. After standing for 14 days in cyclohexane solution, λ_{max} 257, 302, 325 (inflect.) mμ; log ε 3.72, 3.85, 3.17.

Anal. Calcd. for $C_8H_2N_4Cl_2$: C, 35.9; H, 1.0; N, 27.9. Found: C, 36.1; H, 1.3; N, 27.5.

2,4-Dichloro-5,6,7,8-tetrahydropteridine (III). Method A.—2,4-Dichloropteridine was prepared as described above, and the crude product was sublimed directly onto the walls of a 100 × 25 mm. Pyrex column fitted at both ends with standard-taper joints. The column was then capped at the bottom with a small flask and fitted with a reflux condenser at the top. The resulting reaction vessel was filled with anhydrous ether to a level which covered the sublimed 2,4-dichloropteridine, 0.100 g. of lithium aluminum hydride added, the condenser fitted with a drying tube, and the mixture heated under reflux for 10 hours. Excess lithium aluminum hydride was then decomposed by the addition of water and the mixture was filtered. The collected salts were extracted with boiling acetone, and the combined ether and acetone filtrates taken to dryness. Sublimation of the residue at 200° (0.4 mm.) yielded a yellow solid which was recrystallized four times from cyclohexane with the use of charcoal to yield 0.0029 g. (11%), of colorless needles, m.p. 210°.

Method B.—A solution of 15.5 g. (0.0575 mole) of 2,4,6,7-tetrachloropteridine (II) in 100 ml. of dry tetrahydrofuran was added slowly to a stirred solution of 8.75 g. (0.231 mole) of lithium aluminum hydride in 150 ml. of dry tetrahydrofuran. A stream of dry nitrogen was passed through the reaction mixture during the addition. After the resulting exothermic reaction had ceased, water was added cautiously and the mixture was centrifuged. The collected salts were extracted with boiling acetone, and the combined tetrahydrofuran and acetone solutions were treated with charcoal, filtered and the filtrate diluted with an equal volume of water. Evaporation of the resulting solution under reduced pressure resulted in the separation of a colorless, microcrystalline solid which was recrystallized from water to yield 11.3 g. (96%) of white needles, m.p. 210°. The product exhibited an R_f value of 0.88 in 1-butanol–5 *N* acetic acid (2:1), and 0.54 in 3% aqueous ammonium chloride; $\lambda_{max}^{95\% EtOH}$ 248, 254, 282, 318 mμ; log ε 3.36, 3.36, 3.81, 3.89. The products obtained by methods A and B were identical, as judged by a mixture melting point determination and by comparison of ultraviolet and infrared absorption spectra and by paper chromatography.

Anal. Calcd. for $C_6H_6N_4Cl_2$: C, 35.1; H, 3.0; N, 27.3. Found: C, 35.4; H, 3.1; N, 27.5.

2,4-Dimethoxypteridine (VI). Method A.—To a solution of 0.20 g. of 2,4-dichloro-5,6-diaminopyrimidine in 8 ml. of anhydrous methanol was added 0.08 g. of hydrated polyglyoxal resin, 5 g. of anhydrous sodium sulfate and 1 g. of sodium bicarbonate. The mixture was heated under reflux for 25 minutes and then filtered, and the collected salts were washed with methanol. The combined methanol filtrates were evaporated to dryness under reduced pressure and the residue sublimed at 150° (0.1 mm.) to give a small amount of a white crystalline solid, m.p. 190–191°. This material was shown to be identical with a sample of 2,4-dimethoxypteridine prepared by method B below by comparison of ultraviolet absorption spectra.

Method B.—To a solution of 0.40 g. of 2,4-dimethoxy-5,6,7,8-tetrahydropteridine in 200 ml. of anhydrous benzene was added 4.0 g. of freshly prepared manganese dioxide and the mixture was heated with stirring on a steam-bath for 11 hours. The suspension was then treated with charcoal and filtered, and the collected solids extracted with 100 ml. of boiling benzene. Evaporation of the combined benzene filtrates to 5 ml., dilution with 200 ml. of petroleum ether and cooling caused the separation of 0.159 g. of white needles, m.p. 195–197°. An additional 0.178 g. was obtained from the mother liquor to give a total yield of 0.337 g. (86%). Sublimation at 145° (0.1 mm.) raised the melting point to 197–198°; $\lambda_{max}^{95\% EtOH}$ 247 (inflect), 324 mμ; log ε 3.64, 3.78.

