nitro-2,7-dimethylquinoline with stannous chloride and hydrochloric acid led to the formation of what proved to be 8-amino-5-chloro-2,7-dimethylquinoline in addition to the expected amine.[11] Analysis of the crude reaction product indicated a chlorine content of 8.14%, about one-half that calculated (18.50%) for an aminochlorodimethylquinoline. The structure of the by-product (which was not isolated) was established as described in the section on the Sandmeyer reactions. The nitro compound was reduced successfully by the use of iron and acetic acid,[4] with the results indicated in Table III.

Sandmeyer Reactions.—The amines were converted by the Sandmeyer reaction into the corresponding chlorides. The procedure used was similar to that employed by Dikshoorn in the preparation of 5-bromoquinoline.[20] The results of the several Sandmeyer processes are listed in Table IV.

The mixture of amino- and aminochlorodimethylquinoline obtained in the stannous chloride reduction of 8-nitro-2,7-dimethylquinoline was subjected to the Sandmeyer reaction. The steam distilled product melted between 50 and 60° with much prior softening. Six successive crystallizations from petroleum ether gave a colorless substance with the constant melting point 96–97°, which was found to be identical with 5,8-dichloro-2,7-dimethylquinoline.

(20) R. P. Dikshoorn, *Rec. trav. chim.*, **48**, 550 (1929).

HANOVER, N. H.

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. XI. Some 8-Alkyl-7-pteridones[1]

BY GERTRUDE B. ELION AND GEORGE H. HITCHINGS

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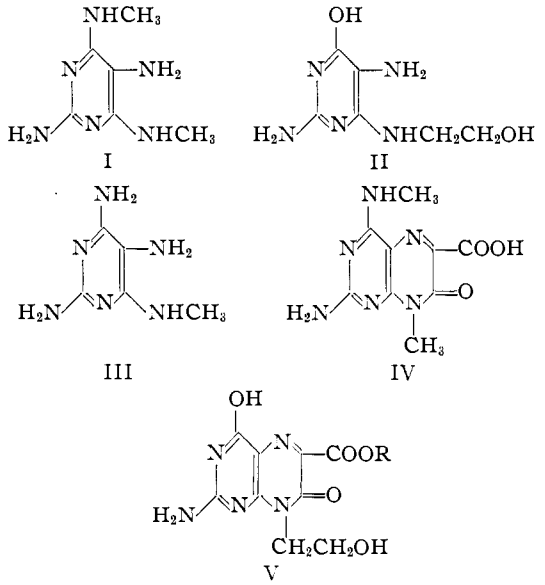
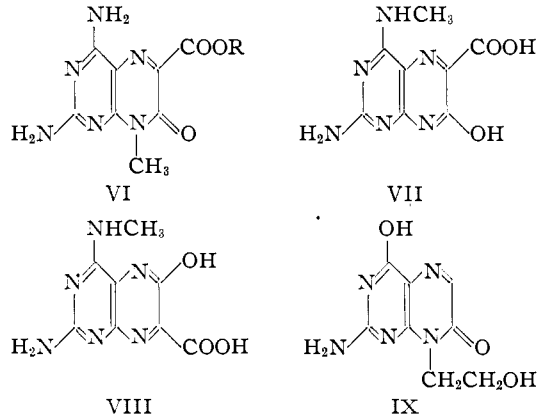
The preparation is described of several 8-alkyl-7-oxo-7,8-dihydro-6-pteridine-carboxylic acids by the condensation of the 2-amino derivatives of 4,5-diamino-6-methylamino-, 5-amino-4,6-bis-(methylamino), and 5-amino-6-hydroxy-4-β-hydroxyethylaminopyrimidine with ethyl oxomalonate. 6-Methylamino-2,4,5-triaminopyrimidine gave two products, for which are proposed the structures ethyl 2,4-diamino-8-methyl-7-oxo-7,8-dihydro-6-pteridinecarboxylate and 2-amino-4-methylamino-7-hydroxy-6-pteridinecarboxylic acid. On heating, 2-amino-4-hydroxy-8-β-hydroxyethyl-7-oxo-7,8-dihydro-6-pteridinecarboxylic acid loses carbon doxide and is converted to the corresponding 7-pteridone.

