(broad s, 1 H, -OH), 2.08 (s, 1 H, C_8 hydrogen), 2.12–2.72 (m, 4 H, thiophene).

Anal. Calcd for $C_{10}H_6OS_2$: C, 58.22; H, 2.93; S, 31.09. Found: C, 58.37; H, 2.83; S, 30.90.

4-Acetoxybenzo[1,2-*b*:4,5-*b'*]dithiophene (33).—A stirred mixture of 2,3′-dithienylmethane-3-carboxylic acid (15 g, 67 mmol), glacial acetic acid (150 ml), acetic anhydride (105 ml), and freshly fused zinc chloride (1.3 g, 9.6 mmol) was heated at reflux for 15 min and while still hot was cautiously diluted with water (255 ml). The resulting yellow crystalline solid was filtered, dried *in vacuo* and purified by sublimation (90°, 0.1 mm). The yield was 12.5 g (75%). An analytical sample was obtained by recrystallization from benzene–hexane: mp 113–115°; uv max (95% C_2H_5OH) 231 mμ (ε 22,900), 246 (44,200), 254 (61,900), 289 (7680), 299 (8500), 323 (9620), 337 (14,900); ir (KBr) 1755 cm^{-1} (acetate C=O); nmr (CCl_4) τ 1.96 (s, 1 H, C_8 proton), 2.60–3.00 (m, 4 H, thiophene), 7.62 [s, 3 H, $-OC(=O)CH_3-$].

Anal. Calcd. for $C_{12}H_8O_2S_2$: C, 58.04; H, 3.25; S, 25.83. Found: C, 57.97; H, 3.39; S, 25.83.

Registry No.—**4k**, 31936-79-5; **5k**, 31981-26-7; **6e**, 31936-80-8; **7e**, 31936-81-9; **8e**, 31936-82-0; **12**, 31936-83-1; **13**, 17965-66-1; **14**, 31936-85-3; **16**, 31936-86-4; **17**, 31936-87-5; **18**, 31936-88-6; **21**, 31936-89-7; **22**, 31936-90-0; **23**, 31936-91-1; **25**, 31936-92-2; **27**, 31936-93-3; **27** tetrabromide, 31936-94-4; **28**, 31936-95-5; **29**, 31936-96-6; **30**, 17964-88-4; **31**, 17965-56-9; **32**, 31936-99-9; **33**, 31937-00-5.

Acknowledgment.—The authors wish to thank Dr. C. G. McCarty and Dr. J. Gruninger for their aid in the preparation of this manuscript and Mr. Robert Smith for recording some of the nmr spectra.

Pteridines. XXVI. Preparation and Properties of Some 3,4- and 5,6-Dihydropteridines[1,2]

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Treatment of 8-alkyl-7(8*H*)-pteridinone-6-carboxylic acid derivatives (substituted at position 4 with hydrogen or methyl) with sodium borohydride leads to the formation in high yield of bright yellow dihydro compounds which are 10,000 times weaker acids, and exhibit uv absorption maxima some 50–60 nm higher, than the starting pteridinones. The influence of 2 and 4 substituents on this reduction has been carefully examined, and evaluation of both spectroscopic (uv, ir, and nmr) and chemical data has shown conclusively that these reduction products are 3,4-dihydro derivatives, and not 4,8- (or 5,8-) dihydro derivatives as previously suggested. By contrast, catalytic reduction of the same series of 8-alkyl-7(8*H*)-pteridinone-6-carboxylic acids and esters has been shown to give 5,6-dihydro compounds with very different chemical and physical properties. It has been demonstrated that the 3,4-dihydro compounds rearrange quantitatively and irreversibly to the 5,6-dihydro isomers in trifluoroacetic acid solution. The preparation of 22 new 8-alkyl-7(8*H*)-pteridinone-6-carboxylic acids and esters, as well as the requisite pyrimidine precursors, is described.

Dihydropteridines are attracting considerable current attention because of their role as naturally occurring cofactors in one-carbon transfer reactions involving the folic acid coenzymes,[3] the enzymatic hydroxylation of phenylalanine to tyrosine,[4] and a variety of other oxygenase reactions,[5] and as intermediates in photosynthetic electron transport processes in higher plants and photosynthetic bacteria.[6] Previous uncertainties as to the location of the hydrogen atoms in certain dihydropteridines (such as drosopterin, isodrosopterin, neodrosopterin, dihydrofolic acid, etc.)[7] have led to numerous efforts to prepare model dihydropteridines of known structure. For these reasons we have reinvestigated and extended our finding of several years ago[8,9] that a number of 7(8*H*)-pteridinone-6-carboxylic acid derivatives were reduced with sodium borohydride to dihydro compounds with unusual chemical and physical properties. The present work was undertaken in an effort to delineate the structural features (primarily the substitution pattern in the pyrimidine ring) necessary for sodium borohydride reduction of 7(8*H*)-pteridinone-6-carboxylic acids to these novel dihydro derivatives and to settle the controversy which has developed concerning their structure.[10] We describe herein the preparation of the requisite pteridine precursors, and the pyrimidine intermediates required for their preparation, the reduction experiments carried out on these pteridines, both with sodium borohydride and with hydrogen in the presence of various catalysts, and, finally, both spectroscopic and chemical evidence which firmly establishes the sodium borohydride reduction products as 3,4-dihydro derivatives, and the catalytic reduction products as their 5,6-dihydro isomers.

Synthesis of Intermediates. Pyrimidines.—Most of the requisite 4-alkylamino-5-aminopyrimidines required in this work were prepared by standard procedures and used directly in the pteridine preparations. Some special cases are described below.

(1) For the previous paper in this series, see E. C. Taylor and K. Lenard, *Justus Liebigs Ann. Chem.*, **726**, 100 (1969).

(2) A part of this work was supported by a grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

(3) R. L. Blakley, "The Biochemistry of Folic Acid and Related Pteridines," Wiley–Interscience, New York, N. Y., 1969.

(4) S. Kaufman, *J. Biol. Chem.*, **242**, 3934 (1967).

(5) Summarized by S. Kaufman, *Ann. Rev. Biochem.*, **36**, 171 (1967).

(6) (a) N. A. Nugent and R. C. Fuller, in "Chemistry and Biology of Pteridines," K. Iwai, M. Akino, M. Goto, and Y. Iwanami, Ed., International Academic Printing Co., Ltd., Tokyo, 1970, pp 371–379. (b) R. C. Fuller and N. A. Nugent, *Proc. Nat. Acad. Sci. U. S.*, **63**, 1311 (1969).

(7) W. Pfleiderer and E. C. Taylor, Ed., "Pteridine Chemistry," Pergamon Press, Oxford, 1964.

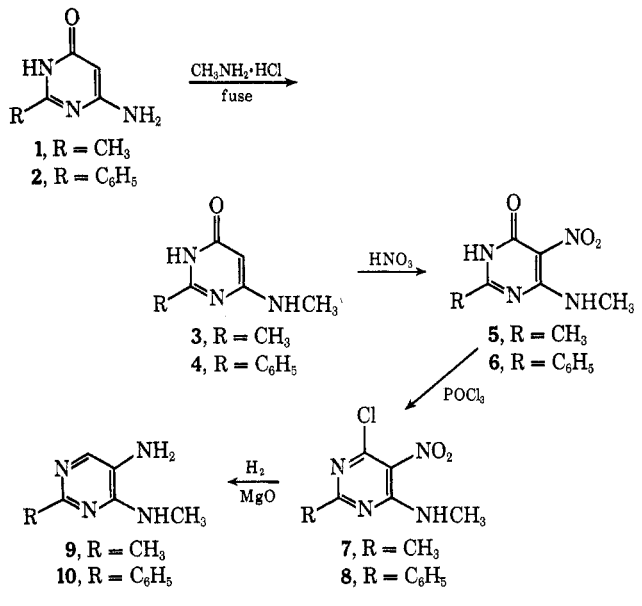
(8) W. Pfleiderer and E. C. Taylor, *J. Amer. Chem. Soc.*, **82**, 3765 (1960).

(9) E. C. Taylor, M. J. Thompson, and W. Pfleiderer, ref 7, pp 181–205.

(10) Reference 7, pp 205–210.

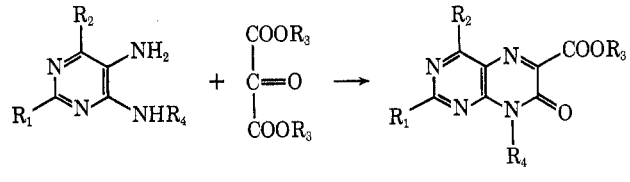
Although 2-methyl-4-methylamino-6(1*H*)-pyrimidinone (**3**) has been prepared previously[11] by a three-step sequence (21% overall yield) from 2-methyl-4,6(1*H*,3*H*)-pyrimidinedione,[12] it seemed that a simpler procedure would be transamidation[13-16] with the readily accessible 2-methyl-4-amino-6(1*H*)-pyrimidinone (**1**).[17] Fusion of this latter compound with methylammonium acetate gave a mixture containing the 4-amino-, 4-methylamino-, and 4-acetamido derivatives, but fusion with methylamine hydrochloride at 200° resulted in the formation of a more homogeneous product which, by nmr, consisted primarily of the desired 2-methyl-4-methylamino-6(1*H*)-pyrimidinone (**3**) (90%), along with a small amount of unreacted starting material. Nitration of this mixture with fuming nitric acid in glacial acetic acid, however, gave pure 2-methyl-4-methylamino-5-nitro-6(1*H*)-pyrimidinone (**5**). Treatment with phosphorus oxychloride then gave the 6-chloro compound **7** which upon reduction in aqueous ethanol containing magnesium oxide[18] underwent simultaneous dehalogenation and reduction of the nitro group to yield the desired 2-methyl-4-methylamino-5-aminopyrimidine (**9**). The same sequence of reactions, applied to 2-phenyl-4-amino-6(1*H*)-pyrimidinone (**2**),[19] gave 2-phenyl-4-methylamino-5-aminopyrimidine (**10**). These reactions are summarized in Scheme I.

SCHEME I



2-Dimethylamino-4-phenyl-5-amino-6-ethylaminopyrimidine (**16**) was prepared as follows. Condensation of dimethylguanidine with ethyl benzoylacetate in the presence of sodium ethoxide gave 2-dimethylamino-4-phenyl-6(1*H*)-pyrimidinone (**11**) in about 40% yield (a competing base-catalyzed cleavage of ethyl benzoylacetate to give acetophenone is apparently responsible for the low yield). This was converted to the 5-nitro compound **13** either by direct nitration with fuming nitric acid in glacial acetic acid at 20° (these conditions do not cause nitration of the 4-phenyl substituent) or by nitrosation to give 2-dimethylamino-4-phenyl-5-nitroso-6(1*H*)-pyrimidinone (**12**) followed by oxidation with pertrifluoroacetic acid.[20] Chlorination with phosphorus oxychloride to **14** followed by reaction with aqueous ethylamine then gave 2-dimethylamino-4-phenyl-5-nitro-6-ethylaminopyrimidine (**15**), which was reduced catalytically to the desired 5-amino derivative **16**. These reactions are summarized in Scheme II.

Pteridines.—All of the ethyl 8-alkyl-7(8*H*)-pteridinone-6-carboxylates utilized in the reduction experiments were prepared by the condensation of diethyl mesoxalate with the appropriate 4-alkylamino-5-aminopyrimidine (often prepared *in situ* by catalytic reduction of the appropriate 5-nitropyrimidine; see Experimental Section). The corresponding methyl esters were prepared from the ethyl esters by transesterification utilizing a large excess of methanol as solvent; this transesterification was particularly facile and complete because of the insolubility of the methyl esters in methanol. Free carboxylic acids were prepared either by condensation of the appropriate diaminopyrimidine with sodium mesoxalate or by alkaline hydrolysis of the esters. The 8-alkyl-7(8*H*)-pteridinone-6-carboxylic acid derivatives are listed, along with pertinent uv data, in Table I (for ir and nmr data, see Experimental Section).



Reduction Experiments with Sodium Borohydride.—Reduction of a series of 4-unsubstituted 8-alkyl-7(8*H*)-pteridinone-6-carboxylic acids and their corresponding ethyl (or methyl) esters, with the 2 position substituted by CH_3, C_6H_5, CH_3NH, $(CH_3)_2N$,[8] CH_3O, and HO, was effected by addition of sodium borohydride to a solution of the pteridinone in ethanol or dimethylformamide, followed by careful acidification with dilute acetic acid. In each instance, a yellow dihydro derivative, which exhibited a characteristic high wavelength absorption maximum between 402 and 453 nm, was obtained in high yield. Physical (see Table II and Experimental Section) and chemical evidence firmly establishing that these yellow compounds are 3,4-dihydro derivatives will be discussed later.