Anal. Calcd. for $C_8H_8N_4O_2$: C, 50.0; H, 4.2; N, 29.2. Found: C, 50.2; H, 4.4; N, 29.3.

2,4-Dimethoxy-5,6,7,8-tetrahydropteridine (VII). Method A.—A mixture of 0.20 g. of 2,4-dichloro-5,6-diaminopyrimidine, 0.08 g. of hydrated polyglyoxal resin, 5 g. of anhydrous sodium sulfate, 1 g. of sodium bicarbonate and 8 ml. of anhydrous methanol was heated under reflux for 30 minutes. The solvent was then removed by distillation under reduced pressure and the residue extracted several times with anhydrous ether. To the ether extracts was added an excess of lithium aluminum hydride and the resulting mixture was heated under reflux for one hour. Water was then added cautiously, the mixture was filtered and the collected solids extracted with boiling acetone. The combined ether and acetone filtrates were then evaporated to dryness under reduced pressure and the yellow residue sublimed at 110° (0.3 mm.) to give a small amount of colorless crystals, m.p. 142–143° (hot-stage).

Method B.—A solution of 1.00 g. of 2,4-dichloro-5,6,7,8-tetrahydropteridine in 50 ml. of 10% sodium methoxide solution was heated under reflux while a slow stream of dry, oxygen-free nitrogen gas was passed over the surface of the reaction mixture. After 15 hours of refluxing, the amber-colored solution was filtered from the precipitated sodium chloride (0.504 g., 88.5%). The filtrate turned green on cooling; heating changed the color to yellow, and this thermochromic change was reversible. This solution was evaporated to dryness under reduced pressure and the dry green-colored residue extracted with four 120-ml. portions of boiling anhydrous benzene. The colorless benzene extracts were concentrated to 25 ml. under reduced pressure and diluted with 200 ml. of petroleum ether. Cooling caused the separation of 0.48 g. (50%) of white needles, m.p. 142–143° (hot-stage), 146–147.5° (capillary). This material was shown to be identical with the product obtained by method A above by a mixture point determination and by comparison of ultraviolet absorption spectra; $\lambda_{max}^{95\% EtOH}$ 261(s), 292 mμ; log ε 3.65, 3.91.

Anal. Calcd. for $C_8H_{12}N_4O_2$: C, 49.0; H, 6.2; N, 28.6. Found: C, 49.0; H, 6.1; N, 28.7.

2,4-Dichloro-6-hydroxy-7,8-dihydropteridine (VIII). Method A.—A solution of 1.5 g. of 2,4,6,7-tetrachloropteridine, 70 ml. of dry benzene and 1.5 g. of palladium chloride-on-carbon catalyst was shaken under three atmospheres of hydrogen at room temperature for 20 hours. Filtration of the colorless reduction solution yielded a mixture of catalyst and product which was extracted with boiling ethanol. Cooling yielded 1.0 g. (82%) of colorless needles of 2,4-dichloro-6-hydroxy-7,8-dihydropteridine, m.p. 302–303° dec. (to a red liquid); $\lambda_{max}^{0.1 N HCl}$ 300 mμ, log ε 3.96; $\lambda_{max}^{0.1 N NaOH}$ 308 mμ, log ε 3.99. The product was soluble in polar organic solvents and slightly soluble in hot water. It dissolved readily in dilute sodium hydroxide but separated as its sodium salt from stronger alkaline solutions. *Anal.* Calcd. for $C_6H_4N_4Cl_2O$: C, 32.9; H, 1.8; N, 25.6. Found: C, 32.9; N, 2.1; N, 25.6.

Method B.—A solution of 1.0 g. of 2,4,6,7-tetrachloropteridine in 50 ml. of dry benzene containing 0.4 g. of dry, freshly prepared platinum-black catalyst was shaken under three atmospheres of hydrogen at room temperature for 20 hours. The hydrogenation flask was evacuated with an oil-pump prior to flushing with nitrogen, and precautions were taken to keep the reduction mixture under nitrogen as it was filtered from the catalyst. The dark purple filtrate was evaporated under reduced pressure to dryness to yield a crude purple solid. This solid was very soluble in all organic solvents, but when these solutions were allowed to stand in the presence of air, gradual decolorization occurred and VIII was formed. Stirring a solution of this purple solid in 95% ethanol in the presence of air proved to be a rapid and convenient method for carrying out this conversion, and VIII separated as colorless needles, m.p. 302–303° dec., from the bleached ethanol solution in essentially quantitative yield. Extraction of the platinum catalyst and hydrogenation vessel with boiling ethanol followed by cooling of the ethanol extracts yielded a small additional amount of VIII.

