the other was best crystallized from alcohol. In Table I are listed the properties of the compounds involved in proceeding to the 3,5- and 3,7-dimethyl-4-chloroquinolines. The structure of the two series was clarified by dehalogenation of the 4-chloro compound of m.p. 59.5–60° in alcohol containing one equivalent of sodium hydroxide employing Busch–Stöve catalyst[15] under 50 lb./sq. in. hydrogen pressure. The crude product was directly converted to the picrate, which melted at 221° after crystallization from acetone. Manske, *et al.*[10] have given the melting point of 3,5-dimethylquinoline picrate as 220° while that salt of 3,7-dimethylquinoline melted at 244°.

3-Amino-4-iodoanisole in the Conrad–Limpach Synthesis.—4-Amino-3-nitroanisole was diazotized and treated with potassium iodide after the manner of Reverdin[11,16,17] to give 4-iodo-3-nitroanisole in 86–92% crude yield. It crystallized from Skellysolve C or aqueous alcohol as orange needles, m.p. 62.5–63°. The reduction of the nitro group was best accomplished by the method of West[11,18] using aqueous ethanol as the solvent. Crude *yields of 65–73% resulted, the* 3-amino-4-iodoanisole being a reddish-brown oil. The crude material was used in subsequent work, for while a trial batch gave a fair recovery of a reddish liquid, b.p. *ca.* 90–115° (0.2 mm.), another sample exploded when distillation was attempted, much iodine vapor being noted afterward. This occurrence has also been witnessed recently by Tarbell *et al.*[11]

The condensation of crude 3-amino-4-iodoanisole with ethyl α-ethoxalylpropionate was carried out in the usual manner, the product resulting in 69–80% yield. All attempts to cyclize the anil in Dowtherm A led to copious evolution of iodine vapor. When the crude reaction product was crystallized from ethanol and from acetone several times, using Darco G-60 liberally, fine white needles were obtained, m.p. 192–192.5°. Analysis and mixed melting point with an authentic sample (prepared from 3-anisidine by the method described by Hauser, *et al.*[7]) showed this compound to be ethyl 4-hydroxy-7-methoxy-3-methylquinoline-2-carboxylate. The yields obtained (from the anil) were 52–66%.

(15) Busch and Stöve, *Ber.*, **49**, 1064 (1916).

(16) Reverdin, *ibid.*, **29**, 2595 (1896).

(17) Hata, Tatematsu and Kubota, *Bull. Chem. Soc.* (*Japan*), **10**, 425 (1935).

(18) West, *J. Chem. Soc.*, 494 (1925).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.78; N, 5.37. Found: C, 64.45; H, 6.06; N, 5.36.

Further Study of 5-Iodo-3-methylquinolines.—In a previous contribution in this series,[2d] it was reported that a halogen-free compound, m.p. 251° dec., was obtained by the action of boiling 5% caustic upon ethyl 4-hydroxy-5-iodo-3-methylquinoline-2-carboxylate. This substance was re-examined and found to contain iodine when boiled with *n*-amyl alcohol and sodium for some while. The low solubility of the material in the common solvents led to the use of 2-methyl-2,4-pentanediol, but satisfactory analyses could not be obtained. Decarboxylation of the yellow acid in either Dowtherm A or mineral oil led to a white solid which melted vaguely around 286° after crystallization from alcohol. This alleged 4-hydroxy-5-iodo-3-methylquinoline failed to give concordant analyses, but merely indicated that more iodine was lost during the reaction. Ultimately, the 4-hydroxy-3-methylquinoline type so obtained was interacted with phosphorus oxychloride. The result of extensive purification of the product by crystallization from Skellysolve B and sublimation was a small quantity of white needles, m.p. 61.5–62.5°, which was free of iodine. A melting point of 60° has been reported for 4-chloro-3-methylquinoline.[2a]

Acknowledgment.—The authors wish to express their appreciation to Mrs. N. P. Gorman, Mr. E. V. Ryan and Mr. A. J. Holland for technical assistance. All analyses were carried out by the analytical staff of this Institute under the direction of Mr. M. E. Auerbach.

