denced by mixture melting point and infrared determinations.

The tetrahydroquinoxaline reported in Table I was prepared by this method, m.p. 98.5–100.5°. Its infrared spectrum showed a single band at 3.08 μ.

dl-trans-**2,3-Dimethyl-1,2,3,4-tetrahydroquinoxaline.**—This authentic sample was prepared by the method of Gibson,[7] m.p. 104–105°. A mixture melting point with the lithium aluminum hydride reduction product was 78–85°. The infrared spectra of this authentic *trans* compound showed a single peak in the NH region at 3.02 μ both in potassium bromide pressing and in carbon disulfide solution, while the *cis* product showed a well defined doublet at 2.96 and 3.02 μ in potassium bromide pressing but a singlet at 2.98 μ in carbon disulfide solution.

The authentic *trans* compound was dissolved in ether and treated with lithium aluminum hydride in the same manner as during the reduction of the quinoxaline. The recovered product melted at 104–105°, did not depress the melting point of the starting material, but lowered the melting point of the *cis* compound to 93–98°.

dl-cis-**2,3-Dimethyl-1,2,3,4-tetrahydro-1,4,5-triazanaphthalene.**—By the same lithium aluminum hydride method as used for 2,3-dimethylquinoxaline there was obtained a 70% yield of this tetrahydro derivative from 2,3-dimethyl-1,4,5-triazanaphthalene,[1,14] m.p. 111.5–112.5° (Kofler).

Anal. Calcd. for $C_9H_{13}N_3$: C, 66.22; H, 8.03; N, 25.75. Found: C, 66.35; H, 7.96; N, 25.69.

dl-cis-**2,3-Dimethyl-1,2,3,4-tetrahydro-1,4,6-triazanaphthalene.**—By the same procedure 2,3-dimethyl-1,4,6-triazanaphthalene[1] (3.20 g., 0.02 mole) was reduced to the tetrahydro compound, 1.80 g. (55%), which was purified by crystallization from benzene–petroleum ether and sublimation, m.p. 149–150°.

Anal. Calcd. for $C_9H_{13}N_3$: C, 66.22; H, 8.03; N, 25.75. Found: C, 66.6; H, 7.8; N, 25.6.

Acknowledgment.—We are indebted to the Eastman Kodak Co., Research Laboratories, Rochester, N. Y., for most of the spectral determinations, to Miss Thelma Davis for help with the spectral correlations and to Mr. John Stenberg for the catalytic hydrogenations.

(14) V. Petrow and J. Saper, *J. Chem. Soc.*, 1389 (1948).

STANFORD, CALIF.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Pteridines. XXII. 5,8-Dihydropteridines by Sodium Borohydride Reduction[1,2]

BY WOLFGANG PFLEIDERER AND EDWARD C. TAYLOR

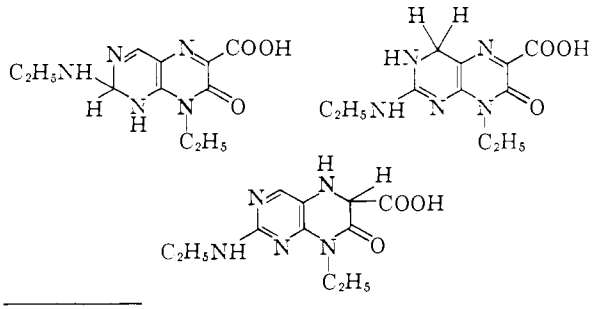
RECEIVED OCTOBER 6, 1959

Sodium borohydride reduction of a number of 8-substituted-7(8*H*)-pteridinone-6-carboxylic acids has been shown to lead to derivatives of 7-hydroxy-5,8-dihydropteridine-6-carboxylic acid. These compounds possess remarkable chemical stability due to intramolecular hydrogen bonding between the 7-hydroxy group and the carbonyl oxygen of the 6-carboxyl group, and their high ultraviolet absorption maxima (405 mμ) are ascribed to the presence in these compounds of a new pteridine chromophoric system. It is suggested that some naturally-occurring reduced pteridines may also be 5,8-dihydro derivatives.

A recent paper from this Laboratory described a new synthetic route to pteridine-6-carboxylic acids which involved the condensation of a 4,5-diaminopyrimidine with alloxan in basic solution, and which proceeded *via* the intermediate formation of a 6-*spiro*pteridine.[3] Certain of the pteridine-6-carboxylic acids prepared during an extension of that study underwent a novel reduction with sodium borohydride, and the present paper describes our investigations on the structure and properties of these dihydropteridines.

The condensation of 2,4-bis-(ethylamino)-5-aminopyrimidine (I) with alloxan in basic solution, or with the disodium salt of mesoxalic acid, proceeded smoothly to give 2-ethylamino-8-ethyl-7-(8*H*)-pteridinone-6-carboxylic acid (II). The structure of II was confirmed by decarboxylation, either by vacuum sublimation or by heating at 200°, to 2-ethylamino-8-ethyl-7(8*H*)-pteridinone (III), which was synthesized independently by condensation of I with ethyl glyoxalate ethyl hemi-acetal. Treatment of II with sodium borohydride in dilute alkaline solution then yielded a dihydro derivative (IV) with rather remarkable physical properties. It exhibited an intense blue fluorescence in solution, possessed a bright yellow color, and comparison of its pK_a with that of the starting material showed that it was 10,000 times a weaker acid. Furthermore, its ultraviolet absorption spectrum exhibited an absorption maximum 48 mμ *higher* than the starting material, and at a wave length (404 mμ) almost unprecedented among simple pteridines.

This latter observation is surprising indeed, for one would intuitively expect disruption of the aromatic system by reduction to result in a hypsochromic shift in the ultraviolet absorption spectrum. Since sodium borohydride does not reduce a carboxyl or amide carbonyl group, there would appear to be only three possible structures for the dihydro acid; namely, the 1,2-, 3,4- or 5,6-dihydro derivatives. Reduction of the 9,10- ring fusion double bond is excluded because of the presence of a second N–H band in the infrared spectrum of the reduced acid. Since it is well known that pyrazine rings are always reduced in preference to pyrimidine rings,[4,5]



(1) For the preceding paper in this series, see E. C. Taylor and C. C. Cheng, *J. Org. Chem.*, **25**, in press (1960).

