Anal. Calcd. for $C_{22}H_{36}O_6$: C, 66.64; H, 9.15; O, 24.21; active hydrogen 4H, 1.01; 5C–CH_3, 18.9; mol. wt., 396.51. Found: C, 66.68, 66.53; H, 9.04, 9.09; O, 24.34, 24.47; active hydrogen 1.07; C–CH_3, 18.9; mol. wt. (Rast), 416, 394.

Oligomycin B Diacetate.—The diacetate of oligomycin B was prepared in a similar manner to that for oligomycin A. After recrystallization from benzene–cyclohexane (1:1), it melted at 135.5–136.5°. The optical rotation was $[\alpha]^{25}D$ −66.6 (*c* 0.63, dioxane).

A sample was dried at 80°, 0.01 mm., and analyzed.

Anal. Calcd. for $C_{26}H_{40}O_8$: C, 64.98; H 8.39; mol. wt., 480.6. Found: C, 65.29; H, 8.45; mol. wt. (Rast), 488.

Oligomycin C.—The material from fraction 2 (Table I) was recrystallized twice from ether–petroleum ether mixture (1:1). The rod shaped crystals melted at 198–200° and had a rotation, $[\alpha]^{28}D$ −80.7 (*c* 3.70, dioxane).

Anal. Calcd. for $C_{28}H_{46}O_6$: C, 70.26; H, 9.69; 6C–CH_3, 18.8; mol. wt., 478.64. Found: C, 69.9; H, 9.8; C–CH_3, 19.3; mol. wt. (Rast), 496.

Absorption Spectra.—Ultraviolet measurements were made in absolute ethanol on a Cary model 11 automatic recording spectrophotometer. Each component showed two main bands at 225 and 232 ± 0.5 mμ, with inflections at 220, 240 ± 0.5, 285 (A and C) and 295 mμ (B). The corresponding molar extinction values, were, for A: 20200, 18200, 18100, 11100, 64; for B: 18800, 17000, 17400, 10800, 59; for C: 23200, 21600, 21700, 13100, 64, respectively.

The infrared data were obtained in 10% chloroform solution with a Baird IR model B automatic recording spectrophotometer and a sodium chloride prism. Main bands for each component were, for A: 3440–3500, 1700, 1638 cm.$^{-1}$; for B: 3446–3500, 1712, 1690, 1640 cm.$^{-1}$; for C: 3500, 1700 and 1640 cm.$^{-1}$.

NOTE ADDED IN PROOF.—For the purpose of further verifying the molecular weights of the two compounds, single crystal X-ray diffraction measurements were made on oligomycin B and oligomycin A. Oligomycin B is orthorhombic, with lattice constants a = 16.92 Å., b = 26.34 Å., c = 10.25 Å., and a pycnometric density of 1.152 g./cc. The molecular weight calculated for eight molecules per unit cell is 396.2, to be compared with a value of 396.5 based on the formula $C_{22}H_{36}O_6$. Isothermal distillation for the molecular weight determination gave a value of 416 for oligomycin B and 407 for dihydroöligomycin B, using chloroform and acetone as solvent, respectively.

Rotation and Weissenberg pictures of oligomycin A also revealed an orthorhombic unit cell with lattice constants a = 17.7 Å., b = 27.5 Å., and c = 10.1 Å. An observed density of 1.15 g./cc. was obtained by the flotation method. These data together with the assumption of eight molecules per unit cell give a calculated molecular weight of 426 which is in good agreement with the value 424.6 based on the formula $C_{24}H_{40}O_6$. Isothermal distillation data gave a molecular weight of 433.

The similarity of the crystal structures of oligomycin B and oligomycin A as indicated by the lattice constants, symmetry, and the same number of molecules per unit cell (eight) suggests a fairly close relationship both in the carbon skeleton and molecular arrangement of the two compounds in the solid state.