Pteridines with a substituent in the 8-position are of interest because the analogous position is the site of attachment of a sugar moiety in the purine nucleosides, riboflavin and vitamin B_{12}. During the course of these experiments, the synthesis of some 8-substituted pteridines was reported[2,3] in which ethyl oxalate, benzoin and chloroacetic acid were the carbonyl reagents used. The present report deals with the condensation of ethyl oxomalonate with the three types of pyrimidine exemplified by structures I, II and III. With pyrimidine I, the substituents at positions 4 and 6 are the same so that when ring closure occurs, only one product is possible, namely, IV. With pyrimidine II ring closure with ethyl oxomalonate likewise gives only one product, V (R = C_2H_5), since there is an hydroxyl group in the 4-position. Because the nitrogen on the 6-position of I and II has a substituent, it is not possible in either case to form the isomeric 6-hydroxy-7-pteridinecarboxylic acid, such as is formed when 6-hydroxy-2,4,5-triaminopyrimidine is condensed with ethyl oxomalonate.[4] Compound III is however, theoretically capable of reacting with this ester to give three products VI, VII and VIII, only one of which VI is an 8-substituted pteridine. Since 4-alkylamino-6-amino-5-thioformamidopyrimidines give 9-substituted purines exclusively on ring closure,[5] it was expected that the primary product would be the 8-substituted pteridine. Furthermore, 2,4,5,6-tetraaminopyrimidine with ethyl oxomalonate gives exclusively the 7-hydroxypteridine rather than a mixture of the





(1) Presented before the XIIth International Congress of Pure and Applied Chemistry, New York, September, 1951.

(2) H. S. Forrest, R. Hull, H. J. Rodda and A. R. Todd, *J. Chem. Soc.*, 3 (1951).

(3) D. B. Cosulich, B. Roth, J. M. Smith, Jr., M. E. Hultquist and R. P. Parker, THIS JOURNAL, **74**, 3252 (1952).

(4) R. Purrmann, *Ann.*, **548**, 284 (1941).

(5) J. Baddiley, B. Lythgoe, D. McNeil and A. R. Todd, *J. Chem. Soc.*, 383 (1943).

6- and 7-hydroxy isomers.[6] Nevertheless, two distinct pteridines were isolated from the condensation of III with the ester. The first of these separated readily from the acidic reaction mixture and was extremely insoluble in hot water. This product was tentatively identified as VII, since its ultraviolet absorption spectrum strongly resembles that of 2,4-diamino-7-hydroxy-6-pteridinecarboxylic acid,[6] except that the band in the 360 mμ region shows no shift with a change in *p*H. Its identity was confirmed by its transformation to isoxanthopterin-6-carboxylic acid on hydrolysis with 6 *N* hydrochloric acid. The second product obtained from the condensation of III with ethyl oxomalonate was soluble in hot water and had an ultraviolet absorption spectrum similar to that of IV, with some difference in the position of the band *ca.* 380 mμ at *p*H 1. When analysis showed that the compound contained a carbethoxyl group, this discrepancy in the spectrum was explained and the compound was assigned the structure VI (R = C_2H_5). Its identity was confirmed when acid hydrolysis produced a compound with a spectrum almost identical with that of V (R = H).

The stability of the ester linkages in V and VI is markedly greater than that of the 8-unsubstituted derivatives since both isoxanthopterin-6-carboxylic acid[4] and its 4-amino analog[6] are the primary products of the condensation of oxomalonic ester with the N-unsubstituted pyrimidines at *p*H 5.

The ultraviolet absorption spectra of the 8-alkyl-7-oxo-7,8-dihydro-6-pteridinecarboxylic acids are similar to those of other 7-hydroxy-6-pteridinecarboxylic acids[6] although the aromatic character of the pyrazine ring would appear to be destroyed by substitution on the 8-position. However, N-methyl-α-pyridones also show the selective absorption of aromatic compounds.[7] The introduction of an alkyl group on the 8-position of the 7-hydroxy-6-pteridinecarboxylic acids has the effect of intensifying and shifting the band in the near ultraviolet 100–200 mμ toward the longer wave lengths.