Method C.—To a vigorously stirred suspension of 3.09 g. of 2,4-dichloro-6,7-dihydroxypteridine in 30 ml. of water was added in small portions 38 g. of 4% sodium amalgam, which had been ground as finely as possible under toluene. The temperature of the reaction was maintained below 40° by regulating the rate of addition of the amalgam and by use of an ice-bath. At the start of the reduction, complete solution of the reactants was achieved, but after half the amalgam had been added, a tan-colored solid separated from the solution. When all the amalgam had been added and the exothermic reaction had ceased, the suspension of

tan solid was decanted from the mercury and filtered. The collected solid (0.965 g., 28% recovery) was shown to be the sodium salt of unreacted 2,4-dichloro-6,7-dihydroxypteridine by acidification and recrystallization of the resulting free acid from water. The product thus obtained was shown to be identical with the starting material by a mixture melting point determination and by comparison of infrared absorption spectra.

The filtrate above was acidified with concentrated hydrochloric acid to give a tan-colored solid which was collected by filtration, washed well with water and dried; yield 1.159 g. Upon heating this solid at 200° (0.2 mm.), 0.02 g. (0.7%) of colorless sublimate, m.p. 303°, was obtained, which was shown by means of a mixture melting point determination and by comparison of ultraviolet absorption spectra to be identical with the samples of 2,4-dichloro-6-hydroxy-7,8-dihydropteridine prepared above by methods A and B.

2,4,6-Trihydroxy-7,8-dihydropteridine (VIIIa).—The solid above which did not sublime was dissolved in 1 *N* sodium hydroxide and the resulting solution treated with charcoal and filtered. Acidification of the filtrate with hydrochloric acid yielded 1.139 g. (47%) of a light tan-colored microcrystalline solid, m.p. < 360°. The product was soluble in dimethylformamide and in dilute alkali, but was essentially insoluble in water and dilute acid; $\lambda_{max}^{0.1\ N\ HCl}$ 296 mμ, log ε 3.98; $\lambda_{max}^{0.1\ N\ NaOH}$ 309 mμ, log ε 4.05.

Anal. Calcd. for $C_6H_6N_4O_3$: C, 39.5; H, 3.3; N, 30.8. Found: C, 39.3; H, 3.0; N, 30.9.

6-Hydroxy-7,8-dihydropteridine (X).—A mixture of 0.5 g. of 2,4-dichloro-6-hydroxy-7,8-dihydropteridine, 0.5 g. of palladium chloride-on-carbon catalyst and 50 ml. of absolute methanol was shaken under three atmospheres of hydrogen at 40° for 15 hours. The reduction mixture was filtered from the catalyst and the light yellow methanol filtrate concentrated to a small volume and cooled. The precipitated solid (0.25 g.) was dissolved in 35 ml. of water, a small amount of unreacted 2,4-dichloro-6-hydroxy-7,8-dihydropteridine was removed by filtration, and an aqueous solution of sodium acetate added to the filtrate. Standing caused the separation of 0.1 g. of 6-hydroxy-7,8-dihydropteridine, m.p. > 325°. The ultraviolet spectra of this compound in 0.1 *N* hydrochloric acid and 0.1 *N* sodium hydroxide were identical with the reported values.[15]

5,6,7,8-Tetrahydropteridine (XI). Method A.—A solution of 1.00 g. of 2,4-dichloro-5,6,7,8-tetrahydropteridine in 100 ml. of absolute methanol containing 1.0 g. of 5% palladium chloride-on-carbon catalyst was shaken under 3 atmospheres of hydrogen for 15 hours. The catalyst was then removed by filtration and the filtrate was shaken with three 1-g. portions of freshly prepared silver oxide. The resulting solution was treated with charcoal and filtered and the filtrate evaporated to dryness under reduced pressure. Sublimation of the residue at 125° (0.1 mm.) yielded 0.40 g. (60%) of a white, crystalline solid which sintered at 140° and melted at 144–146°. This material showed three blue-fluorescing spots at R_f 0.00, 0.57 and 0.72 on paper chromatography with 3% aqueous ammonium chloride, and was consequently purified by column chromatography.