The authors are indebted to R. R. Pfeiffer and A. Van Camp, Eli Lilly and Co., for the above data on oligomycin B and to L. F. Dahl and G. L. Dawes, Chemistry Department, University of Wisconsin for the measurements on oligomycin A.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, PEARL RIVER LABORATORIES, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

Pteridine Chemistry. III. 2-Amino-1(and 3)6,7-trimethyl-4-pteridones and Some Related Compounds

BY WILLIAM V. CURRAN AND ROBERT B. ANGIER

RECEIVED JUNE 30, 1958

The structure of a previously reported ring methylated pteridine has been shown to be 2-amino-1,6,7-trimethyl-4(1H)-pteridone (I, R = CH_3) by alkaline hydrolysis to the known 2-hydroxy derivative (II, R = CH_3). 2-Amino-3,6,7-trimethyl-4(3H)-pteridone (IV, R = CH_3) has been synthesized by two unequivocal routes. Attempted alkaline hydrolysis of the latter compound led to the rearranged product, 2-methylamino-4-hydroxy-6,7-dimethylpteridine (VIII, R = CH_3).

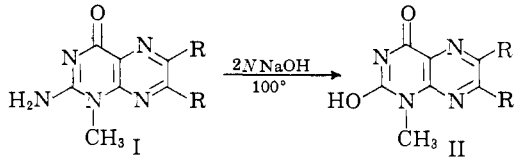
In connection with another problem under investigation in this Laboratory, it was necessary to synthesize 2-amino-1,6,7-trimethyl-4(1H)-pteridone (I, R = CH_3) and 2-amino-3,6,7-trimethyl-4-(3H)-pteridone (IV, R = CH_3). Roth, *et al.*,[1] have described the synthesis of 2-methylamino-4-hydroxy-6,7-dimethylpteridine (VIII), R = CH_3) and also a ring methylated 2-amino-4-pteridone, the structure of which was not proved. By treating methylguanidine with ethyl cyanoacetate they obtained two pyrimidines which were separated by means of solubility differences. After nitrosation and reduction the resulting 4,5-diaminopyrimidines were condensed with biacetyl to give the corresponding 6,7-dimethylpteridines. On the basis of the infrared and ultraviolet spectra of these compounds, structure VIII (R = CH_3) was assigned to the lower melting pteridine obtained from the more soluble pyrimidine and structure IV (R = CH_3) to the higher melting isomer obtained from the less soluble pyrimidine. The ultraviolet spectrum of VIII (R = CH_3) in 0.1 *N* sodium hydroxide was practically the same as the parent 2-amino-4-hydroxy-6,7-dimethylpteridine except that both maxima were shifted toward longer wave lengths. Subsequent workers[2] have confirmed the fact that alkylation of the 2-amino group in the pteridine series produces a bathochromic shift in the ultraviolet spectrum. The ultraviolet spectrum of the product assigned structure IV (R = CH_3) was completely different from the 2-amino-4-hydroxy-6,7-dimethylpteridine in 0.1 *N* sodium hydroxide.

We reinvestigated the ring methylated isomer and found that by refluxing for five minutes in 2 *N* sodium hydroxide it was converted into a new pteridine. Elemental analyses and the infrared spectrum of this product indicated that the 2-amino group had been hydrolyzed to a 2-hydroxy group. 2-Hydroxy-1,6,7-trimethyl-4(1H)-pteridone (II, R = CH_3) was synthesized by known

(1) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, THIS JOURNAL, **73**, 2864 (1951).

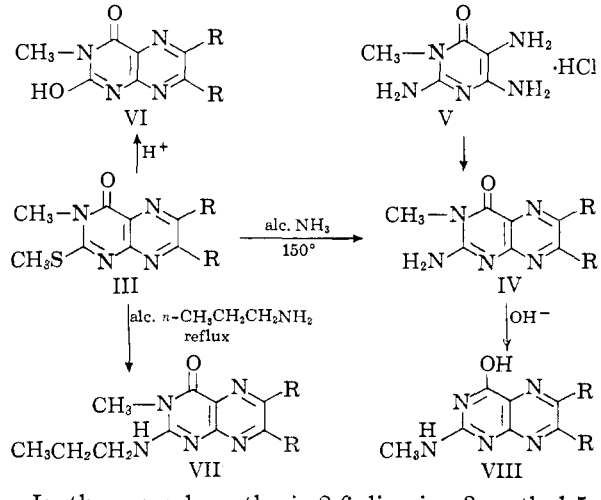
(2) E. C. Taylor and C. K. Cain, *ibid.*, **74**, 1644 (1952).

methods.[3] The infrared and ultraviolet spectra of this compound were identical with those of the above-mentioned hydrolysis product showing that the 2-amino compound from which it was obtained was the 1-methyl isomer (I, R = CH_3).



