CHEMISTRY OF PTERIDINE N-OXIDES (REVIEW)*

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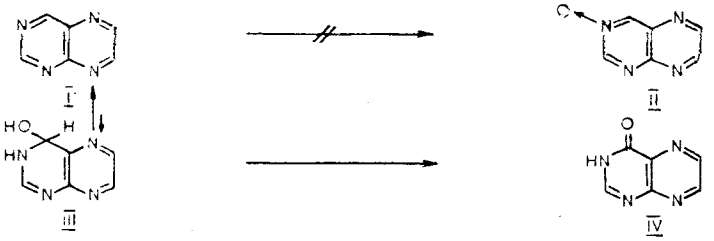
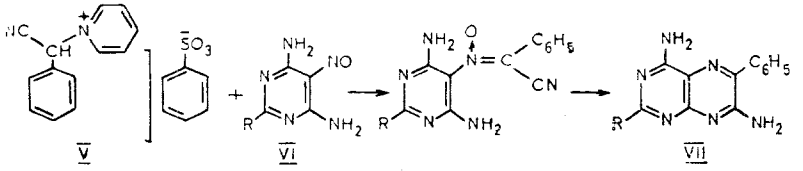
Reactions involving the direct oxidation of pteridine derivatives to their N-oxides are examined. The relationship between the structures of the N-oxides and their physicochemical properties (UV spectra and pK_a values) is discussed.

Albert in 1961 first attempted to synthesize pteridine N-oxide by reaction of pteridine (I) itself with monoperphthalic acid [1]. However, it was found that the oxidation does not lead to the 3-N-oxide (II), as was initially assumed, but rather primarily to 4-oxo-3,4-dihydropteridine (IV) [2]. The formation of the latter is apparently explained by dehydrogenation of the hydrated form (III).



The first authentic N-oxides of the pteridine series (VII) with an N-oxide function in the 5 position were obtained by Pachter and co-workers [3, 4] from 4-amino-5-nitroso pyrimidines (VI) and phenacyl-, acetonyl-, or α-cyanobenzylpyridinium salts.



Pteridine 8-N-oxides were also obtained via an unambiguous route consisting in cyclization of N-oxides of the pyrazine series to 2,4-diaminopteridine (IX), pterine (X), and lumazine 8-N-oxides (XI) [5-8].

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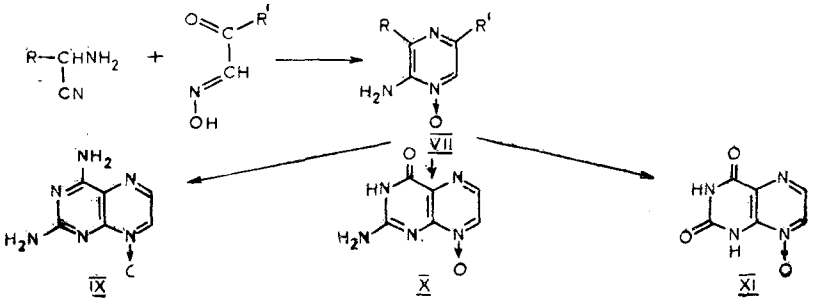
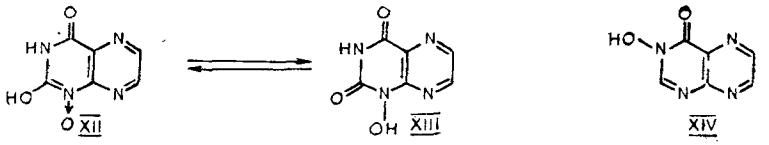


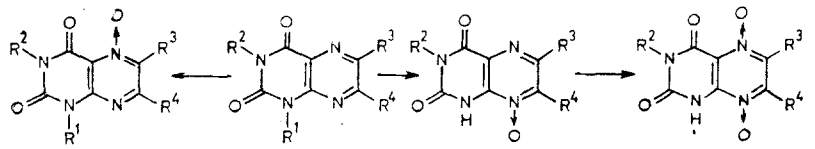
In its tautomeric N-hydroxy form (XIII), the lumazine 1-oxide (XII) described by Brown [9] should be considered to be a cyclic hydroxamic acid similar to 3-hydroxy-4-oxo-3,4-dihydropteridine (XIV) [10].



We first reported the successful direct oxidation of pteridines in 1965 [11], and since that time only one paper [12] in which this same method was used has come to our attention.

Inasmuch as we set out to localize the N-oxide function in the pyrazine portion of the pteridine molecule, lumazine (XVa) itself and its N-methyl, C-alkyl, or aryl derivatives were selected as the initial subjects for the investigation.

Performance of the reaction in formic acid with the gradual addition of a two- to sixfold molar excess of 30% hydrogen peroxide at room temperature proved to be quite favorable for the formation of N-monoxides. Raising the temperature leads not only to lowering of the yields but also to the formation of side products, and this very much complicates the isolation of the N-oxides in pure form. Comparison of the results (reaction times and yields) indicates that the accumulation of N- and C-methyl groups promotes the formation of the N-oxide. While unsubstituted lumazine (XVa) reacts with the formation of N-monoxide XVIIa in 7 days, 1,3,6,7-tetramethyl-lumazine (XVe) is oxidized almost quantitatively to N-oxide XVIe in 2 days. It was subsequently ascertained that the reaction proceeds unambiguously only when there is a methyl group in the 1 position, while further oxidation is usually observed up to the completion of the formation of the N-monoxide in the case of 1-H derivatives.



XVI c,e,f,i-l XV a-l XVII a,b,d,g,h XVIII b,j,k

XV, XVI a $R^1=R^2=R^3=R^4=H$; b $R^1=R^2=H$, $R^3=R^4=CH_3$; c $R^1=R^3=R^4=CH_3$, $R^2=H$; d $R^1=H$, $R^2=R^3=R^4=CH_3$; e $R^1=R^2=R^3=R^4=CH_3$; f $R^1=R^3=H$, $R^2=CH_3$, $R^4=t\text{-}C_4H_9$; g $R^1=R^2=R^4=H$, $R^3=C_6H_5$; h $R^1=R^4=H$, $R^2=CH_3$, $R^3=C_6H_5$; i $R^1=R^2=CH_3$, $R^3=C_6H_5$, $R^4=H$; j $R^1=R^2=R^3=H$, $R^4=C_6H_5$; k $R^1=R^3=H$, $R^2=CH_3$, $R^4=C_6H_5$; l $R^1=R^2=CH_3$, $R^3=H$, $R^4=C_6H_5$; XVII, XVIII a $R^2=R^3=R^4=H$; b $R^2=H$, $R^3=R^4=CH_3$; d $R^2=R^3=R^4=CH_3$; g $R^2=R^4=H$, $R^3=C_6H_5$; h $R^2=CH_3$, $R^3=C_6H_5$, $R^4=H$; j $R^2=R^3=H$, $R^4=C_6H_5$; k $R^2=CH_3$, $R^3=H$, $R^4=C_6H_5$

As in the case of XVb, the chief side product is N,N-dioxide XVIIIb, which can be obtained both by subsequent oxidation of N-monoxide XVIIb and directly from XVb under

more severe conditions (85% hydrogen peroxide in trifluoroacetic acid).