The crude 5,6,7,8-tetrahydropteridine was placed on a 20 × 100 mm. column of Florisil (Floridin Co., Tallahassee, Fla.) in ethanol-cyclohexane (1:8). Washing the column with this solvent resulted in the elution of a blue-fluorescing band (300 mμ ultraviolet lamp). Evaporation of the eluates yielded a trace amount of solid, which showed an R_f value of 0.00 in 3% aqueous ammonium chloride. Pure 5,6,7,8-tetrahydropteridine was then eluted from the column with ethanol–hexane (3:2), and was purified by sublimation at 115° (0.01 mm.) to give white crystals, m.p. 144–146°. It showed an R_f value of 0.78 in 3% aqueous ammonium chloride; $\lambda_{max}^{pH\ 8.2}$ 206, 268, 304 mμ; log ε 4.04, 3.68, 3.81.

Anal. Calcd. for $C_6H_8N_4$: C, 52.9; H, 5.9; N, 41.1. Found: C, 53.0; H, 5.9; N, 40.8.

The picrate had m.p. 200–201°. *Anal.* Calcd. for $C_6H_8N_4C_8H_3N_3O_7$: C, 39.5; H, 3.0; N, 26.9. Found: C, 39.7; H, 3.0; N, 26.7.

A monoacetate of 5,6,7,8-tetrahydropteridine was prepared by heating under reflux a mixture of 0.30 g. of 5,6,7,8-tetrahydropteridine hydrochloride, 0.3 g. of sodium acetate, 5 ml. of pyridine and 20 ml. of acetic anhydride. The crude product was recrystallized from benzene and then sublimed at 180° (2 mm.) to give colorless crystals, m.p. 184–185° (uncor.).

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.9; H, 5.7; N, 31.4. Found: C, 54.0; H, 5.5; N, 31.7.

A hydrochloride of 5,6,7,8-tetrahydropteridine was readily prepared by passing hydrogen chloride through a methanolic solution of 5,6,7,8-tetrahydropteridine followed by evaporation and chilling. The crude product sublimed incompletely at 200° (0.1 mm.) to give a white solid, m.p. 223–224°. It was extremely hygroscopic and good microanalytical results were not obtained. A picrate prepared from this material, however, was identical with an authentic sample of the picrate of 5,6,7,8-tetrahydropteridine.

Method B.—A solution of 0.10 g. of pteridine[30] in 35 ml. of absolute ether was added in one portion to a stirred suspension of 0.10 g. of lithium aluminum hydride in 25 ml. of absolute ether and the resulting solution was heated under reflux for 16 hours. Water was added to decompose excess lithium aluminum hydride and the mixture was filtered. The residual lithium and aluminum salts were extracted with boiling chloroform, the combined ether filtrate and chloroform extracts treated with charcoal, and the filtrate evaporated to dryness. Sublimation of the resulting residue yielded 0.06 g. (58%) of white crystals, m.p. 146–147.5°. A mixture melting point determination with a sample of 5,6,7,8-tetrahydropteridine obtained by method A above showed the two products to be identical. The ultraviolet absorption spectrum of the product was identical with the spectrum of authentic 5,6,7,8-tetrahydropteridine kindly supplied by Dr. G. R. Ramage.[11]

Attempted Oxidation of 5,6,7,8-Tetrahydropteridine to Pteridine.—Numerous attempts under a variety of oxidation conditions were made to effect this conversion, but they led either to destruction of the molecule or to recovery of unreacted starting material. Among these unsuccessful attempts were: (a) treatment with manganese dioxide in refluxing benzene for 30 hours, (b) treatment with potassium permanganate at *p*H 7, (c) treatment with potassium ferricyanide at *p*H 8.5, (d) sodium dichromate, (e) 10% ferric chloride, (f) methylene blue, (g) sublimation over 5% palladium-on-carbon at 130° (0.2 mm.), (h) fusion with sulfur at 120°, (i) 5% palladium-on-carbon and diethyl maleate in refluxing benzene for 24 hours, (j) 5% palladium-on-carbon and maleic acid in aqueous solution under reflux for 24 hours.[31]