The decarboxylation of isoxanthopterincarboxylic acid at 260° leads to the formation of isoxanthopterin.[4] It has also been shown that when this carboxylic acid is first reduced with zinc and alkali or with sodium amalgam, the resultant dihydro compound decarboxylates spontaneously.[8] Substitution on the 8-position of isoxanthopterincarboxylic acid, *e.g.*, V (R = H), has very little effect on the ease of decarboxylation. This compound is stable at 140° but loses carbon dioxide at 240°; the product IX has a spectrum markedly different from that of the starting material (Table II). The spectrum of this β-hydroxyethyl derivative of isoxanthopterin likewise differs noticeably from that of isoxanthopterin[8] itself at *p*H 11 in having its long wave length band at 357 mμ rather than at 342 mμ. This difference at *p*H 11 is to be expected since, in the 8-hydroxyethyl compound, the 7-oxo group can not assume the enolate form.

Like 2,4-diamino-7-hydroxy-6-pteridinecarboxylic acid, which does not decarboxylate at 260°,[6] the 4-methylamino derivative VII darkens but its spectrum does not change after one hour at 260°. Similarly, the 8-methyl derivative IV of the latter decomposes somewhat but does not decarboxylate at 240°. The resistance of these pteridines to decarboxylation is in marked contrast to the ease with which 5,6-dihydro-6-pteridinecarboxylic acids decarboxylate.[8]

The starting pyrimidine for the synthesis of the 8-substituted pteridines was 2-amino-4,6-dichloropyrimidine. The appropriate groups were introduced into the 4- and 6-positions as follows: (1) reaction with methylamine to give a 2-amino-4,6-bis-(methylamino)-pyrimidine, (2) alkaline hydrolysis followed by heating with β-hydroxyethylamine to give 2-amino-4-hydroxy-6-β-hydroxyethylaminopyrimidine, (3) heating with ammonia at 150°, followed by treatment with methylamine to give a 2,4-diamino-6-methylaminopyrimidine.[9]

The 5-amino group was introduced by coupling with *p*-chlorobenzene diazonium chloride[8,10] followed by reduction with zinc dust.[8,11] The 5-aminopyrimidines of types I, II and III are extremely soluble in water and unlike 6-hydroxy-2,4,5-triaminopyrimidine and 2,4,5,6-tetraaminopyrimidine, form sulfates which are relatively soluble. For this reason they were used in solution, directly after the reduction step, after their identity had been verified by comparison of their absorption spectra with those of 2,4,5,6-tetraaminopyrimidine and 6-hydroxy-2,4,5-triaminopyrimidine.

Experimental

2-Amino-4,6-bis-(methylamino)-pyrimidine.[9]—A mixture of 10 g. of 2-amino-4,6-dichloropyrimidine, 50 ml. of 25% aqueous methylamine solution and 5 ml. of 2 *N* hydrochloric acid was heated at 150° in a sealed tube for 4.5 hours. The reaction mixture was taken to dryness on the steam-bath, and then extracted with two 100-ml. portions of boiling acetone to remove an unreacted 2-amino-4,6-dichloropyrimidine. The acetone-insoluble residue was washed with 50 ml. of water and dried in a vacuum desiccator. The crude product was converted to its hydrochloride by treatment with excess alcoholic hydrogen chloride. After filtration, washing with absolute alcohol and drying in a vacuum desiccator, the hydrochloride of 2-amino-4,6-bis-(methylamino)-pyridine (6.0 g.) melted at 326°. This crude product was used for the next step without further purification.

2-Amino-4,6-bis-(methylamino)-5-*p*-chlorobenzeneazopyrimidine.—To a solution of 9.2 g. of 2-amino-4,6-bis-(methylamino)-pyrimidine hydrochloride in 200 ml. of water, kept at 5° in an ice–salt-bath, was added a solution of diazotized *p*-chloroaniline (from 7 g. of *p*-chloroaniline) and a cold solution of 35 g. of sodium bicarbonate in 400 ml. of water to bring the *p*H to 5. The mixture was allowed to stand in the ice-bath for one hour and filtered. The orange-yellow precipitate was washed with water and dried in a vacuum desiccator (10.3 g.). After recrystallization from aqueous methanol, the product (6.85 g.) melted at 193–195°.