Substituents in the 4 position of the pyrimidine ring had a dramatic effect on the course of the sodium borohydride reduction. In fact, the only substituent besides hydrogen which yielded a 3,4-dihydro derivative under the above conditions was methyl; thus, methyl 2-methylamino-4,8-dimethyl-7(8*H*)-pteridinone-6-carboxylate (**27**) (and its corresponding acid **28**) underwent smooth reduction with sodium borohydride to give yellow 3,4-dihydro derivatives (**45** and **46**, respectively), but no reduction was observed when the 4 position was occupied by oxygen [2-amino-8-ethyl-4,7(3*H*,8*H*)-

(11) H. Hirano and H. Yonemoto, *J. Pharm. Soc. Jap.*, **76**, 234 (1956); *Chem. Abstr.*, **50**, 13043 (1956).
(12) H. R. Henze, W. J. Clegg, and C. W. Smart, *J. Org. Chem.*, **17**, 1320 (1953).
(13) E. C. Taylor and C. K. Cain, *J. Amer. Chem. Soc.*, **73**, 4384 (1951).
(14) D. J. Brown, *J. Appl. Chem.*, **7**, 109 (1957).
(15) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **28**, 2672 (1963).
(16) C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, **82**, 3971 (1960).
(17) A. Maggiolo, A. P. Phillips, and G. H. Hitchings, *ibid.*, **73**, 106 (1951).
(18) C. G. Overberger and I. C. Kogon, *ibid.*, **76**, 1879 (1954).
(19) R. Andrisano and L. Maioli, *Gazz. Chim. Ital*, **83**, 264 (1953).
(20) E. C. Taylor and A. McKillop, *J. Org. Chem.*, **30**, 3153 (1965).

SCHEME II

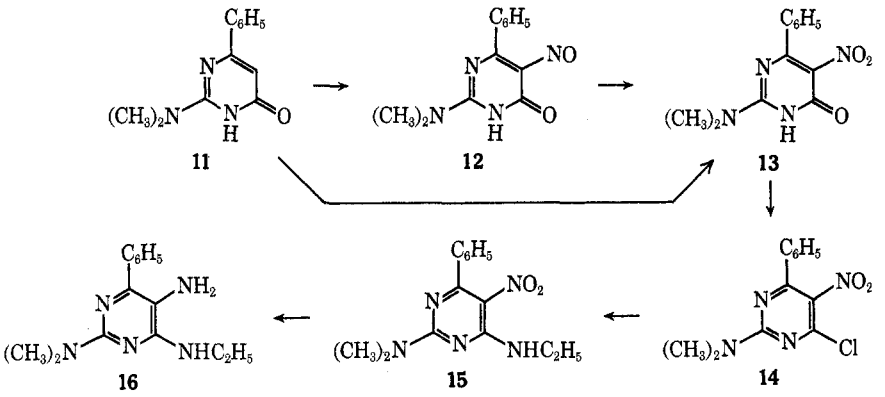
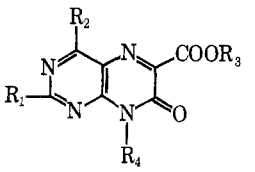


TABLE I

8-ALKYL-7(8*H*)-PTERIDINONE-6-CARBOXYLIC ACID DERIVATIVES



Compd no.	R_1	R_2	R_3	R_4	Uv spectra: λ_{max}, nm	Uv spectra: Log ϵ	Solvent
21	CH_3	H	C_2H_5	CH_3			
22	CH_3	H	CH_3	CH_3	245 (sh), 265, 275 (sh), 323	3.80, 3.55, 3.49, 4.01	C_2H_5OH
23	C_6H_5	H	C_2H_5	CH_3	228, 245 (sh), 290 (sh), 345	4.25, 3.92, 3.73, 4.27	C_2H_5OH
24	C_6H_5	H	CH_3	CH_3	227, 245 (sh), 290 (sh), 347	4.44, 3.97, 3.85, 4.29	C_2H_5OH
25	$(CH_3)_2N$	C_6H_5	C_2H_5	C_2H_5	230, 257 (sh), 295, 395	4.33, 4.16, 4.15, 4.35	C_2H_5OH
26	CH_3NH	CH_3	C_2H_5	CH_3	224, 245 (sh), 298, 378	4.50, 4.02, 3.72, 4.35	C_2H_5OH
27	CH_3NH	CH_3	CH_3	CH_3	222, 243 (sh), 295, 377	4.48, 3.98, 3.62, 4.36	C_2H_5OH
28	CH_3NH	CH_3	H	CH_3	222, 240, 293, 395	4.44, 4.07, 3.65, 4.36	C_2H_5OH
29	CH_3NH	H	C_2H_5	CH_3	238, 288, 354	4.47, 4.09, 4.10	pH −1
					225, 297, 387	4.50, 3.74, 4.40	pH 4
30	CH_3NH	H	CH_3	CH_3	225, 245 (sh), 303, 378	4.43, 3.97, 3.70, 4.37	C_2H_5OH
					238, 290, 355	4.48, 4.09, 4.11	pH −1
					225, 297, 388	4.51, 3.73, 4.41	pH 3
31	CH_3NH	H	H	CH_3	223, 245 (sh), 300, 385	4.16, 3.73, 3.56, 4.09	C_2H_5OH
					236, 288, 353	4.51, 4.10, 4.11	pH −1
					225, 288, 391	4.46, 3.86, 4.26	pH 2
					222, 240 (sh), 300, 366	4.45, 3.95, 3.80, 4.30	pH 6
32	CH_3O	H	C_2H_5	CH_3	257, 277 (sh), 283, 329	3.70, 3.66, 3.67, 4.17	C_2H_5OH
33	HO	H	H	CH_3	235 (sh), 291, 356	3.93, 3.72, 4.29	C_2H_5OH
34	HO	H	C_2H_5	CH_3	233 (sh), 291, 355	3.93, 3.72, 4.29	C_2H_5OH
35	H_2N	H	C_2H_5	CH_3	220, 294, 364	4.39, 3.53, 4.18	C_2H_5OH
					234, 280, 340	4.54, 4.0, 4.15	pH −1
					222, 290, 373	4.57, 3.72, 4.35	pH 7
36	H_2N	H	CH_3	CH_3	232, 280, 340	4.50, 4.01, 4.15	pH 1
					222, 290, 373	4.55, 3.71, 4.36	pH 3
37	H_2N	H	H	CH_3	291, 350	3.80, 4.18	pH 10
38	H	$(CH_3)_2N$	C_2H_5	CH_3	218, 230 (sh), 270, 380	4.31, 4.25, 4.00, 4.03	C_2H_5OH
39	H	$(CH_3)_2N$	H	CH_3	219, 272, 389	4.37, 4.03, 4.02	C_2H_5OH
40	H	C_2H_5NH	C_2H_5	C_2H_5	218, 264, 379	4.32, 3.97, 3.97	C_2H_5OH
41	H	C_2H_5NH	H	C_2H_5	219, 268, 335–350 (sh), 404	4.37, 3.96, 3.63, 4.01	C_2H_4OH
42	H	H	C_2H_5	CH_3	252 (sh), 258, 269 (sh), 319	3.59, 3.58, 3.48, 3.95	C_2H_5OH

pteridinedione-6-carboxylic acid (**64**)[21]], dimethylamino [ethyl 4-dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**38**), and the free acid **39**], ethylamino [ethyl 4-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (**40**), and the free acid **41**], or phenyl [ethyl 2-dimethylamino-4-phenyl-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (**25**)]. It should be noted that these substituents (methyl is a borderline case) are known to prevent covalent hydration at the site of substitution both in the quinazoline and pteridine ring systems.[22]

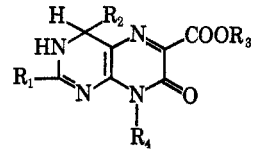
Catalytic Reduction Experiments.—In contrast to sodium borohydride, which yields yellow 3,4-dihydro derivatives exhibiting bathochromic ultraviolet absorption maxima, catalytic reduction of 8-alkyl-7(8*H*)-pteridinone-6-carboxylic acid derivatives yields isomeric 5,6-dihydro derivatives (*vide infra*) which exhibit

(21) E. C. Taylor and H. M. Loux, *J. Amer. Chem. Soc.*, **81**, 2474 (1959).

(22) A. Albert, *Angew. Chem. Int. Ed. Engl.*, **6**, 919 (1967).

TABLE II

3,4-DIHYDRO-8-ALKYL-7(8*H*)-PTERIDINONE-6-CARBOXYLIC ACID DERIVATIVES



Compd no.	R_1	R_2	R_3	R_4	Uv spectra: λ_{max}, nm	Uv spectra: Log ε	Solvent
43	CH_3	H	CH_3	CH_3	245, 270, 437	3.26, 3.09, 3.85	C_2H_5OH
44	C_6H_5	H	CH_3	CH_3	225 (sh), 260, 330 (sh), 453	3.96, 3.91, 3.54, 3.91	C_2H_5OH
45	CH_3NH	CH_3	CH_3	CH_3	263, 290, 410	3.59, 3.43, 3.99	C_2H_5OH
46	CH_3NH	CH_3	H	CH_3	265, 285, 412	3.80, 3.74, 4.20	C_2H_5OH
47	CH_3NH	H	CH_3	CH_3	245 (sh), 298, 402	3.40, 3.33, 3.64	C_2H_5OH
48	CH_3NH	H	H	CH_3	265, 288, 408	3.88, 3.78, 4.43	C_2H_5OH
49	CH_3O	H	C_2H_5	CH_3	263, 326–338 (sh), 416	3.79, 2.94, 4.34	C_2H_5OH
50	HO	H	H	CH_3	225 (sh), 253–260, 285, 402	3.85, 3.67, 3.66, 4.39	C_2H_5OH
51	HO	H	C_2H_5	CH_3	238, 269, 276–285 (sh), 425	3.88, 3.84, 3.82, 4.33	C_2H_5OH

marked hypsochromic shifts in their long wavelength absorption maxima and which are generally colorless. The preparation and properties of these latter dihydro derivatives, as well as experiments designed to probe possible interconversions between the two dihydro isomers, are described below.

Reduction of ethyl 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (**52**) with hydrogen and platinum oxide as catalyst resulted in the absorption of 1 mol of hydrogen and the formation of a precipitate which, upon isolation, proved to be identical with the sodium borohydride reduction product **53**[8] of the same pteridinone. However, examination of the uv spectrum of the filtrate showed the presence of a compound with an absorption maximum at 358 nm (compared with 390 nm for the nonreduced pteridinone **52** and 408 nm for the sodium borohydride reduction product **53**). Attempts to isolate and characterize this reduction product (which is shown later to be the 5,6-dihydro derivative **54**) led only to starting material. This lability toward air oxidation contrasts sharply with the stability of the borohydride reduction product **53**, which was indefinitely stable toward air.[8]

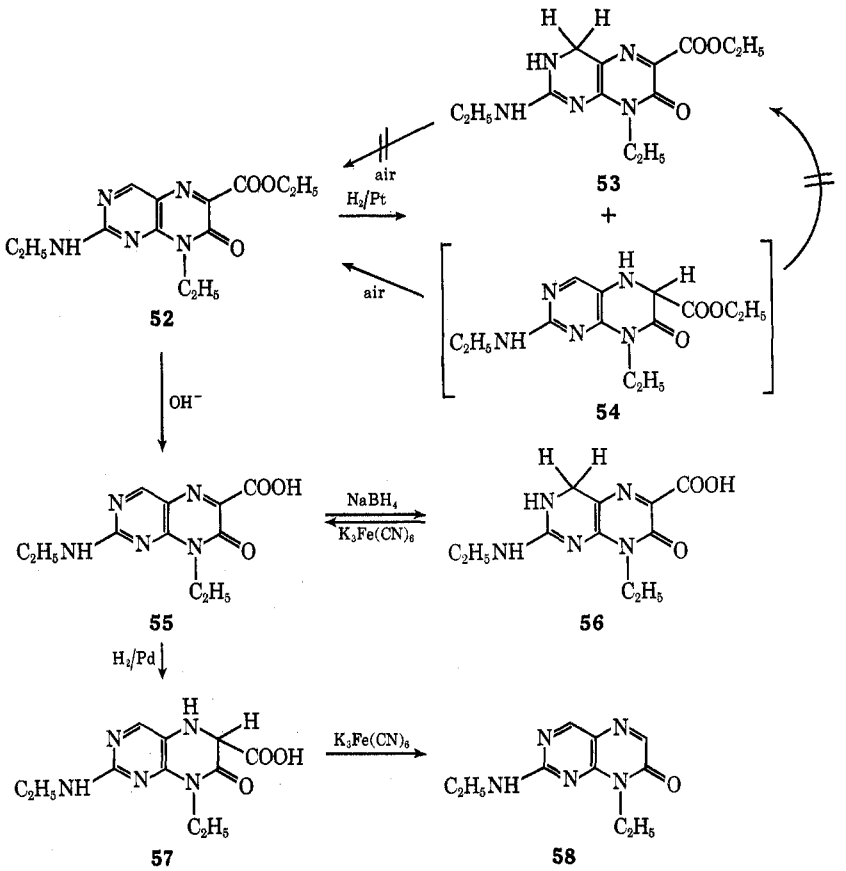
Since **53** was much less soluble than the product of catalytic reduction (*i.e.*, **54**), this system appeared to be a favorable one in which to explore possible isomerization of the latter into the former (it is conceivable that the 3,4-dihydro derivative may have been formed by initial borohydride reduction to give some other isomer, followed by tautomerization). However, the yield of the yellow 3,4-dihydro isomer **53** never exceeded 20% in catalytic reduction experiments, regardless of reaction conditions. Reductions were attempted under conditions designed to favor tautomerism (reduction in alkaline solution, reduction followed by addition of sodium borohydride), but in no case could an increase in the amount of the yellow, less soluble isomer be observed. One must conclude that, under the above conditions, there is no isomerization of the more soluble, colorless 5,6-dihydro isomer **54** to the less soluble, yellow 3,4-dihydro isomer **53**.