The selective formation of the N-oxide is due mainly to steric factors and has certain analogies in the heterocyclic series. Thus it has been found [13-15] for various systems that even a hydrogen atom in the peri position may have a similar effect. It should have been expected that a substituent in the 1 position in lumazine derivatives hinders attack at the peri nitrogen atom to such an extent that initial oxidation proceeds only in the 5 position in this case. Another possibility of lowering or even complete suppression of the reactivities of both pyrazine nitrogen atoms in lumazine derivatives by the creation of unfavorable steric conditions consists in the introduction of isopropyl, tert-butyl, or phenyl groups into the 6 and 7 positions. Thus, in the case of 2,3-diisopropylquinoxaline it has been shown [16-17] that it is not oxidized to the N-oxide by either monoperphthalic acid or hydrogen peroxide in hot acetic acid, while the nitrogen atom in the meta position (but not in the ortho position) is primarily attacked in the case of 2-monosubstituted compounds [18-21].

It is precisely for this reason that 7-tert-butyl-3-methyllumazine (XV*f*) forms 7-tert-butyl-3-methyllumazine 5-oxide (XVI*f*) during oxidation with hydrogen peroxide in trifluoroacetic acid.

The effect of a phenyl substituent in the 6 and 7 positions on N-oxidation has also been investigated in detail. In general, a decrease in reactivity was observed. The phenyl group hinders oxidation of the adjacent nitrogen atom [22]. Because of this, 6-phenyllumazines XVg,h form 8-N-oxides XVIIg,h, while the isomeric 7-phenyllumazines (XVj-*l*) are oxidized to 5-oxides XVIj-*l*. In addition 5,8-dioxides (XVIIIj,k, which, because of their high acidity may be readily isolated from the N-monoxides, are formed in the case of XVj,k.

The establishment of the structure of lumazine N-monoxides was difficult because of the close reactivities of both of the nitrogen atoms of the pyrazine rings [23]. Unsymmetrical substitution of the latter by an annelated pyrimidine ring to give a pteridine system makes it possible to expect a definite difference in chemical behavior for the 5 and 8 positions. This difference may be additionally reinforced by the introduction of electron-donor substituents of the amino or hydroxyl type into the 2 and 4 positions. Proceeding from the fact that the formation of the N-oxide, as electrophilic substitution, is formally similar to quaternization, on the basis of the available data [24, 25], the nitrogen atom in the 8 position can be considered to be more reactive. In addition to this alkyl and aryl substituents in the ortho and peri positions may affect the course of the reaction, such that (as in the related quinoxaline systems [18-21] steric factors will have a substantial effect.

The attempt to obtain chemical proof of the structure that we previously made [11] (the Katada rearrangement [26, 27], which occurs when the N-oxide is refluxed in acetic anhydride) was not very conclusive in the pteridine series, inasmuch as the formation of the 6- or 7-oxo derivative does not make it possible to draw an unambiguous conclusion regarding the presence of an N-oxide function in the ortho position. Thus Taylor [28] recently demonstrated that pterine 8-N-oxide is rearranged completely to xanthopterine, the 6-oxo isomer, without forming any appreciable amounts of isoxanthopterine.

We therefore used the UV spectra and pK_a values as the principal methods for the establishment of the structure and identification of lumazine N-oxides, inasmuch as a comparison of these physical properties makes it possible to readily establish the structural similarity between the investigated compounds (Table 1).

The pK_a values indicate that lumazine N-monoxides, with respect to the degree of increase in acidity as compared with the starting lumazine, form two series, one of which is characterized by a change in the acidity by approximately 1 pK unit, the other of which is characterized by a change of approximately 3 pK units. Inasmuch as the reaction proceeds only at N_5 to give oxide XVI*f* for steric reasons in the oxidation of 7-tert-butyl-3-methyllumazine (XV*f*), and as a result of this the acidity increased by 1 pK unit, it is clear that the N-oxide function in the 8 position reinforces the acid

TABLE 1. Physical Properties of Lumazine Derivatives

Compound	pK_a (H_2O, 20°)	λ_{max}, nm *	log ε	pH	Molecular characteristics†
Lumazine (XVa)	7,95	228 325 215 236 269 346	4,03 3,86 3,97 4,03 3,98 3,71	5,8 10,0	0 —
6,7-Dimethyl-(XVb)	8,40	208 245 327 215 236 272 348 [365]	4,27 3,93 4,01 4,20 4,13 4,10 3,86 [3,79]	6,0 11,0	0 —
1,6,7-Trimethyl- (XVc)	9,21	[225] 250 333 246 280 340	[4,28] 3,97 3,98 4,27 3,45 4,05	5,0 11,0	0 —
3,6,7-Trimethyl- (XVd)	8,52	232 328 245 271 360	4,21 4,03 4,25 4,06 3,87	5,0 11,0	0 —
1,3,6,7-Tetramethyl- (XVe)		237 [253] 333	4,16 [3,92] 3,92	CH_3OH	0
7-tert-Butyl-3-methyl- (XVf)	8,50	228 323 244 270 358	4,16 4,02 4,29 3,95 3,88	5,0 11,0	0 —
6-Phenyl- (XVg)	7,93	272 356 293 373	4,35 4,00 4,37 3,93	5,0 11,0	0 —
3-Methyl-6-phenyl- (XVh)	8,40	[245] 273 354 252 294 383	[4,17] 4,32 4,01 4,14 4,38 3,96	5,0 11,0	0 —
1,3-Dimethyl-6-phenyl- (XVi)		[252] 278 357	[4,16] 4,33 3,94	CH_3OH	0
7-Phenyl- (XVj)	8,05	222 [270] 349 230 273 365	4,33 [3,82] 4,32 4,30 4,23 4,09	5,0 11,0	0 —
3-Methyl-7-phenyl- (XVk)	7,99	223 [272] 349 233 272 376	4,37 [3,85] 4,32 4,34 4,28 4,07	5,0 11,0	0 —
1,3-Dimethyl-7-phenyl- (XVl)		229 [255] 278 357	4,33 [3,95] 3,92 4,24	CH_3OH	0
1,6,7-Trimethyl-5-oxido- (XVIc)	8,51	238 287 349 244 289 353	4,40 3,71 3,84 4,38 3,83 3,88	6,0 11,0	0 —