Anal. Calcd. for $C_{12}H_{14}N_7Cl\cdot H_2O$: C, 46.5; H, 5.2; H_2O, 5.8. Found: C, 46.5; H, 5.1; H_2O, 6.0.

2,5-Diamino-4,6-bis-(methylamino)-pyrimidine (I).—To a boiling suspension of 6.5 g. of the above 5-*p*-chlorobenzeneazo compound in 200 ml. of water was added 14 g. of

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(7) E. R. Riegel and M. C. Reinhard, *ibid.*, **48**, 1334 (1926).

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TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF 2-AMINOPYRIMIDINE INTERMEDIATES

Pyrimidine 4	5	6	Concn., mg./l.	pH 1 $\lambda_{max.}$, mμ	pH 1 Optical density	pH 11 $\lambda_{max.}$, mμ	pH 11 Optical density
NH_2		Cl	10	298	0.52	282	0.52
NH_2		NH_2	10	272	1.58	268	.90
NH_2		CH_3NH	6.0	277	0.94	270	.51
CH_3NH		CH_3NH	8.0	280	1.03	272	.62
OH		Cl	10	284	0.59	275	.48
OH		NH_2	10	265	1.60	265	.99
OH		$HOCH_2CH_2NH$	8.2	268	1.05	268	.79
NH_2	NH_2	NH_2	5.5	272	0.54	240	.14
						280	.275
CH_3NH	NH_2	CH_3NH	χ	280	.55	240	.38
						282	.41
NH_2	NH_2	CH_3NH	χ[a]	275	.46	240	.54
						280	.40
NH_2	NH_2	OH	10	263	.85	240	.39
						280	.46
$HOCH_2CH_2NH$	NH_2	OH	χ[a]	270	1.37	233	1.7
						280	0.8

[a] Solution contains *p*-chloroaniline.

zinc dust and 10 ml. of 10 *N* sulfuric acid. After boiling for 2 minutes, the solution was filtered. The hot filtrate was treated with Darco, refiltered and allowed to stand at 4° overnight. No precipitate formed. An ultraviolet absorption spectrum of the solution indicated that approximately 3 g. of the 2,5-diamino-4,6-bis-(methylamino)-pyrimidine was present (Table I). The solution was used directly for condensation with ethyl oxomalonate.

It was also found possible to reduce the azo compound catalytically at 50° in aqueous methanol containing an excess of hydrochloric acid, using Adams platinum catalyst. However, the uptake of hydrogen was very slow, only 66% of the theoretical amount having been taken up in 50 hours. The product had the same spectrum as that obtained by the zinc reduction.

2-Amino-4-methylamino-8-methyl-7-oxo-7,8-dihydro-6-pteridinecarboxylic Acid (IV).—To the aqueous solution of 2,5-diamino-4,6-bis-(methylamino)-pyrimidine prepared by zinc reduction was added 3 ml. of 10 *N* sulfuric acid, to bring the *p*H to 3, and 10 ml. of ethyl oxomalonate. The mixture was refluxed for two hours, a small amount of oily material was filtered off and the filtrate was taken almost to dryness *in vacuo*. The residue was treated with 250 ml. of absolute ethanol and the insoluble material removed. To the alcoholic filtrate was added 3 volumes of ether. The yellow-orange precipitate was collected by centrifugation, washed with ether and dried in a vacuum desiccator (2.3 g.). This crude product was about 70% pure as judged by its ultraviolet absorption spectrum. A 900-mg. portion was recrystallized from 40 ml. of hot water and dried at 140°. Although the compound does not lose its water of crystallization at 140°, closure of the pyrazine ring is indicated by the spectrum (Table IV).