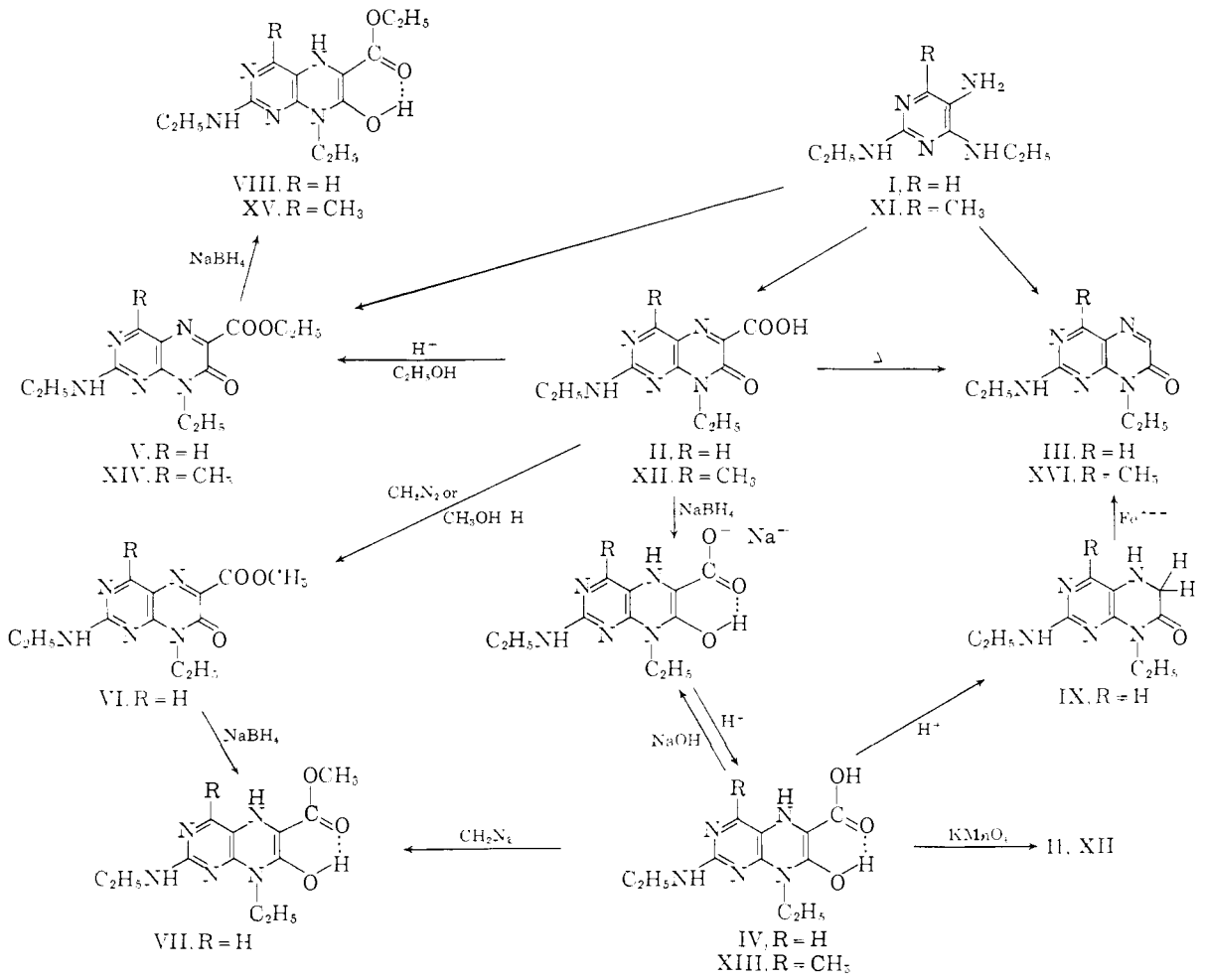
(2) This work was supported in part by a grant to Princeton University from the American Cancer Society.

(3) E. C. Taylor and H. M. Loux, THIS JOURNAL, **81**, 2474 (1959).

(4) E. C. Taylor and W. R. Sherman, *ibid.*, **81**, 2464 (1959).

(5) A. Albert, *Quart. Revs.*, **6**, 197 (1952).

CHART I



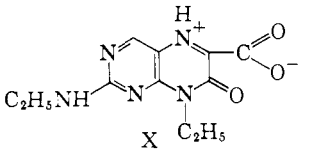
the 5,6-dihydro derivative would appear to be favored, but consideration of such a structure offers no explanation for the unusual physical properties of the compound.

Esterification of II with diazomethane or with methanol and sulfuric acid yielded a methyl ester (VI). When this compound was dissolved in ethanol and sodium borohydride added, reduction took place rapidly, and within one minute a brilliant yellow dihydro ester (VII) separated. The same dihydro ester (VII) could be prepared from the dihydro acid IV by esterification with diazomethane. Reduction of VI to VII was also accompanied by a bathochromic shift in the absorption spectrum; it is significant that the spectra of the dihydro acid IV and the dihydro ester VII are almost identical. The above reactions demonstrate conclusively that the abnormal absorption spectrum of IV cannot be due to a zwitterionic form of the 6-carboxyl group, and that the reduction itself cannot involve the carboxyl group. Furthermore, it was readily shown that no structural alteration of the pteridine ring or its substituents had taken place during the sodium borohydride reduction, since the dihydro acid IV could readily be oxidized back to the parent 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (II) with potassium permanganate.

Esterification of II with ethanol in the presence of sulfuric acid yielded an ethyl ester (V), which was prepared independently from 2,4-bis-(ethylamino)-5-aminopyrimidine (I) and the diethyl ester of mesoxalic acid. Reduction of V with sodium borohydride then yielded a dihydro ethyl ester (VIII) with properties analogous to those previously described for VII.

Attempts to esterify the dihydro acid IV under normal Fischer conditions led only to decomposition, but this difficulty was readily traced to a striking acid lability of IV. Thus, when IV was heated for one minute in 1 *N* hydrochloric acid, smooth decarboxylation took place to yield 2-ethylamino-8-ethyl-5,6-dihydro-7(8*H*)-pteridinone (IX). This dihydro pteridine, however, possessed none of the stability of IV; it underwent rapid oxidation even upon recrystallization from water and was quantitatively converted to 2-ethylamino-8-ethyl-7(8*H*)-pteridinone (III) upon treatment with ferric chloride. Comparison of the ultraviolet absorption spectra of IX and III showed the normal hypsochromic shift in the reduced compound IX, indicating that this dihydro compound must lack the structural feature of the parent dihydro acid responsible for its unusual spectral properties. Both the spectral properties and the stability of IV must, therefore,

be intimately associated with the presence of the 6-carboxyl group. Final evidence for the structure of the dihydro acid IV was deduced as follows: the decarboxylated dihydro pteridine IX possesses in all probability a 5,6-dihydrostructure, since (a) it is readily oxidized to 2-ethylamino-8-ethyl-7(8*H*)-pteridinone (III) and (b) its ultraviolet absorption spectrum is shifted to shorter wave lengths relative to the oxidized pteridine. Therefore, it would appear that IV cannot be a simple 5,6-dihydropteridine, and we propose that the unusual chemical and physical properties of this compound can best be explained by a 5,8-dihydro structure, which presumably arises by an initial reduction of the 5,6-double bond, followed by enolization to the intramolecularly hydrogen bonded 5,8-dihydro structure. The following observations are in agreement with this proposal: (a) all the dihydro acid derivatives (IV, VII and VIII) are capable of internal stabilization *via* intramolecular hydrogen bonding between the 7-hydroxyl group and the carbonyl oxygen of the carboxyl group, and thus possess an unusual degree of stability relative to the decarboxylated dihydro pteridine IX; (b) examination of the ultraviolet absorption data (Table I) reveals that the long wave length absorption maximum of 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (II), either as the acid or as its monoanion, is considerably displaced to shorter wave lengths compared with the maximum of its ethyl or methyl ester (V and VI, respectively). Compound II therefore probably exists as a zwitterion (X). Reduction of II to the dihydro acid IV eliminates the resonance stabilization possessed by the zwitterionic form X, since the carboxyl group is no



X

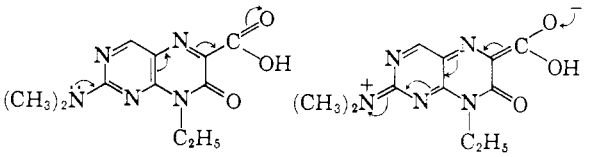
longer conjugated with the pteridine ring, and thus the dihydro acid IV possesses the same long wave length absorption maximum as its anion, or, indeed, as its methyl or ethyl ester. This result as well as the decrease in acid strength of IV as compared with II, is the logical consequence of elimination of resonance-stabilized zwitterionic forms of type X, and again establishes the position of reduction in the pyrazine ring. (c) The remarkable bathochromic shift in the ultraviolet absorption spectrum which accompanies reduction of II to IV certainly cannot be explained on the basis of a 5,6-dihydro structure. The proposed 5,8-dihydro hydrogen-bonded enol structure, which may be considered as a heterocyclic analog of a condensed *p*-benzoquinone system, appears to represent a new type of pteridine chromophore.