2,4-Diamino-5,6,7,8-tetrahydropteridine (XIII).—A mixture of 80 ml. of liquid ammonia and 3.0 g. of 2,4-dichloro-5,6,7,8-tetrahydropteridine was sealed in a steel hydrogenation bomb and heated at 200° for 10 hours. The bomb was cooled to about 80°, the excess ammonia vented in a hood, and the crude reaction product extracted with two 150-ml. portions of boiling ethanol. The combined hot extracts were treated with charcoal and filtered. The ethanol filtrate exhibited thermochromism similar to that observed with 2,4-dimethoxy-5,6,7,8-tetrahydropteridine, being yellow when hot and green when cold. This solution was concentrated to about 50 ml. under reduced pressure and the precipitated yellow solid collected by filtration; yield 2.07 g. (85%), m.p. 209°. Attempted recrystallization of this material from ethanol resulted in partial air oxidation; it was therefore characterized by deliberate oxidation to 2,4-diaminopteridine (see below). $\lambda_{max}^{0.1\ N\ HCl}$ 240, 282, 324 (inflect), 332, 343 (inflect) mμ; log ε 4.04, 3.73, 3.84, 3.88, 3.79; $\lambda_{max}^{95\%\ EtOH}$ 243, 284(s), 291, 331 mμ; log ε 4.09, 3.82, 3.83, 3.65.

2,4-Diaminopteridine (XV).—A mixture of 0.10 g. of 2,4-diamino-5,6,7,8-tetrahydropteridine, 1.0 g. of freshly prepared manganese dioxide and 50 ml. of dimethylformamide was heated on a steam-bath with stirring for 11 hours. The reaction mixture was then treated with charcoal and filtered through Filter-Cel. Evaporation of the filtrate to 5 ml. followed by the addition of 100 ml. of benzene resulted in the separation of 0.077 g. (79%) of a yellow crystalline solid, m.p. 319–320° (uncor.). A mixed melting point determination with an authentic sample of 2,4-diaminopteridine[32] showed no depression. The ultraviolet absorption spectrum ($\lambda_{max}^{0.1\ N\ HCl}$ 240, 285, 332 mμ; log ε 4.06, 3.68, 3.93; $\lambda_{max}^{H_2O}$ 224, 255, 364 mμ; log ε 4.03, 4.25, 3.80)

(30) We are deeply indebted to Professor Adrien Albert of the Australian National University, Canberra, Australia, for a generous gift of this material.

(31) S. Akabori and K. Saito, *Ber.*, **63**, 2245 (1930).

(32) M. F. Mallette, E. C. Taylor and C. K. Cain, THIS JOURNAL, **69**, 1814 (1947).

agrees with previously published values for 2,4-diaminopteridine.[32]

2,4-Diaminodihydropteridine (XIV).—A partial solution of 7.78 g. of 2,4-diaminopteridine in 1 l. of dimethylformamide at 80° was poured into a solution of 36.3 g. of sodium borohydride in 350 ml. of water. The solution was heated on a steam-bath for 2.5 hours, by which time hydrogen evolution had ceased. The solvents were removed by evaporation under reduced pressure and the residue was extracted with hot isopropyl alcohol. Cooling of the extracts overnight at 0° yielded 7.45 g. (97%) of an orange solid which was recrystallized from isopropyl alcohol. The product was obtained as an orange microcrystalline solid, m.p. 271–275° dec. It showed a blue fluorescing spot with R_f 0.42 when run on a paper chromatogram with 3% aqueous ammonium chloride; $\lambda_{max}^{H_2O}$ 290, 329 mμ; log ε 3.86, 3.64.

Anal. Calcd. for $C_6H_8N_6$: C, 43.9; H, 4.9; N, 51.2. Found: C, 43.8; H, 4.9; N, 51.1.

2,4-Dichloro-6,7-diaminopteridine (XVI) was prepared by a modification of the method previously described by Schenker.[6]

To 80 ml. of liquid ammonia was added slowly and in small portions 1.00 g. of finely-ground 2,4,6,7-tetrachloropteridine. The product began to separate immediately. After the reaction mixture had stood at −70° for 6 hours, the ammonia was evaporated off and the solid residue suspended in water and filtered. The yield of yellow, microcrystalline solid, m.p. >360°, was 0.79 g. (92%); λ_{max}^{DMF} 348 mμ, log ε 4.05.