Anal. Calcd. for $C_9H_{10}N_6O_3 \cdot H_2O$: C, 40.3; H, 4.5; N, 31.3. Found: C, 40.8; H, 4.0; N, 31.0.

2-Amino-6-hydroxy-4-β-hydroxyethylaminopyrimidine.—A mixture of 1 g. of 2-amino-4-chloro-6-hydroxypyrimidine[2] and 1 g. of β-hydroxyethylamine was heated in an oil-bath at 140° for one-half hour. The clear melt was cooled, diluted with 40 ml. of absolute ethanol, made strongly acidic by the addition of 2 ml. of 18% ethanolic hydrogen chloride and allowed to stand in an ice-bath for one hour. The precipitate was collected by centrifugation, washed with 20 ml. of ethanol, 10 ml. of ether and dried at room temperature. The 2-amino-6-hydroxy-4-β-hydroxyethylaminopyrimidine hydrochloride (0.9 g.) melted at 203°.

Anal. Calcd. for $C_6H_{10}N_4O_2 \cdot HCl$: C, 34.9; H, 5.3; N, 27.1. Found: C, 35.3; H, 5.0; N, 26.7.

The ultraviolet absorption spectrum (Table I) is in agreement with that expected for the assigned structure of the product. It was not further purified before use in the next reaction.

2-Amino-5-*p*-chlorobenzeneazo-6-hydroxy-4-β-hydroxyethylaminopyrimidine.—A solution of 2.06 g. of 2-amino-6-hydroxy-4-β-hydroxyethylaminopyrimidine hydrochloride in 50 ml. of water, below 5°, was coupled with *p*-chlorobenzenediazonium chloride (from 1.28 g. of *p*-chloroaniline) in the usual way. After one hour in an ice-bath, the orange precipitate was filtered, washed with water and dried at 120°. This crude azo compound (2.85 g.) melted at 267–268°.

2,5-Diamino-6-hydroxy-4-β-hydroxyethylaminopyrimidine (II).—To a suspension of 2.8 g. of the above crude 5-*p*-chlorobenzeneazopyrimidine in 50 ml. of hot water was added 1.5 g. of zinc dust and 7 ml. of 10 *N* sulfuric acid. After boiling for two minutes, the mixture was filtered. No precipitate formed on cooling but the ultraviolet absorption spectrum (Table I) indicated that the reduction had taken place. This solution was used directly for the condensation with ethyl oxomalonate.

Ethyl 2-Amino-4-hydroxy-8-β-hydroxyethyl-7-oxo-7,8-dihydro-6-pteridinecarboxylate (V, R = C_2H_5).—The aqueous solution (90 ml.) of 2,5-diamino-6-hydroxy-4-β-hydroxyethylaminopyrimidine (containing about 1.2 g. of the pyrimidine) was brought to *p*H 5 with 7 ml. of 2 *N* sodium hydroxide solution and then refluxed with 5 ml. of ethyl oxomalonate for one hour. After standing for several days at room temperature the yellow crystalline precipitate was filtered off, washed with water, alcohol and ether. The 2.1 g. of crude product was recrystallized from 600 ml. of water, giving 1.4 g. of the dihydrate of the ester. The water is lost at 140°.

Anal. Calcd. for $C_{11}H_{13}N_5O_5 \cdot 2H_2O$: C, 39.9; H, 5.1; N, 21.2; H_2O, 10.9. Found: C, 39.7; H, 5.2; N, 20.8; H_2O, 10.9.

2-Amino-4-hydroxy-8-β-hydroxyethyl-7-oxo-7,8-dihydro-6-pteridinecarboxylic Acid (V, R = H).—A solution of 130 mg. of V (R = C_2H_5) in 14 ml. of 0.06 *N* sodium hydroxide was heated in a boiling water-bath for 1.5 hours. The solution was diluted to 50 ml. with water and brought to *p*H 5 with 2 *N* hydrochloric acid. The precipitate (100 mg.) was collected and dissolved in 20 cc. of hot water, 0.5 cc. of 2 *N* hydrochloric acid was added, and the solution cooled. The yellow precipitate was filtered off, washed with water, alcohol and ether and dried in a vacuum desiccator. The monohydrate loses its water of crystallization at 140°.