The present work thus establishes without question that reduction of the pteridine nucleus can be effected with sodium borohydride, and structural assignments which do not take this possibility into consideration should be reviewed.[6,7]

(6) M. Viscontini, *Helv. Chim. Acta*, **41**, 1299 (1958).
(7) M. Viscontini and E. Möhlmann, *ibid.*, **42**, 836 (1959).

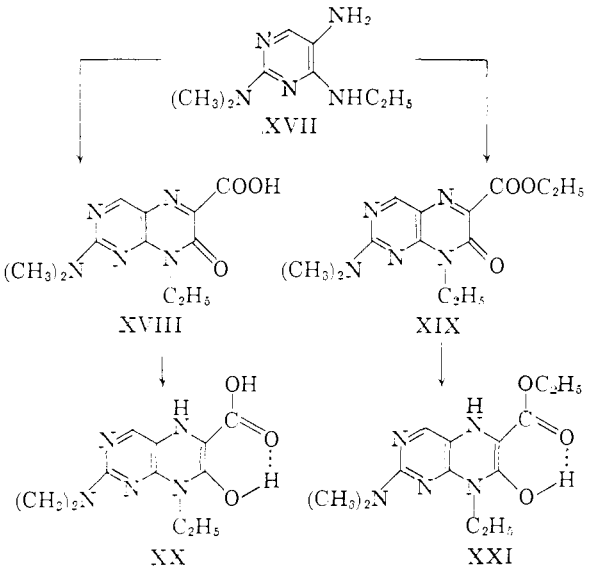
An analogous series of pteridine derivatives was prepared from 2,4-bis-(ethylamino)-5-amino-8-methylpyrimidine (XI), as depicted in the accompanying flow sheet (Chart 1). The properties of these 4-methylpteridines correspond in every way with those of the des-methyl derivatives discussed above.

Early in this investigation, it was thought that the remarkable bathochromic shift in the absorption maximum accompanying reduction of II to IV might in some way be associated with tautomerism involving the 2-ethylamino grouping. In order to examine this possibility, a third series of pteridine derivatives was prepared starting with 2-dimethylamino-4-ethylamino-5-aminopyrimidine (XVII). As outlined in Chart 2, condensation of XVII with the disodium salt of mesoxalic acid yielded 2-dimethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (XVIII), and condensation with the diethyl ester of mesoxalic acid yielded the 6-carbethoxy derivative XIX. Reduction of XVIII and XIX with sodium borohydride then gave the dihydro derivatives XX and XXI, respectively. Comparison of the ultraviolet absorption spectrum of XVIII with its dihydro derivative XX reveals, however, that *no* bathochromic shift has accompanied the reduction. However, since XX has 1/10,000 the acid strength of XVIII, it is obvious that a structural change comparable to that observed in the conversion of II to IV must have taken place. The long wave length absorption maximum of XVIII must therefore be due to resonance interaction between the carboxyl group and the 2-dimethylamino group. This explanation is greatly

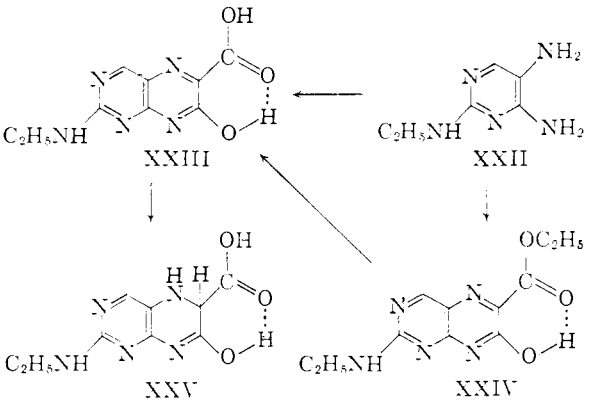


strengthened by the observation that conversion of XVIII to its anion (which cannot participate in such resonance interactions) is accompanied by a marked hypsochromic shift. The fact that the 2-dimethylamino ester XIX absorbs at longer wave lengths than the 2-ethylamino esters V and VI is a further indication of the greater ability of the dimethylamino grouping to participate in resonance interactions of the type pictured above. It is extremely significant, moreover, that *all* the dihydro acid derivatives (IV, VIII, XIII, XV, XX, XXI) have their maximum absorption at approximately the same wave length regardless of the nature of the substituent in the 2-position. This observation is only compatible with a structure for the dihydro derivatives in which conjugation of the carboxyl function with the pyrimidine ring is excluded.

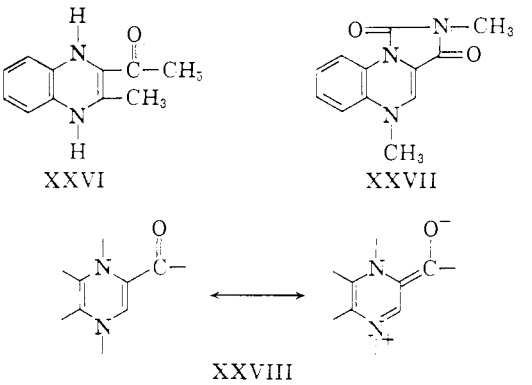
Indirect confirmation for the proposed 5,8-dihydro quinone-like enol structures for the above dihydropteridine acid derivatives was obtained as follows. 2-Ethylamino-4,5-diaminopyrimidine (XXII), prepared from 2-chloro-4-amino-5-nitropyrimidine by reaction with ethylamine, was con-



densed with the disodium salt of mesoxalic acid to give 2-ethylamino-7-hydroxypteridine-6-carboxylic acid (XXIII). Alternatively, XXIII was obtained by alkaline hydrolysis of ethyl 2-ethylamino-7-hydroxypteridine-6-carboxylate (XXIV), which in turn was prepared by condensation of 2-ethylamino-4,5-diaminopyrimidine with the diethyl ester of mesoxalic acid. Reduction of XXIII with sodium borohydride then yielded a dihydro acid, for which the structure 2-ethylamino-5,6-dihydro-7-hydroxypteridine-6-carboxylic acid (XXV) is proposed. Since it has been shown that 7-hydroxypteridine-6-carboxylic acids exist exclusively in the enolized lactim form (probably because of stabilization by intramolecular hydrogen bonding between the 7-hydroxyl group and the carbonyl oxygen of the carboxyl group,[8] it would be expected that reduction with sodium borohydride should yield a 5,6-dihydro acid which, since it is already stabilized by internal hydrogen bonding, should not undergo further tautomerization. Reduction in this instance should therefore be accompanied by a *hypsochromic* shift in the absorption spectrum. Examination of the data in Table I shows that this expectation was realized; although 2-ethylamino-7-hydroxypteridine-6-carboxylic acid (XXIII) exhibits its maximum absorption at 354 mμ (*p*H 0.0), the dihydro acid has its absorption maximum shifted down to 339 mμ (*p*H 5).