After the completion of this work, Boon and Bratt[4] published a proof of structure of the ring methylated pteridine by a synthesis of 1-methyl-2-amino-6,7-diphenyl-4(3H)-pteridone (I, R = C_6H_5) by amination of the corresponding 2-mercapto compound. In addition, these authors claim to have synthesized 2-amino-3-methyl-6,7-diphenyl-4(3H)-pteridone (IV, R = C_6H_5), "by unambiguous methods." No details as to the method of synthesis or properties of this compound were given either in the discussion or the experimental part of the paper. We have now synthesized 2-amino-3,6,7-trimethyl-4(3H)-pteridone (IV, R = CH_3) by two unequivocal methods.

In the first approach, 2-methylmercapto-3-methyl-5,6-diamino-4(3H)-pyrimidone[5] was condensed with biacetyl to give pteridine III (R = CH_3). Treatment with ethanolic ammonia at 150° in a bomb for 4-5 hours led to the desired compound (IV, R = CH_3) in low yield. The 2-methylmercapto group of III (R = CH_3) also was replaced rather readily by propylamine to give VII (R = CH_3) by refluxing in ethanolic propylamine for eighteen hours on a steam-bath. Furthermore, III (R = CH_3) was converted into the corresponding 2-hydroxy derivative (VI, R = CH_3) by the action of hot 6 *N* hydrochloric acid.



In the second synthesis 2,6-diamino-3-methyl-5-formamido-4(3H)-pyrimidone was prepared according to Traube and Dudley.[6] Hydrolysis of the formyl group by cold concentrated hydrochloric acid gave the triamine hydrochloride V which was readily converted into the desired pteridine (IV, R = CH_3).

In contrast to the 1-methyl isomer (I, R = CH_3) which was hydrolyzed easily to its 2-hydroxy analog in alkali, the 3-methyl derivative (IV, R = CH_3) when treated with hot 1 *N* sodium hydroxide readily underwent a rearrangement to give 2-methylamino-4-hydroxy-6,7-dimethylpteridine (VIII, R = CH_3). Several similar type rearrangements have been reported in the literature involving other heterocyclic nuclei. For example, Elion[7] reported that treatment of the 1-methyl derivative of 6-mercaptopurine with alcoholic ammonia at 160° gave 6-methylaminopurine. In addition, Brown, *et al.*,[8] have described the rearrangement of 1-methyl-2-iminopyrimidine hydroiodide to 2-methylaminopyrimidine by the action of warm aqueous base. Experiments are in progress to obtain more information regarding the rearrangement reported in this paper.

Table I lists the R_f values in several different solvent systems and the type of fluorescence along with the ultraviolet absorption data for the various pteridine derivatives. It will be noted that in 0.1 *N* sodium hydroxide all of the 3-methyl compounds reported here (III, IV, VI and VII, R = CH_3) possess maxima in the range 273-285 mμ with molar extinction coefficients (ϵ_{max}) from 10,500 to 17,100. The 1-methyl isomers (I and II, R = CH_3), the 2-methylamino analog (VII, R = CH_3) and 2-amino-4-hydroxy-6,7-dimethylpteridine do not absorb in this region.

Acknowledgment.—We are indebted to Mr. L. Brancone and staff for the microanalyses reported and to Mr. W. Fulmor and staff for spectral data.

Experimental[9]

2-Hydroxy-1,6,7-trimethyl-4(1H)-pteridone (II).—2-Amino-1,6,7-trimethyl-4(1H)-pteridone (0.5 g., 2.4 mmoles)[1] was refluxed for 5 minutes in 10 ml. of 2 *N* sodium hydroxide and acidified hot with 1.5 ml. of concentrated hydrochloric acid. On cooling, the product crystallized as yellow needles; yield 0.35 g. (70%). This compound gave the same ultraviolet and infrared spectra as the synthetic material.[3]

Anal. Calcd. for $C_9H_{10}O_2N_4$ (206.2): C, 52.5; H, 4.89; N, 27.2. Found: C, 52.31; H, 5.10; N, 26.85.

2-Methylmercapto-3,6,7-trimethyl-4(3H)-pteridone (III).—2-Methyl-mercapto-3-methyl-5,6-diamino-4(3H)-pyrimidone (4.8 g., 21.5 mmoles)[5] and 4 ml. of diacetyl were refluxed for two hours in 500 ml. of absolute alcohol. After concentrating *in vacuo* and chilling overnight the product was collected by filtration; yield 4.55 g. (78%). This product was recrystallized from water to give 3.6 g. (62%), m.p. 184–187°. For analysis a small portion was recrystallized from ethanol.

