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Pteridines, LXXVIII[1] Reactions and Properties of 4-Thiolumazine Derivatives

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The reactivity of the 4-thioxo function towards nucleophiles in the 1- (*X*) and 3-methyl- (*XI*) and 1,3-dimethyl-6,7-diphenyl--4-thiolumazine (*XII*) series was examined, showing easy displacements under mild conditions. Special structural and electronical features became obvious with 3-methyl-6,7-diphenyl-4-thiolumazine (*XI*), which reacted analogously to the corresponding 1,3-dimethyl derivative (*XII*) with amines to the 4-imino tautomers (*XVIII*—*XXIV*) and with hydrazines to the corresponding 4-hydrazones (*XXVI*—*XXX*). The latter compounds are very light sensitive and react by photooxidation to the corresponding 6,7-diphenyllumazines (*VI*—*VIII*). Nucleophilic displacement of the sulfur in the 4-thioamide group by alkoxides and under $HgBr_2$ catalysis yielded the unusual 4,4-di-O-alkyl amidacetals (*XXXIII*——*XXXVI*). The acetal function is prone to easy substitution by C—H acidic compounds, giving from *XXXIV* the 4-dicyanomethylen-1,3-dimethyl-2-oxo-6,7-diphenyl-tetrahydropteridine (*XXXIX*).

The newly synthesized compounds have been characterized by elementary analysis, ^{1}H-NMR and UV spectra based on pK_a-values.

INTRODUCTION

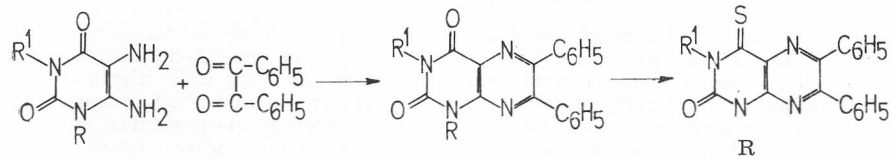
Studying the reactions of anhydronucleosides we were interested in the synthesis of C-4 modified pteridine-*N*-3-nucleosides by way of 4,2'-anhydronucleosides. Starting from different C-2, O-, S- and N-substituted pteridine--*N*-3-nucleosides, however, only 2,2'-cyclization but no 4,2'-cyclization was observed.[2,3] In order to evaluate an alternative possibility to synthesize C-4 modified pteridine-*N*-3-nuclesides by nucleophilic displacement reactions of the 4-thioxo and 4-methylthio function, model studies with 3-methyl-6,7--diphenyl-4-thiolumazine (*XI*) and related compounds were undertaken.

Gorizdra[4] was the first to document in the lumazine series the much higher reactivity of the 4-thioamide function towards nucleophiles compared to the corresponding 2-thioamide function. In analogy to the synthesis of 6,7-diphenyl-4-thiolumazine (*IX*) and its 1,3-dimethyl derivative (*XII*), extension to the 1-methyl- (*X*) and 3-methyl-6,7-diphenyl-4-thiolumazine (*XI*) was performed and their chemical and physical properties studied in more detail.

RESULTS AND DISCUSSION

The starting materials 6,7-diphenyl-lumazine (*V*) and its 1-methyl- (*VI*), 3-methyl- (*VII*) and 1,3-dimethyl derivative (*VIII*) were obtained by Gabriel-

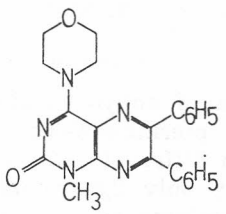
-Isay-condensation[5] of the suitable 5,6-diaminouracils *I*—*IV* with benzil.[6] 1-Methyl-(*II*)[8], 1,3-dimethyl-(*IV*)[8] and 5,6-diaminouracil (*I*)[9] itself were prepared in a classical Traube synthesis[7], starting from *N*-methylurea, *N,N'*--dimethylurea and urea, respectively. For the preparation of 3-methyl-5,6--diaminouracil (*III*)[8,10] an improved synthesis was performed, starting with a condensation of thiourea with ethyl cyanoacetate to yield 6-amino-2-thiouracil[7], which was then methylated with dimethylsulfate to 6-amino-3-methyl-2-methylthio-4-oxo-1,2-dihydropyrimidine followed by base hydrolysis to give 6-amino-3-methyluracil.[11] Subsequent nitrosation to 6-amino-3-methyl-5-nitrosouracil and reduction by ammonium sulfide afforded high yields of very pure and almost colourless *III*. Thiation of the lumazine derivatives *V, VI, VII* and *VIII* was performed with diphosphorous penta-



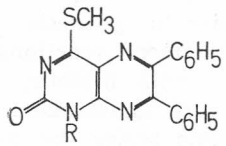
	R	R^1
I	H	H
II	CH_3	H
III	H	CH_3
IV	CH_3	CH_3

	R	R^1
V	H	H
VI	CH_3	H
VII	H	CH_3
VIII	CH_3	CH_3

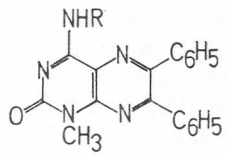
	R	R^1
IX	H	H
X	CH_3	H
XI	H	CH_3
XII	CH_3	CH_3



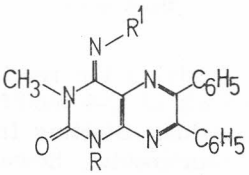
XV



	R
XIII	H
XIV	CH_3



	R
XVI	H
XVII	CH_3



	R	R^1
XVIII	H	H
XIX	CH_3	H
XX	H	CH_3
XXI	CH_3	CH_3
XXII	H	C_2H_5
XXIII	H	C_4H_9
XXIV	CH_3	C_4H_9

sulfide in boiling dioxan[4] to form the orange-coloured 4-thiolumazines *IX*, *X*, *XI*, and *XII* in yields from 80 to 90%.

In contrast to their precursors, the better soluble 4-thiolumazines *IX*—*XII* do not show blue fluorescence and are light-sensitive. Their yellow solutions with a long wave absorption band at about 400 nm are decoloured when irradiated aerobically with light, and a quantitative formation of the corresponding lumazines is observed (Figure 1).

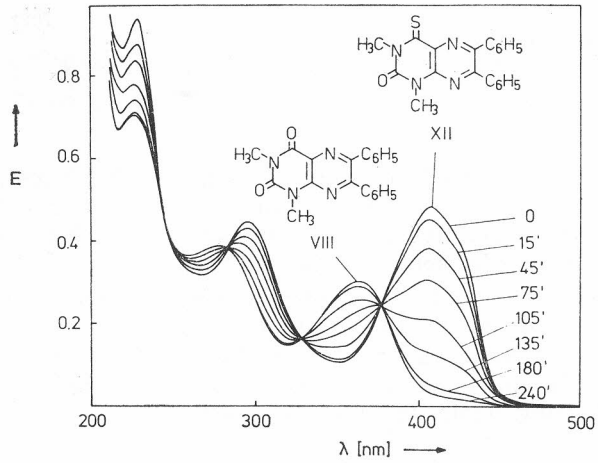


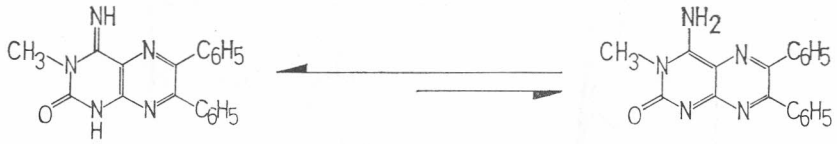
Figure 1. Aerobic interconversion of 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (*XII*) (1 mg in 100 ml methanol) into *VIII* on irradiation with light.

The S/O exchange by photooxidation[12] may proceed *via* various alternative pathways including the intermediary sulfines[13,14], thia-1,2-dioxetanes[14-16] and sulfinic acids[12]. The involvement of singlet oxygen can be explained by selfsensitization of the pteridine itself. Anaerobic irradiation of 4-thio-lumazine solutions decolourize also very fast, but there is no isosbestic UV-kinetic, demonstrating a more complex degradation to so far unknown products.

The high chemical reactivity of the 4-thioamide function in the lumazine system is revealed by the easy conversion of 1-methyl-6,7-diphenyl-4-thiolumazine (*X*) to the corresponding-4-amino-(*XVI*)[6] and 4-methylamino derivative *XVII* by reaction with ammonia and methylamine, respectively, at room temperature. This nucleophilic displacement reaction occurred even more easily when the 4-thioxo function was first methylated. The fluorescing 1-methyl-4-methylthio-2-oxo-6;7-diphenyl-1,2-dihydropteridine (*XIV*), for example, which was prepared from 6,7-dipenyl-4-thiolumazine (*IX*) and its 1-methyl derivative *X*, respectively, showed a very smooth displacement with primary and secondary amines to give *XV*—*XVII* in about 80% yield.