Finally, additional strong support for the 5,8-dihydro structures assigned to the sodium borohydride reduction products above is found in the recent observation[9] that catalytic reduction of 2-acetyl-3-methylquinoxaline gives a red dihydro derivative (λ_{max}^{EtOH} 489.5 mμ) which was conclusively shown to be 1,4-dihydro-2-acetyl-3-methylquinoxaline (XXVI). Furthermore, it has been reported[10] that 3-methyl-1-(*o*-methylamino)-phenylhydantoin upon treatment with sodium and ethyl formate yields an orange-yellow compound XXVII in which the 1,4-dihydro structure is fixed by substitution on both the 1- and 4-nitrogen atoms. The chromophoric system of these 1,4-dihydro derivatives (XXVIII) is the same as is found in the 5,8-dihydropteridines discussed above, and in each case is characterized by high wave length ultraviolet absorption maxima.



Considerable attention has been given recently to naturally-occurring reduced pteridines because of an increased understanding of their importance in numerous biological reactions.[11] In addition to derivatives related to pteroylglutamic acid, however, various reduced pteridines have been isolated for which no specific biological role is as yet known. Some of these latter derivatives[7,12] possess unusually high ultraviolet absorption maxima (>400 mμ), and we would like to suggest that such high absorption maxima could be due to the presence of a stabilized 5,8-dihydropteridine chromophoric system. We plan to provide evidence bearing on this hypothesis by extending the present work to a study of the sodium borohydride reduction of 2-amino-4-hydroxypteridines.

(8) W. Pfleiderer, *Ber.*, **90**, 2617 (1957).

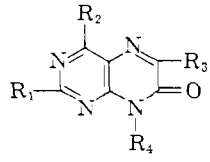
(9) J. A. Barltrop, C. G. Richards and D. M. Russell, *J. Chem. Soc.*, 1423 (1959).

(10) F. E. King and J. W. Clark-Lewis, *ibid.*, 3080 (1951).

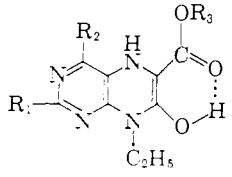
(11) For discussions and references to recent work, see (a) J. R. Totter in "Annual Review of Biochemistry," ed. by J. M. Luck, F. W. Allen and G. Mackinney, Annual Reviews, Inc., Palo Alto, Calif., Vol. 26, 1957, p. 192; (b) H. P. Broquist, *ibid.*, Vol. 27, 1958, p. 285; (c) J. M. Peters and D. M. Greenberg, THIS JOURNAL, **80**, 6679 (1958); (d) Viscontini and H. R. Weilenmann, *Helv. Chim. Acta*, **41**, 2170 (1958).

(12) (a) M. Viscontini and E. Mohlmann, *ibid.*, **42**, 1679 (1959); (b) H. S. Forrest, D. Hatfield and C. VanBaalen, *Nature*, **183**, 1269 (1959); (c) H. S. Forrest, C. VanBaalen and J. Myers, *Arch. Biochim. Biophys.*, **83**, 508 (1959).

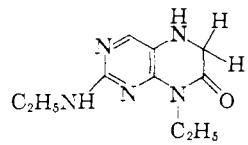
TABLE I



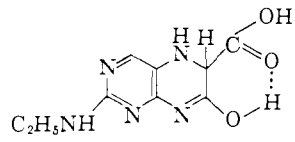
R_1	R_2	R_3	R_4	pK	λ_{max}, mμ	log ε	pH	Form
C_2H_5NH	H	H	C_2H_5	2.50 ± 0.1	234, 270, 338	4.42, 4.22, 3.90	0.0	+
					228, 296, 358	4.26, 3.73, 4.22	5.0	0
C_2H_5NH	H	COOH	C_2H_5	3.35 ± 0.03	239, 289, 356	4.48, 4.09, 4.08	0.0	0
					225, 300, 365	4.39, 3.79, 4.29	6.0	−
C_2H_5NH	H	$COOCH_3$	C_2H_5		227, 295, 390	4.45, 3.72, 4.39	6.0	0
C_2H_5NH	H	$COOC_2H_5$	C_2H_5		226, 298, 390	4.47, 3.73, 4.41	6.0	0
C_2H_5NH	CH_3	H	C_2H_5	2.97 ± 0.07	233, 268, 342	4.42, 4.22, 3.99	0.0	+
					221, 293, 360	4.46, 3.74, 4.21	5.5	0
C_2H_5NH	CH_3	COOH	C_2H_5	3.82 ± 0.02	238, 295, 358	4.47, 4.05, 4.10	1.0	0
					222, 298, 367	4.50, 3.82, 4.30	7.0	−
C_2H_5NH	CH_3	$COOC_2H_5$	C_2H_5		224, 293, 388	4.51, 3.75, 4.40	6.0	0
$(CH_3)_2N$	H	H	C_2H_5	2.30 ± 0.1	236, 272, 344	4.43, 4.31, 3.83	0	+
					223, 246, 284, 300, 370	4.33, 4.18, 3.76, 3.75, 4.20	5	0
$(CH_3)_2N$	H	COOH	C_2H_5	3.31 ± 0.03	231, 241, 287, 407	4.34, 4.35, 4.03, 4.12	1.0	0
					225, 248, 304, 378	4.33, 4.19, 3.80, 4.28	6.0	−
$(CH_3)_2N$	H	$COOC_2H_5$	C_2H_5		224, 300, 402	4.50, 3.81, 4.43	6.0	0
C_2H_5NH	H	H	H	7.50 ± 0.1	216, 242, 296, 357	4.29, 4.09, 3.71, 4.23	5	0
					232, 276, 353	4.54, 3.86, 4.20	10	−
C_2H_5NH	H	COOH	H	3.00 ± 0.03	233, 289, 354	4.46, 4.05, 4.06	0	0
				5.89 ± 0.02	242, 300, 366	4.13, 3.86, 4.29	4.5	−
					233, 282, 360	4.40, 3.87, 4.26	8	..
C_2H_5NH	H	$COOC_2H_5$	H	7.00 ± 0.1	220, 242, 300, 381	4.35, 4.10, 3.73, 4.34	5	0
					237, 286, 370	4.56, 3.86, 4.20	10	−



R_1	R_2	R_3	pK	λ_{max}, mμ	log ε	pH	Form
C_2H_5NH	H	H	7.14 ± 0.02	265, 285, 404	3.91, 3.87, 4.36	4.0	0
				252, 284(s), 404	3.73, 3.64, 4.42	9.5	−
C_2H_5NH	H	CH_3		266, 285(s), 405	4.03, 3.90, 4.42	6.0	0
C_2H_5NH	H	C_2H_5		265, 286(s), 405	4.02, 3.94, 4.43	6.0	0
C_2H_5NH	CH_3	H	6.96 ± 0.03	265, 285(s), 403	3.77, 3.73, 4.22	4.5	0
				253, 282(s), 401	3.82, 3.67, 4.43	9.5	−
C_2H_5NH	CH_3	C_2H_5		264, 285(s), 404	4.02, 3.96, 4.47	6.0	0
$(CH_3)_2N$	H	H	7.25 ± 0.03	268, 289, 405	3.95, 3.99, 4.44	4.5	0
				257, 284, 406	3.86, 3.78, 4.45	9.5	−
$(CH_3)_2N$	H	C_2H_5		266, 290, 408	3.97, 3.96, 4.46	6	0



5.13 ± 0.03	246, 360	4.58, 3.69	2.6 +
	234, 350	4.40, 3.71	8.0 0



7.16 ± 0.06	231, 339	3.93, 4.19	5 0
	287, 363	3.76, 4.27	10 −

Experimental

2,4-Bis-(ethylamino)-5-nitropyrimidine.—2,4-Dichloro-5-nitropyrimidine was prepared from 52 g. of 5-nitrouracil by the procedure described by Brown,[14] except that the ether solution was used directly without isolation of the dichloropyrimidine. To the ether solution (approximately 2 l.) with stirring was added 500 ml. of aqueous 30% ethylamine. A mildly exothermic reaction ensued and a yellow-orange solid separated. This two-phase system was stirred for 2 hours at room temperature and then filtered to give 32.8 g. The two layers of the filtrate were separated, the aqueous layer extracted with two 200-ml. portions of ether, and the combined ether layer and extracts evaporated to dryness to give an additional 16.5 g.; total yield 49.3 g., m.p. 166–170°. Recrystallization from ethanol gave yellow crystals, m.p. 175°.