Anal. Calcd. for $C_9H_9N_5O_5 \cdot H_2O$: C, 37.9; H, 3.9; H_2O, 6.3. Found: C, 37.8; H, 3.7; H_2O, 6.3.

2-Amino-4-hydroxy-8-β-hydroxyethyl-7-oxo-7,8-dihydropteridine (IX).—After 2 g. of 2-amino-4-hydroxy-8-β-hydroxyethyl-7-oxo-7,8-dihydro-6-pteridinecarboxylic acid had been heated at 240–250° for one hour, the residue was dissolved in 35 ml. of 0.3 *N* sodium hydroxide. This solution was filtered into 40 ml. of hot dilute acetic acid, cooled and filtered. After being washed with water, alcohol and ether, the precipitate (1.4 g.) was dried at 120°.

Anal. Calcd. for $C_8H_9N_5O_3$: C, 43.0; H, 4.0; N, 31.4. Found: C, 42.6; H, 4.1; N, 31.0.

2,4-Diamino-6-methylaminopyrimidine.[9]—A mixture of 5 g. of 6-chloro-2,4-diaminopyrimidine[12] and 25 ml. of a 25% aqueous solution of methylamine was heated at 150° in a sealed tube for 4.5 hours. The reaction mixture was taken to dryness on the steam-bath. To the oily residue was added 100 ml. of absolute ethanol and 25 ml. of 36% ethanolic hydrogen chloride. The yellow precipitate was filtered off, washed with absolute alcohol and ether and dried in a vacuum desiccator (3.2 g.). The crude product gave a spectrum consistent with the expected product (Table I).

5-*p*-Chlorobenzeneazo-2,4-diamino-6-methylaminopyrimidine.—To a cold solution of 3.8 g. of the crude 2,4-diamino-6-methylaminopyrimidine dihydrochloride in 50 ml. of water was added the diazotized solution from 2.56 g. of *p*-chloroaniline and 100 ml. of a 10% sodium bicarbonate solution. The mixture was kept at 0 to 5° for one hour and the bright yellow precipitate (5.25 g.) collected, washed with water, and dried in a vacuum desiccator.

6-Methylamino-2,4,5-triaminopyrimidine (III).[9]—To a hot suspension of 5 g. of the crude *p*-chlorobenzeneazo compound, prepared above, in 200 ml. of water and 50 ml. of methanol was added 2.5 g. of the zinc dust. The mixture was boiled for five minutes, filtered and cooled. A small yellow precipitate (0.4 g.) of unreduced azo compound formed on cooling and was filtered off. The filtrate (340 ml.) contained about 2 g. of 6-methylamino-2,4,5-triaminopyrimidine judging from the ultraviolet absorption spectrum (Table I).

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF PTERIDINES

Compound	*p*H 1 Maxima λ, mμ	*E*m	Minima λ, mμ	*E*m	*p*H 11 Maxima λ, mμ	*E*m	Minima λ mμ	*E*m
IV	268	9,500	255	8700	270	14,200	248	8,800
	302	8,050	288	7200	379	15,750	312	3,100
	386	17,700	320	2700				
V, R = C_2H_5	270	7,950	252	6950	265	14,200	242	7,750
	292	7,950	280	6950	380	20,400	302	2,000
	378	25,300	308	1800				
V, R = H	268	7,500	245	5350	262	12,000	245	6,700
	290	6,700	282	6150	367	16,900	302	2,300
	382	23,000	310	1600				
IX	262	5,600	245	4250	258	8,900	245	7,250
	290	6,250	275	4500	282	4,250	278	4,150
	345	9,050	307	3450	357	9,750	305	2,900
VII	263	13,100	245	9800	265	14,300	248	10,400
	298	6,500	285	6100	362	14,700	300	3,300
	360	15,100	315	3900				
VI, R = C_2H_5	268	7,300	265	7200	272	16,700	245	6,200
	300	10,300	280	6800	387	21,500	300	2,500
	372	20,600	315	3700				
VI, R = H	272	7,700	268	7500	265	12,600	248	9,900
	300	7,900	286	6500	370	14,400	305	3,100
	380	15,800	320	3600				