Also, 1,3-dimethyl-6-7-diphenyl-4-thiolumazine (*XII*) reacted with primary amines very easily to the corresponding 4-imino derivatives *XIX*, *XXI* and *XXIV*, whereas an analogous conversion with secondary amines to the corresponding immonium-type structure could not be observed. Interestingly enough, 3-methyl-6,7-diphenyl-4-thiolumazine (*XI*) reacted again only with primary amines to products *XVIII*, *XX* and *XXIII*, which possess according

to UV-, NMR, and pK_a-data the 4-imido-2-oxo-1,2,3,4-tetrahydropteridine structure. These findings indicate that, despite the presence of an unblocked amide function, the usually observed prototropy towards a thermodynamically more favoured 4-amino-1,2-dihydropteridin-2-one does not take place here due to an energetically unfavourable quinonoid-type-π-electron arrangement in the pyrazine moiety.



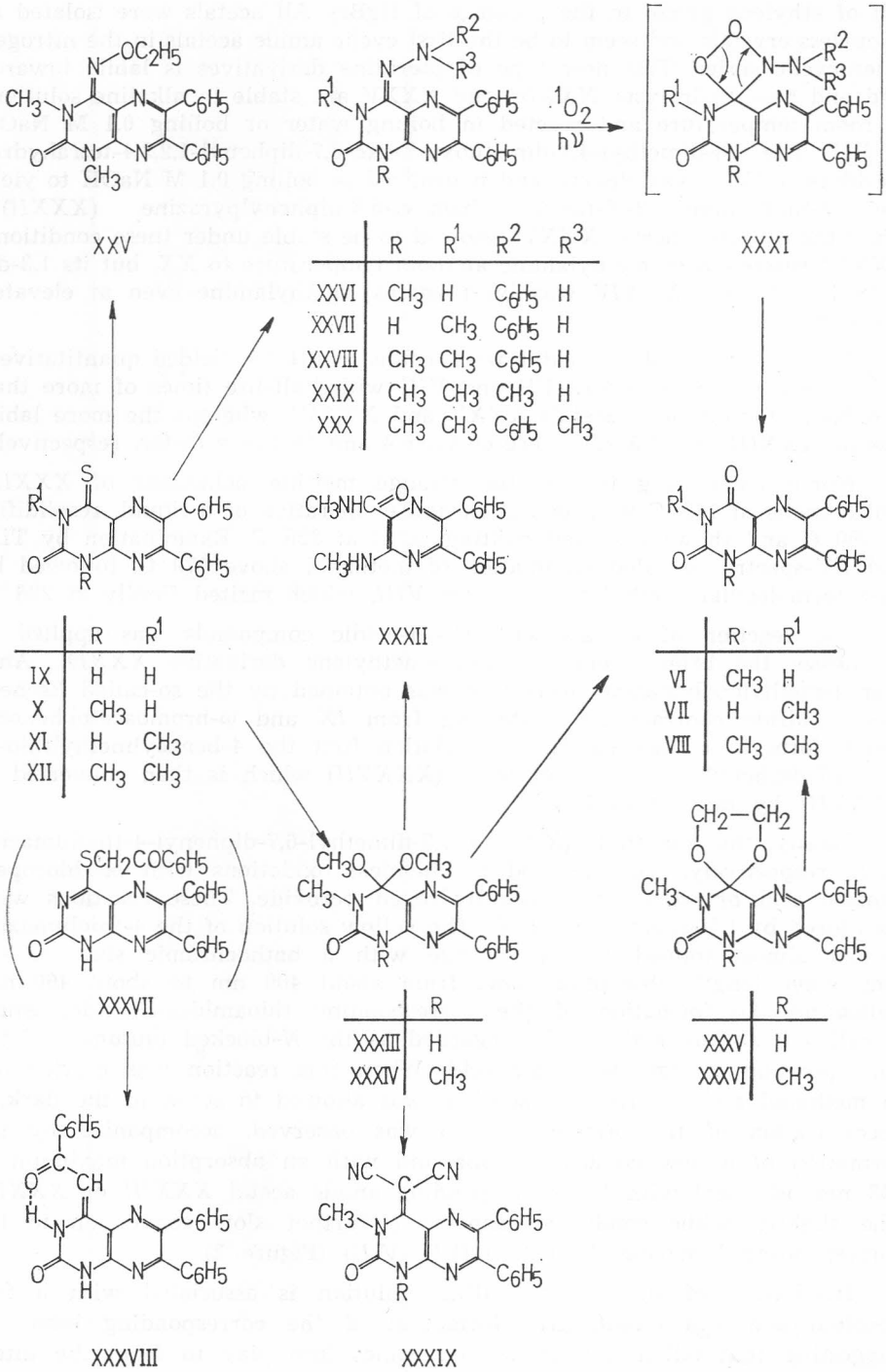
These electronic as well as steric reasons in the 3-methyl group are responsible that the boiling of *XI* in diethylamine for several hours led only to the 4-ethylimino derivative *XXII* on account of ethylamine impurities in the reagent but no displacement by the secondary amines could be observed.

In order to facilitate the nucleophilic displacement reaction we tried to methylate the 4-thioxo function in *XI* with different methylation reagents, including methyl iodide/K_2CO_3, dimethylsulfate/KOH and dimethylformamide dimethylacetal[17]; in all cases no *S*- but only *N*-1-methylation forming *XII* took place, reflecting again the special structural and electronical features of *XI*.

Further reactions of *XII* with *O*-ethyl hydroxylamine furnished the oxime *XXV*, while hydrazines converted the 4-thiolumazines *X*, *XI* and *XII* into the corresponding hydrazones *XXVI*—*XXX* (Scheme 3).

The red coloured phenyl- and methylhydrazones *XXVI*—*XXIX* showing long wave length absorption bands in the visible region are extremely light--sensitive compounds under aerobic conditions, yielding quantitatively with half-life times of 6, 30, 40 and 15 minutes, respectively, the corresponding lumazine derivatives *VI*, *VII* and *VIII* when irradiated with light in the presence of oxygen. Aerobic photooxidation was accelerated by singlet oxygen sensitizers like methylene blue, while anaerobic irradiation left these compounds *XXVI*—*XXIX* unchanged. This fact indicates an involvement of singlet oxygen in the degradation mechanism, which very likely proceeds via a dioxazetidine intermediate *XXXI*[18] followed by a cycloreversion process and including the pteridine hydrazone derivative itself as a photosensitizer. In contrast to the phenyl- and methylhydrazones *XXVI*—*XXIX*, the deep violet coloured 4-*N*-methyl-*N*-phenylhydrazone *XXX* proved to be photostable under aerobic conditions, thus underlying no self-sensitized autoxidation. However, addition of the singlet oxygen sensitizer methylene blue converted *XXX* back into the lumazine *VIII*, suggesting the same singlet oxygen induced process via *XXXI*. The blue fluorescent and colourless oxime *XXV* turned out to be stable against autoxidation with and without addition of singlet oxygen sensitizers.

Nucleophilic displacement reactions with alkoxide ions failed completely with 3-methyl- and 1,3-dimethyl-6,7-diphenyl-4-thiolumazines even on applying drastic conditions; addition of mercury-II-bromide, however, catalyses this reaction to form the unusual amide acetals *XXXIII* and *XXXIV*. The ethy-


XXV
XXVI
XXVII
XXVIII
XXIX
XXX
XXXI
XXXII
IX
X
XI
XII
VI
VII
VIII
XXXIII
XXXIV
XXXV
XXXVI
XXXVII
XXXVIII
XXXIX

lene acetals *XXXV* and *XXXVI* were obtained analogously using the disodium salt of ethylene glycol in the presence of $HgBr_2$. All acetals were isolated as colourless crystals and seem to be the first cyclic amide acetals in the nitrogen heterocyclic series. This new type of pteridine derivatives is labile towards acid and base hydrolysis. *XXXIII* and *XXXV* are stable in alkaline solutions at room temperature and reacted in boiling water or boiling 0.1 M NaOH to *VII*. The 1,3-dimethyl-4,4-dimethoxy-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine *XXXIV* was cleaved and hydrolized in boiling 0.1 M NaOH to yield the 3-methylamino-2-*N*-methylcarbamoyl-5,6-diphenylpyrazine (*XXXII*)[19], while the ethylene acetal *XXXVI* showed to be stable under these conditions. *XXXIII* reacted with methylamine at room temperature to *XX*, but its 1,3-dimethyl derivative *XXXIV* was inert against methylamine even at elevated temperatures.

Acid hydrolysis of all synthesized acetals at pH 3.4 yielded quantitatively the corresponding lumazines *VII* and *VIII* with half-life times of more than two hours for ethylene acetals *XXXV* and *XXXVI*, whereas the more labile acetals *XXXIII* and *XXXIV* were cleaved 4 and 40 times faster, respectively.

Worth mentioning is also the strange melting behaviour of *XXXIII*, which melts at 179 °C with evolution and evaporation of a liquid, resolidifies at 190 °C and shows a second melting point at 226 °C. Examination by TLC and UV-spectra revealed elimination of methanol above 179 °C, followed by an intermolecular methylation to form *VIII*, which melted finally at 226 °C.