Anal. Calcd. for $C_{10}H_{12}ON_4S$ (236.3): C, 50.9; H, 5.13; N, 23.7. Found: C, 50.76; H, 5.22; N, 23.93.

2,5,6-Triamino-3-methyl-4(3H)-pyrimidone Hydrochloride (V).—2,6-Diamino-3-methyl-5-formamido-4(3H)-pyrimidone (16.75 g., 0.092 mmoles)[6] was dissolved in 140 ml. of cold, concentrated hydrochloric acid and allowed to stand at room temperature for 30 minutes. After chilling several hours the crystals were filtered off and washed with cold concentrated hydrochloric acid, ethanol, and ether; yield 14.7 g. (83%). The mother liquor was allowed to stand in the cold several days to give an additional 2.6 g. (99% total

(3) F. Sachs and G. Meyerheim, *Ber.*, **41**, 3957 (1908).
(4) W. R. Boon and G. Bratt, *J. Chem. Soc.*, 2159 (1957).
(5) C. O. Johns and B. M. Hendrix, *J. Biol. Chem.*, **20**, 153 (1915).
(6) W. Traube and H. W. Dudley, *Ber.*, **46**, 3845 (1913).
(7) G. B. Elion, "The Chemistry and Biology of Purines," A Ciba Foundation Symposium, J. and A. Churchill Ltd., London, England, 1957, p. 44.
(8) D. J. Brown, E. Hoerger and S. F. Mason, *J. Chem. Soc.*, 4035 (1955).
(9) Melting points are corrected.

TABLE I

Pteridine derivative	R_f values[a] 0.5% Na_2CO_3	3% NH_4Cl	Butanol–5 *N* acetic acid (7–3)	Ultraviolet absorption spectra[b] 0.1 *N* NaOH λ_{max}, mμ	$\epsilon_{max} \times 10^{-4}$	0.1 *N* HCl λ_{max}, mμ	$\epsilon_{max} \times 10^{-4}$
2-Amino-4-hydroxy-6,7-dimethylpteridine	0.50B	.....	0.57B	250	1.97	215	1.85
				356	0.75	252	0.84
						320	0.92
2-Methylamino-4-hydroxy-6,7-dimethyl-pteridine (VIII)	.55B	0.57B	.65B	258	2.17	217	2.10
				363	0.88	252	1.09
						322	0.94
2-Amino-3,6,7-trimethyl-4(3H)-pteridone (IV)	.56P	.57P	.54P	242	1.68	219	2.10
				277	1.39	248S	0.92
				352	0.73	323	1.10
2-Amino-1,6,7-trimethyl-4(1H)-pteridone (I)	.68DP	.70DP	.64DP	240	1.47	216	1.86
				330–340P	0.84	253	0.87
						321	0.95
2-Hydroxy-1,6,7-trimethyl-4(1H) pteridone (II)	.77P	.67P	.79P	244	1.77	225S	1.28
				341	1.07	250	0.97
						333	0.98
2-Hydroxy-3,6,7-trimethyl-4(3H)-pteridone (VI)	.68B	.72YG	.74YG	247	1.65	232	1.35
				273	1.05	329	1.03
				360	0.71		
2-Methylmercapto-3,6,7-trimethyl-4(3H)-pteridone (III)	.62DP	.65DP	.84DP	247	1.48	247	1.53
				286	1.32	286	1.48
				333	0.80	336	0.79
2-*n*-Propylamino-3,6,7-trimethyl-4(3H)-pteridone (VII)	.70B	.71B	.....	244	1.54	222	1.56
				282	1.71	252S	1.03
				358	0.68	280–290P	0.56
						323	.74
						330S	.68

[a] B = blue fluorescence, P = purple fluorescence, YG = yellow-green fluorescence, DP = dark purple fluorescence. Viewed with an ultraviolet lamp provided with a filter to give mainly light of 254 mμ. Descending technique employed using Whatman No. 1 filter paper. [b] P = plateau, S = shoulder.

yield), m.p. >300° dec. The compound was recrystallized (platelets) by dissolving in warm water and adding an equal volume of ethanol.

Anal. Calcd. for $C_5H_9N_5O.HCl$ (191.6): C, 31.4; H, 5.26; N, 36.6. Found: C, 31.61; H, 5.28; N, 36.84.