1,3,6,7-Tetramethyl-5-oxido- (XVIe)	−2,67		247 241	287		353 351		4,22 4,45	3,87		3,85 3,83	−4,9 7,0	+ 0
7-tert-Butyl-3-methyl-5-oxide-(XVIf)	7,44	224	235 253	286 [270]	[295]	342 376	4,28	4,41 4,40	3,93 [4,24]	[3,76]	3,86 3,75	4,0 10,0	0 —
1,3-Dimethyl-6-phenyl-5-oxido- (XVIi)			252	274		367		4,40	4,37		3,87	CH_3OH	0
7-Phenyl-5-oxido- (XVIj)	7,19	229	253 256	274	296 [300]	370 385	4,26	4,41 4,45	4,47	4,07 [4,07]	4,20 3,93	4,0 10,0	0 —
3-Methyl-7-phenyl-5-oxido- (XVIk)	7,08	228	252 256	273	296 [300]	363 390	4,26	4,38 4,44	4,49	4,04 [4,01]	4,19 3,96	4,0 10,0	0 —
1,3-Dimethyl-7-phenyl-5-oxido- (XVII)		205	[243]	259	300	370	4,39	[4,26]	4,43	4,08	4,07	CH_3OH	0
Lumazine 8-oxide (XVIIa)	5,34	234	244 245	270 266	[285]	345 387	4,26	4,27 4,10	3,73 4,23	[3,95]	3,84 3,86	2,0 8,0	0 —
6,7-Dimethyl-8-oxido- (XVIIb)	6,02	239	240	[276] 267	[285]	342 380	4,37	4,13	[3,67] 4,14	[4,10]	3,86 3,89	3,0 9,0	0 —
3,6,7-Trimethyl-8-oxido- (XVIId)	6,15	238 [239]		266	[281]	343 382	4,44 [4,18]		4,33	[3,96]	3,88 3,90	3,0 9,0	0 —
6-Phenyl-8-oxido- (XVIIg)	5,14		[250] 245	282	295	370 405		[4,27] 4,16	4,46	4,49	3,83 3,88	2,0 8,0	0 —
3-Methyl-6-phenyl-8-oxido- (XVIIh)	5,12		[253] 254	280	294	367 403		[4,37] 4,25	4,47	4,47	3,88 3,92	2,0 9,0	0 —
6,7-Dimethyl-5,8-dioxido- (XVIIIb)	4,98		237 250	263 268	312 317	386 407		4,21 4,28	4,37 4,33	3,97 3,91	3,75 3,84	3,0 8,0	0 —
7-Phenyl-5,8-dioxido- (XVIIIj)	4,50		240 265	287 293	[340] [330]	395 418		4,22 4,28	4,40 4,42	[3,82] [3,89]	3,70 3,82	2,0 7,0	0 —
3-Methyl-7-phenyl-5,8-dioxido-(XVIIIk)	4,38		242 263	288 293	[340] [330]	395 422		4,21 4,34	4,47 4,43	[3,84] [3,93]	3,77 3,86	2,0 9,0	0 —

*The characteristics of the inflections are given in parentheses.

†A zero denotes a neutral molecule, a minus sign denotes a monoanion, and a plus sign denotes a cation.

TABLE 2. Chemical Shifts of the Aromatic Protons of 6- and 7-Phenyllumazines and Their N-Oxides

Compounds	δ, ppm (rel. intensity)		Compounds	δ, ppm (rel. intensity)	
	in neutral media	in trifluoroacetic acid		in neutral media	in trifluoroacetic acid
XVg	7,50—7,80 (3)	7,90—8,30 (2)	XVIIj	7,60—7,90 (3)	8,00—8,30 (2)
XVj	7,50—7,80 (3)	8,10—8,35 (2)	XVIIh	7,50—7,70 (3)	8,00—8,20 (2)
XVh	7,50—7,80 (3)	7,90—8,25 (2)	XVIk	7,75—8,05 (3)	8,30—8,55 (2)
XVk	7,40—7,80 (3)	8,00—8,30 (2)	XVIi	7,60—8,00 (5)	
XVi	7,40—7,75 (3)	7,85—8,15 (2)	XVI1	7,60—8,00 (3)	8,20—8,50 (2)
XVl	7,50—7,80 (3)	7,90—8,25 (2)	XVIIIj	7,50—8,10 (5)	
XVIIg	7,40—7,75 (3)	7,85—8,15 (2)	XVIIIk	7,60—8,00 (5)	

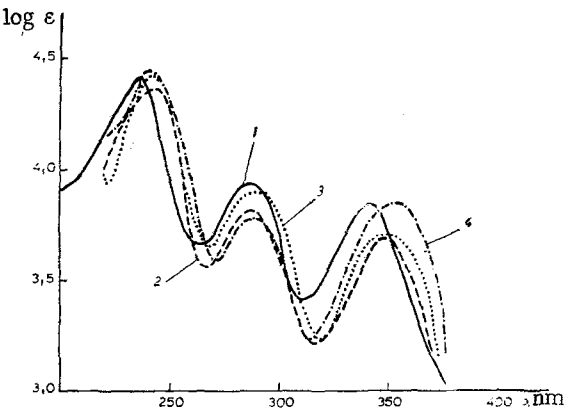


Fig. 1

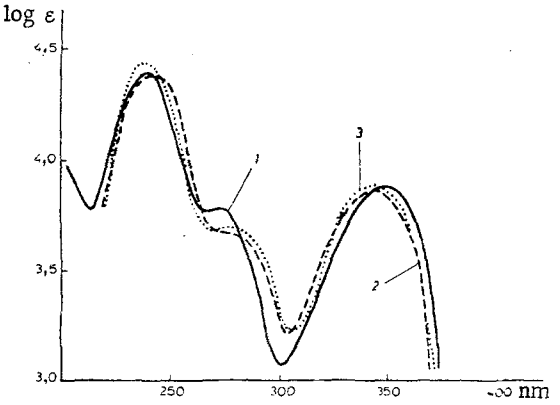
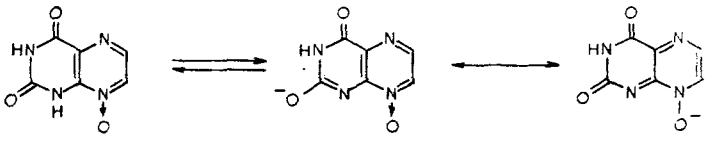


Fig. 2

Fig. 1. UV spectra of neutral 7-tert-butyl-3-methyl- (XVIf) (1, pH 4.0), 1-methyl- (XVIm) (2, pH 5.0), 1,3-dimethyl- (3, pH 5.0), and 1,3,6,7-tetramethyllumazine 5-oxides (XVIe) (4, pH 7.0).

Fig. 2. UV spectra of neutral 3-methyl- (1, pH 2.0), 6,7-dimethyl- (XVIIb) (2, pH 3.0), and 3,6,7-trimethyllumazine 8-oxides (XVIId) (3, pH 3.0).

character to a great degree. This is natural, inasmuch as the N-oxide group in the corresponding anion may manifest a mesomeric effect, while it displays only an inductive effect in the 5-oxides.



Similar conclusions may also be drawn in the case of 1-unsubstituted 6- or 7-phenyllumazine N-oxides. The former (XVIIg, h) are considerably more acidic than the starting XVg,h, and they therefore should be considered to be 8-N-oxides, while the isomeric 7-phenyl derivatives (XVIj-l) have an N-oxide group in the 5 position. Thus, the phenyl ring directs attack of the reagent to the nitrogen atom in the meta position. This sort of orientation is apparently due primarily to steric peculiarities, inasmuch as the adjacent nitrogen atom is shielded because of possible coplanarity of the phenyl and pteridine rings. The coplanarity is confirmed by the characteristic splitting of the signal of the aromatic protons in the PMR spectrum into two-proton multiplets; a broad five-