The reaction of acetals with C—H-acidic compounds was applied to synthesize the bright yellow-4-dicyanomethylene derivative *XXXIX*. Another 4-methylenelymazine derivative was obtained by the so-called Eschenmoser sulfide contraction,[20,21] starting from *IX* and ω-bromoacetophenone, which form in a base catalysed alkylation first the 4-benzoylmethylthio-2--oxo-6,7-diphenyl-1,2-dihydropteridine (*XXXVII*) which is then converted to *XXXVIII* by heating in DMF.

Finally, the 3-methyl- (*XI*) and 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (*XII*), respectively, were applied to chemical oxidations with *m*-chloroperbenzoic acid or with formic acid/hydrogen peroxide. These reactions were monitored by UV-spectra and TLC. The yellow solution of the 4-thiolumazine turned almost immediately to orange with a bathochromic shift of the long wave length absorption band from about 400 nm to about 460 nm, indicating the formation of the corresponding thioamides-*S*-oxide, which is called a sulfine and can be regarded as the *N*-blocked tautomer of the corresponding lumazin-4-sulfenic acid. When this reaction was carried out in methanol and the reaction solution was allowed to stand in the dark, a decolouration of the orange solution was observed, accompanied by the formation of a new colourless compound with an absorption maximum at 345 nm, identical with the corresponding amide acetal *XXXIII* or *XXXIV*. The slightly acidic conditions effected a further slow conversion to the corresponding lumazine derivative (*VII*, *VIII*) (Figure 2).

Irradiation of the orange sulfine solution is associated with a fast decolouration and quantitative formation of the corresponding lumazine, suggesting that either singlet oxygen comes into play to form the inter-

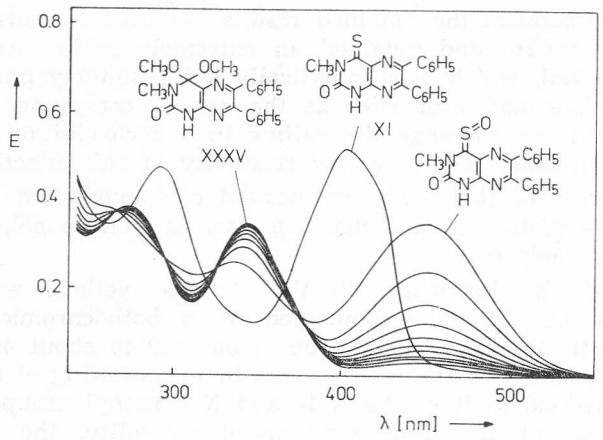
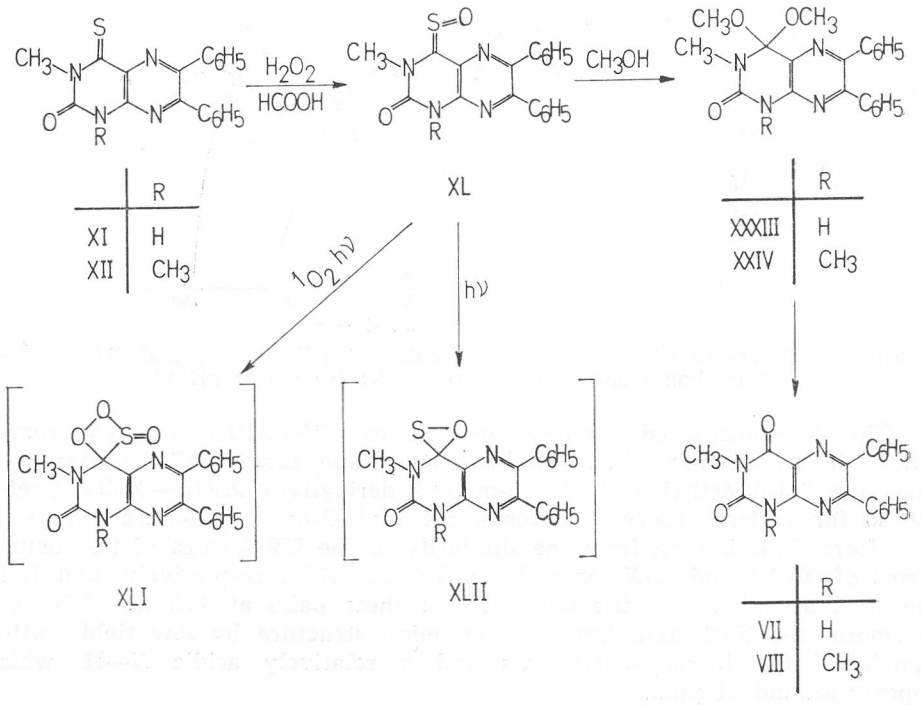


Figure 2. UV-Spectra of the oxidation of 3-methyl-6,7-diphenyl-4-thiolumazine (*XI*) with H_2O_2/HCOOH in methanol in the dark. UV-Spectra are taken every two minutes.

mediary thiadioxetane-*S*-oxide (*XLI*), prone to a subsequent cycloreversion with extrusion of SO_2, or electrocyclization to an oxathiirane type intermediate (*XLII*)[22,23] is followed by sulfur extrusion.



In order to support the obtained results we tried to isolate the sulfine *XXXX* (R = R^1 = CH_3) and obtained an extremely labile, orange coloured, amorphous material, which was analytically not absolutely pure but showed the same reactions and properties as the orange compound in methanolic solution. Attempts to scavange the sulfine in a cycloaddition reaction with dienes failed, probably due to a low reactivity of this function.

The structures of the newly synthesized compounds are based on UV- (Table I), NMR- (Table II), and mass spectra, as well as pK_a-measurements and elementary analysis.

Thiation of the lumazines *V—VIII* to the yellow, non fluorescent 4-thiolumazines *IX—XII* is accompanied by a bathochromic shift of the long wave length absorption band from about 360 to about 400 nm (Figure 3), by an enhancement of the acidity, seen in the lowering of the pK_a-values and by a down-field shift of the *N*-1- and *N*-3-methyl group in the NMR--spectra. Because of the diminished water solubility, the pK_a-values of 4-thiolumazines had to be determined in water solutions containing 30 to 50% methanol.

It is noteworthy that anion formation of *X* and *XI* (respectively) effects the same bathochromic shifts and leads to almost identical spectra, whereas in the lumazine series a *N*-1 and *N*-3 substitution can be distinguished in this manner.

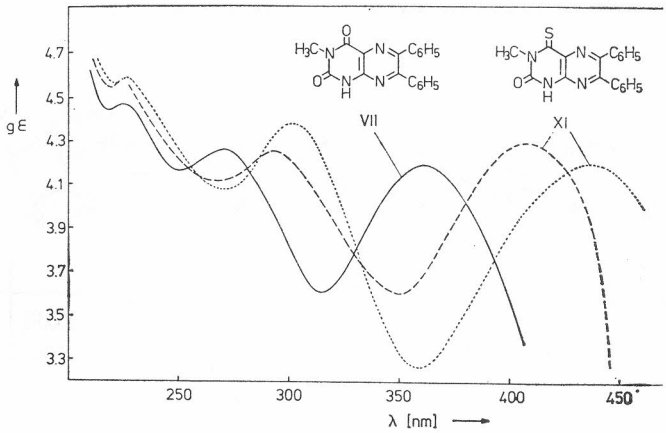


Figure 3. UV-Spectra of the neutral molecules of *VII* (———) and *XI* (— — —) in methanol and of the anion of *XI* (· · · ·) at pH 10.

The *N*-1-substituted isopterin derivatives *XV—XVIII* are best represented in the 4-amino-2-oxo-1,2-dihydropteridine form while, contrary to that, the 1,3-dimethyl and the 3-methyl derivatives *XVIII—XXIV* prefer the so far seldom observed tautomeric 4-imido-2-oxo-1,2,3,4-tetrahydropteridine form. This is seen from the similarity of the UV-spectra of the neutral forms of *XVIII* and *XIX*, as well as *XX* and *XXI*, respectively, and from the good accordance of the basic pK_a of these pairs at 5.55 and 6.0. Furthermore, the NMR-data indicate the imino structure by low field shifted signals of the imino substituents and a relatively acidic *N*—H which appears around 11 ppm.

