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Pteridines, LXXVII.[1] C-Acylations of Pteridines by Homolytic Heteroaromatic Substitution

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Homolytic substitution reactions with acyl radicals proceed with 2,4-diamino- (*VI—VIII*) and 4-amino-2-methylthiopteridines (*XXVII—XXIX*) selectively at position 7 to give the corresponding 7-acyl derivatives *IX—XV* and *XXX—XXXV*, respectively, in moderate to good yields. The ketone character of these new pteridines is demonstrated by carbonyl reactions forming a hydrazone (*XVIII*) and oximes (*XVI, XVII*), as well as 7-(1-hydroxyalkyl)--pteridine derivatives (*XIX, XX*) on sodium borohydride reduction.

Characterization of the newly synthesized compounds has been achieved by elementary analysis, ^{1}H-NMR and UV spectra.

INTRODUCTION

The pteridine ringsystem can be regarded as a prototype of a π-electron--deficient *N*-heterocycle, which is, therefore, not prone to direct elektrophilic substitution reactions at the ring-C-atoms. Homolytic substitutions using radicals, which are of nucleophilic nature, however, reveal an interesting new approach to the formation of new C—C bonds in the heterocyclic field, as shown by Minisci *et al.*[2,3] in their fundamental investigations. This alternative turned out to be also successful with pteridines, as recently demonstrated by homolytic acylations of various lumazine derivatives.[4] In order to prove the general applicability of this reaction to other pteridines, various 2,4-disubstituted derivatives have been treated with acyl radicals derived from the corresponding aldehydes by the redox system *tert.* butylhydroperoxid/Fe^{++} salts in acidic medium.

SYNTHESES

2,4-Diaminopteridine (*VI*) turned out to be an interesting starting material due to the fact that this substitution at the pyrimidine moiety of the molecule reveals potential biological activity as seen from the antineoplastic drugs aminopterin and methotrexate[5], as well as the diuretic triamterene[6]. Reactions of *VI* with acetyl, propionyl, butyryl, isobutyryl, and dihydrocinnamoyl radical in acetic acid or trifluoroacetic acid proceeded smoothly at 5 °C or slightly elevated temp. to give 30—61% yield of the corresponding 7-acyl-

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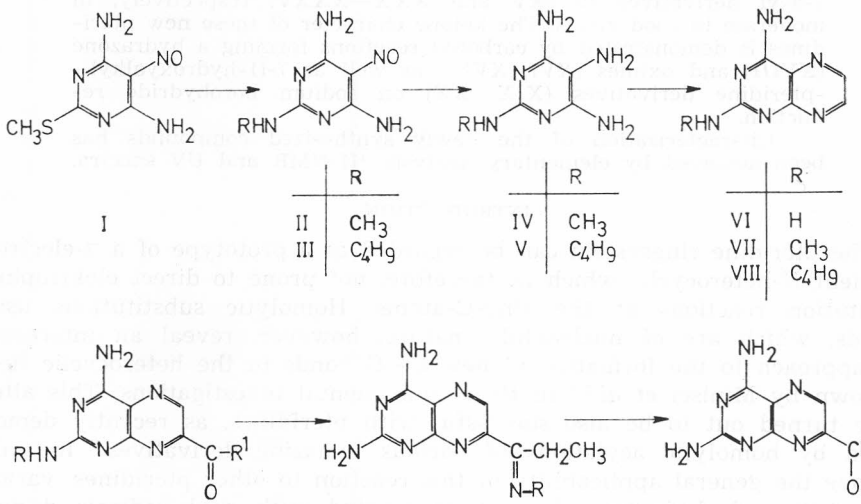
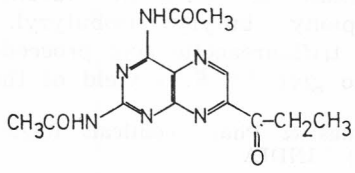
-2,4-diaminopteridines (*IX*—*XIII*). 4-Amino-2-methyl-amino-(*VII*) and 4-amino--2-*n*-butylaminopteridine (*VIII*), which had been synthesized from 4,6-diamino--2-methylmercapto-5-nitrosopyrimidine (*I*) first by nucleophilic displacement of the methylmercapto group by methylamine and *n*-butylamine to give *II* and *III* respectively, then reduction to the corresponding 5-amino derivatives *IV* and *V* followed by condensation with glyoxal, reacted analogously with the propionyl radical to form 4-amino-2-methylamino- (*XIV*) and 4-amino-2--*n*-butylamino-7-propionylpteridine (*XV*) in 33 and 51% yield, respectively. The ketone character of the newly synthesized compounds is revealed in carbonyl reactions yielding, with hydroxylamine and *O*-methylhydroxylamine, the oxime (*XVI*) and *O*-methyl oxime (*XVII*), respectively, whereas *tert.* butylhydrazine gives rise to hydrazone formation (*XVIII*). Sodium borohydride reduction takes also place at the carbonyl function to form 7-(1'--hydroxyalkyl) derivatives (*XIX, XX*), as shown in two cases. Finally,