Summary

The preparation of 4-(4-diethylamino-1-methylbutylamino)-7-ethoxy-3-methylquinoline from 3-phenetidine has been described.

The properties of a number of 3,5- and 3,7-dimethylquinoline derivatives have been reported and the structures proven. Certain experiences with iodinated compounds in the Conrad–Limpach synthesis have been described.

RENSSELAER, NEW YORK RECEIVED SEPTEMBER 20, 1948

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AND THE SCHOOL OF NUTRITION AT CORNELL UNIVERSITY]

Pteridines. IV. Derivatives of 2,4-Diamino-6,7-diphenylpteridine[1]

BY C. K. CAIN, E. C. TAYLOR, JR., AND LOUISE J. DANIEL

In the course of a study of substituted pteridines, it was found that those compounds which have amino groups in both the 2- and 4-positions of the pteridine nucleus exhibit a high degree of antifolic acid activity against several bacteria.[2,3] However, the diaminopteridines studied showed very low solubility in water and in all of the common organic solvents tested. Since it appeared desirable to have available for biological testing compounds of this type which could be administered in aqueous solution, several experiments have been carried out to modify these compounds in such a way that solubility in water or alcohol would result with the retention of a high degree of antifolic acid activity.

Of the various pteridines previously reported,[4] 2,4-diaminophenanthro(9,10-e)pteridine had the maximum antifolic acid activity against *S. faecalis*. The preparation of a derivative of this compound having a sulfonic acid group on the phenanthrene nucleus has been carried out. The resulting compound is fairly soluble in aqueous sodium bicarbonate solution but shows very little antifolic acid activity. Since it was thought for a variety of reasons that 2,4-diamino-6,7-diphenyl-

(1) The work presented in this paper was undertaken in collaboration with the Office of Naval Research, Navy Department, Washington, D. C., and was aided by a grant to Cornell University by the Nutrition Foundation, Inc., New York City. It represents a part of a collaborative project on "Newer Members of the B Group of Vitamins."

(2) Daniel, Norris, Scott and Heuser, *J. Biol. Chem.*, **169**, 689 (1947).

(3) Daniel and Norris, *ibid.*, **170**, 747 (1947).

(4) Mallette, Taylor and Cain, THIS JOURNAL, **69**, 1814 (1947).

TABLE I

SOLUBILITY CHARACTERISTICS AND INHIBITORY INDICES OF SYNTHETIC PTERINS

Compound	Name	Solubility[a] H_2O	C_2H_5OH	0.1 *N* HCl	0.1 *N* NaOH	Inhibitory index *vs. S. faecalis*[b]
1	2,4-Diamino-6,7-diphenylpteridine	I	s	S	I	10
2	2-Amino-4-acetamido-6,7-diphenylpteridine	I	SS	S	Hyd.	30
3	2,4-Diacetamido-6,7-diphenylpteridine	I	S	I	Hyd.	60
4	2-Amino-4-methylamino-6,7-diphenylpteridine	I	SS	S	s	4500
5	2,4-Diamino-6,7-bis-(*p*-aminophenyl)-pteridine	I	S	SS	I	3500
6	2,4-Diamino-6,7-bis-(*p*-acetamidophenyl)-pteridine	I	S	S	Hyd.	10,000
7	2,4-Diamino-6,7-bis-(*p*-sulfitomethylaminophenyl)-pteridine, disodium salt	SS	I	s	SS	8000
8	2,4-Diamino-6,7-bis-(*p*-sulfinomethylaminophenyl)-pteridine, disodium salt	SS	I	s	SS	5000
9	2,4-Diacetamido-6,7-bis-(*p*-acetamidophenyl)-pteridine	I	SS	S	Hyd.	150,000
10	2,4-Diamino-6,7-bis-(*p*-hydroxyphenyl)-pteridine	s	s	S	SS	3500
11	2,4-Diamino-6,7-bis-(*m*-nitrophenyl)-pteridine	I	I	I	I	70
12	2,4-Diamino-6,7-bis-(*m*-aminophenyl)-pteridine	I	S	SS	I	500
13	2,4-Diamino-6,7-bis-(*m*-sulfinomethylaminophenyl)-pteridine, disodium salt	S	I	s	SS	3000
14	2,4-Diaminophenanthro(9,10-e)pteridine-8(or 11)-sulfonic acid	s	s	I	SS	50,000
15	2,4-Diaminophenanthro-(9,10-e)pteridine	I	I	I	I	2