This conclusion was reinforced by an experiment carried out with the corresponding free acid [2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid, **55**]. Reduction with sodium borohydride has been shown to give the yellow 3,4-dihydro derivative **56**, which can be reoxidized to starting material with potassium permanganate or ferricyanide.[8] On the other hand, reduction of **55** with hydrogen in the presence of Pd/C resulted in the absorption of 1 mol of hydrogen and the formation of a colorless solution which exhibited a hypsochromic ultraviolet absorption maximum (354 nm, as contrasted with 365 nm for the starting material). Treatment of this reduction product (presumably the 5,6-dihydro derivative **57**) with potassium ferricyanide, however, resulted in loss not only of the two hydrogens but also of the carboxylic acid grouping giving 2-ethylamino-8-ethyl-7(8*H*)-pteridinone (**58**) (Scheme III). This difference in stability of the two isomeric dihydro acids is striking and emphasizes the lack of interconversion between them under the reaction conditions employed.

Isolation and characterization of the colorless 5,6-dihydro esters resulting from these catalytic reductions proved to be extremely difficult because of their lability toward reoxidation to starting material, particularly in the presence of alkali (see Experimental Section), and it was impossible to isolate the pure dihydro acids. For example, catalytic reduction of 4-dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylic acid (**39**) gave 4-dimethylamino-8-methyl-7(8*H*)-pteridinone (**61**), presumably *via* initial reduction followed by spontaneous decarboxylation and subsequent reoxidation. Parallel results were obtained in attempts to reduce 4-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (**41**); 4-ethylamino-8-ethyl-7(8*H*)-pteridinone (**63**) was the only product isolated. It is certain that decarboxylation in the above two instances takes place with the dihydro acids, and not prior to reduction, since the starting acids can be sublimed without decarboxylation.

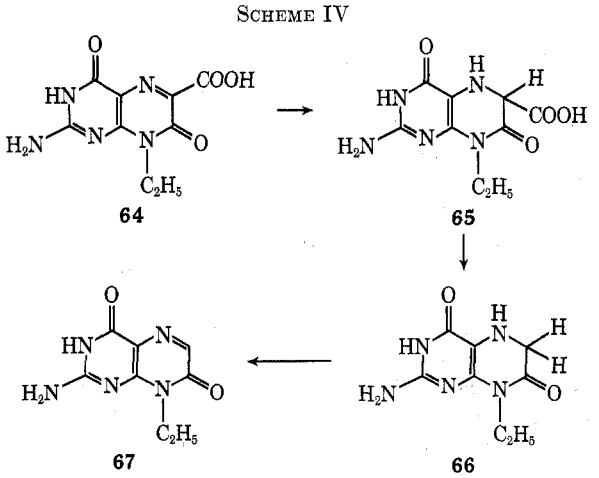
Analogous behavior was noted with 2-amino-8-ethyl-4,7(3*H*,8*H*)-pteridinedione-6-carboxylic acid (**64**),[21] which upon catalytic reduction with hydrogen and Pd in aqueous potassium hydroxide solution gave 2-amino-8-ethyl-4,7(3*H*,8*H*)-pteridinedione (**67**). The ultraviolet absorption spectrum of the initial alkaline solution before reduction showed a maximum at 366 nm which shifted to 325 nm immediately upon reduction. After acidification of the reduction mixture, however, it shifted slowly to 340 nm, and the resulting spectrum was identical with that given by a solution of 2-amino-8-ethyl-4,7(3*H*,8*H*)-pteridinedione (**67**) prepared by

SCHEME III



catalytic reduction of **64** followed by deliberate oxidation with potassium ferricyanide. Catalytic reduction of **67** resulted in loss of its bright blue fluorescence, but isolation of the (presumed) 5,6-dihydro derivative **66** was not possible because of rapid air oxidation back to starting material. We thus conclude (see Scheme IV)

SCHEME IV

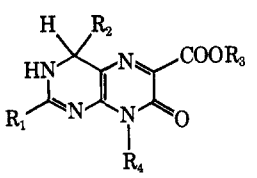


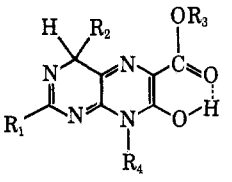
that catalytic reduction of **64** first yields the 5,6-dihydro derivative **65** (similar in structure to the other colorless 5,6-dihydro compounds, *i.e.*, **57**, discussed above), which first decarboxylates to **66** and then oxidizes to give the observed product **67**. Similar instability of dihydropteridine-6-carboxylic acids has been noted many times previously. For example, 2,4-diamino-7(8*H*)-pteridinone-6-carboxylic acid, on reduction with sodium amalgam or with zinc and alkali, yields an unstable dihydro acid which readily loses carbon dioxide to give the (presumed) 5,6-dihydro derivative.[23] Similarly, 2-amino-4,7(3*H*,8*H*)-pteridinedione-6-carboxylic acid has been reduced with zinc and alkali to give a mixture of the 5,6-dihydro acid and the decarboxylated 5,6-dihydro derivative; heating of either *in vacuo* at 150° results in ready decarboxylation and dehydrogenation to give isoxanthopterin.[23] Again, the contrast between the instability of the 5,6-dihydro acids (produced by catalytic reduction) and the stability of the isomeric 3,4-dihydro acids (produced by reduction with sodium borohydride) is remarkable.

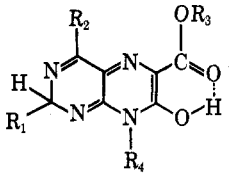
Structures of the Isomeric Dihydropteridines.—One of the most striking spectroscopic features of the dihydropteridines resulting from sodium borohydride treatment is their characteristic long wavelength uv absorption maxima, representing a bathochromic shift of some 50–60 nm as compared with the nonreduced pteridines. It is clear that a new, extended conjugated system has been introduced which, at the same time, must accommodate the observed 10,000-fold increase in base strength. Since borohydride does not normally reduce a carboxyl or amide carbonyl group (independent evidence, in any event, excludes reduction of the 6-carboxyl grouping[8]), there appear to be five structures (A–E) which must be considered (structure F is excluded by the uv data).

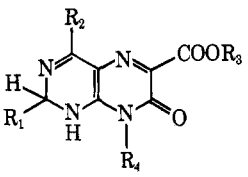
Nmr studies on the sodium borohydride reduction products clearly limit a choice to A or B. It will be seen from the data given in the Experimental Section that in a representative series of 4-unsubstituted 8-al-

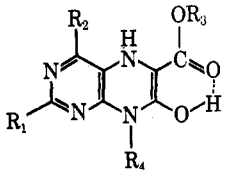
(23) G. B. Elion and G. H. Hitchings, *J. Amer. Chem. Soc.*, **74**, 3877 (1952).

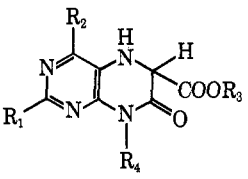

A (3,4-dihydro)


B (4,8-dihydro)


C (2,8-dihydro)


D (1,2-dihydro)


E (5,8-dihydro)


F (5,6-dihydro)

kyl-7(8*H*)-pteridinone-6-carboxylic acid derivatives the aromatic C-4 proton appears between 9.1 and 9.6 ppm, while in their respective dihydro derivatives resulting from borohydride reduction this signal disappears and is replaced by a two-proton singlet at *ca.* 5.0 ppm (CH_2 adjacent to N). Unequivocal evidence that C-4 is the site of reduction is provided by an examination of the spectrum of methyl 2-methylamino-4,8-dimethyl-7(8*H*)-pteridinone-6-carboxylate (**27**) and its sodium borohydride reduction product **45**. The C-4 methyl group, which appears as a sharp singlet at 2.96 ppm in the former compound, appears as a doublet (1.66 ppm) in the latter, while the methine proton introduced by reduction now appears as a quartet at 5.00 ppm. Analogous results were obtained with the corresponding carboxylic acid (*cf.* **28** and **46**). The nmr spectra of methyl 2,8-dimethyl-7(8*H*)-pteridinone-6-carboxylate (**22**) and its sodium borohydride reduction product **43** confirm the fact that reduction has indeed taken place at C-4 and that C-2 is unaffected.

The position of the second added hydrogen, which must reside either on nitrogen (structure A) or on oxygen (structure B), cannot be determined by nmr, since the dihydro compounds are insoluble in DMSO and other aprotic solvents, and spectra could only be obtained in trifluoroacetic acid solution. However, the ir spectra of the starting pteridinones and their sodium borohydride reduction products provide a possible criterion for this choice. All of the 7(8*H*)-pteridinone-6-carboxylic acid esters studied show the presence of two carbonyl bands, one in the 1724–1754-cm^{-1} region (ester) and the other in the 1667–1684-cm^{-1} region (cyclic lactam). In the yellow dihydro esters, however, only *one* carbonyl band appearing from 1692 to 1709 cm^{-1} is observed, and this must be due to the ester function, which is known from independent chemical evidence to be still present, unaffected by the borohydride reduction.[8] Interpreted in terms of the 4,8-dihydro structure B, the observed lowering of the frequency of the ester carbonyl band could be attributed to intramolecular hydrogen bonding of the 7-hydroxyl group to the carbonyl oxygen of the ester function.[24] It is striking (and fortuitous) that the amount of the observed shift is in approximate agreement with the shift observed in analogous systems when a hydroxyl group is introduced into a position ortho to an ester function.[25]

A similarly consistent interpretation in terms of structure B is possible when the corresponding carboxylic acids are considered. Thus, in contrast to the corresponding esters, all of the 7(8*H*)-pteridinone-6-carboxylic acids show only one carbonyl band between 1736 and 1767 cm^{-1}, which must be due to the carbonyl grouping. As a result of intramolecular hydrogen bonding between the amide carbonyl and the acid hydroxyl group, the amide band could be considered to be shifted to much lower frequencies where it would not be readily identified, with the acid carbonyl band occurring at the same frequency as the corresponding ester. In the reduction products, this single band would be shifted to much lower frequencies (1678–1706 cm^{-1}); in terms of structure B, this would be explicable as a result of a reversal of the hydrogen bonding so that the carbonyl oxygen participating is that of the carboxyl group.

On the other hand, the ir spectra of all of the sodium borohydride reduction products show a *sharp* new band at *ca.* 3300 cm^{-1}, certainly at variance with the broad band at lower frequencies expected of a strongly hydrogen-bonded –OH group.[24] This feature of their ir spectra is certainly more reasonably interpreted in terms of the 3,4-dihydro structure A. The observed shifts of the carbonyl frequencies upon reduction are also consistent with structure A; the lowered carbonyl frequency of the ester and carboxylic acid groupings is consistent with the change of environment to a vinylogous urethane, and the "disappearance" of the amide carbonyl band (present in the nonreduced pteridine esters at 1667–1684 cm^{-1}) could be due to a shift to lower frequencies because of its vinylogous urea character. The observed 10,000-fold increase in base strength[8] is better explained by the amidine structure A; this interpretation has strong precedent in the much greater base strength of the covalent hydrate of quinazoline, and of 3,4-dihydroquinazoline, as compared with quinazoline itself.[22]

The high wavelength uv absorption maxima found for all of the sodium borohydride reduction products are consistent with either structure A or B and appear to be characteristic of the system $-NR(CH{=}CH)_xC{=}O$; many examples are known which support this generalization.[26] Although the conjugated system present in structure A is considerably longer than in the examples cited,[26] competitive amide resonance involving the 7-carbonyl grouping and the 8 nitrogen must introduce dipole–dipole repulsions which would be expected to lower the importance of the former. An observation

(24) M. Tichy, *Advan. Org. Chem.*, **5**, 115 (1965).

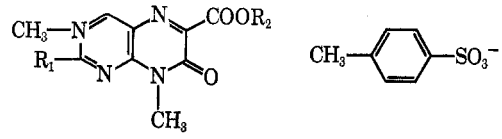
(25) The following examples are illustrative of this effect.

Ester	C=O band, cm^{-1}	Δ, cm^{-1}
Methyl benzoate	1730	47
Methyl salicylate	1683	
Methyl 1-naphthoate	1724	69
Methyl 2-hydroxy-1-naphthoate	1655	
Ethyl 2-naphthoate	1726	58
Ethyl 1-hydroxy-2-naphthoate	1668	

(26) See ref 7, p 204.