Scheme 1



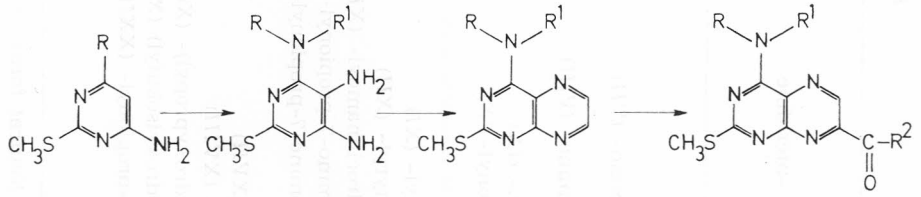


acylation of 2,4-diamino-7-propionylpteridine (*X*) afforded a diacetyl derivative, to which structure *XXI* is assigned for analogy reasons[7] and its spectroscopic data.

Comparisons of physical data of the 7-acyl-2,4-diaminopteridines with those of 2,4-diaminopteridine itself (*VI*) show the expected changes. The basicity of *VI* drops from 5.32 to 4.63 in X due to the elctron-attracting properties of the acyl group and the UV-absorption of the long wavelength band is red-shifted in the neutral form by about 30 nm, expressing a longer chromophoric system (Table I). Alkylation of the 2-amino group is associated with an increase in basicity and bathochromicity. Reduction of the carbonyl group leads back to the 2,4-diaminopteridine type molecule and acetylation at the amino groups neutralizes the electron-donating power of these substituents.

Another series of 7-acylpteridines have been derived from 4-amino-2-methylmercapto.pteridine (*XXVII*) and its 4-methylamino- (*XXVIII*) and 4--dimethylamino derivative (*XXIX*). The yield of *XXVII*[8] in the condensation step of 4,5,6-triamino-2-methylmercaptopyrimidine with glyoxal has been improved substantially from 32 to 89%. The syntheses of *XXVIII* and *XXIX* were achieved from 6-amino-4-chloro-2-methylmercaptopyrimidine (*XXII*)[9], first by reaction with methylamine and dimethylamine, respectively, to form in a nucleophilic displacement reaction *XXIII* and *XIV*[10], followed by nitrosation and subsequent reduction with ammonium sulfide to 5,6-diamino-4--methylamino-2-methylmercapto- (*XXV*) and 5,6-diamino-4-dimethylamino-2--methylmercaptopyrimidine (*XXVI*)[10], which condensed with glyoxal in high yield to *XXVIII* and *XXIX*, respectively.

Homolytic acylations with *XXVII—XXIX* proceeded unexpectedly well and gave high yields for this type of reaction, ranging from 53—86%. The methylmercapto group seems to have a good electronic influence on the reaction and its hydrophobic character allows an easy isolation and purification of the reaction products (*XXX—XXXV*).



	R
XXII	Cl
XXIII	$NHCH_3$
XXIV	$N(CH_3)_2$

	R	R^1
XXV	H	CH_3
XXVI	CH_3	CH_3

	R	R^1
XXVII	H	H
XXVIII	H	CH_3
XXIX	CH_3	CH_3

	R	R^1	R^2
XXX	H	H	CH_3
XXXI	H	H	C_2H_5
XXXII	H	H	C_3H_7
XXXIII	H	H	$CH_2CH_2C_6H_5$
XXXIV	H	CH_3	C_2H_5
XXXV	CH_3	CH_3	C_2H_5