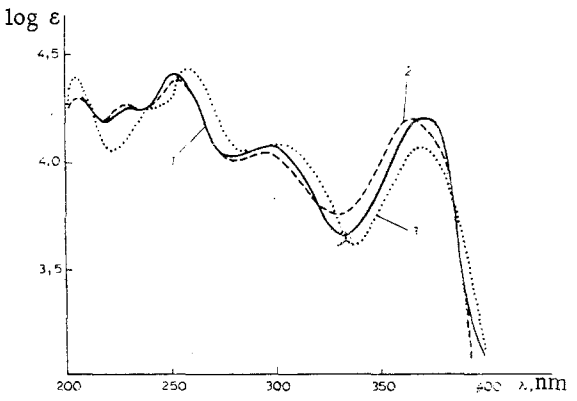


Fig. 3

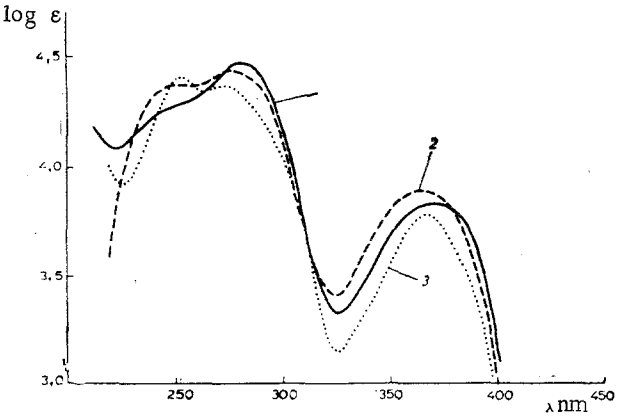


Fig. 4

Fig. 3. UV spectra of neutral 7-phenyl- (XVIj) (1, pH 4.0), 3-methyl-7-phenyl- (XVIk) (2, pH 4.0), and 1,3-dimethyl-7-phenyllumazine 5-oxides (XVIl) (3, methanol).

Fig. 4. UV spectra of neutral 6-phenyl- (XVIIg) (1, pH 2.0) and 3-methyl-6-phenyllumazine 8-oxides (XVIIh) (2, pH 2.0) and 1,3-dimethyl-6-phenyllumazine 5-oxide (XVIi) (3, methanol).

proton signal is observed in the absence of coplanarity (Table 2).

It is natural that the pK values cannot be used for the establishment of the structure of 1-methyl- and 1,3-dimethyllumazine N-oxides, so that the structural proofs in these cases were based on a comparison of the UV spectra. Inasmuch as the spectra of neutral 6,7-H- or 6,7-dialkyl derivatives are similar to the spectrum of 7-tert-butyl-3-methyllumazine 5-oxide (XVIf) (Fig. 1), it can be concluded that all of them have an oxide group in the 5 position and that a substituent in the 1 position hinders reaction in the 8 peri position. The smooth oxidation of 1-methyl-substituted lumazines and the absence of 5,8-dioxides are also in agreement with this. The UV spectra of lumazine 8-oxides are very similar to one another (Fig. 2) and have a characteristic difference from the spectra of the 5-oxides (shoulder at 270 nm).

The spectral differences between the 5- and 8-oxides in the series of 6- or 7-phenyl derivatives are considerably greater because of the mutual effect of the phenyl ring and the heteroring, so that a comparison of the spectra in these cases makes it possible to easily establish the structure of the N-oxide (Figs. 3 and 4).

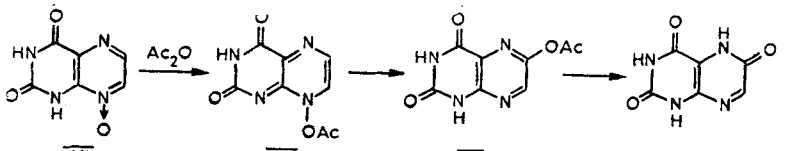
The product of oxidation of 1,3-dimethyl-6-phenyllumazine (XVi) seems of special interest, inasmuch as the reactivities of both N_5 and N_8 (a methyl group in the 1 peri position) are reduced in this case. The different UV spectra of XVIi and XVIIh as well as the absence of splitting of the signal of the aromatic protons in the PMR spectrum (Table 2) may be explained only by the fact that a 5-N-oxide in which the phenyl ring is removed from the plane of the molecule is formed in this case.

The properties of 5,8-dioxides XVIII are characterized by the additive effect of both N-oxide functions, which are reflected both in a decrease in the pK_a value to 4-5 and in intensification of the long-wave absorption at 390 nm.

Still another method for the establishment of the structures of heterocyclic N-oxides is the study of their mass-spectrometric fragmentation, during which the presence of α-alkyl substituents can be detected from the intensity ratio (M-17)/(M-16) > 1 ("ortho effect") [29]. This method was used to establish the structures not only of the lumazine N-oxides under discussion here, but was also used to confirm the correctness of the structure of the 1,3,6-trimethyllumazine 5-oxide obtained in [12].

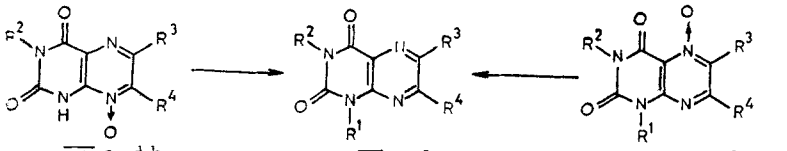
We have found that when the Katada rearrangement [26, 27], which occurs on treatment of various lumazine N-oxides with acetic anhydride, is carried out, the duration of

the reaction varies markedly as a function of the position of the N-oxide function. Lumazine 8-oxide (XVII*a*) is rearranged in good yield to 6-oxo-5, 6-dihydrolumazine (XXI*a*), apparently through a step involving the formation of 8-acetoxy- (XIX) and 6-acetoxylumazine (XX) only after refluxing for 10 h and subsequent saponification in acidic media. At the same time, the reaction with 1-methyl lumazine 5-oxide (XVIm) is complete after 1-2 h, and the intermediate 6-acetoxy-1-methyllumazine (XXIb) can be isolated. Hydrolysis of the latter gives 1-methyl-6-oxo-5,6-dihydrolumazine (XXIc) [30].



XVII a XIX XX XXI a

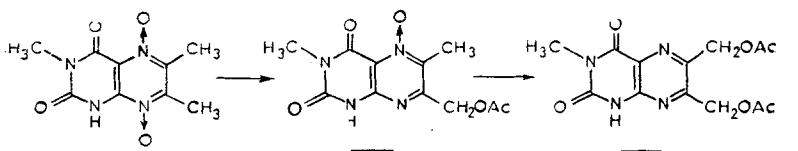
The rearrangement of 7-phenyllumazine 5-oxides XVIk,*l* to the corresponding 6-oxo derivatives XXId, e proceeds just as readily. 3-methyl-6-phenyllumazine 8-oxide (XVIIh) and 1,3-dimethyl-6-phenyllumazine 5-oxide (XVIi), which form 7-oxo isomers XXI*f*,g, behave similarly.