Anal. Calcd. for $C_8H_{13}N_5O_2$: C, 45.5; H, 6.2; N, 33.2. Found: C, 45.2; H, 6.1; N, 33.4.

2,4-Bis-(ethylamino)-5-aminopyrimidine (I) Sulfate.—A suspension of 10 g. of 2,4-bis-(ethylamino)-5-nitropyrimidine and 3 g. of Raney nickel in 150 ml. of ethanol was hydrogenated in a Parr apparatus at 60 p.s.i. and at 50°. Hydrogen uptake was complete in two hours. The catalyst was removed by filtration and the filtrate treated with 50% sulfuric acid to convert the free pyrimidine base into its sulfate. Filtration yielded 12 g. of glossy white flakes which were recrystallized from aqueous ethanol; m.p. 217° dec.

Anal. Calcd. for $C_8H_{13}N_5 \cdot H_2SO_4$: C, 34.4; H, 6.1; N, 25.1. Found: C, 34.6; H, 5.9; N, 24.95.

2-Ethylamino-8-ethyl-7(8*H*)pteridinone-6-carboxylic Acid (II) Method A.—To a solution of 2.0 g. of 2,4-bis-(ethylamino)-5-aminopyrimidine sulfate in 50 ml. of 1 *N* sodium hydroxide was added 1.6 g. of alloxan monohydrate, and the mixture was heated under reflux for 17 hours. The reaction mixture was treated with charcoal, filtered and the filtrate acidified with dilute hydrochloric acid to *p*H 1. The precipitated yellow solid was collected by filtration, washed with water and dried to give 1.15 g., m.p. 215° dec. Recrystallization from water raised the decomposition point to 217° and afforded 1.0 g. of pure product.

Method B.—A mixture of 2.7 g. of 2,4-bis-(ethylamino)-5-aminopyrimidine sulfate, 3.1 g. of the disodium salt of mesoxalic acid and 50 ml. of water was heated under reflux for 1 hour. The resulting dark yellow solution was treated with charcoal and the filtrate was acidified with dilute hydrochloric acid to *p*H 1 to yield 1.4 g. of product, m.p. 215° dec.

Method C.—A mixture of 12 g. of 2,4-bis-(ethylamino)-5-aminopyrimidine sulfate, 12 g. of the disodium salt of mesoxalic acid and 150 ml. of 0.5 *N* sodium hydroxide was heated under reflux for 1 hour, treated with charcoal, and the filtrate acidified to yield 8 g. of product, m.p. 212° dec.

Method D.—A mixture of 0.2 g. of ethyl 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate and 10 ml. of 1 *N* sodium bicarbonate was heated under reflux for 10 minutes and then acidified with hydrochloric acid to *p*H 1. Recrystallization of the precipitated solid from water yielded 0.13 g. of product, m.p. 217° dec.

Method E.—To a suspension of 0.26 g. of 2-ethylamino-7-hydroxy-8-ethyl-5,8-dihydropteridine-6-carboxylic acid in 20 ml. of 0.5 *N* sodium hydroxide at room temperature was added dropwise and with stirring a dilute solution of aqueous potassium permanganate until the solution remained green. The reaction mixture was then stirred for an additional 15 minutes, filtered and the filtrate acidified with 1.5 ml. of concentrated hydrochloric acid. The yellow solid which separated was collected by filtration and recrystallized from water to give 0.15 g. of product, m.p. 217° dec.

Anal. Calcd. for $C_{11}H_{13}N_5O_3$: C, 50.2; H, 5.0; N, 26.6. Found: C, 50.4; H, 5.0; N, 26.5.

Ethyl 2-Ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (V) Method A.—A mixture of 1 g. of 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid, 100 ml. of absolute ethanol and 1 ml. of concentrated sulfuric acid was heated under reflux for 5 hours. The reaction mixture was treated with charcoal, filtered and the filtrate evaporated to 30 ml. volume under reduced pressure. Addition of 50 ml. of water then initiated separation of a solid. The mixture was allowed to stand overnight and was then filtered to give 0.9 g., m.p. 139°. The product was purified either by sublimation at 110° (0.5 mm.) or by recrystallization from aqueous ethanol to yield yellow needles, m.p. 144°.

Anal. Calcd. for $C_{13}H_{17}N_5O_3$: C, 53.6; H, 5.9; N, 24.0. Found: C, 53.5; H, 5.8; N, 24.2.

Method B.—A solution of 2.8 g. of 2,4-bis-(ethylamino)-5-aminopyrimidine sulfate and 2.0 g. of the diethyl ester of mesoxalic acid in 100 ml. of water was heated on a steam-bath for 30 minutes. The product separated as yellow needles from the reaction mixture upon cooling; yield 0.5 g., m.p. 138°.

Methyl 2-Ethylamino-8-ethyl-7(8H)-pteridinone-6-carboxylate (VI) Method A.—A mixture of 1 g. of 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid, 100 ml. of absolute methanol and 1 ml. of concentrated sulfuric acid was heated under reflux for 5 hours. Evaporation of the reaction mixture to about 5 ml. under reduced pressure and addition of 40 ml. of water resulted in the separation of a yellow solid which was collected by filtration and dried; yield 0.85 g., m.p. 165°. Recrystallization from water with the use of charcoal yielded yellow needles, m.p. 170°.

Method B.—To a suspension of 1 g. of 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid in 30 ml. of absolute methanol was added dropwise and with stirring a solution of diazomethane in ether (prepared from 10 g. of nitrosomethylurea). Complete solution of the suspended solid was not achieved, but an apparent change in the appearance of the solid did take place. The reaction mixture was allowed to stand overnight and was then evaporated to dryness. The residue was suspended in water, filtered, and was then evaporated to dryness. The residue was suspended in water, filtered, and the collected solid recrystallized from water to yield 0.4 g. of yellow needles, m.p. 170°.

Anal. Calcd. for $C_{12}H_{15}N_5O_3$: C, 52.0; H, 5.45; N, 25.3. O-methyl, 11.2. Found: C, 51.9; H, 5.5; N, 25.3; O-methyl, 10.9.

2-Ethylamino-8-ethyl-7(8*H*)-pteridinone (III) Method A.—A solution of 2.6 g. of 2,4-bis-(ethylamino)-5-aminopyrimidine sulfate in 50 ml. of water was adjusted to *p*H 6 with sodium bicarbonate solution and then 2 g. of ethyl glyoxalate ethyl hemiacetal was added. The resulting mixture was heated under reflux for 30 minutes. Cooling resulted in the separation of a solid which was collected by filtration; yield 1.0 g., m.p. 150°. Recrystallization from a large amount of water yielded 0.7 g. of yellow crystals, m.p. 155°.

Method B.—Two grams of 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid was heated in a Pyrex tube at 200° for 48 hours and the sublimate collected; yield 0.95 g., m.p. 154°. Resublimation of this material yielded 0.8 g. of pure product, m.p. 155°.