TABLE I

Physical Data of Pteridine Derivatives

		pK_a in water	UV — Absorption Spectra λ_{max} (nm)			lg ε			pH	Molecular Species
6,7-Diphenyllumazine	(*V*)[8]	8.09 ± 0.04	220	272	361	4.43	4.16	4.17	5	○
			[220]	288	376	[4.41]	4.30	4.06	11	○
1-Methyl-6,7-diphenyllumazine	(*VI*)[8]	8.64 ± 0.10	222	276	365	4.44	4.21	4.18	6	○
			[220]	266	367	[4.32]	4.25	4.16	11	○
			225	278	365	4.40	4.20	4.14	MeOH	○
3-Methyl-6,7-diphenyllumazine	(*VII*)[8]	8.01 ± 0.07	223	270	361	4.44	4.16	4.19	2	○
			[240]	288	384	[4.41]	4.19	4.18	11	○
			226	271	362	4.46	4.20	4.19	MeOH	○
1,3-Dimethyl-6,7-diphenyllumazine	(*VIII*)[8]		226	276	365	4.41	4.19	4.18	7	○
6,7-Diphenyl-4-thiolumazine	(*IX*)		225	293	407	4.49	4.12	4.21	MeOH	○
1-Methyl-6,7-diphenyl-4-thiolumazine	(X)	7.77 ± 0.15	226	292	403	4.53	4.20	4.28	3.9	○
			[227]	301	435	[4.53]	4.37	4.17	10.8	○
			226	292	402	4.54	4.20	4.25	MeOH	○
3-Methyl-6,7-diphenyl-4-thiolumazine	(*XI*)	7.49 ± 0.13[b]	225	291	403	4.53	4.20	4.28	1	○
			[229]	302	435	[4.51]	4.37	4.19	10	○
			226	291	401	4.57	4.23	4.28	MeOH	○
1,3-Dimethyl-6,7-diphenyl-4--thiolumazine	(*XII*)		226	294	406	4.54	4.23	4.27	1—10	○
4-Methylthio-2-oxo-6,7-diphenyl--1,2-dihydropteridine	(*XIII*)		222	282	388	4.53	4.24	4.26	MeOH	○
1-Methyl-4-methylthio-2-oxo-6,7--diphenyl-1,2-dihydropteridine	(*XIV*)		223	284	393	4.67	4.40	4.38	MeOH	○
1-Methyl-4-morpholino-2-oxo-6,7--diphenyl-1,2-dihydropteridine	(*XV*)	1.46 ± 0.08[a]	224	287	396	4.45	4.30	4.24	—1	○+
			222	276	377	4.47	4.29	4.23	5	○
			222	277	377	4.46	4.32	4.24	MeOH	○
4-Amino-1-methyl-2-oxo-6,7--diphenyl-1,2-dihydropteridine	(*XVI*)[24]		222	282	393	4.46	4.23	4.18	0	○+
			222	278	374	4.36	4.30	4.20	7	○

Table I to be continued

Table I continued

		pK_a in water	UV — Absorption Spectra λ_{max} (nm)				lg ε				pH	Molecular Species
4-Methylamino-1-methyl-2-oxo-6,7-diphenyl-1,2-dihydropteridine	(*XVII*)	2.69 ± 0.08[a]	223	274	383		4.46	4.25	4.23		0	+
			222	276	377		4.47	4.29	4.23		5	○
			222	277	377		4.46	4.32	4.24		MeOH	○
4-Imino-3-methyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XVIII*)		220	278	377		4.49	4.20	4.22		0	+
			224	277	366		4.45	4.16	4.18		MeOH	○
			[223]	292	394		[4.44]	4.19	4.06		14	⊖
4-Imino-1,3-dimethyl-2-oxo-6,7-diphenil-1,2,3,4-tetrahydropteridine	(*XIX*)	5.64 ± 0.09[c]	225	282	382		4.49	4.22	4.20		3	+
			224	284	370		4.47	4.18	4.21		8	○
			224	283	369		4.49	4.20	4.22		MeOH	○
4-Methylimino-3-methyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XX*)	5.55 ± 0.12[c]	222	273	379		4.45	4.25	4.19		1	+
		10.84 ± 0.09[c]	228	297	373		4.48	4.27	4.02		7.2	○
			233	312	400		4.44	4.19	4.08		13	⊖
			227	286	367		4.47	4.14	4.13		MeOH	○
4-Methylimino-1,3-dimethyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXI*)	6.14 ± 0.17[c]	226	282	386		4.45	4.27	4.20		1	+
			228	292	370		4.48	4.15	4.17		7	○
			228	292	370		4.47	4.14	4.16		MeOH	○
4-Ethylimino-3-methyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXII*)		226	284	366		4.48	4.15	4.13		MeOH	○
4-*n*-Butylimino-3-methyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXIII*)	5.44 ± 0.14[d]	222	274	382		4.47	4.28	4.21		1.6	+
		11.36 ± 0.04[d]	227	286	368		4.47	4.13	4.14		MeOH	○
			[292]	312	401		[4.15]	4.17	4.06		14	⊖
4-*n*-Butylimino-1,3-dimethyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXIV*)		228	292	370		4.48	4.14	4.16		MeOH	○
4-(*O*-ethylhydroxy)-imino-1,3-dimethyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXV*)		230	298	376		4.56	4.06	4.25		MeOH	○
1-Methyl-2-oxo-6,7-diphenyl-4-phenylhydrazino-1,2,3,4-tetrahydropteridine	(*XXVI*)	2.02 ± 0.10[d]	225	282	393		4.46	4.13	4.11		0	+
		10.53 ± 0.14	226	264	346	464	4.28	4.35	3.76	4.02	5.7	○
			222	268	337	492	4.33	4.27	3.80	3.97	13	⊖
3-Methyl-2-oxo-6,7-diphenyl-4-phenylhydrazino-1,2,3,4-tetrahydropteridine	(*XXVII*)	11.95 ± 0.06[d]	[262]	345	464	535	[4.36]	3.85	4.06	3.63	5	⊖
			275		352	505	4.56		3.87	4.17	14	⊖
			222	264	341	485	—	—	—	—	MeOH	○

Table I to be continued

Table I continued

		pK_a in water	UV — Absorption Spectra λ_{max} (nm)				lg ε				pH	Molecular Species
1,3-Dimethyl-2-oxo-6,7-diphenyl-4-phenylhydrazino-1,2,3,4-tetrahydropteridine	(*XXVIII*)		264 267	340 346	464 496	535	4.39 4.49	3.78 3.93	4.10 4.22	3.75	0—13 $CHCl_3$	○ ○
1,3-Dimethyl-4-methylhydrazino-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXIX*)	3.62 ± 0.20[d]	226 228 229	286 [247] [246]	376 323 323	 426 418	4.43 4.52 4.45	4.26 [4.44] [4.36]	4.18 3.91 3.87	 4.02 3.94	0.7 MeOH 6.8	○+ ○ —
1,3-Dimethyl-4-*N*-methyl-*N*-phenylhydrazino-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXX*)	2.72 ± 0.10[d]	228 224 227	282 260 260	387 360 360	 496 490	4.55 4.46 4.45	4.28 4.42 4.43	4.21 4.07 4.08	 3.71 3.69	0.7 MeOH 5—13	○+ ○ ○
4,4-Dimethoxy-3-methyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXXIII*)	10.77 ± 0.16[a]	228 [240] 228	268 291 275	340 370 340		4.41 [4.28] 4.43	4.14 4.30 4.14	4.17 4.07 4.17		8 14 MeOH	○ — ○
4,4-Dimethoxy-1,3-dimethyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXXIV*)		228	278	340		4.38	4.16	4.16		MeOH	○
Spiro[1,3-dioxolane-2,4'-(3'-methyl-2'-oxo-6',7'-diphenyl-1',2',3',4'-tetrahydropteridine)]	(*XXXV*)	11.40 ± 0.04[a]	227 302	276 366	338		4.45 4.22	4.11 4.08	4.16		MeOH 14	○ —
Spiro[1,3-dioxolane-2,4-(1',3'-dimethyl-2'-oxo-6',7'-diphenyl-1',2',3',4'-tetrahydropteridine)]	(*XXXVI*)		229	280	339		4.43	4.16	4.19		MeOH	○
4-Benzoyl-methylene-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXXVIII*)	9.21 ± 0.04[d]	228 237 228	310 324 310	422 463 422	[440] 486 [440]	4.54 4.49 4.23	4.28 4.30 3.96	4.45 4.47 4.23	[4.46] 4.48 [4.16]	3 11.6 MeOH	○ — ○
4-Dicyanomethylene-1,3-dimethyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXXIX*)		231	265 [434]	303	421	4.58	4.17 [4.30]	4.27	4.34	MeOH	○
1,3-Dimethyl-6,7-diphenyl-4-thiolumazine-*S*-oxide	(*XL*)		[260]	348		457	[4.26]	4.03		4.18	$CHCl_3$	○

[ ] = Shoulder; ○ = neutral form; — = monoanion; + = cation.
a) = 10% CH_3OH; b) = 30% CH_3OH; c) = 50% CH_3OH; d) = 70% CH_3OH.