2,4,6,7-Tetraminopteridine (XVII) Hydrochloride.—To 80 ml. of liquid ammonia contained in a glass liner for a steel high-pressure hydrogenation bomb, was added slowly, with external cooling in an acetone–Dry Ice-bath, 5.0 g. of 2,4,6,7-tetrachloropteridine. The liner was then sealed in the steel bomb and heated with shaking at 150° for 8 hours. The bomb was cooled, the excess ammonia bled off and the bronze-colored residue was dissolved in boiling 0.1 *N* hydrochloric acid. Cooling yielded 4.02 g. (95%) of the light yellow monohydrochloride of 2,4,6,7-tetraminopteridine, m.p. > 360°; $\lambda_{max}^{0.1\,N\ HCl}$ 235, 305, 360 mμ; log ε 3.19, 3.88, 4.05.

Anal. Calcd. for $C_6H_8N_8 \cdot HCl$: C, 31.5; H, 4.0; N, 49.0. Found: C, 31.7; H, 3.9; N, 49.3.

2,4,6,7-Tetraminopteridine hydrochloride is slightly soluble in boiling water, and moderately soluble in liquid ammonia and boiling ethylene glycol. Dilute aqueous solutions exhibit a brilliant blue fluorescence when exposed to ultraviolet light. The material possesses an R_f of 0.30 in butanol–morpholine–water (3:1:3) and an R_f of 0.15 in 3% aqueous ammonium chloride. A product of sufficient purity for subsequent reactions (one spot on paper chromatography) was readily obtained without recourse to recrystallization by suspending the crude, water-washed reaction product in a small amount of boiling dilute hydrochloric acid and cooling.

Triaminohydroxypteridine.—A suspension of 1.0 g. of 2,4,6,7-tetraminopteridine hydrochloride in 50 ml. of 0.3 N sodium hydroxide was heated under reflux overnight. Ammonia was evolved and complete solution was achieved. The light red solution was treated with charcoal and filtered and the light yellow filtrate was adjusted to *p*H 5 with concentrated hydrochloric acid. The resulting yellow gel was digested on a steam-bath for one hour and then filtered to give 0.934 g. (93%) of a light yellow solid. It was further purified by recrystallization from aqueous dimethylformamide. The product does not melt or decompose below 360°. Paper chromatography in butanol–morpholine–water (3:1:3) showed one bright-blue fluorescing spot at R_f 0.36; $\lambda_{max}^{0.1\,N\ HCl}$ 227, 313, 347 mμ; log ε 4.18, 4.07, 4.03; $\lambda_{max}^{0.1\,N\ NaOH}$ 222, 239, 286, 293(s), 349 mμ; log ε 4.24, 4.20, 3.76, 3.74, 4.06.

Anal. Calcd. for $C_6H_7N_7O$: C, 37.3; H, 3.6; N, 50.8. Found: C, 37.5; H, 3.4; N, 50.8.

2,4-Diamino-7,9-dihydroxypteridyl(6,7-g)pteridine (XIX).—A mixture of 2.00 g. (0.00875 mole) of 2,4,6,7-tetraminopteridine hydrochloride, 1.40 g. (0.00875 mole) of alloxan hydrate and 100 ml. of water was heated under reflux for 17 hours. The reaction mixture was then cooled and filtered and the collected olive-green intermediate anil XXII washed with water followed by acetone; yield 2.87 g.