[a] Solubility expressed as follows: SS, greater than 10 mg./ml.; S, 1–10 mg./ml.; s, 0.1–1 mg./ml.; I, less than 0.1 mg./ml. [b] Ratio of concentration of inhibitor (pterin) to the concentration of metabolite (folic acid) at which complete inhibition of growth of the organism occurs.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF SYNTHETIC PTERINS

Compound		Maxima mμ	Log ε	Minima mμ	Log ε
1	(d)	267	4.25	250	4.14
		370	4.19	318	3.54
2		257	4.29	247	4.28
	(a)	288	4.26	279	4.25
		370	4.08	332	3.76
	(b)	274	4.22	255	4.12
		365	4.19	318	3.69
3	(c)	278	4.27	257	4.18
		365	4.27	321	3.81
4	(d)	275	4.28	253	4.13
		374	4.27	325	3.64
	(e)	285	4.37	257	4.13
		395	4.15	336	3.48
5	(d)	267	4.29	247	4.13
		367	4.22	315	3.59
		235	4.35	247	4.31
	(e)	263	4.38	360	3.75
		415	4.17		
6		268	4.44	240	4.31
	(a)	295	4.45	280	4.39
		400	4.13	355	3.75
	(b)	274	4.22	255	4.21
		370	4.12	330	3.80
7	(d)	267	4.07	247	3.94
		365	3.97	315	3.43
		230	4.17	225	4.16
	(e)	262	4.19	248	4.10
		415	3.95	360	3.55
8	(f)	275	4.22	260	4.20
		423	4.03	369	3.83
	(e)	265	4.25	248	4.21
		415	4.03	363	3.76
9	(a)	265	4.53	235	4.41
		400	4.25	353	3.81
	(b)	274	4.33	255	4.27
		370	4.24	330	3.87
10	(d)	Shoulder at 245–255	4.35	345	3.76
		392	4.12		
		240	4.34	225	4.30
	(e)	275	4.32	258	4.30
		432	4.13	370	3.84
11	(g)	268	4.54	245	4.39
		365	4.26	320	3.83
12	(d)	294	4.08	288	3.92
		369	4.15	321	3.70
	(e)	225	4.55	325	3.78
		Shoulder at 255–265	4.29		
		380	4.11		
13	(d)	262	4.14	250	4.11
		368	4.00	322	3.64
	(e)	230	4.35		
		390	3.90	340	3.67
14		Shoulder at 243–255	3.44		
	(e)	265	3.46	355	3.42
		428	4.01		

Solvents for absorption spectra

[a] Methyl alcohol. [b] Methyl alcohol made 0.1 *N* in hydrochloric acid. [c] Ethylene glycol made 0.1 *N* in hydrochloric acid. [d] 0.1 *N* Hydrochloric acid. [e] 0.1 *N* Sodium hydroxide. [f] Water. [g] 1 *N* Hydrochloric acid.

pteridine would be a more suitable molecule to modify for solubility, several compounds have been prepared which might be considered as derivatives of this parent molecule. These compounds, together with their absorption spectra in solution, some solubility characteristics and antifolic acid activity against *S. faecalis*, are listed in Tables I and II.