TABLE I

Physical Data of 2,4-Diaminopteridine Derivatives

-pteridine	pK_a in H_2O	UV — Absorption Spectra									pH	Molecular form
		λ_{max} (nm)					lg ε					
2,4-Diamino- (*VI*)	5.32		239	282	331		4.10	3.71	3.98		3.0	+
		225	254			363 4.03	4.31			3.86	9.0	0
4-Amino-2-methylamino- (*VII*)	4.97	204	243	292	337		4.36	4.13	3.79	3.98	1.0	+
		223	263	[302]		372 4.06	4.31	[3.31]		3.82	8.0	0
4-Amino-2-*n*-butylamino- (*VIII*)	5.06	211	244	296	340		4.36	4.17	3.83	4.02	1.0	+
		228	265	[304]		376 4.10	4.37	[3.32]		3.85	8.0	0
7-Acetyl-2,4-diamino- (*IX*)		217	[240]	271		390 4.35	[4.15]	4.14		3.77	MeOH	0
2,4-Diamino-7-propionyl- (*X*)	4.63		248	[305]	349			3.87	[3.62]	3.94	0.0	+
			[240]	268		393		[4.05]	4.04	3.70	8.0	0
		218	[243]	269		390 4.23		[4.05]	4.08	3.73	MeOH	0
2,4-Diamino-7-butyryl- (*XI*)		217	[240]	270		390 4.32		[4.15]	4.16	3.81	MeOH	0
2,4-Diamino-7-isobutyryl- (*XII*)		219	[244]	272		393 4.30		[4.11]	4.14	3.80	MeOH	0
2,4-Diamino-7-dihydrocinnamoyl- (*XIII*)		217	[243]	270		392 4.28		[4.14]	4.16	3.82	MeOH	0
4-Amino-2-methylamino-7-propionyl- (*XIV*)			244	278		400		4.19	4.26	3.82	MeOH	0
4-Amino-2-*n*-butylamino-7-propionyl- (*XV*)		223		280		406 4.27			4.24	3.77	MeOH	0
X-Oxime (*XVI*)		220		264		377 4.30			4.30	3.96	MeOH	0
X-*O*-Methyloxime (*XVII*)		221		265		380 4.32			4.31	3.97	MeOH	0
X-*t*-butylhydrazone (*XVIII*)		220		255		392 4.23			4.27	4.13	pH 8	0
2,4-Diamino-7-(1-hydroxypropyl)- (*XIX*)		225		254		365 4.07			4.32	3.93	MeOH	0
2,4-Diamino-7-(1-hydroxyisobutyl) (*XX*)		224		254		364 4.08			4.34	3.94	MeOH	
2,4-Diacetylamino-7-propionyl- (*XXI*)	1.51	214	254	288	345		4.41	4.09	3.90	4.05	—1.0	+
		218	254		356		4.37	4.38		4.03	4.0	0
		219	257		357		4.37	4.39		3.99	MeOH	0

[ ] = Shoulder. 0 = Neutral form; + = cation.

The newly synthesized compounds have been characterized by elementary analysis, UV- and ^{1}H-NMR-spectra proving the assigned structures. In two cases (*XXVII*, *XXX*) the pK_a-values have been determined to get an idea about the basic properties of the starting material in comparison to its 7-acyl derivative.

The physical properties of this series run parallel to the 2,4-diaminopteridine series, since acylation lowers basicity on the one hand and effects a bathochromic shift of the UV-spectrum on the other hand (Table II). The gradual substitution of the 4-amino group in 4-amino-2-methylmercapto-7--propionylpteridine (*XXXI*) by a methylamino (*XXXIV*) and dimethylamino group (*XXXV*), respectively, is again reflected in the UV-spectra by a redshift accounting for an increasing electronic interaction.

BIOLOGICAL ACTIVITIES

The structural relationship of the 7-acyl-2,4-diamino-pteridines with 2,4,7-triamino-6-phenylpteridine, the diuretic triamterene, prompted us to test this group of compounds regarding their diuretic activity. It was found that 7-acyl-2,4-diaminopteridines act as potassium-neutral diuretics. Especially 2,4--diamino-7-butyryl-pteridine (*XI*) showed on intravenous and oral application, respectively, in rat and dog an elevated excretion of urine, sodium and chloride, not influencing, however, the potassium excretion (Figure 1). The oral LD_{50} in the rat was determined with 3050 mg/kg. In comparison with triamterene, the natrium diuretic potency of the new pteridine derivative is about 1/5—1/3 in rats. However, in dogs the diuretic effect with a 20 mg/kg dose is about three times stronger than with triamterene (Figure 2).

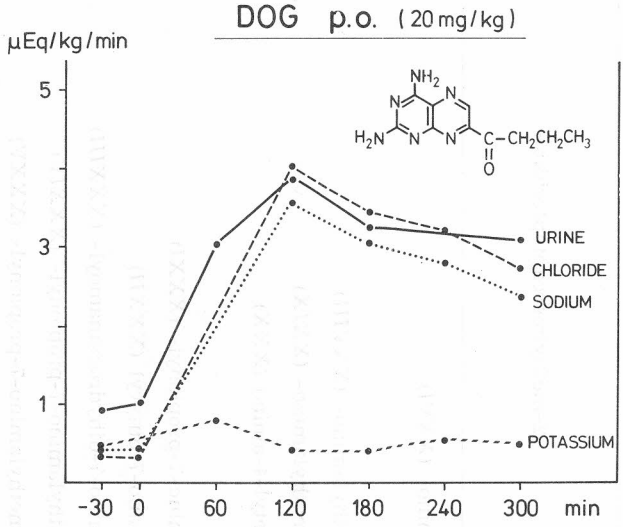


Figure 1. — Excretion of Na^+, K^+, Cl^- and urine in dog after oral application of 20 mg/kg 2,4-diamino-7-butyryl-pteridine (*XI*).