Method C.—To a boiling solution of 0.2 g. of 2-ethylamino-8-ethyl-5,6-dihydro-7(8*H*)-pteridinone in 15-ml. of water was added 0.5 g. of ferric nitrate. The color of the reaction mixture changed rapidly to reddish-brown and 2-ethylamino-8-ethyl-7(8*H*)-pteridinone started to separate directly from the boiling solution. The mixture was cooled, filtered and the collected solid recrystallized from water to give 0.12 g. of product, m.p. 155°.

Anal. Calcd. for $C_{10}H_{13}N_5O$: C, 54.8; H, 6.0; N, 31.95. Found: C, 54.8; H, 6.0; N, 31.9.

2-Ethylamino-7-hydroxy-8-ethyl-5,8-dihydropteridine-6-carboxylic Acid (IV).—To a solution of 5 g. of 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid in 100 ml. of 0.2 *N* sodium hydroxide was added a solution of 10 g. of sodium borohydride in 30 ml. of water. Considerable foaming took place and after 30 minutes separation of a yellow solid commenced. The reaction mixture was allowed to stand at room temperature overnight and was then filtered. The collected yellow solid was suspended in 100 ml. of warm water and the suspension acidified with acetic acid with stirring. The chilled acidified mixture was filtered to give 4.0 g., m.p. 222° dec. Recrystallization from a large amount of ethanol yielded 3.3 g. of yellow crystals, m.p. 227° dec.

Anal. Calcd. for $C_{11}H_{15}N_5O_3$: C, 49.8; H, 5.7; N, 26.4. Found: C, 49.9; H, 5.8; N, 26.4.

Sodium 2-Ethylamino-7-hydroxy-8-ethyl-5,8-dihydropteridine-6-carboxylate.—A suspension of 0.3 g. of 2-ethylamino-

(13) We are indebted to Dr. Joseph F. Alicino, Metuchen, N. J., for the microanalyses. All melting points are corrected.

(14) D. J. Brown, *J. Appl. Chem.*, **2**, 239 (1952).

7-hydroxy-8-ethyl-5,8-dihydropteridine-6-carboxylic acid in 15 ml. of 1 *N* sodium hydroxide was boiled for 1 minute and then cooled and filtered. Recrystallization of the collected solid from water yielded 0.25 g. of yellow crystals, m.p. 222–223° dec.

Anal. Calcd. for $C_{11}H_{14}N_5O_3Na \cdot 0.5\ H_2O$: C, 44.6; H, 5.2; N, 23.6; Na, 7.8. Found: C, 44.8; H, 5.1; N, 23.3; Na, 7.9.

Ethyl 2-Ethylamino-7-hydroxy-8-ethyl-5,8-dihydropteridine-6-carboxylate (VIII).—To a suspension of 0.5 g. of ethyl 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate in 20 ml. of ethanol was added 0.5 g. of sodium borohydride. Complete solution took place within 1–2 minutes and the solution turned orange. Within an additional minute a yellow solid started to separate from the reaction mixture. After 15 minutes, the mixture was filtered and the collected solid washed with water followed by ethanol and dried; yield 0.4 g., m.p. 268°. Recrystallization from dimethylformamide yielded 0.3 g. of yellow crystals, m.p. 282° dec.

Anal. Calcd. for $C_{13}H_{19}N_5O_3$: C, 53.2; H, 6.5; N, 23.9. Found: C, 53.6; H, 6.3; N, 23.7.

Methyl 2-Ethylamino-7-hydroxy-8-ethyl-5,8-dihydropteridine-6-carboxylate (VII) Method A.—Reduction of 0.5 g. of methyl 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate with sodium borohydride by the method described above yielded 0.38 g. of yellow crystals, m.p. 268–270° dec.

Method B.—To a suspension of 1 g. of 2-ethylamino-7-hydroxy-8-ethyl-5,8-dihydropteridine-6-carboxylic acid in 50 ml. of methanol was added a solution of diazomethane in ether (prepared from 10 g. of nitrosomethylurea). The mixture was stirred at room temperature overnight and then filtered to give 1 g. of crude product, m.p. 250° dec. Recrystallization from dimethylformamide yielded yellow crystals, m.p. 268–270° dec.

Anal. Calcd. for $C_{12}H_{17}N_5O_3$: C, 51.6; H, 6.1; N, 25.1; O-methyl, 11.1; N-ethyl, 20.8. Found: C, 51.75; H, 6.1; N, 25.0; O-methyl, 10.9; N-ethyl, 21.0.

2-Ethylamino-8-ethyl-5,6-dihydro-7(8*H*)-pteridinone (IX).—A mixture of 0.5 g. of 2-ethylamino-7-hydroxy-8-ethyl-5,8-dihydropteridine-6-carboxylic acid, 50 mg. of sodium hydrosulfite and 10 ml. of 1 *N* hydrochloric acid was heated under reflux for 10 minutes, cooled to 50° and neutralized with ammonium hydroxide to *p*H 7–8. The precipitate which separated on standing was collected by filtration, washed with ice-water and dried; yield 0.32 g., m.p. 118–121°. Recrystallization from 15 ml. of water containing 50 mg. of sodium hydrosulfite afforded 0.25 g. of yellow crystals, m.p. 121–122°.

Anal. Calcd. for $C_{10}H_{15}N_5O$: C, 54.3; H, 6.8; N, 31.7. Found: C, 54.45; H, 6.5; N, 31.7.

2,4-Bis-(ethylamino)-5-nitro-6-methylpyrimidine.—Eighty grams of 5-nitro-6-methyluracil was chlorinated as previously described,[15] and the ether solution containing the desired 2,4-dichloro-5-nitro-6-methylpyrimidine intermediate was poured into 500 ml. of 33% aqueous ethylamine solution. The mixture was stirred overnight at room temperature and then filtered to give 67 g. of product, m.p. 125°. A second crop was obtained by separation of the ether layer above, evaporation to dryness and crystallization of the residue from aqueous ethanol; yield 14 g., m.p. 125°. The product was purified either by recrystallization from aqueous ethanol or by vacuum sublimation; m.p. 128°.

Anal. Calcd. for $C_9H_{15}N_5O_2$: C, 48.0; H, 6.7; N, 31.1. Found: C, 47.7; H, 7.0; N, 31.0.

2,4-Bis-(ethylamino)-5-amino-6-methylpyrimidine (XI) Sulfate.—A solution of 10 g. of 2,4-bis-(ethylamino)-5-nitro-6-methylpyrimidine in 100 ml. of ethanol containing 3 g. of Raney nickel catalyst was hydrogenated at 60 p.s.i. and at 50° until hydrogen uptake was complete (about 2 hours). The catalyst was removed by filtration and the filtrate was acidified with 50% sulfuric acid. Filtration then yielded 11.5 g. of colorless crystals, m.p. 185°, which were recrystallized from water without change in the melting point.

Anal. Calcd. for $C_9H_{17}N_5 \cdot H_2SO_4$: C, 36.8; H, .65; N, 23.9. Found: C, 36.8; H, 6.4; N, 23.6.

The free base was prepared by treatment of a suspension of 3 g. of 2,4-bis-(ethylamino)-5-amino-6-methylpyrimidine sulfate in water with 20 ml. of 1 *N* sodium hydroxide. The sulfate dissolved completely and shortly afterward the free base separated as glittering colorless plates; yield, 1.6 g., m.p. 122–124°. Recrystallization from water yielded 1.2 g. of pure product, m.p. 126°.

Anal. Calcd. for $C_9H_{17}N_5$: C, 55.35; H, 8.8; N, 35.8. Found: C, 55.5; H, 9.0; N, 35.7.