Inspection of Table I leads to several interesting conclusions in regard to the relation of structure and antifolic acid activity. First, there seems to be no direct correlation between alcohol solubility, which we assume is related to lipid solubility, and antifolic acid activity. Extreme examples of this may be found in Compounds 2 and 9 of Table I. Second, acetylation of the amino groups in either the 4- or both the 2- and 4-positions of the pteridine ring has very little effect on the activity, the difference between the mono- and the diacetate probably being one of ease of hydrolysis by the organism. Third, substitution on the phenyl group, regardless of the nature of the substituting group, decreases the activity. Moreover, the position of the substituent on the phenyl group also has a marked effect on the activity, as shown by Compounds 5 and 12. Fourth, the introduction of any of the various water-solubilizing groups employed results in a considerable decrease in the activity, as shown by Compounds 7, 8 and 13. Fifth, replacement of the 4-amino group by a 4-methylamino group lowers the activity, as shown by Compounds 1 and 4.

It is also of interest to point out that the replacement of phenyl groups in the 6- and 7-positions of the pteridine nucleus by *p*-aminophenyl groups affects the reactivity of the amino groups in the 2- and 4-positions. As described in the Experimental Section, acetylation of 2,4-diamino-6,7-bis-(*p*-aminophenyl)-pteridine under mild conditions gives the tetraacetyl derivative, all four of the amino groups present in the molecule being attacked. In contrast to this behavior, the acetylation of the 4-amino group of 2,4-diamino-6,7-diphenylpteridine requires rather vigorous conditions while the acetylation of both the 2- and 4-amino groups in this compound requires much more strenuous conditions.

The assignment of structure of the monoacetyl derivative of 2,4-diamino-6,7-diphenylpteridine as 2-amino-4-acetamido-6,7-diphenylpteridine is based upon a comparison of the absorption spectrum of this compound with that of 2-amino-4-methylamino-6,7-diphenylpteridine.

Experimental

2-Amino-4-acetamido-6,7-diphenylpteridine.—A mixture of 1.0 g. of 2,4-diamino-6,7-diphenylpteridine and 50 ml. of acetic anhydride was heated under reflux for sixteen hours, the acetic anhydride removed by distillation under reduced pressure, and the residue taken up in 100 ml. of boiling alcohol and filtered. The dark orange filtrate was treated twice with Norit and the alcohol concentrated to 15 ml. on a steam-bath. Addition of 75 ml. of hot water and cooling gave 620 mg. (55%) of a light yellow microcrystalline solid. It was recrystallized by dissolving in alcohol, adding hot water to the point of precipitation, and allowing to cool slowly. On heating, the compound melts slowly at 140–150° to a clear red liquid.

Anal. Calcd. for $C_{20}H_{16}N_6O$: N, 23.6. Found: N, 23.6.

2,4-Diacetamido-6,7-diphenylpteridine.—A solution of 0.5 g. (0.0016 mole) of 2,4-diamino-6,7-diphenylpteridine in 3 ml. of concentrated sulfuric acid was treated with 10 ml. of acetic anhydride and the clear red solution heated on a steam-bath for one hour. It was then poured onto ice, diluted to 100 ml. with water and allowed to stand at 0° for one day. The light yellow solid was filtered off and washed first with water and then with alcohol. Recrystallization by dissolving in boiling dimethylformamide, adding hot water to precipitation and cooling gave 0.43 g. (68%) of a light yellow microcrystalline solid, which decomposed slowly on heating above 190°.

Anal. Calcd. for $C_{20}H_{18}N_6O_2$: C, 66.3; H, 4.6; N, 21.1. Found: C, 66.5; H, 4.8; N, 21.2.

2-Amino-4-chloro-6,7-diphenylpteridine Hydrochloride.—A suspension of 1.0 g. (0.0032 mole) of dry 2-amino-4-hydroxy-6,7-diphenylpteridine in 60 ml. of freshly distilled phosphorus oxychloride containing 5 g. of phosphorus pentachloride was refluxed for two hours in an oil-bath to give a clear red solution. After filtering through a sintered glass filter, the solvent was removed by distillation under diminished pressure and the excess phosphorus pentachloride destroyed by addition of ice. After standing for one-half hour, the bright yellow solid was filtered off and washed thoroughly with water to give 0.95 g. (81%). All attempts to recrystallize it resulted in the hydrolysis of the 4-chloro group to give 2-amino-4-hydroxy-6,7-diphenylpteridine.