TABLE II

Physical Data of 4-Amino-2-methylmercapto-pteridine Derivatives

-2-methylmercaptopteridine	pK_a in H_2O	UV — Absorption Spectra										pH	Molecular form
		λ_{max} (nm)					lg ε						
4-Amino- (*XXVI*)	2.52	223	264	299	340	[352]	4.15	4.19	4.01	4.08	[4.01]	—1.0	+
		206	242	262		352	4.14	4.08	4.30		3.87	5.0	0
		205	243	273		355	4.14	4.11	4.32		3.86	MeOH	0
4-Methylamino- (*XXVIII*)		210	241	278		365	4.15	4.17	4.32		3.95	MeOH	0
4-Dimethylamino- (*XXIX*)			241	283		370		4.29	4.21		3.92	MeOH	0
7-Acetyl-4-amino (*XXX*)	2.31	216	253	270	[318]	358	4.26	4.06	4.12	[3.88]	4.05	0.0	+
		209	256	284		377	4.25	4.16	4.20		3.80	5.0	0
		228	256	284		380	4.13	4.16	4.18		3.77	MeOH	0
4-Amino-7-propionyl- (*XXXI*)			256	284		380		4.22	4.26		3.85	MeOH	0
4-Amino-7-butyryl (*XXXII*)		227	258	285		382	4.21	4.25	4.28		3.87	MeOH	0
4-Amino-7-dihydrocinnamoyl- (*XXXIII*)		227	257	285		382	4.24	4.25	4.27		3.87	MeOH	0
4-Methylamino-7-propionyl- (*XXXIV*)		231	256	291		387	4.26	4.24	4.19		3.86	MeOH	0
4-Dimethylamino-7-propionyl- (*XXXV*)			244	296		394		4.41	4.15		3.95	MeOH	0

[ ] = Shoulder; 0 = Neutral form; + = cation.

TABLE III

^{1}H-NMR Spectra of 2,4-Diamino- and 4-Amino-2-methylthiopteridine Derivatives in D_6DMSO (δ-values in ppm)

	2-Substituent	4-Substituent	6-H (1H)	7-Substituent
VII	7.04bs(2H)	7.65bs(2H); 2.85d(3H)	8.68d	8.28bs(1H)
VIII	7.08bs(2H); 3.34m(2H); 1.53m(2H); 1.35m(2H); 0.90t(3H)	7.66bd(2H)	8.66d	8.26d(1H)
IX	6.80s(2H)	7.90bd(2H)	8.66s	2.63s(3H)
X	6.84bs(2H)	7.90bd(2H)	8.67s	3.34q(2H); 1.11t(3H)
XI	6.83bs(2H)	7.89bd(2H)	8.67s	3.33t(2H); 1.66m(2H); 0.95t(3H)
XII	6.85s(2H)	7.90bd(2H)	8.67s	3.95m(1H); 1.15d(6H)
XIII	6.83s(2H)	7.90bd(2H)	8.67s	7.28m(5H); 3.50t(2H); 2.97t(2H)
XIV	7.25(1H); 2.88(3H)	7.80(2H)	8.70s	3.20q(2H); 1.10t(3H)
XV	7.28(1H); 3.19m(2H); 1.56m(2H); 1.36m(2H); 0.91t(3H)	7.90bd(2H)	8.67s	3.35t(2H); 1.10t(3H)
XVI	6.64bs(2H)	7.76bs(2H)	8.70s	2.89q(2H); 1.08t(3H); 12.00s(1H, N—OH)
XVII	7.17(2H)	8.20(2H)	8.73s	4.04s(3H); 2.80q(2H); 1.06t(3H)
XIX	6.57s(2H)	7.64bd(2H)	8.40s	5.58d(1H, OH); 4.56q(1H); 1.750(2H); 0.89t(3H)
XX	6.58s(2H)	7.60bd(2H)	8.37s	5.56d(1H, OH); 4.38pt(1H); 2.10o(2H); 0.85t(6H)
XXI	10.68s(1H); 2.37s(3H)	10.87s(1H); 2.55s(3H)	9.15s	3.30q(2H); 1.15t(3H)
XXVII	2.53s(3H)	8.33bd(2H)	8.97d	8.68d(1H)
XXVIII	2.54s(3H)	8.94m(1H); 3.00d(3H)	8.95d	8.66d(1H)
XXIX	2.53s(3H)	3.60bs(6H)	8.87d	8.65d(1H)
XXX	2.56s(3H)	8.50bd(2H)	9.04s	2.71s(3H)
XXXI	2.56s(3H)	8.48bd(2H)	9.04s	3.25q(2H); 1.14t(3H)
XXXII	2.49s(3H)	8.42(2H)	8.97s	3.17t(2H); 1.62m(2H); 0.91t(3H)
XXXIII	2.53s(3H)	8.49(2H)	9.03s	7.25m(5H); 3.56t(3H); 2.97t(3H)
XXXIV	2.53s(3H)	9.03(2H); 2.97d(3H)	8.97s	3.20ä(2H); 1.11t(3H)
XXXV	2.53s(3H)	3.79s(6H)	8.99s	3.21ä(2H); 1.11t(3H)