Condensation of 6-Methylamino-2,4,5-triaminopyrimidinopyrimidine with Ethyl Oxomalonate.—The solution from the zinc reduction above was brought to *p*H 3–4 with 23 ml. of 2 *N* sodium hydroxide solution, 5 ml. of ethyl oxomalonate was added and the mixture was refluxed for one and one-half hours. After cooling to 10°, the yellow precipitate formed during the reflux period was collected, washed with water and dried at room temperature. The precipitate was dissolved in 200 ml. of hot water containing 10 ml. of concentrated ammonium hydroxide, filtered and acidified to a *p*H < 3 with hydrochloric acid. After standing overnight at room temperature, the yellow precipitate was collected by centrifugation, washed with water, alcohol and ether and dried at 110° (0.6 g.). This compound was assigned the structure VII on the basis of ultraviolet absorption spectrum, analysis and conversion to isoxanthopterin carboxylic acid.

Anal. Calcd. for $C_8H_8N_8O_3 \cdot {}^1/_2H_2O$: C, 39.2; H, 3.7; N, 34.3; H_2O, 3.7. Found: C, 40.0; H, 3.6; N, 34.3; H_2O, 3.3.

The reaction mixture filtrate was brought to *p*H 6 by the addition of 40 ml. of 2 *N* sodium hydroxide. The bright yellow precipitate was filtered off, washed with water and dried in a vacuum desiccator (1.3 g.). On boiling with 250 ml. of water, a portion (0.4 g.) of this precipitate remained undissolved. After filtration of the hot aqueous solution, a pale yellow crystalline precipitate separated slowly on cooling. It was collected, washed with water, alcohol and ether and dried in a vacuum desiccator (0.2 g.). The structure proposed on the basis of the spectrum is ethyl 2,4-diamino-8-methyl-7-oxo-7,8-dihydro-6-pteridinecarboxylate (VI, R = C_2H_5). After recrystallization from 30 parts of water it was dried at 120°.

Anal. Calcd. for $C_{10}H_{12}N_6O_3$: C, 45.5; H, 4.5. Found: C, 46.1; H, 4.3.

By concentration of various mother liquors a compound was isolated which was recrystallized by solution in hot dilute alkali and acidification to *p*H 5 with hydrochloric acid. It was dried at 140°. This compound (0.4 g.) was shown to be VI (R = H) by its analysis and ultraviolet absorption spectrum. Its spectrum differs from that of the corresponding ester reported above in the relative positions of the 370–380 mμ bands in acid and alkaline solutions.

Anal. Calcd. for $C_8H_8N_6O_3$: C, 40.7; H, 3.4. Found: C, 41.2; H, 3.3.

Acid Hydrolysis of VII.—One hundred mg. of VII was heated with 40 ml. of 6 *N* hydrochloric acid for four hours under reflux. The mixture was allowed to cool, and the pale yellow precipitate filtered off, washed with water, alcohol and ether and dried at room temperature (36 mg.). The product had an ultraviolet absorption spectrum identical with that of an authentic specimen of isoxanthopterin-6-carboxylic acid.[8] The acid filtrate contained mainly unhydrolyzed VII, according to the ultraviolet absorption spectrum, indicating that the hydrolysis had been only about 40% complete after four hours.

Acid Hydrolysis of VI (R = C_2H_5).—Approximately 10 mg. of VI (R = C_2H_5) was boiled with 6 *N* hydrochloric acid for four hours. The solution was then taken to dryness on the steam-bath. The residue was dissolved in 50 ml. of water containing 0.1 ml. of 2 *N* sodium hydroxide. The ultraviolet absorption spectrum of this solution very closely resembled that of V (R = H) and its identity as an 8-substituted pteridine was thereby established.

Ultraviolet absorption spectrum: at *p*H 1, λ_{max} = 275, 295, 377 mμ (o.d. = 0.26, 0.25, 0.49); at *p*H 11, λ_{max} = 265, 367 mμ (o.d. = 0.38, 0.51).

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