XVII a, d,h XXI a-h XVI c,e,i,k-m

XVI c $R^1=R^3=R^4=CH_3$, $R^2=H$; e $R^1=R^2=R^3=R^4=CH_3$; i $R^1=R^2=CH_3$, $R^3=C_6H_5$, $R^4=H$; k $R^1=R^3=H$, $R^2=CH_3$, $R^4=C_6H_5$; l $R^1=R^2=CH_3$, $R^3=H$, $R^4=C_6H_5$; m $R^1=CH_3$, $R^2=R^3=R^4=H$; XVII a $R^2=R^3=R^4=H$; d $R^2=R^3=R^4=CH_3$; h $R^2=CH_3$, $R^3=C_6H_5$, $R^4=H$; XXI a $R^1=R^2=R^4=H$, $R^3=OH$; b $R^1=CH_3$, $R^2=R^4=H$, $R^3=OAc$; c. $R^1=CH_3$, $R^2=R^4=H$, $R^3=OH$; d $R^1=H$, $R^2=CH_3$, $R^3=OH$, $R^4=C_6H_5$; e $R^1=R^2=CH_3$, $R^3=OH$, $R^4=C_6H_5$; f $R^1=H$, $R^2=CH_3$, $R^3=C_6H_5$, $R^4=OH$; g $R^1=R^2=CH_3$, $R^3=C_6H_5$, $R^4=OH$; h $R^1=H$, $R^2=R^3=CH_3$, $R^4=CH_2OA$

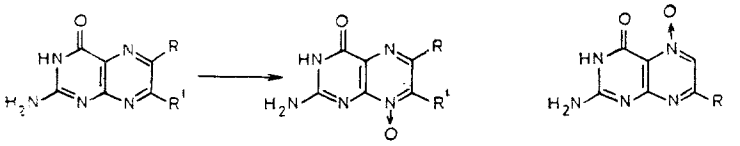
3,6,7-Trimethyllumazine 8-oxide (XVIId) rearranges similarly, probably to 7-acetoxymethyl-3,6-dimethyllumazine (XXIh) [31, 32], while the reaction can be carried out in steps in the case of 5,8-dioxide XXII. After refluxing for 5 min in acetic anhydride, 7-acetoxymethyl-3,6-dimethyllumazine 5-oxide (XXIII), the structure of which is confirmed by the characteristic relatively high pK_a value of 7.20 and the similarity between its UV spectra and the spectra of the 5-oxide, is initially formed. When the reaction is allowed to continue, 6,7-bis(acetoxymethyl)-3-methyllumazine (XXIV) is obtained.



XXII XXIII XXIV

The realization of similar oxidation processes in the pterine and 2,4-diaminopteridine series suggests itself. However, it was found that because of the low solubility of pterines, the reaction is most expediently carried out in trifluoroacetic acid with 30-85% hydrogen peroxide. Other experimental difficulties consisting in the fact that further oxidation of the monoxide and the N,N-dioxide occurs relatively easily in these series, followed by the oxidative destruction of the molecule, were also observed; this usually leads to mixtures of reaction products that are difficult to separate.

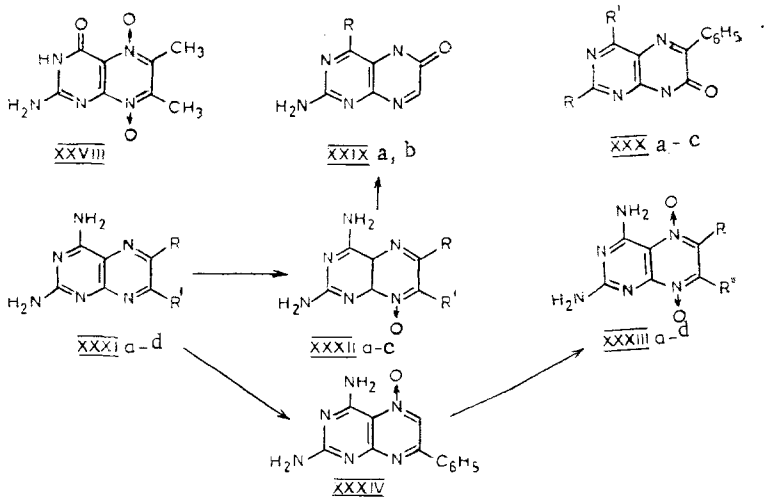
However, if the reaction is carried out under special conditions and with chromatographic monitoring, the process may stop at the step involving the formation of the monoxide or the N,N-dioxide, which are obtained in good yields. Oxidation in the pterine and 2,4-diaminopteridine series proceeds primarily in the 8 position, and N_5 is initially attacked in the 7 position to give oxide XXVII only when sterically demanding substituents of the tert-butyl (XXVe) or phenyl (XXVg) types are present. When a substituent is present in the 1 position, the N_8 peri atom is strongly shielded, just as in the lumazine series, so that 1,6-7-trimethylpterine (XXXV) is oxidized smoothly to 5-oxide XXXVI.



XXV a-g XXVI a-d, f XXVII a, b

XXV, XXVI a R=R′=H; b R=CH_3, R′=H; c R=H, R′=CH_3; d R=R′=CH_3; e R=H, R′=t-C_4H_9; f R=C_6H_5, R′=H; g R=H; R′=C_6H_5; XXVII a R=t-C_4H_9; b R=C_6H_5

In the establishment of the structure of pterine N-monoxides XXVI and XXVII, it was found to be essential that 6-methyl- (XXVIb) and 6-phenylpterine 8-oxide (XXVI*f*) be identical to the preparations obtained by Taylor via an unambiguous path [5-8]. The Katada rearrangement [26, 27] cannot be used in this series as a method of proof of the structures, inasmuch as pterine 8-oxide (XXVI*a*) is rearranged to xanthopterine (XXIX*a*), the 6-oxo isomer, on treatment with acetic anhydride as a result of meta substitution,

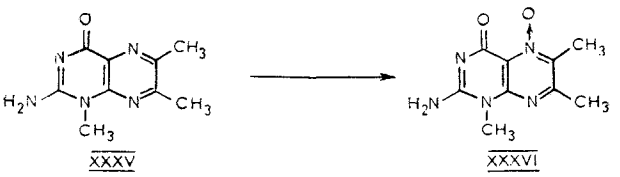


XXVIII XXIX a, b XXX a-c

XXXI a-d XXXII a-c XXXIII a-d

XXXIV

XXIX a R=OH; b R=NH_2; XXX a R=NH_2, R′=OH; b R=R′=NHAc; c R=R′=NH_2; XXXI—XXXIII a R=R′=H; b R=R′=CH_3; c R=C_6H_5, R′=H; d R=H, R′=C_6H_5



XXXV XXXVI

while 6-phenylpterine 8-oxide (XXVI*f*) is rearranged to 6-phenyl-isoxanthopterine (XXX*a*), the "normal" 7-oxo isomer.

On oxidation with hydrogen peroxide, 2,4-diaminopteridine (XXXI*a*) and its 6- and 7-alkyl- or -aryl-substituted derivatives (XXXIb-d) behave exactly like pterines. Hy-

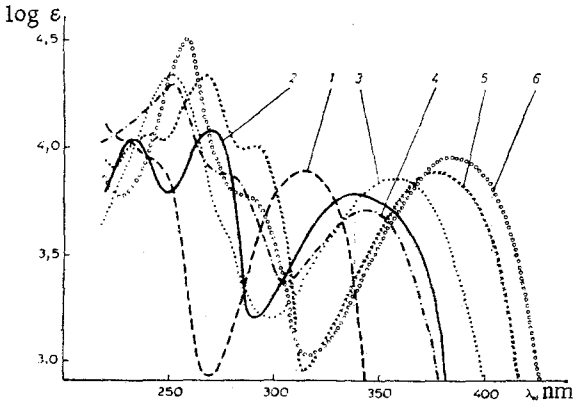


Fig. 5

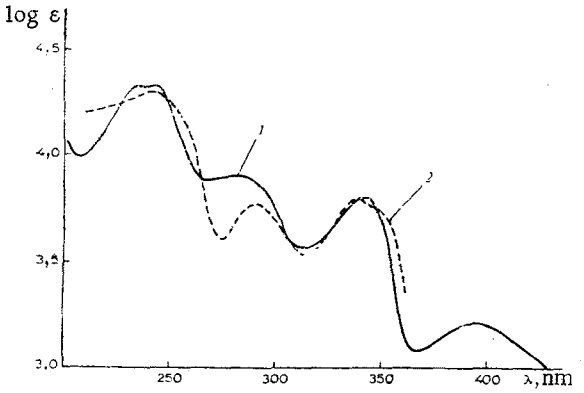


Fig. 6

Fig. 5. UV spectra of cations, neutral molecules, and monoanions of pterine (XXV*a*) (1, pH 0.0; 2 pH 5.0; 3 pH 10) and pterine 8-oxide (XXVI*a*) (4, pH 2.0; 5, pH 4.0; 6, pH 10.0).