2-Amino-4-methylamino-6,7-diphenylpteridine.—A mixture of 1.0 g. (0.002 mole) of 2-amino-4-chloro-6,7-diphenylpteridine hydrochloride, 30 ml. of alcohol, and 10 ml. of methylamine was heated in a glass bomb at 155° for sixteen hours. After cooling, the reaction mixture was filtered and the clear yellow filtrate evaporated to dryness under diminished pressure. The yellow residue was extracted with hot 0.5 *N* hydrochloric acid and filtered. The filtrate was treated with Norite and adjusted to *p*H 9 with ammonium hydroxide. The resulting precipitate was crystallized by dissolving in hot alcohol and adding hot water to the point of precipitation which gave 0.27 g. (27%) of bright yellow crystals in the form of rectangular platelets exhibiting parallel extinction and melting at 237–238° (cor.).

Anal. Calcd. for $C_{19}H_{16}N_6$: C, 69.5; H, 4.9; N, 25.6. Found: C, 69.6; H, 5.0; N, 25.8.

2,4-Diamino-6,7-bis-(*p*-aminophenyl)-pteridine.—To a solution of 2.00 g. (0.0084 mole) of 2,4,5,6-tetraminopyrimidine sulfate in 90 ml. of water was added 2.00 g. (0.0049 mole) of *p,p'*-diaminobenzil sulfate,[5] and the mixture refluxed for one hour to give a clear, cherry red solution. After treatment with Norit, it was poured into boiling dilute ammonium hydroxide of sufficient strength so that the final solution was distinctly alkaline (*p*H 11). Orange crystals of the desired product separated at once. After filtering, washing with water, and drying, 1.73 g. (quantitative) was obtained. Recrystallization from 50% ethanol gave bright orange prisms exhibiting parallel extinction, and decomposing sharply at 308–309° (cor.).

Anal. Calcd. for $C_{18}H_{16}N_8$: C, 62.8; H, 4.7; N, 32.6. Found: C, 63.0; H, 4.6; N, 32.6.

2,4-Diamino-6,7-bis-(*p*-acetamidophenyl)-pteridine.—A solution of 1.10 g. (0.00785 mole) of 2,4,5,6-tetraminopyrimidine in 75 ml. of water and a solution of 1.35 g. (0.00417 mole) of *p,p'*-diacetamidobenzil in 100 ml. of ethanol were mixed and refluxed for seven hours. After treatment with Norit, the ethanol was removed by dis-

(5) We should like to express our thanks to Calco Chemical Division of American Cyanamid Company for this material.

tillation under reduced pressure. Upon cooling and filtering, 1.46 g. (82%) of yellow crystals was obtained. Recrystallization from 50% aqueous acetic acid gave small, slender needles showing oblique extinction, m. p. 234–237° (cor.).

Anal. Calcd. for $C_{22}H_{20}N_8O_2$: C, 61.7; H, 4.7; N, 26.2. Found: C, 61.4; H, 4.8; N, 26.2.

2,4-Diamino-6,7-bis-(*p*-hydroxymethylaminophenyl)-pteridine.—To a suspension of 0.1 g. of 2,4-diamino-6,7-bis-(*p*-aminophenyl)-pteridine in 4 ml. of boiling water, sufficient concentrated hydrochloric acid was added to cause solution, and then 0.2 ml. of 40% formaldehyde was added slowly. The addition product separated at once. The mixture was adjusted to *p*H 7.5 with sodium bicarbonate, cooled to 0°, filtered, and washed thoroughly with water to give 115 mg. (quantitative) of the bright orange product. The solid did not melt below 300°.

2,4-Diamino-6,7-bis-(*p*-sulfitomethylaminophenyl)-pteridine Disodium Salt.—The product obtained above was suspended in 30 ml. of water and 0.15 g. of sodium bisulfite added. The mixture was refluxed for three hours to give a clear, light red solution. Removal of three-quarters of the water by distillation under reduced pressure and addition of two volumes of acetone precipitated 0.148 g. (88%) of the orange product. The solid did not melt below 300°.