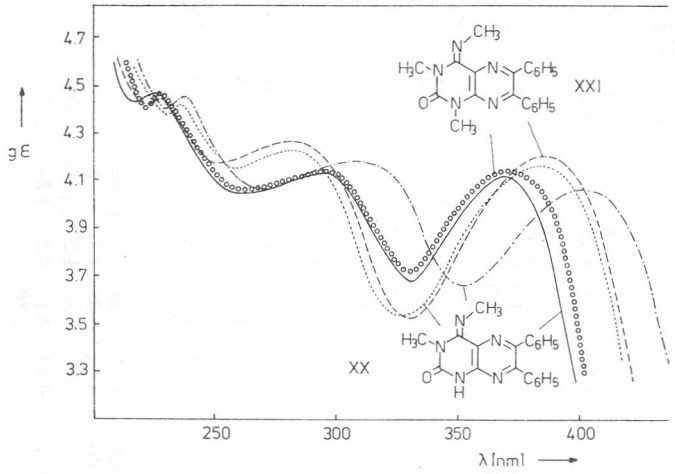


Figure 4. UV-Spectra of the neutral forms of *XX* (———) and *XXI* (oooo) in methanol, of their cations at pH 1 *XX* (• • • •) and *XXI* (— — —) and of the anion of *XX* (—•—•—) at pH 13.

The big difference in the base and acid strength of the imino group and the amide function can be regarded as a second reason for the missing proton transfer from the *N*-1 to the exocyclic imino group and formation of the amino tautomer.

UV-spectra of the anionic species from the fluorescent 4-imido derivatives *XVIII*, *XX* and *XXIII* again show the characteristic bathochromic shift of the *N*-3-methyllumazine series, as also found with the amide acetales *XXXIII* and *XXXV*. NMR-Spectra of the amide acetals *XXXIII*—*XXXVI* show high field shifted signals for the *N*-1- and the *N*-3-methyl groups, indicating a less electron deficient pyrimidine moiety compared to the lumazines and 4-thiolumazines, respectively. This electronic effect is also reflected by the lower acidity of *XXXIII* and *XXXV* in comparison with the corresponding lumazines.

Since all phenylhydrazones *XXVI*, *XXVII*, *XXVIII* and *XXX* show similar UV-spectra with the long wave absorption band at about 490 nm, alike structures representing the tautomeric hydrazone form have to be assumed. The base strength of the hydrazones *XXVI*, *XXIX* and *XXX* is relatively low in the region of 2.0 to 3.6 and cation formation is associated with a drastic hypsochromic shift of the long wavelength absorption band of about 100 nm to 380—390 nm. The cation species of the phenylhydrazones show almost identical UV-spectra to the corresponding 4-imino derivatives, indicating that protonation takes place at the same position — the imino nitrogen. The acidic properties of the phenylhydrazones are expectedly also very weak and deprotonation could only be achieved in basic medium, forming bathochromically shifted anions.

Further structure elucidations were performed by IR-spectra, which showed the 4-C=N stretching band for the hydrazones at 1600 cm^{-1}, while the 4-C=N stretching band of the 4-imino derivatives was in the region of about 1635 cm^{-1}.

TABLE II

NMR-Data of Pteridine Derivatives

		Substituents at C-6	C-7	N-1	N-3	Other Substituents	Solvent
1,3-Dimethyl-6,7-diphenyl-lumazine	(*VIII*)	7.2—7.6 m(10)		3.75 s(3)	3.53 s(3)		$CDCl_3$
1,3-Dimethyl-6,7-diphenyl-4-thio--lumazine	(*XII*)	7.2—7.6 m(10)		**3.96** s(3)	3.80 s(3)		$CDCl_3$
4-Imino-3-methyl-2-oxo-6,7--diphenyl-1,2,3,4-tetrahydro-pteridine	(*XVIII*)	7.2—7.4 m(10)		10.70 s(1)	3.39 s(3)	9.08 s(1), 4-N=H	$CDCl_3/D_6DMSO$
4-Imino-1,3-dimethyl-2-oxo-6,7--diphenyl-1,2,3,4-tetrahydro-pteridine	(*XIX*)	7.2—7.6 m(10)		3.66 s(3)	3.59 s(3)	9.27 s(1), 4-N=H	$CDCl_3$
4-Methylimino-3-methyl-2-oxo--6,7-diphenyl-1,2,3,4-tetrahydro-pteridine	(*XX*)	7.2—7.4 m(10)		11.47 s(1)	3.27 s(3)	3.83 s(3), 4-N=CH_3	D_6DMSO
4-Methylimino-1,3-dimethyl-2--oxo-6,7-diphenyl-1,2,3,4-tetra-hydropteridine	(*XXI*)	7.2—7.6 m(10)		3.62 s(3)	3.44 s(3)	3.91 s(3), 4-N=CH_3	$CDCl_3$
4-*n*-Butylimino-3-methyl-2-oxo--6,7-diphenyl-1,2,3,4-tetrahydro-pteridine	(*XXIII*)	7.2—7.4 m(10)		11.28 s(1)	3.24 s(3)	4.20 t(2), 1.2—1.8 m(4), 0.92 t(3), 4-*n*-butyl	D_6DMSO
4-*n*-Butylimino-1,3-dimethyl-amino-2-oxo-6,7-diphenyl-1,2,3,4--tetrahydropteridine	(*XXIV*)	7.2—7.6 m(10)		3.63 s(3)	3.46 s(3)	4.27 t(2), 1.3—1.9 m(4), 0.96 t(3), 4-*n*-butyl	$CDCl_3$
4-(*O*-Ethylhydroxy)-imino-1,3--dimethyl-2-oxo-6,7-diphenyl--1,2,3,4-tetrahydropteridine	(*XXV*)	7.2—7.6 m(10)		3.61 s(3)	3.61 s(3)	4.36 q(2), OCH_2 1.36 t(3), CH_3	$CDCl_3$
1-Methyl-2-oxo-6,7-diphenyl-4--phenylhydrazino-1,2,3,4-tetra-hydropteridine	(*XXVI*)	7.2—7.4 m(10)		3.45 s(3)	exch.	7.23 t(2), 7.08 d(2), 6.77 t(1), phenylhydrazino	D_6DMSO/D_2O
3-Methyl-2-oxo-6,7-diphenyl-4--phenylhydrazino-1,2,3,4-tetra-hydropteridine	(*XXVII*)	7.3—7.5 m(10)		exch.	3.20 s(3)	7.28 t(2), 6.98 d(2), 6.78 t(1), phenylhydrazino	D_6DMSO/D_2O

Table II to be continued

Table II continued

		Substituents at C-6	C-7	N-1	N-3	Other Substituents	Solvent
1,3-Dimethyl-2-oxo-6,7-diphenyl--4-phenylhydrazino-1,2,3,4-tetrahydropteridine	(*XXVIII*)		7.2—7.5 m(10)	3.63 s(3)	3.53 s(3)	7.24 t(2), 7.02 d(2), 6.82 t(1), 12.77 s(1), phenylhydrazino	$CDCl_3$
1,3-Dimethyl-4-methylhydrazino--2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXIX*)		7.3—7.5 m(10)	3.43 s(3)	3.23 s(3)	9.55 q(1), 3.00 d(3), methylhydrazino	D_6DMSO
1,3-Dimethyl-4-*N*-methyl-*N*--phenylhydraziono-6,7-diphenyl--1,2,3,4-tetrahydropteridine	(*XXX*)		7.2—7.5 m(10)	3.69 s(3)	3.25 s(3)	7.25 t(2), 7.06 d(2), 6.85 t(1), 3.69 s(3), methyl-phenyl-hydrazino	$CDCl_3$
4,4-Dimethoxy-3-methyl-2-oxo--6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXXIII*)		7.2—7.4 m(10)	10.96 s(1)	2.92 s(3)	3.09 s(6), OCH_3	D_6DMSO
4,4-Dimethoxy-1,3-dimethyl-2--oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	(*XXXIV*)		7.2—7.4 m(10)	3.51 s(3)	3.03 s(3)	3.17 s(6), OCH_3	$CDCl_3$/D_6DMSO
Spiro[1,3-dioxolane-2,4'-(3'--methyl-2'-oxo-6',7'-diphenyl--1',2',3',4'-tetrahydropteridine]	(*XXXV*)		7.2—7.4 m(10)	10.82 s(1)	3.00 s(3)	4.3—4.6 m(4), CH_2—CH_2	$CDCl_3$/D_6DMSO
Spiro[1,3-dioxolane-2,4'-(1',3'--dimethyl-2'-oxo-6',7'-dimethyl--1',2',3',4'-tetrahydropteridine)]	(*XXXVI*)		7.2—7.5 m(10)	3.59 s(3)	3.18 s(3)	4.2—4.6 m(4), CH_2CH_2	$CDCl_3$
4-Dicyanomethylene-1,3-dimethyl-2-oxo-6,7-diphenyl--1,2,3,4-tetrahydropteridine	(*XXXIX*)		7.2—7.6 m(10)	3.95 s(3)	3.75 s(3)		$CDCl_3$

s = Singlet, d = doublet, t = triplet, m = multiplet; all values in ppm, TMS as in ternal standard.