TABLE III

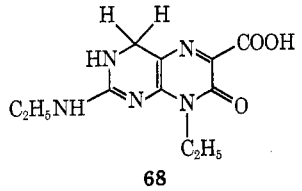
3,8-DIMETHYL-6-CARBALKOXY-7-OXO-7,8-DIHYDROPTERIDINIUM TOSYLATES



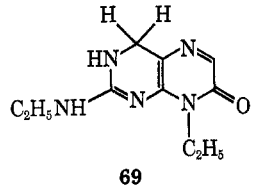
Compd no.	R_1	R_2	pK_a value[a]	Uv spectra: λ_{max}, nm	Uv spectra: Log ϵ	Solvent	Species
70	H_2N	CH_3	5.21 ± 0.06	229, 278, 339	4.56, 3.98, 4.17	pH 3	Cation
				262, 280 (sh), 393	3.97, 3.72, 4.51	pH 8	Pseudobase
71	H_2N	C_2H_5	5.13 ± 0.03	230, 278, 340	4.57, 4.00, 4.17	pH 3	Cation
				262, 280 (sh), 394	4.00, 3.75, 4.53	pH 8	Pseudobase
72	CH_3NH	CH_3	5.99 ± 0.03	230, 237, 289, 351	4.47, 4.46, 4.06, 4.14	pH 3	Cation
				264, 280 (sh), 394	4.05, 3.94, 4.47	pH 8	Pseudobase
73	CH_3NH	C_2H_5	6.06 ± 0.04	229, 237, 290, 352	4.47, 4.47, 4.07, 4.15	pH 3	Cation
				264, 280 (sh), 395	4.03, 3.85, 4.52	pH 8	Pseudobase

[a] Determined spectrophotometrically.

compatible only with structure A, and not with structure B, is the fact that 2-ethylamino-3,4-dihydro-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (**68**) and its decarboxylation product **69** (formed by sublimation of **68** *in vacuo* at 175°) have approximately the same long wavelength uv maxima.[8,27]



68



69

Conclusive evidence that the sodium borohydride reduction products are 3,4-dihydro derivatives (A) and not the 4,8-dihydro tautomers (B) was obtained as follows. A series of 8-alkyl-7(8*H*)-pteridinone-6-carboxylates substituted at position 2 with $-NH_2$, $-NHCH_3$, and $-N(CH_3)_2$ was heated with methyl *p*-toluenesulfonate. In all cases except with ethyl 2-dimethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate,[8] crystalline monomethylated pteridinium tosylates **70–73** were obtained (see Table III). The fact that the 2-dimethylamino compound was recovered unchanged under the above reaction conditions indicates that methylation probably took place on one of the ring nitrogen atoms adjacent to the 2 position (*i.e.*, N-1 or N-3), which would be expected to be sterically affected by the bulky 2-dimethylamino grouping. (Methylation on oxygen was excluded by the observation that each of the four methylpteridinium tosylates **70–73** contained only one alkoxy (ester) group by a Zeisel determination.) The similarity of the uv spectra and the pK_a values (Table III) determined for all four compounds showed that they all possessed analogous structures. The position of alkylation was then firmly established as N-3 by the observations that (a) the methylation product **71** of ethyl 2-amino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**35**) was smoothly converted by oxidation with potassium ferricyanide at pH 7 to the known 3,8-dimethylisoxanthopterin-6-carboxylic acid ethyl ester (**78**),[28] and (b) **71** underwent the Dimroth rearrangement[29] in sodium bicarbonate solution at room temperature to give ethyl 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**29**), identical with an authentic sample. Furthermore, heating **71** in pH 9 buffer resulted in a Dimroth rearrangement with accompanying saponification of the ester grouping to give 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylic acid (**31**), again identical with an authentic sample. These conversions and rearrangements are summarized in Scheme V.[30]

Sodium borohydride reduction of these 3,8-dimethylpteridinium tosylates **70–73** then gave bright yellow 3,4-dihydro derivatives (**74–77**) whose uv spectra were essentially superimposable with the uv spectra of the sodium borohydride reduction products of the parent pteridinones (see Tables II and IV). We thus confidently assign the 3,4-dihydro structure to the yellow dihydro compounds resulting from sodium borohydride reduction of all of the pteridinones discussed above. The 4,8- and 5,8-dihydro structures previously discussed[7,8] are in error and should be amended accordingly.

The structures of the colorless dihydro derivatives obtained by catalytic (and occasionally zinc dust; see Experimental Section) reduction of the above series of 8-alkyl-7(8*H*)-pteridinones were evident by examination of their uv and ir spectra, and readily confirmed by examination of their nmr spectra (Table V) to be the 5,6-dihydro isomers (structure F). Thus, the only spectral change which occurred upon catalytic reduction (best carried out in trifluoroacetic acid) of the pteridinones **21–42**, apart from a shift of the C-4 proton singlet (when present) to lower field (from ~9 to 7.7–8.3 ppm) was the appearance of a new one-

(27) It was this observation that led one of us (W. P.) to question the originally assigned 5,8- and 4,8-dihydro structures for the sodium borohydride reduction products and to favor the 3,4-dihydro structure A (see ref 7, p 207). It should be noted that decarboxylation of **68** in aqueous acid gives the isomeric 5,6-dihydro derivative (see ref 8), which arises by rearrangement of the initially formed 3,4-dihydro isomer **69**.

(28) W. Pfleiderer and M. Rukwied, *Chem. Ber.*, **95**, 1591 (1962).

(29) D. J. Brown in "Mechanisms of Molecular Migrations," Vol. 1, B. S. Thyagarajan, Ed., Interscience, New York, N.Y., 1968, p 209.

(30) It is interesting to note that the nmr spectrum of 2-methylamino-3,8-dimethyl-6-carbomethoxy-7-oxo-7,8-dihydropteridinium tosylate (**72**) in trifluoroacetic acid shows the 2-methylamino grouping as a doublet. That the splitting of the methyl signal was due to coupling with the adjacent NH was demonstrated by a decoupling experiment (irradiation at −258 Hz). Apparently proton exchange at the 2-NH group is slow even in trifluoroacetic acid because of steric hindrance by the methyl group. Further evidence for this steric effect is seen in a comparison of the pK_a values for the 3,4-dihydro derivatives **74–77** (Table IV). The two 2-CH_3NH derivatives **76** and **77** are actually *weaker* bases than the 2-NH_2 derivatives **74** and **75**; this observation provides indirect evidence that protonation in these compounds occurs at N-1.

SCHEME V

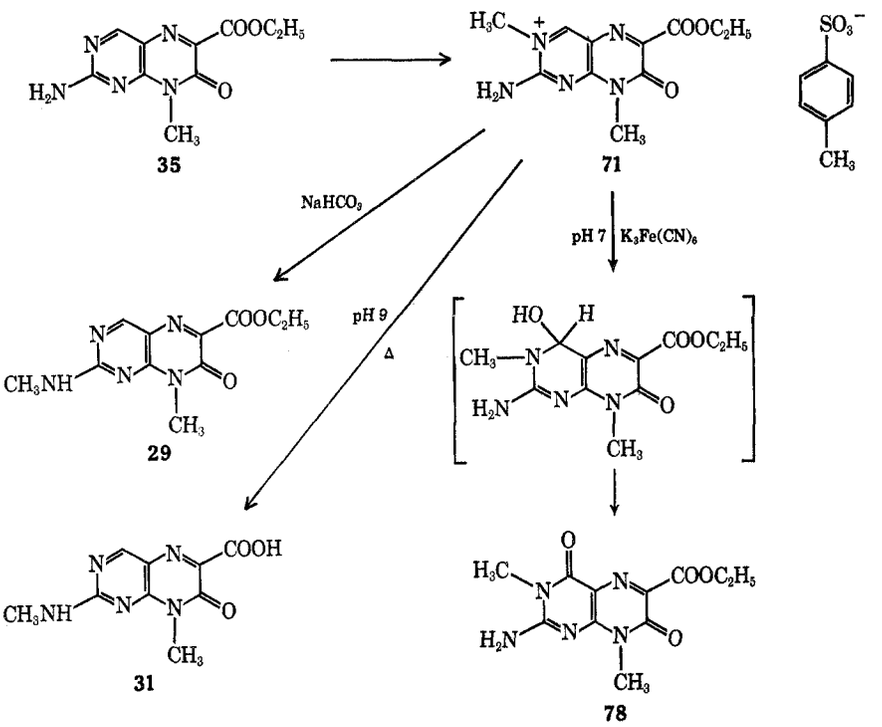
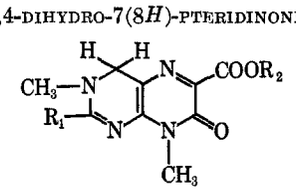


TABLE IV

3,8-DIMETHYL-3,4-DIHYDRO-7(8*H*)-PTERIDINONE-6-CARBOXYLATES



Compd no.	R_1	R_2	pK_a value[a]	Uv spectra: λ_{max}, nm	Uv spectra: Log ϵ	Solvent	Species[b]
74	H_2N	CH_3	1.66 ± 0.12	230, 392	4.05, 4.20	pH −1	Cation
				242, 269, 290 (sh), 408	4.0, 3.9, 3.69, 4.43	pH 6	O
75	H_2N	C_2H_5	1.85 ± 0.05	230, 392	4.05, 4.23	pH 0	Cation
				242, 268, 290 (sh), 408	3.99, 3.90, 3.67, 4.43	pH 6	O
76	CH_3NH	CH_3	0.55 ± 0.05	287, 390	3.61, 4.22	pH −1	Cation
				240, 272, 405	3.84, 4.00, 4.44	pH 4	O
77	CH_3NH	C_2H_5	0.65 ± 0.05	290, 390	3.62, 4.20	pH −1	Cation
				240, 373, 408	3.88, 3.99, 4.44	pH 5	O

[a] Determined spectrophotometrically. [b] O denotes the neutral species.

proton methine singlet at ~5.1 ppm, arising from reduction at C-6.

In an attempt to determine the nmr spectra of the yellow 3,4-dihydro isomers in trifluoroacetic acid, it was noted that a rapid change occurred even at room temperature; the 4-methine signal disappeared and was replaced by a one-proton methine singlet at about 5.1 ppm, while an aromatic one-proton singlet appeared at 7.7–8.3 ppm in the 4-unsubstituted compounds. Indeed, these latter spectra were identical with the spectra of solutions of the starting pteridinones in trifluoroacetic acid which had been reduced with hydrogen and platinum and with the spectra of trifluoroacetic acid solutions of the isolated, colorless 5,6-dihydro compounds obtained by catalytic reduction in water or ethanol (*vide supra*). It is thus evident that rearrangement of the 3,4- to the 5,6-dihydro isomers occurs in trifluoroacetic acid solution; this change represents the long sought isomerization (even if irreversible) between the two series of dihydro compounds.

The various interconversions among the 3,4- and 5,6-dihydro isomers discussed above are summarized in Scheme VI.

Experimental Section[31]

2-Methyl-4-methylamino-6(1*H*)-pyrimidinone (3).—A mixture of 30.0 g of 2-methyl-4-amino-6(1*H*)-pyrimidinone[17] and 120 g of methylamine hydrochloride was heated in an oil bath for 30 min

(31) All melting points were determined on a Thomas-Hoover silicone oil bath apparatus and are uncorrected. Microanalyses were performed by the Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., Spang Microanalytical Laboratories, Ann Arbor, Mich., and Dr. G. Robertson, Florham Park, N. J. Uv spectra were determined on a Cary Model 11 recording ultraviolet spectrophotometer, ir spectra on a Perkin-Elmer Model 237B Infracord by the normal Nujol mull technique, and nmr spectra on a Varian A-60 instrument, using TMS as internal standard in CF_3COOH as solvent (unless otherwise indicated).