2-Amino-3,6,7-trimethyl-4(3H)-pteridone (IV). Method 1.—2,5,6-Triamino-3-methyl-4(3H)-pyrimidone hydrochloride (1.0 g., 5.23 mmoles) was suspended in 25 ml. of water containing a pinch of sodium hydrosulfite and solid sodium bicarbonate added till the *p*H was 6. After warming on a steam-bath to effect solution the *p*H was brought to 7 by adding more sodium bicarbonate. The solution was warmed to 75–80° and 1 ml. of diacetyl added. The solution was heated on a steam-bath for five minutes, then treated with Norite and filtered from a small amount of insoluble material. After chilling, the crystalline product was filtered off, washed with some cold water and dried; yield 0.55 g. (51.5%), does not melt below 300°. For analysis a portion of this product was recrystallized twice from 95% ethanol.

Anal. Calcd. for $C_9H_{11}ON_5$ (205.2): C, 52.8; H, 5.4; N, 34.1. Found: C, 52.79; H, 5.37; N, 34.13.

Method 2.—2-Methylmercapto-3,6,7-trimethyl-4(3H)-pteridone (0.5 g., 2.12 mmoles) was suspended in 50 ml. of absolute ethanol and saturated with anhydrous ammonia in an ice-bath. After heating in a bomb at 150° for five hours, the solvent was removed *in vacuo* and the resulting oil taken up in absolute alcohol which was again evaporated *in vacuo*. This procedure was repeated using 95% ethanol. The product then was crystallized from 20 ml. of 95% ethanol after treating with Norite; crude yield 0.20 g. (46%). Recrystallizing from 15 ml. of 95% ethanol gave 0.15 g. (35%). The ultraviolet absorption spectrum of this product was the same as that obtained in method 1. Paper chromatography in three different solvent systems (see Table I) showed a trace of the 2-hydroxy derivative (VI, R = CH_3) was also present.

2-Methylamino-4-hydroxy-6,7-dimethylpteridine (VIII).—2-Amino-3,6,7-trimethyl-4(3H)-pteridone (1.0 g. 4.9 mmoles) was refluxed for 10 minutes in 10 ml. of 1 *N* sodium hydroxide and acidified while still hot with 0.83 ml. of concentrated hydrochloric acid. After chilling, the crystals were filtered off and washed with water, acetone and ether, yield 0.60 g. (55%). After recrystallizing from 50 ml. of water using Norite there was obtained 0.35 g. (32%). The infrared and ultraviolet spectra of this product were identical to the spectra of the product prepared by the method of Roth, *et al.*[1]

2-Hydroxy-3,6,7-trimethyl-4(3H)-pteridone (VI).—2-Methylmercapto-3,6,7-trimethyl-4(3H)-pteridone (0.50 g., 2.12 mmoles) was heated on a steam-bath for one hour in 50 ml. of 6*N* hydrochloric acid. The solution was evaporated to dryness *in vacuo*, 30 ml. of water added and again taken to dryness. The residue was taken up in 20 ml. of boiling water, treated with Norite, and filtered. On cooling the compound crystallized; yield 0.25 g. (57%), m.p. 268–270°. For analysis a portion of this product was recrystallized from 1-propanol.

Anal. Calcd. for $C_9H_{10}O_2N_4$ (206.2): C, 52.5; H, 4.9; N, 27.2. Found: C, 52.63; H, 4.86; N, 27.35.

2-Propylamino-3,6,7-trimethyl-4(3H)-pteridone (VII).—A solution of 2-methylmercapto-3,6,7-trimethyl-4(3H)-pteridone (0.5 g., 2.12 mmoles) in 5 ml. of propylamine and 10 ml. of absolute alcohol was refluxed for 11 hours on a steam-bath protected with a tube of Drierite. Five ml. of *n*-propylamine was added and refluxed for an additional 7 hours. After chilling overnight the crystals were filtered off, washed with a small amount of cold ethanol, and dried; yield 0.33 g. (63%). An additional 0.10 g. (total 81%) was obtained from the mother liquor. These two crops were combined and recrystallized from 4 ml. of 1-propanol using Norite to give 0.25 g. (47.7%), m.p. 296–298° dec.

Anal. Calcd. for $C_{12}H_{17}ON_5$ (247.5): C, 58.2; H, 6.9; N, 28.2. Found: C, 58.00; H, 7.09; N, 28.15.

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