EXPERIMENTAL

UV-spectra were recorded on a Kontron Spektrometer Uvikon 820, pK_a-values were determined photospectroscopically[25] at 25 °C in 0.01 M buffer[26] at at least 3 analytical wavelengths. ^{1}H-NMR-spectra were measured on a Jeol JNM-NH-100 and on a Bruker Cryospec WM 250 spectrometer with TMS as internal standard. Infrared spectra were recorded on a Perkin-Elmer IR-Spektrometer 621, mass-spectra were obtained from a Finnigan MAT 312. Chromatographical studies were performed on thin layer sheets from Schleicher & Schüll, silica gel F 1500 LS 254 and cellulose F 1440 LS 254. Elution solvents used were chloroform/methanol, chloroform/acetone, SSE (ethylacetate/water/*n*-propanol (4 : 2 : 1), organic layer) on silica gel, while 4% sodiumcitrate and propanol/water/ammonia (7 : 2 : 1) were used on cellulose.

Preparative layer chromatography was performed on glass plates, 400 × 200 mm, coated with 2 mm silica gel 60 PF 254 from E. Merck. Radiation experiments were carried out with a slide projector, light of wavelength < 330 was filtered off. Generally, the substances were dried over P_4O_{10} at elevated temperatures; melting points are not corrected.

5,6-Diamino-3-methyluracil (III)[10]

6-Amino-2-thiouracil was prepared by condensation of thiourea with ethyl cyanoacetate[27] in yields up to 85%. Methylation to 6-amino-3-methyl-2-methylthiouracil with dimethyl sulfate in aqueous sodium hydroxide gave 52%, while 6-amino-4-methoxy-3-methyl-2-thioxo-1,2-dihydropyrimidine was separated by extraction with diethylether. Base hydrolysis of the methylthio group[11] led to 6-amino-3-methyluracil. Nitrosation with sodum nitrite in acidic solution yielded about 90% of 6-amino-5-nitroso-3-methyluracil. 15.6 g (0.1 mol) of this compound then added to a fresh 20% ammonium sulfide solution at 70—80 °C, followed by refluxing for 15 min, which converted the red-violet crystals into a colourless solid. After cooling the precipitate was collected, washed and dried in a vacuum desiccator to give 13.3 g (85%) of m. p. >330 °C. The material was spectroscopically identical with an authentic sample.[10]

1-Methyl-6,7-diphenyl-4-thiolumazine (X)

9.90 g (30 mmoles) of 1-methyl-6,7-diphenyllumazine (*VI*)[6] and 13.0 g of diphosphorous pentasulfide were boiled in 150 ml of dioxan under reflux for 1.25 hours. After cooling the suspension was filtered, the filtrate evaporated and then the remaining residue crystallized from 300 ml of ethanol/dioxan/water (22/5/5) to yield 8.58 g (82%) yellow-orange coloured crystals with m. p. >270 °C.

Anal. $C_{19}H_{14}N_4OS$ (346.41) Calc'd.: C 65.88; H 4.07; N 16.17; S 9.26%
Found: C 65.88; H 3.97; N 16.06; S 9.29%.

3-Methyl-6,7-diphenyl-4-thiolumazine (XI)

3.96 g (12 mmoles) of 3-methyl-6,7-diphenyllumazine (*VII*)[6] and 5.0 g of diphosphorous pentasulfide were boiled under reflux in 150 ml of dioxan for 1.5 hours. After cooling the suspension was filtered, the brown filtrate evaporated and then the remaining residue crystallized from 500 ml of ethanol/dioxan/water (8/1/1) to yield 3.2 g (77%) orange-coloured crystals with m. p. >270 °C.

Anal. $C_{19}H_{14}N_4OS$ (346.41) Calc'd.: C 65.88; H 4.07; N 16.17; S 9.26%
Found: C 65.71; H 4.05; N 16.05; S 9.10%.

1,3-Dimethyl-6,7-diphenyl-4-thiolumazine (XII)

6.90 g (20 mmoles) 1,3-dimethyl-6,7-diphenyllumazine (*VII*)[6] was suspended in 150 ml of dioxan and refluxed with 13.0 g of diphosphorous pentasulfide for 1 hour. After cooling, the yellow suspension was filtered and the filtrate evaporated to dryness. Crystallization of the residue from 250 ml of ethanol/dioxan/water (3/1/1) gave orange crystals, wich further were recrystallized from ethanol to afford 5.60 g (77%) orange crystals of m. p. 229—231 °C. Lit.[4] m. p. 220—221 °C.

Anal. $C_{20}H_{16}N_4OS$ (360.44) Calc'd.: C 66.65; H 4.47; N 15.54; S 8.89%
Found: C 66.46; H 4.44; N 15.39; S 9.05%.

4-Methylthio-2-oxo-6,7-diphenyl-1,2-dihydropteridine (XIII)

0.665 g (2 mmoles) of 6,7-diphenyl-4-thiolumazine (*IX*)[4], 0.2 g of potassium carbonate and 0.3 g methyliodide were stirred at room temperature for 4 hours, in absolute dioxan followed by filtration and evaporation. Crystallization of the resulting residue from 80 ml of ethanol yielded 0.546 g (79%) slightly yellowish crystals with m. p. 212 °C.

Anal. $C_{19}H_{14}N_4OS$ (346.42) Calc'd.: C 65.88; H 4.07; N 16.17%
Found: C 65.53; H 3.86; N 16.03%.

1-Methyl-4-methylthio-2-oxo-6,7-diphenyl-1,2-dihydropteridine (XIV)

0.346 g (1 mmole) 4-methylthio-2-oxo-6,7-diphenyl-1,2-dihydropteridine (*XIII*), 0.1 g potassium carbonate and 0.15 g methyliodide were stirred at room temperature in 50 ml of absolute dioxan overnight. Filtration and evaporation of the filtrate yielded, after crystallization from 60 ml of ethanol, 0.3 g (83%) slightly yellowish crystalls with m. p. 272 °C.

XIV was also prepared directly from 6,7-diphenyl-4-thiolumazine (*IX*) using the twofold equivalent of methyliodide.

Anal. $C_{20}H_{16}N_4OS$ (360.44) Calc'd.: C 66.65; H 4.47; N 15.54%
Found: C 66.58; H 4.54; N 15.58%.

1-Methyl-4-morpholino-2-oxo-6,7-diphenyl-1,2-dihydropteridine (XV)

0.5 g (1.39 mmoles) 1-methyl-4-methylthio-2-oxo-6,7-diphenyl-1,2-dihydropteridine (*XIV*) was suspended in 60 ml of dioxan and stirred with 5 ml of morpholine at room temperature overnight. After evaporation and several coevaporations with methanol, crystallization from 80 ml ethanol with charcoal yielded 0.442 g (79%) of pale yellowish needles with m. p. 252 °C.

Anal. $C_{23}H_{21}N_5O_2$ (399.45) Calc'd.: C 69.16; H 5.29; N 17.53%
Found: C 69.13; H 5.42; N 17.53%.

4-Amino-1-methyl-2-oxo-6,7-diphenyl-1,2-dihydropteridine (XVI)

0.693 g (2 mmoles) 1-methyl-6,7-diphenyl-4-thiolumazine (*X*) was stirred at room temperature in 20 ml 15-% methanolic ammonia for two days. Evaporation and crystallization of the remaining residue from 150 ml dimethylformamide/water (1/1) with charcoal and another recrystallization from 400 ml of ethanol yielded 0.52 g (78%) slightly yellowish crystals, which were identical with an authentic sample.[6]

4-Methylamino-1-methyl-2-oxo-6,7-diphenyl-1,2-dihydropteridine (XVII)

1.50 g (4.33 mmoles) 1-methyl-6,7-diphenyl-4-thiolumazine (*X*) was stirred at room temperature in 80 ml of 25-% ethanolic methylamine solution for two days. Evaporation and crystallization of the remaining residue from ethanol/water (80/20 ml) and then from 75 ml ethanol yielded 1.16 g (79%) pale yellowish crystals with m. p. >270 °C.

Anal. $C_{20}H_{17}N_5O$ (343.39) Calc'd.: C 69.94; H 4.99; N 20.41%
Found: C 69.76; H 5.05; N 20.31%.

4-Imino-3-methyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (XVIII)

0.693 g (2 mmoles) 3-methyl-6,7-diphenyl-4-thiolumazine (*XI*) was stirred at room temperature in 150 ml of 8-% methanolic ammonia for two weeks. The uncompleted reaction was stopped by evaporation and purification was performed on four preparative silica gel plates (400×200×2 mm) with a twofold development using chloroform/methanol (19/1); the main band was eluted and the obtained product rechromatographed in the same manner. Since all crystallizations failed by yielding slightly yellow coloured thick gels, the material was precipitated by dissolving in a little hot dimethylformamide and by dropwise addition, with vigorous stirring, into 150 ml of diethylether. The amorphous solid was difficult to filter and gave, after drying, 0.137 g (20%) of m. p. 267 °C.