SCHEME VI

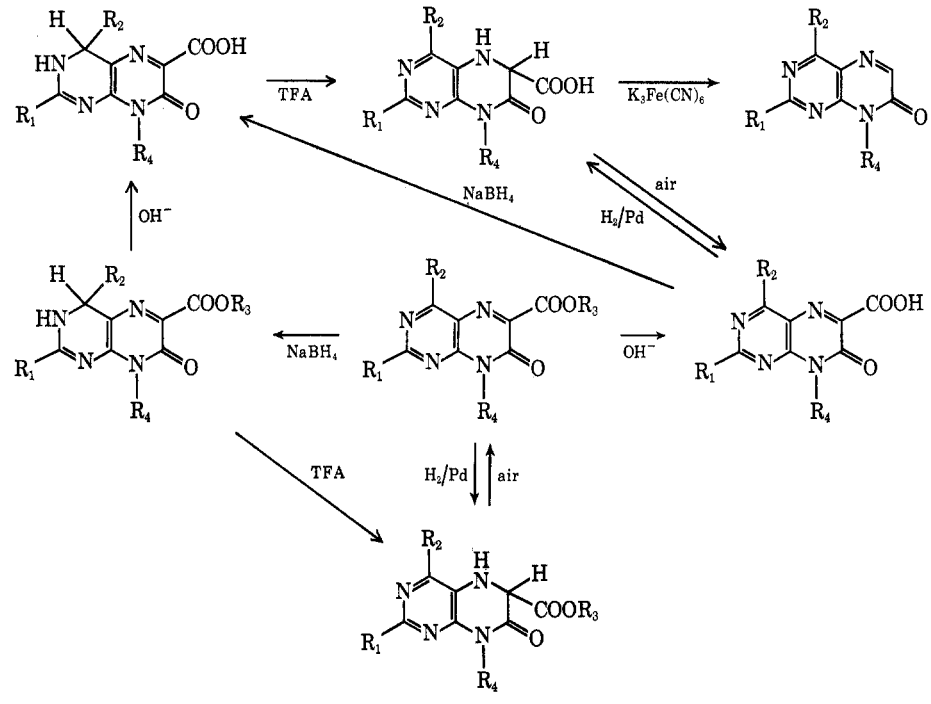
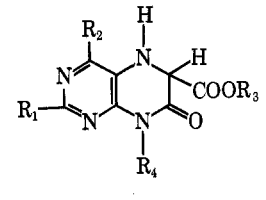


TABLE V

NMR SPECTRA OF REPRESENTATIVE 5,6-DIHYDRO-8-ALKYL-7(8*H*)-PTERIDINONE-6-CARBOXYLIC ACID DERIVATIVES[a]



Substrate compd no.	Chemical shift of substituent, ppm R1	R2	C6-H
22	2.83 (s, 3)	8.15 (s, 1)	5.28 (s, 1)
24	7.70 (m, 3)	8.30 (s, 1)	5.43 (s, 1)
	8.10 (m, 2)		
25	3.40 (s, 6)	7.70 (s, 5)	5.13 (s, 1)
27	3.18 (s, 3)	2.55 (s, 3)	5.15 (s, 1)
28	3.13 (s, 3)	2.50 (s, 3)	5.17 (s, 1)
30	3.20 (s, 3)	7.70 (s, 1)	5.15 (s, 1)
31	3.16 (s, 3)	7.70 (s, 1)	5.20 (s, 1)

[a] These 5,6-dihydro compounds were prepared in CF_3COOH solution by hydrogenation with H_2–Pd/C or H_2–PtO_2. Reduction was complete within 30 min; the catalyst was then removed by filtration and the nmr spectrum of the filtrate determined at room temperature [see A. Bobst and M. Viscontini, *Helv. Chim. Acta*, **49**, 875 (1966)].

with the internal temperature of the melt maintained at 190–195°. At the end of this time, the melt was cooled to about 100° and dissolved in 150 ml of warm water. The resulting solution was cooled to 0°, and the crystals which separated were collected by filtration (25 g) and recrystallized from water, mp 279–281° dec (lit.[11] mp 282° dec), yield 31.2 g (94%). Despite the agreement with the literature melting point, inspection of the nmr spectrum of this product indicated that it contains approximately 5–10% of unchanged 2-methyl-4-amino-6(1*H*)-pyrimidinone. This proved to be inconsequential, however, since the residual starting material was eliminated in the nitration step (see below).

2-Methyl-4-methylamino-5-nitro-6(1*H*)-pyrimidinone (5).—Over a period of 10 min, 6.0 g of 2-methyl-4-methylamino-6(1*H*)-pyrimidinone was added to a mixture of 60 ml of fuming nitric acid and 24 ml of glacial acetic acid at 30–32°. The mixture was stirred at this temperature for an additional 30 min and then poured into ice–water, and the precipitated solid was collected by filtration, washed with water, and dried, yield 4.3 g (55%), mp 301–302° dec. Recrystallization from dimethylformamide did not change the melting point.

Anal. Calcd for $C_6H_8N_4O_3$: C, 39.13; H, 4.38; N, 30.43. Found: C, 39.12; H, 4.51; N, 30.54.

Ethyl 2,8-Dimethyl-7(8*H*)-pteridinone-6-carboxylate (21).—A solution of 3.5 g of 2-methyl-4-methylamino-5-nitro-6(1*H*)-pyrimidinone in 35 ml of phosphorus oxychloride was heated under reflux, with stirring, for 1.5 hr, the excess phosphorus oxychloride removed by distillation under reduced pressure, and the residual gum crystallized from ether. The resulting yellow, crystalline 2-methyl-4-methylamino-5-nitro-6-chloropyrimidine (7) was dissolved in 40 ml of ethanol and 40 ml of water containing 10 g of magnesium oxide and 1 g of palladium-on-carbon catalyst, and the mixture was hydrogenated at 60 psi in a Parr shaker. Hydrogen uptake was very rapid and was complete within 10 min. The reduction mixture was filtered and 3.80 g of diethyl mesoxalate was added to the filtrate. The resulting solution was heated under reflux for 30 min, the ethanol evaporated under reduced pressure, and the residual solid recrystallized from ethanol to give 2.0 g (40%) of yellow crystals, mp 94–95°.

Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.33; H, 4.93; N, 22.50.

Methyl 2,8-Dimethyl-7(8*H*)-pteridinone-6-carboxylate (22).—A solution of 1.0 g of ethyl 2,8-dimethyl-7(8*H*)-pteridinone-6-carboxylate in 25 ml of methanol containing a few crystals of thorium nitrate was heated under reflux for 24 hr and cooled, and the red crystals of the methyl ester were collected by filtration: yield 0.75 g (80%); mp 153–154°; ir 1675 (C_7-C=O), 1725 cm^{-1} (ester); nmr δ 9.41 (s, 1, C_4-H), 3.33 (s, 3, C_2-CH_3).

Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.31; H, 4.37; N, 23.86.

2-Phenyl-4-methylamino-6(1*H*)-pyrimidinone (4).—A mixture of 20 g of 2-phenyl-4-amino-6(1*H*)-pyrimidinone[19] and 80 g of methylamine hydrochloride was stirred and heated at 235–240° (internal temperature) for 45 min. The melt was then cooled to about 100°, digested with 150 ml of warm water, and cooled, and the precipitate was collected by filtration, yield 14.7 g (70%), mp 255–257°. The compound was recrystallized for analysis from dimethylformamide; the crude product (containing some 10% of unchanged starting material by nmr) could be used directly in the next step.

Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.50; H, 5.27; N, 20.79.

2-Phenyl-4-methylamino-5-nitro-6(1*H*)-pyrimidinone (6).—To a mixture of 12 ml of fuming nitric acid and 60 ml of glacial acetic acid at 25–30° was added, over a period of 15 min, 10.8 g of

2-phenyl-4-methylamino-6(1*H*)-pyrimidinone. The mixture was stirred for an additional 15 min and then poured into 150 ml of ice–water. The resulting purple solid was collected by filtration, washed well with water, and then recrystallized from aqueous dimethylformamide to give 9.3 g (78%) of cream-colored crystals, mp 330–332° dec.

Anal. Calcd for $C_{11}H_{10}N_4O_3$: C, 53.64; H, 4.09; N, 22.76. Found: C, 53.47; H, 3.96; N, 22.51.

Ethyl 2-Phenyl-8-methyl-7(8*H*)-pteridinone-6-carboxylate (23).—A suspension of 6.0 g of 2-phenyl-4-methylamino-5-nitro-6-(1*H*)-pyrimidinone in 60 ml of phosphorus oxychloride was heated under reflux with stirring for 2.5 hr. A homogeneous solution resulted after about 1 hr of heating. The excess phosphorus oxychloride was removed by distillation under reduced pressure and the residual solid recrystallized from ether to give 4.35 g of 2-phenyl-4-methylamino-5-nitro-6-chloropyrimidine (**8**). This material was dissolved in 120 ml of 50% aqueous ethanol containing 12 g of magnesium oxide and 2.0 g of Pd/C catalyst and hydrogenated in a Parr apparatus until hydrogen uptake was complete (about 20 min). The reduction mixture was filtered, and to the filtrate was added 4.0 g of diethyl mesoxalate. The mixture was heated under reflux for 30 min and filtered, and the collected colorless solid recrystallized from ethanol to give 2.75 g (58%): mp 203–204°; ir 1690 (C_7-C=O), 1760 cm^{-1} (ester); nmr δ 9.51 (s, 1, C_4-H).

Anal. Calcd for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06. Found: C, 62.05; H, 4.47; N, 18.15.

Methyl 2-Phenyl-8-methyl-7(8*H*)-pteridinone-6-carboxylate (24).—Heating a solution of 1.0 g of ethyl 2-phenyl-8-methyl-7(8*H*)-pteridinone-6-carboxylate for 24 hr in 100 ml of methanol resulted in the separation of 0.95 g of pure methyl ester: mp 202–203°; ir 1675 (C_7-C=O), 1750 cm^{-1} (ester); nmr δ 9.61 (s, 1, C_4-H).

Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.80; H, 4.08; N, 18.91. Found: C, 60.60; H, 4.20; N, 18.82.

2-Dimethylamino-4-phenyl-6(1*H*)-pyrimidinone (11).—A solution of 46 g (0.17 mol) of dimethylguanidine sulfate in 240 ml of methanol containing 8.5 g (0.37 mol) of sodium was heated under reflux for 30 min, the precipitated sodium sulfate filtered off, and 66 g (0.34 mol) of ethyl benzoylacetate added to the filtrate. The resulting solution was heated under reflux for 18 hr, the excess methanol removed by distillation under reduced pressure, and the semicrystalline residue dissolved in water. The pH was adjusted to 6–7 with acetic acid and the precipitated colorless crystals were collected by filtration, yield 26.7 g (37%), mp 240–241° (acetophenone separated from the filtrate as an oil). Recrystallization of the solid from methanol raised the melting point to 242–243°.

Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.52. Found: C, 66.95; H, 6.16; N, 19.80.

2-Dimethylamino-4-phenyl-5-nitroso-6(1*H*)-pyrimidinone (12).—To a solution of 10.5 g of 2-dimethylamino-4-phenyl-6(1*H*)-pyrimidinone in 40 ml of 5 *N* sulfuric acid was added 4.0 g of sodium nitrite dissolved in 15 ml of water. The mixture was stirred at room temperature for 4 hr, solid sodium acetate added to pH 6, and the precipitated solid collected by filtration and washed well with water, yield 11.3 g (92%). The analytical sample melted at 133–134° after recrystallization from ethanol.

Anal. Calcd for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.03; H, 5.07; N, 22.87.

2-Dimethylamino-4-phenyl-5-nitro-6(1*H*)-pyrimidinone (13). Method A.—Aqueous 30% hydrogen peroxide (8 ml) was added dropwise over a period of 1 hr to a stirred solution of 4.0 g of 2-dimethylamino-4-phenyl-5-nitroso-6(1*H*)-pyrimidinone in 40 ml of trifluoroacetic acid.[20] The temperature of the mixture was maintained below 40°. The initial brown solution had become pale yellow after 6 hr of stirring; it was then diluted with 200 ml of cold water and the precipitated solid collected by filtration and washed well with cold water, yield 2.2 g (52%), mp 277–278° dec (after recrystallization from dimethylformamide).

Method B.—To a cooled mixture of 50 ml of glacial acetic acid and 10 ml of fuming nitric acid was added slowly, and with stirring, 10 g of 2-dimethylamino-4-phenyl-6(1*H*)-pyrimidinone; the temperature of the mixture was maintained below 20°. The mixture was stirred at room temperature for 15 min and then poured into 150 ml of ice–water and filtered and the product was washed well with water, yield 9.8 g (75%), mp 274–276° dec.

Anal. Calcd for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.55; H, 4.72; N, 21.60.

2-Dimethylamino-4-phenyl-5-nitro-6-ethylaminopyrimidine (15).—A mixture of 5.5 g of 2-dimethylamino-4-phenyl-5-nitro-6(1*H*)-pyrimidinone and 55 ml of phosphorus oxychloride was heated under reflux for 2 hr and evaporated under reduced pressure, and the residual crystalline 6-chloro compound **14** was dissolved in 500 ml of ether and filtered (to remove a small amount of insoluble impurity). To the cooled, stirred ether solution was added 60 ml of 30% aqueous ethylamine, and the two-phase system was stirred overnight. The ether layer was evaporated, the aqueous solution was diluted with an additional 100 ml of water, and the precipitated yellow crystals were filtered, washed well with water, and dried, yield 5.5 g (92%), mp 123–125°.

Anal. Calcd for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.38. Found: C, 58.32; H, 5.95; N, 24.62.

Ethyl 2-Dimethylamino-4-phenyl-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (25).—A solution of 4.45 g of 2-dimethylamino-4-phenyl-5-nitro-6-ethylaminopyrimidine in 75 ml of ethanol containing 0.4 g of Pd/C catalyst was hydrogenated in a Parr apparatus at room temperature until hydrogen uptake was complete. The mixture was filtered, the filtrate evaporated to 35 ml, 4.0 g of diethyl mesoxalate added, and the solution then heated under reflux for 2 hr. Cooling resulted in the separation of 3.65 g (74%) of orange crystals, mp 132–134°, which were recrystallized from ethanol: ir 1675 (C_7-C=O), 1740 cm^{-1} (ester).