Fig. 6. UV spectra of the cationic forms of 7-tert-butylpterine 5-oxide (XXVII*a*) (1, pH 1.0) and 1,6,7-trimethyl-pterine 5-oxide (XXXVI) (2, pH 0.0).

drolysis reactions and several other transformations were used to prove the structures of monoxides and N,N-dioxides XXXII-XXXIV. When N-oxide XXXII*a* is refluxed in acetic anhydride and subsequently subjected to mild alkaline hydrolysis, 2,4-diamino-6-oxo-5,6-dihydropteridine (XXIXb) is formed, while saponification of it with hot 1 N sodium hydroxide solution gives pterine 8-oxide (XXVI*a*) as a result of substitution of the 4-amino group. Compound XXXIIb is converted to oxopteridine XXVId and XXXIV is converted to XXXVIIb in precisely the same way.

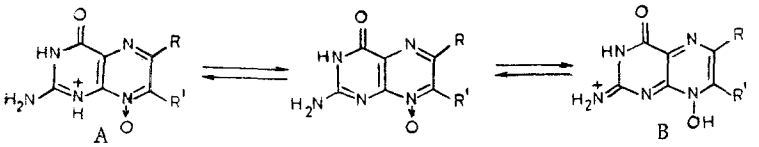
The pK_a values [33] found by spectrophotometry and the UV spectra of solutions of the compounds with different acidities were used for the further characterization of the N-oxides. A comparison of the N-oxides with the starting compounds makes it possible to find a number of interesting characteristic principles that are of general significance for compounds of this type. For example, as expected, the basicity of the system decreases by 1-4 pK units as a function of the position and number of the N-oxide group in the pterine and the 2,4-diaminopteridine series as a result of the formation of N-oxides. Thus in the pterine series the structure may even be established unambiguously, inasmuch as an oxide group in the 8 position, for reasons involving its electronic and steric character, displays a stronger effect as far as lowering the basicity of the N_1 protonation center than an oxide group in the 5 position. In XXVII*a*, the basicity is reduced by 1 pK unit as compared with starting pterine XXVe while in pterine 8-oxide (XXVI*a*) it changes by ~3 units as compared with XXV*a*. Conversion to the 5,8-dioxide leads to a further small reduction in the basicity.

It is interesting that the nature of the substituents in the 6 and 7 position has a strong effect on the NH acidity of the pterines. While a small additive increase in the acidity on passing from monoxides to N,N-dioxides is observed in the case of pterine and 6- or 7-alkyl-substituted derivatives, the effect of a phenyl group in the same position is at least one unit greater.

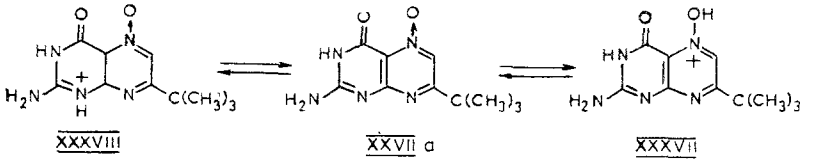
The introduction of an N-oxide group is reflected in the UV spectra as a bathochromic shift of the long-wave band of the starting compound which, depending on the nature of the substituent and its position, is 20-40 nm (Fig. 5).

However, 1,6,7-trimethylpterine 5-oxide (XXXVI) deviates from this series and displays a smaller long-wave shift; this seems completely understandable because of the presence of a substituent in the 1 position and the associated change in the electronic structure as compared with the normal pterine system.

From the fact that a hypsochromic shift of the long-wave band is observed on passing from neutral (XXVIa-d) molecules to the monocations, it can be concluded that protonation occurs at N_1 (A), just as in the starting pteridines, and that partial localization of the π electrons weakens the interaction of the 2-amino group with the system. The appearance of an additional long-wave band of lower intensity at 390 nm is associated with the fact that the second cation form (B), which is formed as a result of protonation of the N-oxide oxygen atom, participates in the equilibrium. The cross-conjugation of the π-electron system that is also observed in a number of the long-wave maxima of 8-substituted pterines and their cations [34] arises in this way.

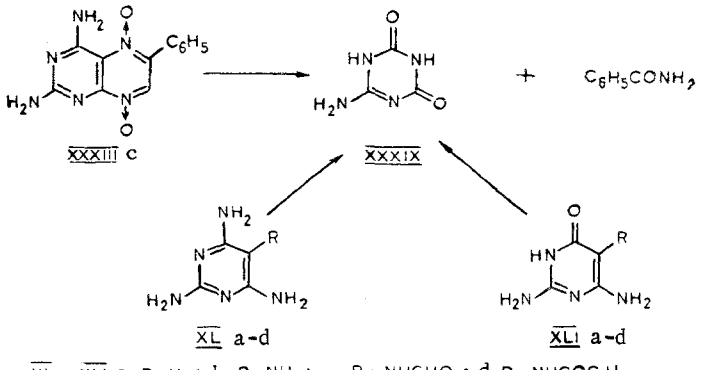


Still another long-wave absorption maximum at 393 nm (Fig. 6), which is due in our opinion, to the presence of a certain amount of 5-o-protonated form XXXVII along with normal cation XXXVIII, is observed in the spectrum of the cationic form of 7-tert-butylpterine 5-oxide (XXVII*a*). The fact that the cation of XXXVI, which is protonated at N_8, has a spectrum similar to the spectra of the cationic forms of oxide (XXVII*a* is evidence in favor of this assumption, inasmuch as it is a structural analog of cation XXXVII. At the same time, quaternization at N_5 is accompanied by a pronounced bathochromic effect. A sharp reduction in the yield was observed in the direct oxidation of 2,4-diamino-6-phenylpteridine (XXXIc) to the corresponding 5,8-dioxide (XXXIIIc) by means of H_2O_2 in formic acid when excess oxidizing agents were used and when the reaction was allowed to proceed for a longer time. It was established by means of chromatography that pteridine XXXIIIc is converted to a mixture of two products, which were identified as 2-amino-4,6-dioxo-3,4,5,6-tetrahydro-sym-triazine (XXXIX) and benzamide.



XXXVIII XXVII a XXXVII

A similar oxidative cleavage of xanthopterine, which upon reaction with hydrogen peroxide also forms the so-called melanuric acid (XXXIX) [35] in addition to leucopterine, is known.