2,4-Diamino-6,7-bis-(*p*-sulfinomethylaminophenyl)-pteridine Disodium Salt.—To a solution of 0.8 g. (0.00232 mole) of 2,4-diamino-6,7-bis-(*p*-aminophenyl)-pteridine in 200 ml. of ethanol was added 0.65 g. of finely powdered sodium formaldehyde sulfoxylate and 50 mg. of sodium hydroxide, and the mixture heated under reflux on a steam-bath for six hours. During this time, the sulfoxylate gradually dissolved and a bright orange solid separated. The reaction mixture was cooled to 0° and the product filtered off and washed thoroughly with hot alcohol to yield 0.96 g. (76%). The solid did not melt below 300°. No satisfactory method of recrystallization could be found. The structure is assigned on the basis of absorption spectrum and ready solubility in water.

2,4-Diacetamido-6,7-bis-(*p*-acetamidophenyl)-pteridine.—A mixture of 0.2 g. of 2,4-diamino-6,7-bis-(*p*-aminophenyl)-pteridine, 1.9 ml. of glacial acetic acid, and 3.2 ml. of acetic anhydride was heated for forty-five minutes at 80°. Addition of 100 ml. of water caused the separation of a flocculent, light yellow solid, which was collected by filtration, washed with ice cold water, and recrystallized from water to give 0.18 g. (56%). The product was dried for analysis at 140° under vacuum over phosphorus pentoxide, but retained one molecule of water of recrystallization.

Anal. Calcd. for $C_{26}H_{24}N_8O_4 \cdot H_2O$: C, 58.9; H, 4.9; N, 21.1. Found: C, 59.0; H, 4.8; N, 20.8.

2,4-Diamino-6,7-bis-(*p*-hydroxyphenyl)-pteridine.—(a) To an ice-cold solution of 0.2 g. of 2,4-diamino-6,7-bis-(*p*-aminophenyl)-pteridine in a mixture of 7 ml. of water and 0.8 ml. of concentrated sulfuric acid was added slowly a solution of sodium nitrite in water until an excess of nitrous acid was present (starch–iodide paper). The excess nitrous acid was destroyed with urea and the reaction mixture was immersed in a water-bath at 60° for fifteen minutes and finally at 100° for one hour. Five ml. of water was added, and the yellow solid filtered off and washed with water to give 0.14 g. (71%). It was purified by dissolving in dilute sodium hydroxide, treating with Norite, and pouring into hot dilute hydrochloric acid, and was finally recrystallized from water to give a yellow microcrystalline solid. (b) A solution of 0.5 g. (0.002 mole) of *p,p'*-dihydroxybenzil, 1.0 g. (0.0045 mole) of 2,4,5,6-tetraminopyrimidine bisulfite, 20 ml. of ethyl methyl ketone, 20 ml. of ethanol, 40 ml. of water, and 6 ml. of concentrated hydrochloric acid was refluxed for sixteen hours. The clear yellow solution was then treated with Norit and concentrated by distillation under reduced pressure until a bright yellow product separated out. It was filtered off, washed with cold water, and recrystallized from water to give 0.6 g. (84%) of a light yellow microcrystalline solid. The absorption spectrum of this product was identical with that obtained by method (a) above.

Anal. Calcd. for $C_{18}H_{14}N_6O_2$: C, 62.4; H, 4.1. Found: C, 62.7; H 4.1.

2,4-Diamino-6,7-bis-(*m*-nitrophenyl)-pteridine.—A solution of 3.0 g. (0.0214 mole) of 2,4,5,6-tetraminopyrimidine and 2.0 g. (0.0066 mole) of 3,3'-dinitrobenzil in a mixture of 70 ml. of ethanol and 15 ml. of ethyl methyl ketone was refluxed for three hours. The heavy yellow solid which had separated from the reaction mixture was filtered off, washed with boiling water, and recrystallized by dissolving in a small amount of glacial acetic acid, treating with Norit, and pouring into a ten-fold excess of boiling water. The product weighed 2.3 g. (quantitative). After two additional recrystallizations, the product was obtained in the form of thin rods and sheets showing oblique extinction, m. p., 307–308° (cor.).