Anal. Calcd for $C_{19}H_{21}N_5O_3$: C, 62.11; H, 5.76; N, 19.06. Found: C, 62.26; H, 5.73; N, 19.19.

2,6-Bis(methylamino)-4-methyl-5-nitropyrimidine (17), mp 234–235°, was prepared by the procedure described[8] for the preparation of 2,6-bis(ethylamino)-4-methyl-5-nitropyrimidine, except that methylamine was employed instead of ethylamine.

Anal. Calcd for $C_7H_{11}N_5O_2$: C, 42.63; H, 5.62; N, 35.52. Found: C, 42.42; H, 5.69; N, 35.60.

Ethyl 2-Methylamino-4,8-dimethyl-7(8*H*)-pteridinone-6-carboxylate (26).—A suspension of 15.0 g of 2,6-bis(methylamino)-4-methyl-5-nitropyrimidine in 150 ml of ethanol containing 1.8 g of 10% Pd/C catalyst was hydrogenated in a Parr apparatus at room temperature until hydrogen uptake was complete (about 15 min). The catalyst was removed by filtration, and to the filtrate was added 14.5 g of diethyl mesoxalate. The mixture was heated under reflux for 15 min, cooled, and filtered to give 17.0 g (81%) of yellow crystals, mp 220–222°, which were recrystallized from ethanol: ir 1675 (C_7-C=O), 1745 cm^{-1} (ester).

Anal. Calcd for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 51.87; H, 5.41; N, 25.32.

The corresponding methyl ester **27**, mp 254–255°, was prepared in the usual manner by transesterification in methanol: nmr δ 2.96 (s, 3, C_2-CH_3).

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.61. Found: C, 50.22; H, 4.95; N, 26.62.

2-Methylamino-4,8-dimethyl-7(8*H*)-pteridinone-6-carboxylic acid (28) was prepared from the ethyl (or methyl) ester by heating for 30 min with 0.1 *N* sodium hydroxide, followed by acidification of the alkaline solution. The free acid was obtained as yellow crystals, mp 259–260° dec, upon recrystallization from dimethylformamide: ir 1765 cm^{-1} (acid); nmr δ 3.07 (s, 3, C_2-CH_3).

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.38; H, 4.52; N, 28.12.

2,4-Bis(methylamino)-5-nitropyrimidine (18), mp 260–261°, was prepared as described[8] for the corresponding 2,4-bis(ethylamino) compound except that methylamine was used instead of ethylamine.

Anal. Calcd for $C_6H_9N_5O_2$: C, 39.34; H, 4.95; N, 38.24. Found: C, 39.58; H, 4.96; N, 38.30.

Ethyl 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (29) was prepared essentially by the method described[8] for the preparation of ethyl 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate except that the ethanol solution of 2,4-bis(methylamino)-5-aminopyrimidine (from the catalytic reduction) was treated directly with diethyl mesoxalate. The product was obtained as glistening yellow needles, mp 197–198° dec, upon recrystallization from ethanol.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.61. Found: C, 50.35; H, 5.02; N, 26.48.

The methyl ester **30**, mp 245–246° (from water), was prepared by transesterification in the usual manner by refluxing in methanol with a crystal of thorium nitrate as catalyst: ir 1675 (C_7-C=O), 1750 cm^{-1} (ester); nmr δ 9.00 (s, 1, C_4-H).

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.31; H, 4.44; N, 28.18.

2-Methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylic acid (31) was prepared from the above methyl ester by heating in 0.5 *N* sodium hydroxide solution for 3 hr, followed by acidification. The free acid, mp 247–248° dec, was recrystallized from dimethylformamide for analysis: ir 1680 (C_7-C=O), 1712 cm^{-1} (acid); nmr δ 9.23 (s, 1, C_4-H).

Anal. Calcd for $C_9H_9N_5O_3$: C, 45.96; H, 3.86; N, 29.78. Found: C, 46.05; H, 3.95; N, 29.72.

Ethyl 2-Methoxy-8-methyl-7(8*H*)-pteridinone-6-carboxylate (32).—A solution of 1.5 g of 2-methoxy-4-methylamino-5-nitropyrimidine[32] in 50 ml of ethanol was reduced under 3 atm of hydrogen, using 5% Pd/C as catalyst. After hydrogen uptake had ceased, the mixture was filtered and 3 ml of diethyl mesoxalate was added to the filtrate. The solution was then heated under reflux for 2 hr and evaporated to a small volume, and 50 ml of water was added to the syrupy residue, whereupon the product separated as a pale yellow solid, mp 99–102°, yield 1.5 g (70%). Recrystallization from water gave white needles: mp 100–102°; ir 1677 (C_7-C=O), 1739 cm^{-1} (ester).

Anal. Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.68; H, 4.52; N, 20.94.

2-Hydroxy-8-methyl-7(8*H*)-pteridinone-6-carboxylic Acid (33). Method A.—A solution of 0.50 g of 2-hydroxy-4-methylamino-5-nitropyrimidine[33] in 50 ml of water containing 2 equiv of sodium hydroxide was reduced under 3 atm of hydrogen, using 5% Pd/C as catalyst, until hydrogen absorption had ceased. The mixture was filtered, 1.0 g of sodium mesoxalate added to the filtrate, and the resulting solution heated under reflux for 2 hr. The mixture was then cooled and hydrochloric acid added to pH 5. Filtration gave 0.46 g (65%) of an orange solid which was purified by reprecipitation from alkaline solution. The pale yellow solid turned green upon heating above 230° and then slowly decomposed without melting up to 320°.

Anal. Calcd for $C_8H_6N_4O_4 \cdot H_2O$: C, 40.00; H, 3.36; N, 23.33. Found: C, 40.32; H, 3.48; N, 23.60.

Method B.—Heating a solution of 0.50 g of ethyl 2-methoxy-8-methyl-7(8*H*)-pteridinone-6-carboxylate in 50 ml of 0.1 *N* sodium hydroxide for 30 min on a steam bath followed by acidification gave 0.40 g (88%) of a yellow solid identical in all respects with the product obtained by method A.

Ethyl 2-Hydroxy-8-methyl-7(8*H*)-pteridinone-6-carboxylate (34).—A solution of 0.50 g of 2-hydroxy-4-methylamino-5-nitropyrimidine in 50 ml of water was reduced as described above, the catalyst removed by filtration, 1.0 ml of diethyl mesoxalate added to the filtrate, and the mixture heated under reflux for 1.5 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residue triturated with water and filtered to give 0.49 g (67%) of a gray solid, mp 253–256° dec. Recrystallization from ethanol gave small brown needles, mp 258–260° dec.

Anal. Calcd for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.02; N, 22.39. Found: C, 47.92; H, 4.28; N, 22.62.

Ethyl 2-Amino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (35).—A suspension of 1.60 g of 2-amino-4-methylamino-5-nitropyrimidine[34] in 100 ml of ethanol was reduced under 3 atm of hydrogen, using 5% Pd/C as catalyst, until hydrogen absorption ceased. The reduction mixture was filtered, 3 ml of diethyl mesoxalate added to the filtrate, and the mixture heated under reflux for 1 hr. Evaporation to a small volume under reduced pressure followed by dilution with water and chilling resulted in the crystallization of 1.71 g (72%) of glistening yellow needles, mp 201–203°. Recrystallization from ethanol did not affect the melting point: ir ($HCCl_3$) 1681 (C_7-C=O), 1739 cm^{-1} (ester).

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.18; H, 4.37; N, 28.19.

Methyl 2-Amino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (36).—This compound was prepared from 2-amino-4-methylamino-5-nitropyrimidine and dimethyl mesoxalate as described above, yield 54%, mp (from water) 237°.

Anal. Calcd for $C_9H_9N_5O_3$: C, 45.96; H, 3.86; N, 29.78. Found: C, 46.11; H, 3.84; N, 29.84.

2-Amino-8-methyl-7(8*H*)-pteridinone-6-carboxylic Acid (37).—A suspension of 1.10 g of 2-amino-4-methylamino-5-nitropyrimidine[34] in 80 ml of ethanol was reduced as described above and filtered, and the filtrate was evaporated to dryness. A solution of 1.5 g of sodium mesoxalate in 30 ml of water was added to the residue, and the mixture was heated under reflux for 2 hr. Acidification with hydrochloric acid resulted in the separation of 0.50 g (35%) of a yellow solid which was purified by acidification of a hot solution of the potassium salt. The product was obtained as fine, mustard-yellow needles, mp 258° dec, which then resolidified and remelted at 293–295°: ir 1754 cm^{-1} (acid).

Anal. Calcd for $C_8H_7N_5O_3$: C, 43.44; H, 3.19; N, 31.67. Found: C, 43.18; H, 3.35; N, 31.76.

4-Methylamino-5-nitro-6-dimethylaminopyrimidine (19).—A suspension of 3.0 g of 4-chloro-5-nitro-6-dimethylaminopyrimidine[35] in 50 ml of ethanol was treated with 10 ml of 25% aqueous methylamine. The reaction mixture became warm and the chloropyrimidine dissolved. Evaporation under reduced pressure followed by crystallization of the residue from water gave 1.7 g (58%) of fine, pale yellow needles, mp 101–101.5° (lit.[36] mp 96–97°).

Anal. Calcd for $C_7H_{11}N_5O_2$: C, 42.63; H, 5.62; N, 35.52. Found: C, 42.80; H, 5.79; N, 35.61.

Ethyl 4-Dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (38).—A solution of 4.0 g of 4-methylamino-5-nitro-6-dimethylaminopyrimidine in 100 ml of ethanol was reduced with hydrogen, using 5% Pd/C as catalyst, until rapid hydrogen absorption ceased. The mixture was filtered to remove the catalyst, 8 ml of diethyl mesoxalate was added to the filtrate, and the resulting solution was heated under reflux for 1 hr. Evaporation under reduced pressure to 30 ml, dilution with water, and chilling to 0° resulted in the separation of 4.3 g (76%) of a bright yellow solid, mp 122–123°. Recrystallization from aqueous ethanol gave fine, canary-yellow needles: mp 124–125°; ir ($HCCl_3$) 1667 (C_7-C=O), 1733 cm^{-1} (ester).

Anal. Calcd for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 52.18; H, 5.54; N, 25.54.

4-Dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylic Acid (39).—A mixture of 2.0 g of ethyl 4-dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate, 2 g of sodium hydroxide and 100 ml of water was allowed to stand at room temperature for 14 hr. The resulting solution was carefully acidified with hydrochloric acid. Filtration then gave 1.6 g (89%) of a yellow solid, mp 209–210°. Recrystallization from aqueous ethanol yielded fine, brilliant yellow needles, mp 210–211°. The acid could be sublimed *in vacuo* without decarboxylation: ir ($HCCl_3$) 1761 cm^{-1} (acid).

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 47.94; H, 4.60; N, 28.22.

4,6-Bis(ethylamino)-5-nitropyrimidine (20).—A solution of 10.0 g of 4,6-dichloro-5-nitropyrimidine in 150 ml of ethanol was treated with an excess of aqueous ethylamine (70%). A vigorous reaction ensued with the separation of 8.2 g (76%) of pale yellow needles, mp 86–87°. Recrystallization from ethanol raised the melting point to 87–88°.

Anal. Calcd for $C_8H_{13}N_5O_2$: C, 45.49; H, 6.20; N, 33.16. Found: C, 45.50; H, 6.39; N, 33.42.

Ethyl 4-Ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (40).—A solution of 2.14 g of 4,6-bis(ethylamino)-5-nitropyrimidine in 100 ml of ethanol was reduced with hydrogen, using 5% Pd/C as catalyst. After hydrogen uptake had ceased, several milliliters of ethanolic hydrogen chloride were added, the mixture filtered, and 3.5 ml of diethyl mesoxalate added to the filtrate. The mixture was heated under reflux for 30 min, the ethanol removed by evaporation under reduced pressure, and the residue triturated with 50 ml of water. Filtration gave 2.30 g (81%) of a yellow-green solid, mp 88–93°. Recrystallization from aqueous ethanol gave long golden-yellow needles: mp 93–95°; ir ($HCCl_3$) 1667 (C_7-C=O), 1733 cm^{-1} (ester).

Anal. Calcd for $C_{13}H_{17}N_5O_3$: C, 53.60; H, 5.88; N, 24.04. Found: C, 53.85; H, 6.02; N, 24.01.

4-Ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic Acid. (41).—A solution of 0.60 g of ethyl 4-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate in 40 ml of water containing 0.6 g of sodium hydroxide was stirred at room temperature overnight, cooled, and acidified with hydrochloric acid. Filtration yielded 0.45 g (83%) of a bright yellow solid, mp 186–189°. Recrystallization from water gave bright yellow needles, mp 191–193°. The acid could be sublimed *in vacuo* without change: ir ($HCCl_3$) 1751 cm^{-1} (acid).