Anal. $C_{19}H_{15}N_5H_2O$ (347.37) Calc'd.: C 65.69; H 4.93; N 20.16%
Found: C 65.88; H 4.45; N 20.46%.

4-Imino-1,3-dimethyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (XIX)

a) 0.36 g (1 mmole) 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (*XII*) and 2.0 g ammonium acetate were heated under reflux in 30 ml of dioxan for 8 hours. Every two hours 1.0 g of ammonium acetate was added. The brown solution was then evaporated and the remaining residue separated by chromatography on two silica gel plates (400×200×2 mm) with chloroform/methanol (49/1). As a side product, 95 mg of 1,3-dimethyl-6,7-diphenyllumazine (*VIII*) were isolated, while crystallization of the main product from 30 ml of ethanol yielded 0.193 g (56%) colourless crystals with m. p. 206—207 °C.

b) 0.72 g (2 mmoles) 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (*XII*) was stirred at room temperature for 3 days in 50 ml of dioxan with 30 ml of 15-% methanolic ammonia. Additional heating under reflux for 1 hour, evaporation and twofold recrystallization from 70 and 60 ml of ethanol, respectively, with traces of water yielded 0.532 g (77%) colourless crystals with m. p. 206—207 °C.

Anal. $C_{20}H_{17}N_5O$ 5343.39) Calc'd.: C 69.94; H 4.99; N 20.41%
Found: C 69.88; H 4.91; N 20.43%.

4-Methylimino-3-methyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (XX)

a) 0.346 g (1 mmole) 3-methyl-6,7-diphenyl-4-thiolumazine (*XI*) was stirred at room temperature in 30 ml of 25-% methanolic methylamine solution overnight under exclusion of light and moisture. Evaporation of the slightly yellowish solution and twofold recrystallization of the remaining residue from dioxan/water yielded 0.256 g (74%) colourless crystals with m. p. >300 °C.

b) 80 mg (0.21 mmoles) 4,4-dimethoxy-3-methyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (*XXXIII*) was stirred for 2 hours at room temperature in 10 ml of 12-% methanolic methylamine solution. Evaporation and purification by chromatography on a silica gel plate (400×200×2 mm) with chloroform/methanol (19/1) yielded after crystallization from dioxan/water 62 mg (86%) of colourless crystals with m. p. >300 °C.

Anal. $C_{20}H_{17}N_5O$ (343.38) Calc'd.: C 69.96; H 4.99; N 20.39%
Found: C 69.73; H 5.11; N 20.32%.

4-Methylimino-1,3-dimethyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (XXI)

0.720 g (2 mmoles) 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (*XII*) was stirred in 80 ml of dioxan together with 15 ml of 12-% ethanolic ammonia for 3 days at room temperature. The solution was then boiled for a few minutes, evaporated and the residue twice recrystallized from 120 and 80 ml of ethanol, respectively, to yield 0.583 g (81%) pale yellowish crystals with m. p. 166 °C.

Anal. $C_{21}H_{19}N_5O$ (357.42) Calc'd.: C 70.57; H 5.36; N 19.59%
Found: C 70.66; H 5.48; N 19.66%.

4-Ethylimino-3-methyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (XXII)

0.693 g (2 mmoles) 3-methyl-6,7-diphenyl-4-thiolumazine (*XI*) was refluxed in 50 ml of absolute dioxan and 30 ml of ethylamine containing impure diethylamine for 3 days. Another 30 ml of the diethylamine were added and boiling continued for another 11 days. Since much of the starting material was unchanged, the dark solution was evaporated and the remaining residue separated by chromatography on 3 silica gel plates (400×200×2 mm) with chloroform/methanol (19/1). The fluorescing band was eluted and the product crystallized from 30 ml of methanol yielding 0.233 g (32%) colourless needles with m. p. 228 °C.

Anal. $C_{21}H_{19}N_5O$ (357.42) Calc'd.: C 70.57; H 5.36; N 19.59%
Found: C 70.56; H 5.18; N 19.35%.

4-n-Butylamino-3-methyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (XXIII)

0.693 g (2 mmoles) 3-methyl-6,7-diphenyl-4-thiolumazine (*XI*) was stirred at room temperature in 50 ml absolute dioxan with 5 ml of *n*-butylamine overnight. The clear solution was evaporated and the residue recrystallized twice from 150 ml of ethanol with charcoal yielding 0.538 g (70%) colourless crystals with m. p. 251 °C.

Anal. $C_{23}H_{23}N_5O$ (385.47) Calc'd.: C 71.66; H 6.01; N 18.17%
Found: C 71.54; H 6.06; N 18.13%.

4-n-Butylamino-1,3-dimethyl-6,7-diphenyl-1,2,3,4-tetrahydropteridine (XXIV)

0.720 g (2 mmoles) 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (*XII*) was stirred with 2 ml *n*-butylamine in 150 ml of dioxan at room temperature for 8 hours, followed by evaporation. The resulting residue was crystallized twice from 120 ml of ethanol with charcoal, yielding 0.508 g (64%) pale yellowish crystals with m. p. 101—102 °C.

Anal. $C_{24}H_{25}N_5O$ (399.50) Calc'd.: C 72.16; H 6.31; N 17.53%
Found: C 72.23; H 6.54; N 17.64%.

4-Ethoximino-1,3-dimethyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (XXV)

0.360 g (1 mmole) 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (*XII*), 0.184 g (2 mmoles) *O*-ethyl-hydroxylaminehydrochloride and 2 ml triethylamine were refluxed in 100 ml of dioxan for 3 days. The solution was evaporated, the residue resolved in 100 ml of chloroform and then shaken three times with 20 ml of 1 M hydrochloric acid each. After drying and evaporation the residue was chromatographed on two silica gel plates (400×200×2 mm) with chloroform. The main band was eluted and yielded, on crystallization from 50 ml of methanol, 0.273 g (70%) pale yellowish crystals with m. p. 157 °C.

Anal. $C_{22}H_{21}N_5O_2$ (387.44) Calc'd.: C 68.20; H 5.46; N 18.08%
Found: C 68.11; H 5.49; N 18.01%.

1-Methyl-2-oxo-6,7-diphenyl-4-phenylhydrazino-1,2,3,4-tetrahydropteridine (XXVI)

0.693 g (2 mmoles) 1-methyl-6,7-diphenyl-4-thiolumazine (*X*) was stirred at room temperature in 20 ml of dioxan with 0.40 g of phenylhydrazine for 24 hours. The red solution was evaporated, the residue dissolved in 30 ml of hot dimethylformamide, treated with charcoal, filtered and then 10 ml of water was added while hot. The precipitate was collected after cooling and then the purification procedure repeated to yield 0.521 g (62%) red crystals with m. p. 269 °C. All procedures were carried out under exclusion of light.

Anal. $C_{25}H_{20}N_6O$ (420.48) Calc'd.: C 71.41; H 4.79; N 19.99%
Found: C 71.56; H 4.82; N 20.06%.

3-Methyl-2-oxo-6,7-diphenyl-4-phenylhydrazino-1,2,3,4-tetrahydropteridine (XXVII)

0.693 g (2 mmoles) 3-methyl-6,7-diphenyl-4-thiolumazine (*XI*) was stirred at room temperature in 20 ml of dioxan and 20 ml of dimethylformamide with 0.4 g of phenylhydrazine for 4 hours. After evaporation, the residue was dissolved in 30 ml of hot DMF, filtered and 5 ml of water was added for crystallization upon cooling. The red precipitate was collected and the crystallization procedure was repeated yielding finally 0.493 g (71%) red crystals with m. p. >270 °C. All procedures were carried out under exclusion of light.

Anal. $C_{25}H_{20}N_6O$ (420.48) Calc'd.: C 71.41; H 4.79; N 19.99%
Found: C 71.15; H 4.62; N 19.89%.

1,3-Methyl-2-oxo-6,7-diphenyl-4-phenylhydrazino-1,2,3,4-tetrahydropteridine (XXVIII)[4]

0.720 g (2 mmoles) 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (*XII*) and 0.4 g phenylhydrazine were refluxed in 50 ml of dioxan for 8 hours. The solution, which turned from yellow to a deep red colour, was evaporated and the resulting residue was dissolved in about 60 ml of hot dimethylformamide. Addition of 10 ml of water and cooling gave a red precipitate, which was collected and further purified by the same procedure to yield 0.458 g (52%) red crystals with m. p. >300 °C. All operations were conducted under exclusion of light.

Anal. $C_{26}H_{25}N_6O$ (434.5) Calc'd.: C 71.87; H 5.10; N 19.34%
Found: C 71.61; H 5.10; N 19.38%.

1,3-Dimethyl-4-methylhydrazino-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (XXIX)

0.72 g (2 mmoles) 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (*XII*) in 50 ml absolute dioxan was stirred at room temperature with 0.92 g (20 mmoles) of methylhydrazine for 30 minutes. The orange-red solution was evaporated and the residue was crystallized twice from 160 ml of ethanol with charcoal, yielding 0.592 g (79%) orange coloured crystals with m. p. 214 °C.