Anal. Calcd. for $C_{18}H_{12}N_8O_4$: N, 27.7. Found: N, 27.5.

2,4-Diamino-6,7-bis-(*m*-aminophenyl)-pteridine.—A solution of 1.0 g. (0.0025 mole) of 2,4-diamino-6,7-bis-(*m*-nitrophenyl)-pteridine in 75 ml. of ethanol containing 5 drops of concentrated hydrochloric acid was shaken with hydrogen at 2.5 atmospheres pressure with platinum oxide catalyst at room temperature. After one hour, reduction was complete, and the yellow reaction mixture was filtered and evaporated to dryness. The residue was dissolved in 15 ml. of water, treated with Norit, and the product precipitated by addition of ammonium hydroxide to give 0.55 g. (65%). After a partial purification by redissolving in dilute hydrochloric acid and precipitating by addition of ammonium hydroxide, the compound was recrystallized from dilute ammonium hydroxide to give an orange-yellow microcrystalline solid. It slowly decomposed on heating above 180°.

Anal. Calcd. for $C_{18}H_{16}N_8$: C, 62.8; H, 4.7; N, 32.6. Found: C, 62.6; H, 4.6; N, 32.7.

2,4-Diamino-6,7-bis-(*m*-sulfinomethylaminophenyl)-pteridine Disodium Salt.—A boiling solution of 0.04 g. (0.000116 mole) of 2,4-diamino-6,7-bis-(*m*-aminophenyl)-pteridine in 75 ml. of absolute alcohol was treated with 0.013 g. (0.00011 mole) of sodium formaldehyde sulfoxylate, and the mixture refluxed for two hours. The white sodium formaldehyde sulfoxylate gradually disappeared, while at the same time an orange solid deposited. After cooling, filtering, and washing with boiling absolute alcohol, 51 mg. (85%) of the desired product was obtained. The material was hygroscopic and rapidly formed the trihydrate in contact with air.

Anal. Calcd. for $C_{20}H_{18}N_8Na_2O_4S_2 \cdot 3H_2O$: C, 40.1; H, 4.0; N, 18.7. Found: C, 39.7; H, 4.5; N, 18.7.

2,4-Diaminophenanthro(9,10-e)pteridine-8-(or 11)-sulfonic Acid.—A solution of 5.0 g. (0.0225 mole) of 2,4,5,6-tetraminopyrimidine bisulfite in 20 ml. of 0.5% sodium hydroxide was added to a solution of 5.0 g. (0.0174 mole) of phenanthrenequinone-3-sulfonic acid in 130 ml. of water and the resulting deep green mixture refluxed for thirty minutes. At the end of this time the color had changed to a deep cherry red. The reaction mixture was treated with Norit and acidified to *p*H 5 with concentrated hydrochloric acid. The bright yellow solid which separated was collected by filtration and washed with water followed by acetone to give 6.0 g. (88%). The product was purified by dissolving in dilute alkali, treating with Norit, and adding an equal volume of 40% sodium hydroxide. The crystalline sodium salt so obtained was dissolved in water and poured into hot dilute hydrochloric acid to give a light yellow microcrystalline product. It does not melt below 360°.

Anal. Calcd. for $C_{18}H_{12}N_6O_3S$: C, 55.1; H, 3.1. Found: C, 55.2; H, 3.0.

Summary

1. A number of derivatives of 2,4-diamino-6,7-

diphenylpteridine have been prepared for the purpose of finding a soluble derivative which would retain a high degree of antifolic acid activity.

The absorption spectra of these compounds in solution, some of their solubility characteristics and their inhibitory indices against *S. faecalis* are reported.

2. It has been found that a sulfinomethylamino group confers water solubility with the retention of antifolic acid activity. The introduction into the 2,4-diamino-6,7-diphenylpteridine molecule of any of the solubilizing groups investigated results in some lowering of antifolic acid activity.