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Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.61. Found: C, 50.32; H, 5.14; N, 26.93.

Ethyl 8-Methyl-7(8*H*)-pteridinone-6-carboxylate (42).—A solution of 2.0 g of 4-methylamino-5-aminopyrimidine[32a] and 5.0 g of diethyl mesoxalate in 10 ml of ethanol was heated under reflux for 2 hr and then diluted with 10 ml of water. Chilling resulted in the separation of 3.5 g (93%) of white needles, mp 115–116°, which were recrystallized from aqueous ethanol: ir (CCl_4) 1695 (C_7-C=O), 1758 cm^{-1} (ester).

Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.30; H, 4.52; N, 23.66.

Reduction with Sodium Borohydride. General Procedure.—A solution of 0.01 mol of the 7(8*H*)-pteridinone-6-carboxylate in 20 ml of dimethylformamide was treated with 0.015 mol of sodium borohydride. The resulting mixture was stirred at room temperature for 30 min and diluted with water and the excess sodium borohydride was decomposed by the cautious addition of dilute acetic acid. The precipitated orange solid was collected by filtration, washed well with water, and dried. The dihydro acids were reduced analogously but in 1 *N* sodium hydroxide solution. When solubility permitted, the 3,4-dihydro compounds were recrystallized from hot dimethylformamide.

Methyl 2,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (43): mp 265–266° dec (75% yield); ir 1705 cm^{-1} (ester); nmr δ 2.75 (s, 3, C_2-CH_3), 5.12 (br s, 2, C_4-H) (at −15°).

Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.61; H, 5.19; N, 23.91.

Methyl 2-phenyl-8-methyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (44): mp 210–211° dec (30% yield); ir (1720 cm^{-1} (ester); nmr δ 5.20 (br s, 2, C_4-H) (at −15°).

Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73; N, 18.78. Found: C, 60.12; H, 4.96; N, 18.65.

Methyl 2-methylamino-4,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (45): mp 242–244° dec (rapid heating) (90% yield); ir 1700 cm^{-1} (ester); nmr δ 5.00 (q, 1, C_4-H) (at room temperature), 1.66 (d, 3, C_4-CH_3) (at −15°).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.70; N, 26.40. Found: C, 49.72; H, 5.86; N, 26.48.

2-Methylamino-4,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylic acid (46): mp 235–237° dec (78% yield); ir 1720 cm^{-1} (acid); nmr δ 5.18 (q, 1, C_4-H), 1.83 (d, 3, C_4-CH_3) (at −15°).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.83; H, 5.09; N, 27.70.

Methyl 2-methylamino-8-methyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (47): mp 278–280° dec (35% yield); ir 1700 cm^{-1} (ester); nmr δ 4.98 (br s, 2, C_4-H) (at −15°).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.76; H, 5.39; N, 27.70.

2-Methylamino-8-methyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylic acid (48): mp 270–272° dec (60% yield); ir 1705 cm^{-1} (acid); nmr δ 4.98 (br s, 2, C_4-H) (at −15°).

Anal. Calcd for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.53. Found: C, 45.68; H. 4.71; N, 29.58.

Ethyl 2-methoxy-8-methyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (49): mp 267–268° dec (36% yield); ir 1709 cm^{-1} (ester).

Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.85; H, 5.42; N, 21.00.

8-Methyl-3,4-dihydro-2,7(1*H*,8*H*)-pteridinedione-6-carboxylic acid (50): mp 277–278° dec (70% yield; the same compound was prepared in 71% yield by alkaline hydrolysis of ethyl 2-methoxy-8-methyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate).

Anal. Calcd for $C_8H_8N_4O_4$: C, 42.86; H, 3.60; N, 24.99. Found: C, 43.03; H, 3.49; N, 25.21.

Ethyl 8-methyl-3,4-dihydro-2,7(1*H*,8*H*)-pteridinedione-6-carboxylate (51): mp 305–307° dec (75% yield).

Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.68; H, 4.92; N, 22.03.

Catalytic Reduction of Ethyl 2-Ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (52).—To a solution of 0.30 g of **52**[8] in 250 ml of ethanol was added 0.2 g of PtO_2 catalyst and the mixture was shaken with hydrogen in a Parr apparatus for 2 hr at room temperature. It was then heated to boiling and filtered, and the filtrate was cooled and filtered to give 0.06 g (19%) of a bright yellow solid, mp 298°, identical with an authentic sample of ethyl 8-ethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (**53**) prepared by the reduction of **52** with sodium borohydride.[8,37]

(37) This compound was described as the 5,8-dihydro derivative in the original publication.[8]

The uv spectrum of the filtrate exhibited a maximum at 358 nm, as contrasted with 390 nm for the starting material, and 405 nm for the 3,4-dihydro ester **53**. An attempt to isolate this presumed 5,6-dihydro ester **54** by evaporation of the filtrate, however, gave only unchanged ethyl 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (**52**), mp 142–144°, resulting from rapid air oxidation of the extremely labile 5,6-dihydro derivative **54**.

2-Ethylamino-8-ethyl-5,6-dihydro-7(8*H*)-pteridinone-6-carboxylic Acid (57).—A solution of 1.0 g of 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (**55**) in 50 ml of water containing 2 equiv of sodium hydroxide was shaken with hydrogen and 5% palladium-on-carbon catalyst until 1 mol of hydrogen had been absorbed. The reduction mixture was filtered and the filtrate was acidified with concentrated hydrochloric acid and then evaporated to dryness under reduced pressure. The residue was triturated with ethanol and filtered to remove sodium chloride. Evaporation of the ethanol filtrate gave a gray-green solid which was dissolved in 10 ml of water. A yellow solid precipitated after a few minutes at 0°. Filtration gave 0.27 g (27%) of a light green solid, mp 175° dec. The product was unstable, for it rapidly turned brown upon standing in the air.

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.70; N, 26.40. Found: C, 49.06; H, 5.82; N, 26.70.

2-Ethylamino-8-ethyl-7(8*H*)-pteridinone (58).—A solution of 0.26 g of 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (**55**) in 10 ml of water containing 1 equiv of sodium hydroxide was shaken with 3 atm of hydrogen, using 5% Pd/C catalyst, until 1 mol of hydrogen had been absorbed. The solution was filtered and 1.0 g of potassium ferricyanide in 10 ml of water was added to the filtrate. After 10 min, the white precipitate which had formed was collected by filtration to give 0.13 g (60%), mp 159–163°. Recrystallization from water raised the melting point to 164–165° (lit.[8] mp 155°).

Ethyl 2-Methoxy-8-methyl-5,6-dihydro-7(8*H*)-pteridinone-6-carboxylate (59).—To a solution of 0.50 g of ethyl 2-methoxy-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**32**) in 25 ml of glacial acetic acid was added, with stirring, zinc dust until the initial yellow color of the solution had disappeared. The mixture was then filtered to remove excess zinc and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 5 ml of ethanol, several pieces of ice were added, and the mixture was stirred until crystallization was complete. Filtration gave 0.40 g (80%) of a light yellow solid, mp 133–135°. Recrystallization from water then gave a white, microcrystalline solid, mp 138–139°. It is apparently stable in air but oxidizes extremely rapidly in solution in the presence of a trace of alkali to regenerate the starting material: $\lambda_{max}^{C_2H_5OH}$ 219 nm (log ϵ 4.44), 337 (3.79); ir ($HCCl_3$) 1709, 1739 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.77; H, 5.32; N, 21.25.

Ethyl 4-Dimethylamino-8-methyl-5,6-dihydro-7(8*H*)-pteridinone-6-carboxylate (60).—A solution of 1.2 g of ethyl 4-dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**38**) in 100 ml of ethanol was reduced with hydrogen, using 5% Pd/C as catalyst, until 1 mol of hydrogen had been absorbed. The reduction mixture was filtered to remove catalyst and the filtrate concentrated under reduced pressure to approximately 5 ml. Addition of 15 ml of water followed by several pieces of solid carbon dioxide resulted in the crystallization of 1.2 g (100%) of fine white needles, mp 76–78°. This dihydro ester is readily oxidized in solution back to the starting material but may be preserved in the solid state by storage in the absence of oxygen. It is considerably less stable than the corresponding 4-ethylamino derivative described below: $\lambda_{max}^{C_2H_5OH}$ 229 nm (log ϵ 4.26), 286 (3.80), 324 (3.79); ir ($HCCl_3$) 1695, 1739 cm^{-1}.

Anal. Calcd for $C_{12}H_{17}N_5O_3$: C, 51.60; H, 6.14; N, 25.08. Found: C, 51.26; H, 6.27; N, 25.35.

4-Dimethylamino-8-methyl-7(8*H*)-pteridinone (61).—A solution of 0.40 g of 4-dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylic acid (**39**) in 30 ml of ethanol was reduced with hydrogen, using 5% Pd/C as catalyst, until 1 mol of hydrogen had been absorbed. This solution then exhibited ultraviolet absorption maxima at 260, 267, and 318 nm. Oxygen was bubbled through the reduction solution for 10 min, the ethanol was removed by evaporation under reduced pressure, and the residue was triturated with cold water. Filtration gave 0.26 g (79%) of fine pale green needles, mp 161–163°. The material was purified by sublimation at 140° (0.05 mm), followed by crystallization from ethanol, and was obtained as fine white needles, mp 161–163° (lit.[36] mp 159–161°). The product exhibited ultraviolet absorp-

tion maxima at 211, 232, 246, 264, 303, and 356 nm. Catalytic reduction of this compound in ethanol solution, using Pd/C catalyst, resulted in the uptake of 1 mol of hydrogen. The uv spectrum of this reduction solution was identical with the spectrum given by the reduction solution of the carboxylic acid, indicating that decarboxylation had apparently accompanied reduction of the latter. 4-Dimethylamino-8-methyl-5,6-dihydro-7(8*H*)-pteridinone was too readily oxidized by air to permit isolation and characterization as a solid.

Anal. Calcd for $C_9H_{11}N_5O$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.98; H, 5.61; N, 34.06.

Ethyl 4-Ethylamino-8-ethyl-5,6-dihydro-7(8*H*)-pteridinone-6-carboxylate (62).—A solution of 1.0 g of ethyl 4-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (**40**) in 50 ml of ethanol was reduced with hydrogen, using 5% Pd/C as catalyst, until 1 mol of hydrogen had been absorbed. The resulting colorless solution was filtered, the filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in water. Chilling resulted in the separation of 1.0 g (100%) of small white plates, mp 129–131°. Recrystallization from aqueous ethanol raised the melting point to 132–133.5°. This dihydro ester was readily oxidized in solution by air back to the starting material, but the solid was more stable and could be preserved without difficulty by storing in the absence of oxygen: $\lambda_{max}^{C_2H_5OH}$ 216 nm (log ϵ 4.32), 228 sh (4.25), 275 (3.89), 317 (3.70); ir ($HCCl_3$) 1689, 1742 cm^{-1}.

Anal. Calcd for $C_{13}H_{19}N_5O_3$: C, 53.23; H, 6.53; N, 23.88. Found: C, 53.42; H, 6.62; N, 23.68.

4-Ethylamino-8-ethyl-7(8*H*)-pteridinone (63).—A solution of 0.20 g of 4-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (**41**) in 20 ml of ethanol was reduced with hydrogen, using 5% Pd/C as catalyst, until 1 mol of hydrogen had been absorbed. This solution exhibited uv maxima at 215, 276, and 317 nm. Evaporation of the ethanol, addition of water to the residue, and filtration give 0.10 g (60%) of a white solid, mp 126.5–127.5°, which exhibited uv maxima at 226, 259, and 353 nm in ethanol solution. Isolation of this material is facilitated if oxygen is bubbled through the reduction solution prior to evaporation. Catalytic reduction of this compound in ethanol solution, using Pd/C catalyst, resulted in the uptake of 1 mol of hydrogen. The uv spectrum of this reduction solution was identical with the spectrum of the reduction solution of the carboxylic acid. However, 4-ethylamino-8-ethyl-5,6-dihydro-7(8*H*)-pteridinone could not be isolated because of the ease with which it is reoxidized by air to 4-ethylamino-8-ethyl-7(8*H*)-pteridinone (**63**).

Anal. Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.95. Found: C, 55.05; H, 6.08; N, 31.70.

2-Amino-8-ethyl-4,7(3*H*,8*H*)-pteridinedione (67).—A solution of 1.0 g of 2-amino-8-ethyl-4,7(3*H*,8*H*)-pteridinedione-6-carboxylic acid (**64**)[21] in 100 ml of water containing 0.6 g of potassium hydroxide was reduced under 3 atm of hydrogen, using 5% Pd/C as catalyst. After 4 hr, the catalyst was removed by filtration and the filtrate treated with a solution of potassium ferricyanide until the color persisted. The solid which precipitated was collected by filtration, washed well with water, and dried to give 0.7 g (78%), mp >300°. An alkaline solution of this material exhibited a bright blue fluorescence. Recrystallization from aqueous ethanol gave colorless plates. The same product was formed in lower yield and more slowly when the reduction mixture was acidified with acetic acid rather than treated with potassium ferricyanide solution.