s = Singlet, bs = broad singlet, d = duplet, bd = broad duplet, t = triplet, q = = quadruplet, o = octet, m = multiplet.

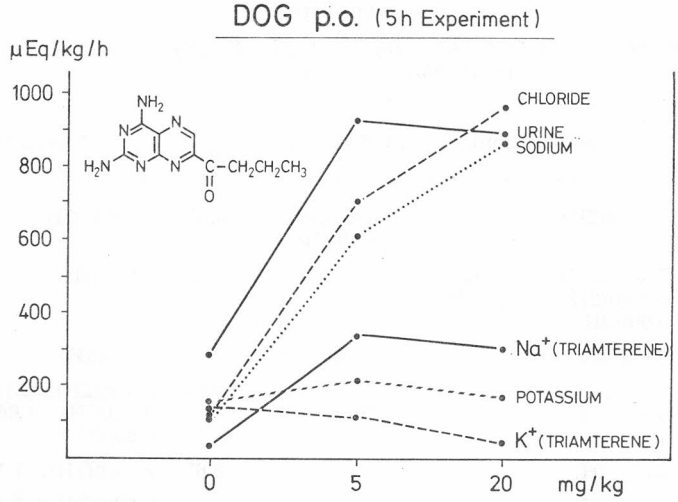


Figure 2. — Comparison of Na^+ and K^+ excretion in dog after application of triamterene and 2,4-diamino-7-butyryl pteridine.

2,4-Diamino-7-dihydrocinnamoylpteridine (*XIII*) possesses a very similar profile of action when orally applied to the rat and dog, respectively.

Acknowledgements. — We thank the Ciba-Geigy AG for testing the pteridine derivatives, Mrs. M. Bischler for the *pK*-determinations and Dr. R. Charubala for measuring the NMR spectra.

EXPERIMENTAL

General Methods

UV-spectra were taken with a Cary-Recording Spectrometer Model 118 from Appl. Phys. Corp. — pK_a-Determinations were performed by the spectrophotometric method[11] at 25 °C in 0.01 M buffer solutions[12]. At least 3 different analytical wavelengths were chosen for the calculations. — NMR-Spectra were determined with a Jeol-JNM-MH 100 and Bruker WM-250 spectrometer. — Chromatography: TLC sheets silica gel F 1500 LS 254 and cellulose F 1440 LS 254 from Schleicher & Schüll. Column chromatography with silica gel (0.05—0.2 mm particles) and preparative thick layer chromatography on silica gel PF_{254} (2 mm thick) from Merck, Darmstadt. — The substances were dried at 100 °C in a drying oven or in a vacuum oven Büchi-TO 50 over P_4O_{10} at room temp. — The melting points have not been corrected.

4,6-Diamino-2-methylamino-5-nitrosopyrimidine (II)

1.85 g (0.01 mol) of 4,6-diamino-2-methylmercapto-5-nitrosopyrimidine (*I*)[13] was suspended in 50 ml of 2 M methylamine in methanol and stirred for 6 h at room temp. The blue colour of the starting material turned red during this procedure. The red precipitate was collected by suction, washed with methanol and dried at 100 °C to give 1.2 g (71%) red crystals of m. p. 299 °C.

Anal. $C_5H_8N_6O$ (168.16) Calc'd.: C 35.71; H 4.80; N 49.98%
Found: C 35.80; H 4.74; N 49.70%.

*4,6-Diamino-2-*n*-butylamino-5-nitrosopyrimidine (III)*

10 g (0.054 mol) of 4,6-diamino-2-methylmercapto-5-nitrosopyrimidine (*I*) were refluxed with 7.3 g (0.1 mol) of *n*-butylamine in 100 ml of methanol for 6 h.

The reaction mixture was cooled, the precipitate collected, washed with methanol and dried to give 6.5 g (56%) red crystals of m. p. 205—207 °C.

Anal. $C_8H_{14}N_6O$ (210.24) Calc'd.: C 45.70; H 6.71; N 39.98%
Found: C 45.61; H 6.68; N 39.82%.