3. Several conclusions have been drawn regarding the effect on antifolic acid activity of certain structural changes in the 2,4-diamino-6,7-diphenylpteridine molecule.

Ithaca, New York Received September 27, 1948

[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

Piperidine Derivatives. XX. The Preparation and Reactions of 1-Methyl-3-piperidone

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The recent report[1] on the reactions of 1-methyl-4-piperidone, particularly those with a variety of aromatic aldehydes, indicated a study of similar reactions with the unsymmetrical isomer, 1-methyl-3-piperidone (VI). The preparation of this latter compound from 1-methyl-4-carbethoxy-3-piperidone (V), obtained by the cyclization of the diester (IV) was reported earlier[2] from this Laboratory. It seemed of special interest to determine the reactivity of VI in the presence of basic catalysts inasmuch as the previous workers[2] had shown that, due to the relative inertness of the α-aminomethylene group, the cyclization of IV produced the keto-ester V rather than the isomer, 1-methyl-2-carbethoxy-3-piperidone.

In the earlier work[2] the diester IV was prepared by the interaction of ethyl γ-bromobutyrate with sarcosine ester. In the present work a more satisfactory preparation of IV has been developed from butyrolactone, which is now commercially available.[3] The complete series of reactions from this lactone to the piperidone VI is

$$OCH_2CH_2CH_2CO \xrightarrow[280°]{CH_3NH_2} CH_3NCH_2CH_2CH_2CO \xrightarrow{HCl}$$

I (90–93%)

$$HCl\cdot CH_3NHCH_2CH_2CH_2COOH \xrightarrow{KOH}$$

II (91%)

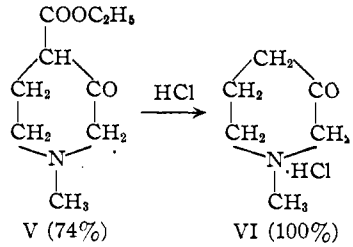
$$CH_3NHCH_2CH_2CH_2COOK \xrightarrow[KOH]{ClCH_2COOK}$$

III

$$CH_3NCH_2CH_2CH_2COOK \xrightarrow[2.\ NH_3]{1.\ C_2H_5OH + HCl}$$

$$\begin{matrix} CH_3NCH_2CH_2CH_2COOC_2H_5 \\ | \\ CH_2COOC_2H_5 \end{matrix}$$

IV (37–46% from II)



V (74%) VI (100%)

The sequence from II to IV was found necessary, as it was not possible to obtain an ester of II; all attempts to prepare the ester gave the pyrrolidone (I). The amino-acid, however, is quite stable in the form of its salts II and III. The cyclization of IV was found to proceed most satisfactorily with sodium ethoxide; sodium hydride, which produced excellent yields of 1-methyl-3-carbethoxy-4-piperidone,[1] gave very poor yields (*ca.* 10%) of V.

The condensation of benzaldehyde with VI in alkaline, 60% ethanol was rapid and a crystalline product, which gave analytical values approximating an equimolecular mixture of the 4-carbinol (VII) and the 4-benzal derivative (VIII), was obtained in approximately 70% yield. No other products could be separated from this reaction. This mixture of VII and VIII could not be separated by recrystallization; a product with a constant melting range, 123–128°, was obtained. However, when this material was converted to the hydrochloride salts, the free bases liberated into ether, and the resulting solution concentrated, the benzal derivative VIII, m. p. 112–113°, separated. From the ether filtrate the carbinol VII was obtained as a glass, which gave a crystalline hydrochloride that melted at 192–202°, indicating that it was a mixture of the two possible racemates. Two other observations are worthy of note: (a) an ethereal solution of the carbinol VII containing a small amount of the benzal derivative (VIII) gave, on standing, a crystalline precipitate, m. p. 123–128°, and (b) this latter product also separated from an alkaline 60% ethanol solution of VII on

(1) McElvain and Rorig, This Journal, **70**, 1820 (1948).
(2) Prill and McElvain, *ibid.*, **55**, 1233 (1933).
(3) From the Cliffs Dow Chemical Company, Marquette, Michigan.