Anal. Calcd for $C_8H_9N_5O_2 \cdot H_2O$: C, 42.66; H, 4.92; N, 31.10. Found: C, 42.90; H, 5.18; N, 30.94.

2-Ethylamino-8-ethyl-3,4-dihydro-7(8*H*)-pteridinone (69).—2-Ethylamino-8-ethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylic acid[8] (1 g) was heated for 3 days at 175° under vacuum (0.1 mm). The sublimate (0.3 g) was identified as 2-ethylamino-8-ethyl-7(8*H*)-pteridinone by comparison with an authentic sample.[8] The orange-yellow residue was repeatedly recrystallized from water with the use of a small amount of decolorizing charcoal to give 0.3 g (36%) of glittering orange-yellow crystals: mp 243–244°; λ_{max}^{pH7} 242 nm (log ϵ 3.76), 280 (3.54), 390 (4.26); pK_a = 3.75 ± 0.04.

Anal. Calcd for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.83; N, 31.66. Found: C, 53.96; H, 6.66; N, 31.78.

2-Amino-3,8-dimethyl-6-carbomethoxy-7-oxo-7,8-dihydropteridinium Tosylate (70).—A mixture of 0.50 g of methyl 2-amino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**36**) and 10 ml of methyl *p*-toluenesulfonate was heated for 1 hr at 120°, cooled, and filtered. The collected solid was washed well with ether and then dried at 100°, yield 0.72 g (81%), mp 233°. The analytical sample was prepared by dissolution of the above solid in methanol followed by precipitation by addition of ether: nmr δ 4.17 (s, 3, N^+-CH_3), 9.03 (s, 1, C_4-H).

Anal. Calcd for $C_{10}H_{12}N_5O_3 \cdot C_7H_7SO_3$: C, 48.45; H, 4.55; N, 16.62; OCH_3, 7.37. Found: C, 48.19; H, 4.65; N, 16.42; OCH_3, 7.58.

2-Amino-3,8-dimethyl-6-carbethoxy-7-oxo-7,8-dihydropteridinium Tosylate (71).—A mixture of 0.70 g of ethyl 2-amino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**35**) and 14 g of methyl *p*-toluenesulfonate was heated for 1.5 hr at 120°, and the fine colorless needles which had separated were collected by filtration (hot) and washed well with ether, yield 0.80 g (66%), mp 245°. An additional 0.25 g of product, mp 240°, was obtained by cooling of the filtrate followed by filtration. The analytical sample, mp 245°, was prepared in the form of colorless, silky needles by recrystallization from ethanol: nmr δ 4.2 (s, 3, N^+-CH_3), 9.00 (s, 1, C_4-H).

Anal. Calcd for $C_{11}H_{14}N_5O_3 \cdot C_7H_7SO_3$: C, 49.65; H, 4.86; N, 16.09; OC_2H_5, 10.13. Found: C, 49.67; H, 4.79; N, 15.84; OC_2H_5, 10.91.

2-Methylamino-3,8-dimethyl-6-carbomethoxy-7-oxo-7,8-dihydropteridinium Tosylate (72).—In the same manner as described above, methyl 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**30**) was methylated by heating with methyl *p*-toluenesulfonate: yield 75%; mp (by precipitation from methanol solution with ether) 246°; nmr δ 4.13 (s, 3, N^+-CH_3), 9.05 (s, 1, C_4-H).

Anal. Calcd for $C_{11}H_{14}N_5O_3 \cdot C_7H_7SO_3$: C, 49.65; H, 4.86; N, 16.09; OCH_3, 7.13. Found: C, 49.80; H, 4.80; N, 15.89; OCH_3, 7.30.

2-Methylamino-3,8-dimethyl-6-carbethoxy-7-oxo-7,8-dihydropteridinium Tosylate (73).—This compound was prepared as described above from ethyl 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**29**) and methyl *p*-toluenesulfonate: yield 73%; mp (from methanol) 249°; nmr δ 4.1 (s, 3, N^+-CH_3), 9.01 (s, 1, C_4-H).

Anal. Calcd for $C_{12}H_{16}N_5O_3 \cdot C_7H_7SO_3$: C, 50.78; H, 5.16; N, 15.58; OC_2H_5, 9.81. Found: C, 50.50; H, 5.11; N, 15.65; OC_2H_5, 11.10.

Methyl 2-Amino-3,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (74).—To a suspension of 0.27 g of **70** in 10 ml of ethanol was added 0.15 g of sodium borohydride, and the mixture was diluted with 10 ml of water and stirred at room temperature for 12 hr. The yellow needles which had separated were collected by filtration, washed well with ether, and dried to give 0.12 g (75%), mp 230–233°. The analytical sample, mp 240°, was prepared by recrystallization first from water and then from methanol: nmr (in DMSO-d_6) δ 2.96 (s, 3, N_3-CH_3), 4.36 (s, 2, C_4-CH_2).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.63; H, 5.33; N, 27.59.

Ethyl 2-Amino-3,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (75).—To a solution of 0.20 g of **71** in 10 ml of water was added 0.10 g of sodium borohydride. The solution foamed slightly and turned yellow. After a few minutes a yellow solid started to separate. The mixture was stirred at room temperature for 3 hr and filtered, and the collected solid was washed well with ether and dried to give 0.12 g (96%), mp 181°. The analytical sample was prepared in the form of yellow, silky needles, mp 194°, by recrystallization from ethanol: nmr (in DMSO-d_6) δ 2.97 (s, 3, N_3-CH_3), 4.36 (s, 2, C_4-CH_2).

Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot {}^1/_2H_2O$: C, 48.52; H, 5.91; N, 25.37. Found: C, 48.22; H, 5.89; N, 25.56.

Methyl 2-Methylamino-3,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (76).—A solution of 0.50 g of **72** and 0.10 g of sodium borohydride in 20 ml of methanol was stirred at room temperature for 30 min and evaporated to dryness, and the residue was triturated with 10 ml of water. Filtration then gave 0.30 g of a yellow solid which was dissolved in 10 ml of hot water; neutralization with a few drops of hydrochloric acid and cooling gave 0.20 g (66%) of yellow needles, mp 233°. The analytical sample, mp 240°, was prepared by recrystallization from methanol: nmr (in DMSO-d_6) δ 2.93 (s, 3, N_3-CH_3), 4.31 (s, 2, C_4-CH_2).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.70; N, 26.40. Found: C, 49.77; H, 5.61; N, 26.24.

Ethyl 2-Methylamino-3,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (77).—To a suspension of 1.1 g of **73** in 50 ml of ethanol was added 0.5 g of sodium borohydride. The mixture foamed slightly and turned greenish yellow and the

suspended solid dissolved. Dilution with 150 ml of water, followed by evaporation under reduced pressure to a small volume, cooling, and filtering gave 0.7 g (97%) of yellow needles, mp 201°. The analytical sample, mp 213°, was prepared by recrystallization from water: nmr (DMSO-d_6) δ 2.94 (s, 3, N_3-CH_3), 4.32 (s, 2, C_4-CH_2).

Anal. Calcd for $C_{12}H_{17}N_5O_3$: C, 48.47; H, 6.44; N, 23.56. Found: C, 48.57; H, 6.13; N, 23.88.

3,8-Dimethylisoxanthopterincarboxylic Acid Ethyl Ester (78).—A solution of 0.108 g of 2-amino-3,8-dimethyl-6-carbethoxy-7-oxo-7,8-dihydropteridinium tosylate (**71**) and 0.165 g of potassium ferricyanide in 27 ml of pH 7 buffer was stirred at room temperature for 4 days and the light yellow precipitate was collected by filtration, washed with ether, and dried, yield 0.033 g (49%), mp 305° (lit.[28] mp 308°). The product was identical (tlc) with an authentic sample of 3,8-dimethylisoxanthopterincarboxylic acid ethyl ester, and its uv spectrum was also in agreement with published data: λ_{max}^{pH6} 266 nm (log ϵ 3.92), 290 (3.87), 375 (4.38) [lit.[28] 265 (3.94), 289 (3.81), 374 (4.38)].

Dimroth Rearrangement of 2-Amino-3,8-dimethyl-6-carbethoxy-7-oxo-7,8-dihydropteridinium Tosylate (71).—A solution of 75 mg of **71** in 10 ml of saturated sodium bicarbonate solution was stirred at room temperature for 3 hr, and the bright yellow solid which had separated was collected by filtration, washed well with water, and dried, yield 19 mg (42%), mp 197–198°. The product was identical with an authentic sample of ethyl 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**29**).

Heating 100 mg of **71** in 10 ml of pH 9 buffer under reflux for 20 min, followed by acidification, gave 25 mg (46%) of 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylic acid (**31**), identical in every respect with an authentic sample.

Registry No.—**4**, 31937-01-6; **5**, 31937-02-7; **6**, 31937-03-8; **11**, 31937-04-9; **12**, 31937-05-0; **13**, 31937-06-1; **15**, 31937-07-2; **17**, 31937-08-3; **18**, 5177-26-4; **20**, 31937-10-7; **21**, 31937-11-8; **22**, 31937-12-9; **23**, 31937-13-0; **24**, 31937-14-1; **25**, 31937-15-2; **26**, 31937-16-3; **27**, 31937-17-4; **28**, 31937-18-5; **29**, 31937-19-6; **30**, 31937-20-9; **31**, 31937-21-0; **32**, 2046-74-4; **33**, 2046-73-3; **34**, 2046-72-2; **35**, 2539-49-3; **36**, 31937-26-5; **37**, 2046-69-7; **38**, 2046-68-6; **39**, 2235-77-0; **40**, 2046-67-5; **41**, 2235-76-9; **42**, 2047-23-6; **43**, 31934-03-9; **44**, 31934-04-0; **45**, 31934-05-1; **46**, 31934-06-2; **47**, 31981-27-8; **48**, 31934-07-3; **49**, 31934-08-4; **50**, 31934-09-5; **51**, 31934-10-8; **52**, 2144-73-2; **53**, 31934-12-0; **57**, 31934-13-1; **59**, 1471-66-5; **60**, 1471-87-0; **61**, 1639-38-9; **62**, 1471-67-6; **63**, 1471-81-4; **67**, 31934-17-5; **69**, 31934-18-6; **70**, 31934-19-7; **71**, 31981-30-3; **72**, 31981-31-4; **73**, 31934-20-0; **74**, 31934-21-1; **75**, 31934-22-2; **76**, 31934-23-3; **77**, 31934-24-4.

Synthesis of the 1,4-Dihydropyrazine Ring System. A Stable 8-π-Electron Heterocycle

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A previous report on the synthesis of the 1,4-dihydropyrazine ring system by the reaction of carboxylic anhydrides with dihydropyrazine **4** has been shown to be incorrect. The tetrahydropyrazine **6** is the product of this reaction. A stable dihydropyrazine **5a** has been prepared from **4** using acetyl chloride. Chemical reactions and physical properties of this 8-π-electron heterocycle are reported.

It has been known since the last century that certain conjugated cyclic molecules, such as benzene, possess unusual properties not consistent with those of simple open-chain conjugated olefins. However, it remained until the 1930's with the advent of quantum mechanics, for a theoretical understanding of these molecules to be developed. Now, due initially to the investigations of Hückel,[1] conjugated cyclic molecules can be divided into two groups. The first group contains molecules possessing $(4n + 2)$ π electrons (where $n = 0, 1, 2, \ldots$). Those molecules are predicted to have additional stability due to the cyclic delocalization of π electrons and should display aromatic properties analogous to benzene. Considerable research effort in recent years has verified this original prediction.[2]

The second group consists of molecules containing $4n$ π electrons (where $n = 1, 2, 3 \ldots$) which were originally predicted not to be stabilized by the cyclic delocalization of π electrons. Therefore, molecules in this group were designated simply as nonaromatic. The best and most classical representative of this group is cyclooctatetraene which behaves as a cyclic polyene.

Molecules containing $4n$ π electrons where the cyclic delocalization of π electrons can occur have recently attracted attention. Simple HMO theory predicts that monocyclic molecules containing $4n$ π electrons should possess zero delocalization. Since some delocalization is predicted for the open-chain analogs containing $4n$ π electrons, the cyclic compared to the noncyclic structures are actually destabilized. For this reason cyclic molecules containing $4n$ π electrons have been designated as antiaromatic.[3]

Most work on the concept of antiaromaticity has been concerned with electronic systems containing 4 π electrons. However, antiaromaticity should also be observed in molecules containing 8 π electrons *if* electron delocalization can occur.

Cyclooctatetraene, 1*H*-azepine, and 1,4-dihydropyrazine potentially all contain 8 π electrons. Since the π overlap of two p orbitals is proportional to cos θ (where θ = angle between the axis bisecting each p orbital),[4] molecular models indicate that little delocalization should occur in cyclooctatetraene. The smaller seven-membered 1*H*-azepine ring is more planar and more delocalization should be possible compared to cyclooctatetraene. However, molecular models indi-

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