2-Ethylamino-4-methyl-8-ethyl-7(8*H*)-pteridinone-6-carboxylic Acid (XII).—A mixture of 3 g. of 2,4-bis-(ethylamino)-5-amino-6-methylpyrimidine sulfate and 3 g. of the disodium salt of mesoxalic acid in 50 ml. of 1 *N* sodium hydroxide was heated under reflux for 1 hour. The hot solution was treated with charcoal and the filtrate acidified with dilute hydrochloric acid to *p*H 1. The yellow solid which separated was collected by filtration, washed with water and dried; yield 1.5 g., m.p. 210° dec. Recrystallization from water yielded 1.2 g. of yellow crystals, m.p. 219° dec.

Anal. Calcd. for $C_{12}H_{15}N_5O_3$: C, 52.0; H, 5.45; N, 25.3. Found: C, 52.2; H, 5.5; N, 25.1.

Ethyl 2-Ethylamino-4-methyl-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (XIV).—A solution of 2 g. of 2,4-bis-(ethylamino)-5-amino-6-methylpyrimidine and 2.5 g. of the diethyl ester of mesoxalic acid in 100 ml. of water was heated under reflux for 15 minutes, cooled and the solid which had separated was collected by filtration; yield 2.6 g., m.p. 121°. Recrystallization from aqueous ethanol gave 2 g. of yellow crystals, m.p. 127°.

Anal. Calcd. for $C_{14}H_{19}N_5O_3$: C, 55.1; H, 6.3; N, 22.9. Found: C, 55.2; H, 6.1; N, 22.7.

2-Ethylamino-4-methyl-8-ethyl-7(8*H*)-pteridinone (XVI). Method A.—One gram of 2-ethylamino-4-methyl-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid in a Pyrex tube was heated at 200° for 24 hours, and the sublimate collected; yield 0.4 g., m.p. 155°.

Method B.—A mixture of 1 g. of 2,4-bis-(ethylamino)-5-amino-6-methylpyrimidine and 1.5 ml. of ethyl glyoxylate ethyl hemiacetal in 50 ml. of water was heated under reflux for 1 hour. The reaction mixture was allowed to stand at room temperature overnight and was then filtered to give 0.75 g., m.p. 155°. Recrystallization from water yielded colorless needles.

Anal. Calcd. for $C_{11}H_{15}N_5O$: C, 56.6; H, 6.5; N, 30.0. Found: C, 56.8; H, 6.5; N, 29.8.

Ethyl 2-Ethylamino-4-methyl-7-hydroxy-8-ethyl-5,8-dihydropteridine-6-carboxylate (XV).—To a solution of 1.5 g. of ethyl 2-ethylamino-4-methyl-8-ethyl-7(8*H*)-pteridinone-6-carboxylate in 25 ml. of ethanol was added 0.2 g. of sodium borohydride. The product started to separate after about 30 minutes of stirring. The mixture was allowed to stand at room temperature overnight and was then filtered to give 1.05 g., m.p. 250–255° dec. Recrystallization from dimethylformamide or from a large volume of ethanol yielded 0.8 g. of yellow crystals, m.p. 274–276° dec.

Anal. Calcd. for $C_{14}H_{21}N_5O_3$: C, 54.7; H, 6.9; N, 22.8. Found: C, 54.4; H, 6.7; N, 22.6.

2-Ethylamino-4-methyl-7-hydroxy-8-ethyl-5,8-dihydropteridine-6-carboxylic Acid (XIII).—To a solution of 1 g. of 2-ethylamino-4-methyl-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid in 25 ml. of 0.1 *N* sodium hydroxide was added a solution of 1 g. of sodium borohydride in 10 ml. of water. Considerable foaming took place and separation of thin colorless needles (the sodium salt of the starting material) commenced. Water was added until complete solution was again achieved, and the reaction mixture was stirred at room temperature for 5 hours. An additional 1 g. of sodium borohydride was then added and the solution was allowed to stand at room temperature overnight. Careful acidification with acetic acid then resulted in the separation of a yellow solid which was collected by filtration, washed with water and dried; yield 0.4 g., m.p. 217–220° dec. Recrystallization from ethanol gave 0.25 g. of yellow crystals which melted with decomposition (effervescence) at 222°, resolidified at 225° and then melted again at 240–242°.

Anal. Calcd. for $C_{12}H_{17}N_5O_3$: C, 51.6; H, 6.1; N, 25.1. Found: C, 51.55; H, 6.05; N, 25.1.

2-Dimethylamino-4-chloro-5-nitropyrimidine was prepared by a modification of the procedure described by Saunders.[16] A mixture of 71 g. of 2-dimethylamino-4-hydroxy-5-nitro-

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

(16) D. G. Saunders, *J. Chem. Soc.*, 3232 (1956).

pyrimidine and 400 ml. of phosphorus oxychloride was heated under reflux for 2 hours, cooled and allowed to stand overnight. Filtration then yielded the desired chloropyrimidine, which was dried in a vacuum desiccator over potassium hydroxide; yield 49 g., m.p. 140°. Evaporation of the filtrate to half its volume and cooling overnight resulted in the separation of an additional 12 g., m.p. 140°. The product was sufficiently pure for subsequent reactions.

2-Dimethylamino-4-ethylamino-5-nitropyrimidine.—A mixture of 17 g. of 2-dimethylamino-4-chloro-5-nitropyrimidine and 70 ml. of aqueous ethylamine solution was heated under reflux for 5 minutes. The oil which separated solidified upon cooling. Filtration then yielded 16 g., m.p. 98°, which was recrystallized from ethanol without change in the melting point.

Anal. Calcd. for $C_8H_{13}N_5O_2$: C, 45.5; H, 6.2; N, 33.2. Found: C, 45.5; H, 6.0; N, 33.5.

2-Dimethylamino-4-ethylamino-5-aminopyrimidine (XVII) Sulfate.—A solution of 16 g. of 2-dimethylamino-4-ethylamino-5-nitropyrimidine in 160 ml. of ethanol was hydrogenated at 60 p.s.i. and at 50° in the presence of 3 g. of Raney nickel. After hydrogen uptake ceased, the catalyst was removed by filtration and the filtrate adjusted to *p*H 3 with 50% sulfuric acid. Scratching induced slow separation of the sulfate salt. The mixture was chilled overnight and filtered to give 16 g., m.p. 170–180°. Recrystallization from ethanol gave colorless crystals, m.p. 195–198°.

Anal. Calcd. for $C_8H_{15}N_5 \cdot H_2SO_4$: C, 34.4; H, 6.1; N, 25.1. Found: C, 35.8; H, 6.2; N, 25.0.

2-Dimethylamino-8-ethyl-7(8*H*)-pteridinone.—A mixture of 2.8 g. of 2-dimethylamino-4-ethylamino-5-aminopyrimidine, 2 ml. of ethyl glyoxalate ethyl hemiacetal, 20 ml. of 1 *N* sodium bicarbonate and 10 ml. of water was heated under reflux for 15 minutes. The oil which separated solidified upon cooling. The reaction mixture was allowed to stand at 0° overnight and was then filtered to give 1.1 g., m.p. 112°. Recrystallization from aqueous ethanol yielded 0.7 g. of yellow neeedles, m.p. 118°.

Anal. Calcd. for $C_{10}H_{13}N_5O$: C, 54.8; H, 6.0; N, 31.95. Found: C, 55.0; H, 6.1; N, 31.7.