4-Amino-2-methylaminopteridine (VII)

3.4 g (0.02 mol) of 4,6-diamino-2-methylamino-5-nitrosopyrimidine (*II*) was treated with 20 ml of a conc. fresh solution of ammonium sulfide with gentle heating till the red colour disappeared. It was evaporated to dryness, the residue was added slowly with stirring till the red colour disappeared. After evaporation to dryness the residue is taken up in 30 ml of water, the insoluble sulfur filtered off and the filtrate, after addition of 2.5 g of trimeric glyoxal hydrate, refluxed for 30 min. After cooling and concentrating to a smaller volume the precipitate was collected and crystallized from water with charcoal to give 1.83 g (52%) yellow powder of m. p. 240 °C.

Anal. $C_7H_8N_6$ (176.18) Calc'd.: C 47.72; H 4.58; N 47.70%
Found: C 47.56; H 4.64; N 47.41%.

*4-Amino-2-*n*-butylaminopteridine (VIII)*

6.3 g (0.03 mol) of 2-*n*-butylamino-4,6-diamino-5-nitrosopyrimidine (*III*) was suspended in 120 ml of water and heated to 60 °C. Then 18.0 g of sodium dithionite are added slowly with stirring until the red color dissappeared. The reduction to *V* was completed by rising the temp. to 75 °C for another 30 min. This mixture was then added to a solution of 4.2 g of trimeric glyoxal hydrate in 60 ml of boiling water and stirred for 30 min. at 90 °C to afford the condensation. The solution was neutralized by ammonia, the yellow precipitate collected on cooling and then crystallized from methanol/water (1/1) to give 2.2 g (34%) yellow crystals of m. p. 190 °C.

Anal. $C_{10}H_{14}N_6$ (218.26) Calc'd.: C 55.03; H 6.47; N 38.50%
Found: C 55.06; H 6.52; N 38.62%.

General Procedure for the Synthesis of 7-Acyl-2,4-diaminopteridines (IX—XV)

0.01 mol of the starting 2,4-diaminopteridine (*VI—VIII*) is dissolved in a mixture of 30 ml of glacial acetic acid or 20 ml of trifluoroacetic acid, respectively, and 20 ml of water. After cooling to 5 °C, 0.03 mol of the appropriate aldehyde is added. To the stirred solution is then added, simultaneously and dropwise through two separate dropping funnels, a solution of 5.6 g (0.02 mol) of ferrous sulfateheptahydrate ($FeSO_4 \cdot 7H_2O$) in 10 ml of water and 1.8 g (0.02 mol) of *tert.* butylhydroperoxide, respectively, within 5—10 min. The mixture is stirred for another 30 min and then partially neutralized by addition of 10—20 ml of half-concentrated ammonia. A yellow precipitate separates, is filtered off by suction and purified by crystallization of the appropriate solvent (Table IV).

General Procedure for the Synthesis of 7-Acyl-4-amino-2-methylthiopteridine (XXX—XXV)

Preparation is made analogously to the preceding procedure by dissolving 0.01 mol of the starting 4-amino-2-methylthiopteridine (*XXVII—XXIX*) in 40 ml of glacial acetic acid and 20 ml of water, addition of 0.03 mol of aldehyde and treatment by 2.8 g $FeSO_4 \cdot 7H_2O$ (0.01 mol) in 10 ml of H_2O and 1.8 of *tert.* butylhydroperoxide. Separation of the reaction product is achieved by addition of 10 ml of half-conc. ammonia to the reaction solution (Table IV).

(2,4-Diaminopteridin-7-yl)-ethyl-ketoxime (XVI)

0.22 g (1 mmol) of 2,4-diamino-7-propionylpteridine (*X*) and 0.15 g hydroxylamine hydrochloride were refluxed for 15 min in 20 ml of water. The clear solution was treated with charcoal, filtered hot and then neutralized with ammonia to give 0.16 g (69%) greenish-yellow crystals of m. p. >253 °C (decomp.).

Anal. $C_9H_{11}N_7O$ (233.23) Calc'd.: C 46.34; H 4.75; N 42.04%
Found: C 46.17; H 4.68; N 41.96%.