Anal. $C_{21}H_{20}N_6O$ (372.43) Calc'd.: C 67.72; H 5.51; N 22.56%
Found: C 67.57; H 5.40; N 22.35%.

*1,3-Dimethyl-4-*N*-methyl-*N*-phenylhydrazino-2-oxo-6,7-diphenyl--1,2,3,4-tetrahydropteridine* (XXX)

0.72 g (2 mmoles) 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (*XII*) and 0.61 g (5 mmoles) *N*-methyl-*N*-phenylhydrazine in 80 ml of dioxan were refluxed under exclusion of moisture and light for 2 days. During that time 1.2 g *m*-chlor-perbenzoic acid was added in portions to the boiling solution. The dark red solution was evaporated, the resulting residue was dissolved in little chloroform and chromatographed on two silica gel plates (400×200×2 mm) with chloroform. The main band was eluted and this material forther purified by another chromatography on plates with twofold development in dichloromethane and crystallization of the eluted main product from 70 ml of ethanol to yield 0.219 g (24%) dark redviolet crystals with m. p. 158 °C.

Anal. $C_{27}H_{24}N_6O$ (448.53) Calc'd.: C 72.30; H 5.39; N 18.74%
Found: C 72.27; H 5.35; N 18.56%.

4,4-Dimethoxy-3-methyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (XXXIII)

1.73 g (5 mmoles) 3-methyl-6,7-diphenyl-4-thiolumazine (*XI*) was dissolved in 100 ml of absolute methanol, containing 0.23 g of sodium. 1.80 g mercury-II-bromide was added to the slightly red coloured solution which turned to yellow and from which a precipitate separated. Stirring overnight, filtration and very careful neutralization of the filtrate with aqueous acetic acid to pH 8—9 gave, on evaporation and crystallization of the residue from 180 ml of ethanol, 1.31 g (69%) colourless crystals. Melting behaviour: at 179 °C melting with evaporation of a liquid, at about 190 °C the melt resolidified and melted again at 226 °C. The substance which was produced at 179 °C and melted at 226 °C was identified as 1,3-dimethyl--6,7-diphenyllumazine (*VIII*).

Anal. $C_{21}H_{20}N_4O_3$ (376.42) Calc'd.: C 67.00; H 5.36; N 14.88%
Found: C 66.75; H 5.50; N 14.79%.

4,4-Dimethoxy-1,3-dimethyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (XXXIV)

1.80 g (5 mmoles) 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (*XII*) was solved in 80 ml of absolute methanol and 100 ml of absolute dioxan containing 0.75 g

sodium. To this slightly red coloured solution, 1.80 g (5 mmoles) of mercury-II--bromide was added, turning the colour to yellow, then to brown, until a grey precipitate was formed. After stirring overnight, the grey suspension was filtered and the slightly yellow filtrate evaporated. The remaining residue was crystallized from 80 ml of absolute methanol with charcoal and then recrystallized from absolute methanol to yield 1.45 g (74%) colourless, unusually large, crystals with m. p. 178—180 °C.

Anal. $C_{22}H_{22}N_4O_3$ (390.44) Calc'd.: C 67.68; H 5.68; N 14.35%
Found: C 67.44; H 5.80; N 14.10%.

Spiro[1,3-dioxolane-2,4'-(3'-methyl-2'-oxo-6',7'-diphenyl--1',2',3',4'-tetrahydropteridine)] (XXXV)

1.55 g (25 mmoles) of ethylene glycol and 1.15 g of sodium were heated under reflux in 100 ml of absolute dioxan overnight. After all of the sodium had dissolved, 1.39 g (4 mmoles) of 3-methyl-6,7-diphenyl-4-thiolumazine (*XI*) and 1.80 g (5 mmoles) of mercury-II-bromide were added at room temperature. The red solution slowly turned yellow, then brown and a grey precipitate appeared. Stirring was continued for an additional 30 hours at room temperature. After filtration, careful neutralization with aqueous acetic acid and evaporation, the resulting residue was crystallized from 400 ml of absolute methanol yielding 1.19 g colourless crystals. Recrystallization from the same solvent yielded finally 0.957 g (64%) pure product with m. p. 288 °C.

Anal. $C_{21}H_{18}N_4O_3$ (374.40) Calc'd.: C 67.37; H 4.85; N 14.96%
Found: C 67.11; H 4.87; N 14.89%.

Spiro[1,3-dioxolane2,4'-(1',3'-dimethyl-2'-oxo-6',7'-diphenyl--1',2',3',4'-tetrahydropteridine)] (XXXVI)

1.55 g (25 mmoles) of ethylene glycol and 1.15 g (50 mmoles) of sodium were heated under reflux in 100 ml of absolute dioxan until all of the sodium had dissolved. 1.80 g (5 mmoles) of 1,3-dimethyl-6,7-diphenyl-4-thiolumazine (*XII*) and 1.80 g (5 mmoles) of mercury-II-bromide were added at room temperature to the clear red solution. A brown-grey precipitate was slowly formed and the reaction took 4 days to be completed (TLC). After filtration and evaporation, the remaining residue was crystallized from 300 ml of methanol with charcoal. Recrystallization from 100 ml of methanol yielded 53 mg (7%) colourless crystals with m. p. 253 °C.

Anal. $C_{22}H_{20}N_4O_3$ (388.43) Calc'd.: C 68.03; H 5.19; N 14.42%
Found: C 68.01; H 5.22; N 14.62%.

4-Benzoyl-methylene-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (XXXVIII)

1.33 g (4 mmoles) 6,7-diphenyl-4-thiolumazine (*IX*) and 0.8 g 2-bromoacetophenone were stirred overnight at room temperature in 100 ml of dioxan in the presence of 5 ml of triethylamine. After evaporation, the remaining residue was boiled under reflux in dimethylformamide for 1 hour. The resulting black solution was evaporated in vacuum and then dissolved in a small amount of chloroform. Chromatography was performed on a silica gel column (15×4 cm) with chloroform/methanol (9/1). Further purification was carried out by twofold chromatography on preparative silica gel plates (400×200×2 mm) with chloroform/methanol (19/1) and crystallization of the chromatographically pure substance from 500 ml dioxan/ /water, yielding 0.753 g (45%) of fine, yellow crystals with m. p. >250 °C.

Anal. $C_{26}H_{18}N_4O_2$(418.46) Calc'd.: C 74.63; H 4.34; N 13.39%
Found: C 74.86 H 4.40; N 13.28%.

4-Dicyanomethylene-1,3-dimethyl-2-oxo-6,7-diphenyl-1,2,3,4--tetrahydropteridine (XXXIX)

0.376 g (1 mmole) 4,4-dimethoxy-1,3-dimethyl-2-oxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine (*XXXIV*) and 5 ml malonitrile were heated in 10 ml of dioxan under reflux for 1 hour. Evaporation of the dark solution was followed by chromato-

graphy on two silica gel plates (400×200×2 mm) with a twofold development in chloroform. The yellow band was eluted and the material chromatographed once more with chloroform/acetone (19/1). Elution of the yellow product and twofold recrystallization from 250 ml of methanol yielded 0.186 g (47%) bright yellow needles with m. p. 281 °C.

Anal. $C_{23}H_{16}N_6O$ (392.42) Calc'd.: C 70.39; H 4.11; N 21.41%
Found: C 70.60; H 4.20; N 21.70%.

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POVZETEK

Pteridini. LXXVIII. Reakcije in lastnosti derivatov 4-tiolumazina

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Pri 1- (*X*), 3-metil-(*XI*) in 1,3-dimetil-6,7-difeniltiolumazinu se 4-tiokso skupina izmenjuje z mukleofilnimi reagenti pod milimi pogoji. Posebne strukturne in elektronske lastnosti se odražajo tudi pri 3-metil-6,7-difenil-4-tiolumazinu (*XI*), ki reagira analogno kot 1,3-dimetil derivat (*XII*) z amini, tako da nastanejo 4-imino tavtomeri (*XVIII—XXIV*) in s hidrazini, s katerimi nastanejo hidrazoni (*XXXVI—XXX*). Te zadnje spojine so občutljive na svetlobo in se fotooksidirajo v ustrezne

6,7-difenillumazine (*VI—VIII*). Pri nukleofilni substituciji žvepla 4-tioamidne skupine z alkoksidi ali pod vplivom $HgBr_2$ katalizatorja nastanejo neobičajni 4,4-di-*O*-alkil amid acetali (*XXXIII—XXXVI*). Acetalna skupina se lahko substituira s C—H kislimi apojinami, tako da nastane iz *XXXIV* 4-dicianometilen-1,3-dimetil-2-okso-6,7-difeniltetrahidropteridin (*XXXIX*).

Nove spojine so bile karakterizirane z elementno analizo, ^{1}H-NMR spektri in UV spektri pri različnih pH vrednostih.