Cyclization was difficult and could not be carried out without some concomitant decomposition. Thus, a suspension of 2.19 g. of the above anil in 400 ml. of cold 1 *N* sodium hydroxide was stirred for a few minutes and then heated rapidly to boiling. Charcoal was added and the solution filtered. The deep red filtrate was adjusted to *p*H 5 with concentrated hydrochloric acid (at *p*H 6–7, the solution fluoresced a brilliant green) and the precipitated solid collected. A solution of this solid in 90% formic acid was heated under reflux for 30 minutes, cooled and the partially cyclized product precipitated by the addition of acetone. Repetition of this procedure finally yielded 0.96 g. (42%) of a yellow microcrystalline solid. This material appeared to be completely cyclized, since it dissolved in dilute alkali to give a light yellow solution and in boiling dilute acid to give a colorless solution. Both these solutions exhibited intense blue fluorescence in ultraviolet light. The material exhibits an R_f of 0.22 in butanol–morpholine–water (3:1:3) and does not melt or decompose below 360°; $\lambda_{max}^{0.1\,N\ HCl}$ 227, 315, 356, 362(s) mμ; log ε 4.33, 4.06, 4.21, 4.21; $\lambda_{max}^{0.1\,N\ NaOH}$ 282, 350, 405, 407(s), 478(s) mμ; log ε 4.11, 4.13, 3.92, 3.91, 2.81.

Anal. Calcd. for $C_{10}H_6N_{10}O_2 \cdot 2.5H_2O$: C, 35.0; H, 3.2; N, 40.8. Found: C, 35.0; H, 3.2; N, 40.8.

2-Amino-4,7,8-trihydroxypyrazino(2,3-g)pteridine (XX).—A finely-ground mixture of 0.645 g. of 2,4,6,7-tetraminopteridine hydrochloride and 3.55 g. of oxalic acid dihydrate was heated for one hour at 150° and then at 200° for an additional hour. The cooled fusion product was ground to a powder and extracted with 100 ml. of hot 0.2 *N* sodium hydroxide, the extract treated with charcoal and filtered. Acidification of the filtrate to *p*H 5 with glacial acetic acid yielded a yellow gel. This gelled mixture was digested for 30 minutes on a steam-bath and then centrifuged. The collected yellow solid was washed with three portions each of water, acetone and ether; yield 0.598 g. (80% based on monohydrate). The material was further purified by dissolution in 90% formic acid followed by addition of ether to complete precipitation. The product did not move on paper chromatograms in 3% aqueous ammonium chloride or butanol–morpholine–water, but even the analytically pure material showed the presence of a very small amount of unchanged starting material, as evidenced by spots at R_f 0.15 and 0.30, respectively. It was soluble in dilute alkali, insoluble in water and dilute acid, and did not melt or decompose below 360°; $\lambda_{max}^{0.1\,N\ HCl}$ 232, 278(s), 365, 373, mμ; log ε 4.26, 3.85, 4.27, 4.27; $\lambda_{max}^{0.1\,N\ NaOH}$ 278, 336(s), 411 mμ; log ε 4.27, 3.35, 4.28.

Anal. Calcd. for $C_8H_5N_7O_3 \cdot H_2O$: C, 36.2; H, 2.7; N, 37.0. Found: C, 36.4; H, 2.7; N, 36.9.

Formyl Derivative of 2,4-Diaminoimidazo(4,5-g)pteridine (XXI).—A suspension of 1.0 g. of 2,4,6,7-tetraminopteridine hydrochloride in 10 ml. of 99% formamide was heated under reflux for 25 minutes. A clear solution was obtained after the first few minutes of refluxing, and the product then started to separate. The reaction mixture was cooled to room temperature, 5 ml. of water was added and the resulting suspension cooled overnight and filtered. This crude product was dissolved in boiling dilute hydrochloric acid, the solution treated with charcoal and the filtrate adjusted to *p*H 8 with concentrated ammonium hydroxide. The resulting yellow gel was centrifuged and the solid washed with water followed by acetone; yield 0.817 g. (79%). An analytical sample was prepared by dissolution in 90% formic acid followed by addition of acetone to complete precipitation. The yellow, microcrystalline product did not melt or decompose below 360°. It was soluble in dilute alkali and dilute acid and exhibited a brilliant blue-green fluorescence in ultraviolet light. It showed an R_f value of 0.24 in butanol–morpholine–water (3:1:3); $\lambda_{max}^{0.1\,N\ HCl}$ 215, 244(s), 292(s), 345 mμ; log ε 4.25, 4.04, 3.46, 4.06; $\lambda_{max}^{0.1\,N\ NaOH}$ 222, 251, 323(s), 374 mμ; log ε 4.25, 4.29, 3.72, 3.98.

Anal. Calcd. for $C_7H_5N_8 \cdot CHO \cdot {}^1/_2H_2O$: C, 40.2; H, 3.0; N, 46.9. Found: C, 40.5; H, 3.1; N, 46.7.

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