TABLE IV

Synthesis of 7-Acyl-2,4-diamino- and 7-Acyl-4-amino-2-methylthiopteridines

Starting material		-aldehyde		Reaction product				Solvent of crystallization	Empirical formula	Molecular weight	Elementary Analysis			
						Yield					Calc'd / Found	C	H	N
	g		g		g	%	m. p. (°C)							
VI	1.62	Acet-	1.32	*IX*	0.67	30	>170(dec.)	water	$C_8H_8N_6O \cdot H_2O$	222.19		43.25 43.03	4.53 4.29	37.82 37.07
VI	1.62	Propion-	1.74	*X*	1.20	55	280	water	$C_9H_{10}N_6O$	218.23		49.53 49.42	4.62 4.46	38.51 38.87
VI	1.62	*n*-Butyr-	2.16	*XI*	0.74	32	223—224	ethanol	$C_{10}H_{12}N_6O$	232.25		51.72 51.20	5.21 5.11	36.19 36.06
VI	1.62	Isobutyr-	2.16	*XII*	1.10	47	240—241	methanol	$C_{10}H_{12}N_6O$	232.25		51.71 51.50	5.21 5.44	36.19 36.30
VI	1.62	Dihydro-cinnamyl-	2.68	*XIII*	0.88	30	220	ethanol	$C_{15}H_{14}N_6O$	294.31		61.21 61.04	4.79 4.82	28.56 28.66
VII	1.76	Propion-	1.74	*XIV*	0.76	33	210—212	*n*-propanol/ /water (1/1)	$C_{10}H_{12}N_6O$	232.25		51.72 51.56	5.21 5.13	36.19 36.06
VIII	2.18	Propion-	1.74	*XV*	1.40	51	152	*n*-propanol/ /water (1/1)	$C_{13}H_{18}N_6O$	274.33		56.92 56.75	6.61 6.59	30.64 30.55
XXVII	1.93	Acet-	1.32	*XXX*	1.75	75	218—220	ethanol	$C_9H_9N_5OS$	235.20		45.95 45.91	3.86 4.20	29.77 29.56
XXVII	1.93	Propion-	1.74	*XXXI*	1.40	56	236	*n*-propanol	$C_{10}H_{11}N_5OS$	249.30		48.18 48.27	4.45 4.42	28.09 28.16
XXVII	1.93	*n*-Butyr-	2.16	*XXXII*	1.53	58	225—227	methanol	$C_{11}H_{13}N_5OS$	263.25		50.18 49.95	4.98 4.93	26.60 26.61
XXVII	1.93	Dihydro-cinnamyl-	2.68	*XXXIII*	1.98	61	225—228	DMF/water	$C_{16}H_{15}N_5OS$	325.32		59.06 59.08	4.65 4.41	21.52 21.61
XXVIII	2.07	Propion-	1.74	*XXXIV*	1.60	53	155—157	methanol	$C_{11}H_{13}N_5OS$	263.25		50.18 50.09	4.98 4.88	26.60 26.54
XXIX	2.21	Propion-	1.74	*XXXV*	2.36	86	181—183	methanol	$C_{12}H_{15}N_5OS$	277.28		51.97 52.09	5.45 5.55	25.24 25.51

(2,4-Diaminopteridin-7-yl)-ethyl-O-methylketoxime (XVII)

0.22 g (0.1 mmol) of 2,4-diamino-7-propionylpteridine (*X*) and 0.15 g *O*-methylhydroxylamine hydrochloride were refluxed in 20 ml of water for 15 min. The hot solution was treated with charcoal, filtered and then neutralized with ammonia. A precipitate separated, was collected after cooling and yielded 0.15 g (61%) yellowish crystals of m. p. 282 °C.

Anal. $C_{10}H_{13}N_7O$ (247.26) Calc'd.: C 48.58; H 5.30; N 39.67%
Found: C 48.37; H 5.33; N 39.60%.

(2,4-Diaminopteridin-7-yl)-ethyl-N-tert.butylketohydrazone (XVIII)

1.09 g (0.005 mol) of 2,4-diamino-7-propionylpteridine (*X*) and 2.5 g of *tert.* butylhydrazine hydrochloride are refluxed in 50 ml of ethanol for 1 hour. The reaction solution is concentrated to a small volume, the yellow precipitate collected and recrystallized from water to give 1.44 g (80%) of dihydrochloride salt in the form of yellow needles of m. p. 210 °C.

Anal. $C_{13}H_{20}N_8 \cdot 2\,HCl$ (361.25) Calc'd.: C 43.23; H 6.14; N 31.03%
Found: C 43.60; H 6.25; N 31.26%.

2,4-Diamino-7-(1-hydroxypropyl)-pteridine (XIX)

4.36 g (0.02 mol) of 2,4-diamino-7-propionylpteridine (*X*) was heated in 200 ml of water to 90 °C and then 1.0 g of sodium borohydride added gradually with stirring. The clear solution was treated with charcoal, filtered and on cooling 3.25 g (80%) of yellowish crystals of m. p. 221—223 °C (decomp.) separated.

Anal. $C_9H_{12}N_6O$ (220.23) Calc'd.: C 49.08; H 5.49; N 38.16%
Found: C 48.91; H 5.52; N 38.08%.