XXXIII c XXXIX + $C_6H_5CONH_2$

XL a-d XLI a-d

XL, XLI a R=H ; b R=NH_2; c R=NHCHO ; d R=$NHCOC_6H_5$

Inasmuch as the key step in this rearrangement, according to the existing concepts, is the formation of a pyrimidine derivative as an intermediate, in order to ascertain the complex mechanism of the process we studied the behavior of various derivatives of 2,4,-6-triamino- (XL) and 2,4-diamino-6-oxodihydropyrimidine (XLI) with respect to hydrogen

TABLE 3. Physical Properties of Pterine and 2,4-Diamino-pteridine N-Oxides

Compound	pK_a (H_2O, 20°)	λ_{max}, nm*						log ε						pH	Molecular characteristics†
Pterine (XXVa)	2,20		[229]	[242]		314			[4,03]	[3,94]		3,89		0,0	+
	7,86		233	270		339			4,04	4,08		3,79		5,0	0
				251		360				4,33		3,85		10,0	—
Pterine 8-oxide (XXVIa)	−0,63			252	[273]	342	[390]			4,29	[3,87]	3,71	[3,19]	−2,0	+
	6,94		242	268	291	376			4,05	4,33	4,01	3,87		4,0	0
				259	[285]	383				4,50	[3,78]	3,95		10,0	—
6-Methylpterine 8-oxide (XXVIb)	−0,05			253	[275]	344	395			4,29	[3,97]	3,74	3,18	−2,0	+
	7,07		241	270	[290]	381			4,05	4,37	[4,08]	3,85		4,0	0
				260	[285]	390				4,50	[3,89]	3,90		10,0	—
7-Methylpterine 8-oxide (XXVIc)	0,03			251	280	332	380			4,38	3,89	3,80	3,15	−2,0	+
	6,94	211	240	268	[290]	365		4,22	4,16	4,45	[3,99]	3,90		3,0	0
				258	[285]	373				4,48	[3,74]	3,94		10,0	—
6,7-Dimethylpterine 8-oxide (XXVId)	0,41			250	[280]	343	390			4,33	[3,88]	3,79	3,19	−2,0	+
	7,24	212	244	270	[287]	370		4,14	4,09	4,42	[4,02]	3,83		3,0	0
		210		259	[283]	378		4,17		4,49	[3,83]	3,93		10,0	—
6,7-Dimethylpterine 5,8-dioxide (XXVIII)	0,22		258	271	310	[355]	394		4,30	4,29	3,84	[3,48]	3,76	−1,0	+
	6,64			272	317	393	[415]			4,39	3,85	3,75	[3,67]	3,0	0
			262	[280]	320	396	[413]		4,42	[4,13]	3,85	3,85	[3,75]	10,0	—
7-tert-Butylpterine (XXVe)	2,54	215	[245]			312		4,32	[3,90]			4,02		0,0	+
	8,54	[215]	[233]	271		338		[4,19]	[4,15]	4,06		3,87		5,0	0
			249	[273]		355			4,33	[3,72]		3,92		11,0	—
7-tert-Butylpterine 5-oxide (XXVIIa)	1,62	[235]	244	283		342	393	[4,32]	4,33	3,90		3,80	3,21	−1,0	+
	7,52	228	250	272	[297]	366		4,30	4,24	4,32	[3,75]	3,74		5,0	0
		223	260		[300]	372		4,27	4,37		[3,74]	3,81		10,0	—
6-Phenylpterine (XXVf)	2,17			275		350				4,35		4,02		0,1	+
	8,22				293	367					4,38	3,96		5,4	0
				271	[295]	379				4,41	[4,16]	4,05		11,3	—
6-Phenylpterine 8-oxide (XXVIf)	−0,54	[213]	248	287		366		[4,13]	4,23	4,44		3,82		−3,0	+
	6,99		243	297		393			4,14	4,51		3,89		4,0	0
				282		402				4,52		3,99		10,0	—

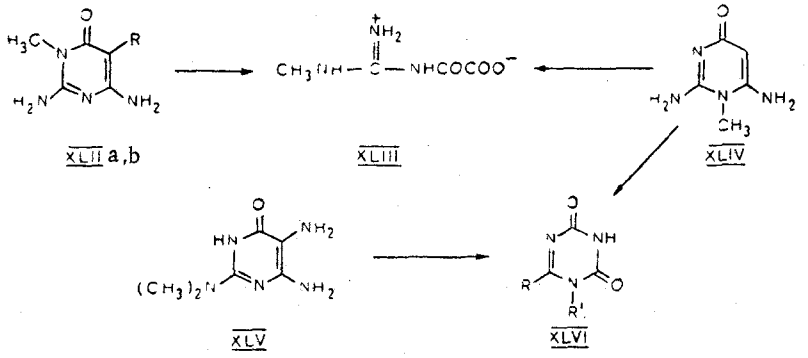
7-Phenylpterine (XXVg)	2,30	225	[255]			348		4,41	[3,91]			4,36		0,1	+
	8,14			275		362				4,24		4,16		5,4	0
			237	264		373			4,32	4,32		4,13		10,4	—
7-Phenylpterine 5-oxide (XXVIIb)	1,35	226	[255]	[277]		348	[395]	4,38	[4,04]	[3,88]		4,32	[3,12]	−1,0	+
	5,21		238	272		365			4,34	4,30		4,13		3,0	0
		220		275		365		4,41		4,42		4,20		8,0	—
1,6,7-Trimethylpterine (XXXV)	3,20	216	253			320		4,30	3,97			4,02		0,0	+
			241			328			4,26			4,06		5,0	0
1,6,7-Trimethylpterine 5-oxide (XXXVI)	−2,95		242		290	337			4,30		3,77	3,80		0,0	+
			242		294	341			4,38		3,90	3,90		5,0	0
2,4-Diaminopteridine (XXXIa)	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
2,4-Diaminopteridine 8-oxide (XXXIIa)	2,17		250	279	351	365			4,55	4,10	4,04	4,00		0,0	+
		[224]	261	[290]		390		[4,09]	4,63	[3,94]		4,07		6,0	0
2,4-Diaminopteridine 5,8-dioxide (XXXIIIa)	1,20	217	258	[292]		383		4,21	4,33	[3,92]		3,88		−1,0	+
		213	266	[283]		378	[390]	4,37	4,53	[4,07]		3,97	[3,94]	4,0	0
2,4-Diamino-6,7-dimethylpteridine (XXXIb)	5,44	[217]	242	277	334	[344]		[4,20]	4,17	3,64	4,08	[4,04]		2,0	+
		230	252	[272]		362		4,14	4,31	[3,82]		3,91		8,0	0
2,4-Diamino-6,7-dimethylpteridine 8-oxide (XXXIIb)	3,04		247	282	346	360			4,53	3,93	3,97	3,92		0,0	+
		213	260	[286]		382		4,20	4,53	[3,86]		3,95		6,0	0
2,4-Diamino-6-7-dimethylpteridine 5,8-dioxide (XXXIIIb)	1,36	219	255			379		4,16	4,35			3,90		−2,0	+
			265			375			4,58			3,94		6,0	0
2,4-Diamino-6-phenylpteridine (XXXIc)	5,07			266		364				4,48		4,11		2,0	+
		216	[234]	276	[302]	388		4,19	[4,02]	4,44	[4,22]	4,04		8,0	0
2,4-Diamino-6-phenylpteridine 8-oxide (XXXIIc)	2,50			274		374				4,46		3,93		0,0	+
				283		407				4,48		3,94		5,0	0
2,4-Diamino-6-phenylpteridine 5,8-dioxide (XXXIIIc)	1,50			273	[294]	385	[420]			4,41	[4,35]	3,84	[3,44]	0,0	+
					291	406					4,52	3,95		5,0	0
2,4-Diamino-7-phenylpteridine (XXXId)	5,36	[227]	252	280	356	[365]		[4,32]	4,05	3,90	4,38	[4,36]		2,0	+
		221	238	265	[305]	380		4,33	4,31	4,32	[3,81]	4,14		9,0	0
2,4-Diamino-7-phenylpteridine 5-oxide (XXXIV)	1,91	221	[235]	275	[305]	371		4,38	[4,34]	4,21	[3,94]	4,24		0,0	+
		224		271		375		4,47		4,43		4,28		5,0	0
2,4-Diamino-7-phenylpteridine 5,8-dioxide (XXXIIId)		[225]		288	[370]	380	[396]	[4,27]		4,60	[3,97]	4,02	[3,99]	CH_3OH	0