2 - Dimethylamino - 8 - ethyl - 7(8*H*) - pteridinone - 6-carboxylic Acid (XVIII).—A mixture of 2.8 g. of 2-dimethylamino-4-ethylamino-5-aminopyrimidine sulfate, 2.5 g. of the disodium salt of mesoxalic acid and 40 ml. of 1 *N* sodium bicarbonate solution was heated under reflux for 1 hour, treated with charcoal and filtered. Acidification of the yellow filtrate with dilute hydrochloric acid to *p*H 1 and cooling yielded yellow needles which were collected by filtration, washed with a little cold water and dried; yield 1.8 g., m.p. 190° dec. Recrystallization from water gave 1.1 g., m.p. 192° dec.

Anal. Calcd. for $C_{11}H_{13}N_5O_3$: C, 50.2; H, 5.0; N, 26.6. Found: C, 49.9; H, 4.9; N, 26.6.

Ethyl 2-Dimethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (XIX).—To a solution of 2.8 g. of 2-dimethylamino-4-ethylamino-5-aminopyrimidine sulfate in 20 ml. of 1 *N* sodium bicarbonate was added 2.2 g. of the diethyl ester of mesoxalic acid in 10 ml. of water followed by 5 ml. of acetic acid, and the mixture was heated under reflux for 3 minutes. The oil which separated from the solution solidified upon cooling and was collected by filtration; yield 1.4 g., m.p. 95–100°. Recrystallization from aqueous methanol gave 1 g. of yellow crystals, m.p. 110°.

Anal. Calcd. for $C_{13}H_{17}N_5O_3$: C, 53.6; H, 5.9; N, 24.0. Found: C, 53.7; H, 5.9; N, 23.8.

2-Dimethylamino-7-hydroxy-8-ethyl-5,8-dihydropteridine-6-carboxylic Acid (XX).—To a solution made up from 4 g. of 2-dimethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid in 50 ml. of water containing 20 ml. of 1 *N* sodium hydroxide was added a solution of 2 g. of sodium borohydride in 10 ml. of water. After standing overnight, the reaction mixture was carefully acidified with acetic acid, and the yellow solid which separated was collected by filtration; yield 2.6 g., m.p. 245° dec. Recrystallization from 1200 ml. of ethanol yielded 2.3 g. of yellow crystals with the same decomposition point.

Anal. Calcd. for $C_{11}H_{15}N_5O_3$: C, 49.8; H, 5.7; N, 26.4. Found: C, 49.8; H, 5.7; N, 26.1.

Ethyl 2-Dimethylamino-7-hydroxy-8-ethyl-5,8-dihydropteridine-6-carboxylate (XXI).—To a solution made of 1 g. of ethyl 2-dimethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate in 15 ml. of ethanol at 35° was added 0.1 g. of sodium borohydride. The color of the solution changed rapidly to dark yellow and a yellow solid started to separate out after 30 minutes. The reaction mixture was allowed to stand at room temperature for 1.5 hours and was then filtered to give 0.8 g., m.p. 190–200°. Recrystallization from ethanol gave 0.5 g. of yellow crystals, m.p. 235–236°.

Anal. Calcd. for $C_{13}H_{19}N_5O_3$: C, 53.2; H, 6.5; N, 23.9. Found: C, 52.8; H, 6.3; N, 23.4.

2-Ethylamino-4-amino-5-nitropyrimidine.—A mixture of 15 g. of 2-chloro-4-amino-5-nitropyrimidine and 100 ml. of 50 % aqueous ethylamine was placed in a pressure bottle and heated 4 hours in a boiling water-bath. A yellow solid separated out on cooling. The mixture was allowed to stand overnight and was filtered to yield 15 g. of yellow crystals, m.p. 170–175°. Recrystallization from water with the use of charcoal raised the melting point to 179°.

Anal. Calcd. for $C_8H_9N_5O_2$: C, 39.3; H, 4.95; N, 38.2. Found: C, 39.05; H, 4.8; N, 38.3.

2-Ethylamino-4,5-diaminopyrimidine (XXII).—A solution of 15 g. of 2-ethylamino-4-amino-5-nitropyrimidine in 150 ml. of ethanol was hydrogenated in a Parr apparatus at 60 p.s.i. and 50° in the presence of 5 g. of Raney nickel catalyst. Hydrogen uptake was complete after 2 hours. The catalyst was removed by filtration and the filtrate, which rapidly turned to a wine-red color, was evaporated to dryness under reduced pressure. The residue was triturated with warm acetone and filtered. The collected solid (9.5 g., m.p. 178°) was dried and used directly.

Ethyl 2-Ethylamino-7-hydroxypteridine-6-carboxylate (XXIV).—A mixture of 1.5 g. of 2-ethylamino-4,5-diaminopyrimidine, 2 g. of the diethyl ester of mesoxalic acid and 40 ml. of water was heated on a steam-bath for 15 minutes. The precipitate which formed was filtered from the hot solution, washed with water and dried; yield 2.5 g., m.p. 286–290°. Recrystallization from dimethylformamide gave 2.0 g. of a light yellow microcrystalline solid, m.p. 290°.

Anal. Calcd. for $C_{11}H_{13}N_5O_3$: C, 50.2; H, 5.0; N, 26.6. Found: C, 50.6; H, 5.15; N, 26.9.

2-Ethylamino-7-hydroxypteridine-6-carboxylic Acid (XXIII) Method A.—A mixture of 1.5 g. of 2-ethylamino-4,5-diaminopyrimidine, 2 g. of the disodium salt of mesoxalic acid and 25 ml. of 1 *N* sodium hydroxide was heated under reflux for 1 hour, treated with charcoal and filtered. Acidification of the filtrate to *p*H 1 precipitated a yellow solid which was collected by filtration, washed with water and dried; yield 2.4 g., m.p 345° dec. Recrystallization from water yielded 1.8 g. of yellow crystals, m.p. 348° dec.

Method B.—A mixture of 1 g. of ethyl 2-ethylamino-7-hydroxypteridine-6-carboxylate and 25 ml. of 1 *N* sodium bicarbonate was heated under reflux for 15 minutes The resulting clear yellow solution was treated with charcoal, filtered, and the filtrate acidified to *p*H 1 with hydrochloric acid. The yellow solid which separated was collected by filtration and recrystallized from water to give 0.5 g., m.p. 348° dec.

Anal. Calcd. for $C_9H_9N_5O_3$: C, 46.0; H, 3.9; N, 29.8. Found: C, 45.4; H, 3.9; N, 30.2.

2-Ethylamino-7-hydroxy-5,6-dihydropteridine-6 carboxylic Acid (XXV).—To a partial solution of 1 g. of 2-ethylamino-7-hydroxypteridine-6-carboxylic acid in 30 ml of water containing 8 ml. of 1 *N* sodium hydroxide was added a solution of 1 g. of sodium borohydride in 5 ml. of water. Considerable foaming took place and a clear solution was obtained. After 15 minutes at room temperature, separation of a yellow solid began. The mixture was allowed to stand overnight and was then filtered to give 0.6 g. of a yellow solid. This material was suspended in 100 ml. of boiling water and acetic acid added to *p*H 5. Cooling and filtering then gave 0.45 g. of yellow crystals, m.p. 281° dec.

Anal. Calcd. for $C_9H_{11}N_5O_3$: C, 45.6; H, 4.7; N, 29.5. Found: C, 45.3; H, 4.3; N, 29.4.

Acknowledgment.—We wish to express our appreciation to Dr. Harvey M. Loux for his help with some of the initial phases of the experimental work, and to Miss I. Fink of the Institute für organische Chemie, Technische Hochschule, Stuttgart, Germany, for the pK_a and ultraviolet absorption spectra determinations.

PRINCETON, N. J.