2,4-Diamino-7-(1-hydroxy-2-methylpropyl)-pteridine (XX)

0.7 g (3 mmol) of 2,4-diamino-7-isobutyrylpteridine (*XII*) was suspended in 20 ml of methanol and 10 ml of water. 0.4 g of sodium borohydride was added gradually with stirring, wihch was continued over night. The colourless precipitate was collected (0.6 g) and yielded on crystallization from 80 ml of water and some ethanol 0.51 g (73%) of slightly yellowish crystals of m. p. 248 °C.

Anal. $C_{10}H_{16}N_6O$ (234.27) Calc'd.: C 52.27; H 6.02; N 35.87%
Found: C 52.30; H 6.12; N 35.71%.

2,4-Diacetamino-7-propionylpteridine (XXI)

0.87 g (4 mmol) of 2,4-diamino-7-propionylpteridine (*X*) was refluxed in 50 ml of acetic anhydride for 20 min. The hot solution was treated with charcoal, filtered while hot and then cooled in an ice-box. The precipitate was collected, washed with ethanol and ether to yield 0.65 g (54%) of yellow crystals of m. p. 225—228 °C (decomp.).

Anal. $C_{13}H_{14}N_6O_3$ (302.29) Calc'd.: C 51.65; H 4.67; N 27.80%
Found: C 51.51; H 4.65; N 27.66%.

4-Amino-2-methylthiopteridine (XXVII)[8]

3.4 g (0.02 mol) of 4,5,6-triamino-2-methylthiopyrimidine and 3.0 g of trimeric glyoxal hydrate were refluxed in 150 ml of water and 5 ml of acetic acid for 30 min. The solution was concentrated to a smaller volume, the precipitate collected and crystallized from water to give 3.43 g (89%) of yellowish crystals of m. p. 211 °C. Lit.[8] m. p. 208 °C.

4-Methylamino-2-methylthiopteridine (XXVIII)

5.0 g (0.028 mol) of 6-amino-4-chloro-2-methylthiopyrimidine (*XXII*)[9] was heated in 20 ml of 6 M methanolic methylamine solution in an autoklave to 120 °C for 8 hours. On cooling the colourless crystals of 6-amino-4-methylamino-2-methylthiopyrimidine (*XXIII*) were collected and dried to give 3.5 g (73%) of m. p. 125 °C.

4.0 g (0.024 mol) of *XXIII* was dissolved in 80 ml of 10% acetic acid, cooled to 5 °C and a solution of 2.8 g sodium nitrite in 20 ml of water added dropwise with stirring. After 1 hour the blue 5-nitroso derivate was filtered off and then reduced in a solution of 100 ml of water and 18 ml of conc. ammonium sulfide by heating to 65 °C with stirring. When the blue colour had disappeared the mixture was cooled and yielded 2.8 (64%) of slightly yellow crystals of 5,6-diamino--4-methylamino-2-methylthiopyridine (*XXV*). This material was then refluxed with 2.1 g of trimeric glyoxal hydrate in 100 ml of water for 30 min. On cooling a precipitate separated, which gave, on crystallization from water, 2.03 g (65%) yellowish crystals of m. p. 140—142 °C.

Anal. $C_8H_9N_5S$ (207.19) Calc'd.: C 46.37; H 4.38; N 33.80%
Found: C 46.51; H 3.99; N 33.60%.

4-Dimethylamino-2-methylthiopteridine (XXIX)

4.5 g (0.023 mol) of 5,6-diamino-4-dimethylamino-2-methylthiopyrimidine (*XXVI*)[10] was dissolved in 200 ml of water, then 4.2 g of trimeric glyoxal hydrate in 50 ml of water added and the mixture stirred for 30 min under gentle boiling. On cooling, 4.90 g (98%) yellow crystals separated, which can be recrystallized from acetone to show m. p. 178—180 °C.

Anal. $C_9H_{11}N_5S$ (221.22) Calc'd.: C 48.85; H 5.01; N 31.65%
Found: C 48.70; H 5.17; N 31.68%.

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POVZETEK

Pteridini. LXXVII. C-Aciliranje pteridinov s homolitsko heteroaromatsko substitucijo

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Homolitske substitucije z acilnimi radikali potekajo pri 2,4-diamino (*VI—III*) in 4-amino-2-metiltiopteridinih (*XXVII—XXIX*) selektivno na mestu 7, tako da nastanejo 7-acil derivati *IX—XV* in *XXX—XXXV* s srednjimi ali dobrimi izkoristki. Ketonski značaj teh novih pteridinov se kaže v tvorbi hidrazona (*XVIII*) in oksimov (*XVI, XVII*), kakor tudi 7-(1-hidroksialkil)pteridinskih derivatov (*XIX, XX*), ki nastanejo pri redukciij z natrievim borovim hidridom.

Nove spojine so bile karakterizirane z elementno analizo, ^{1}H NMR in UV spektri.