*The characteristics of the inflections are given in parentheses.

†A plus sign denotes a monocation, a zero denotes a neutral molecule, and a minus sign denotes a monoanion.

peroxide in formic acid. All of the investigated compounds (XL and XLI) form high yields of triazine XXXIX, regardless of whether there is an amino group in the 5 position. In this connection, the behavior of various N-methyl derivatives was subsequently examined, inasmuch as removal of labile hydrogen atoms might change the direction of the reaction.

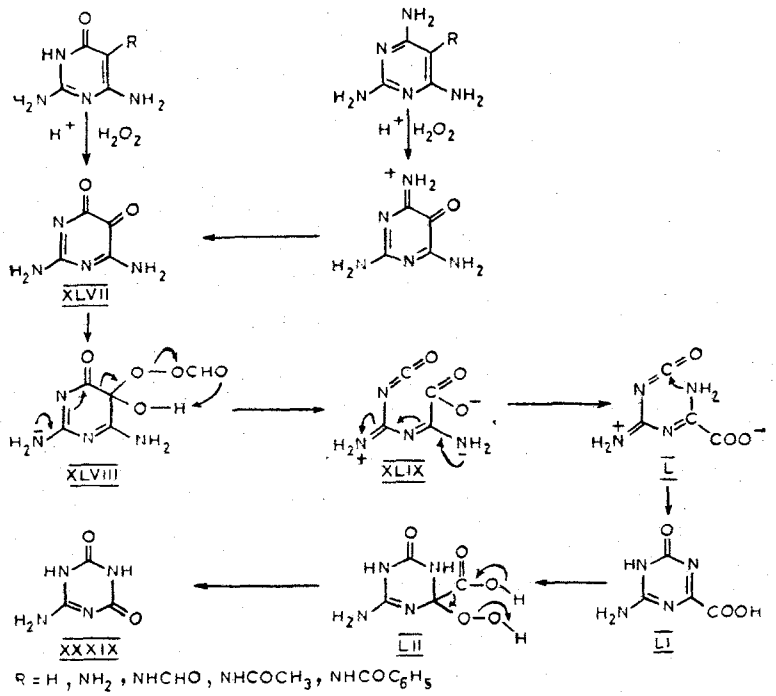
While 4,5-diamino-2-dimethylamino-6-oxo-1,6-dihydropyrimidine (XLV) is converted rapidly in high yield to 2-dimethylamino-4,6-dioxotetrahydro-sym-triazine (XLVI*a*), 2,4-diamino-1-methyl-6-oxodihydropyrimidine (XLII*a*) and its 5-formylamino derivative (XLIIb) is the only isolated product of the reaction with H_2O_2 in formic acid form ω-(methylguanidino)glyoxylic acid (XLIII). On the other hand, the heretofore unknown 2-amino-1-methyl-4,6-dioxotetrahydro-sym-triazine (XLVIb) as a result of rearrangement gives the isomeric (with respect to XLII*a*) 2,4-diamino -3-methyl-6-oxo-dihydropyrimidine (XLIV) along with a small amount of acid XLIII.



XLII a,b — XLIII — XLIV — XLV — XLVI

XLII a R=H; b R=NHCHO, XLVI a R=$(CH_3)_2N$, R'=H, b R=NH_2, R'=CH_3

Consolidation of all of the experimental data makes it possible to propose the following reaction scheme:

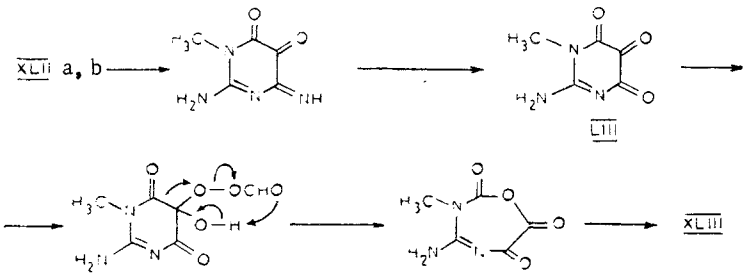


XLVII — XLVIII — XLIX — L — LI — LII — XXXIX

R = H, NH_2, NHCHO, $NHCOCH_3$, $NHCOC_6H_5$

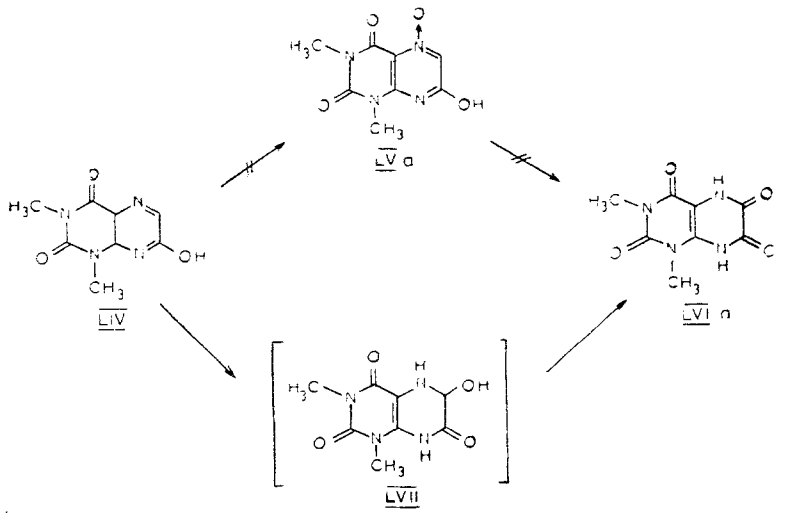
Oxidation initially proceeds in the 5 position to give 2,4-diamino-5,6-dioxodihydropyrimidine (XLVII), to the formally o-quinoid system of which H_2O_2 or peracid adds again. Intermediate XLVIII undergoes the further rearrangement pyrimidine → sym-triaz-

ine, in such a way that the ring is opened initially, and isocyanate XLIX is formed; in the conformer (L) of XLIX the amino group previously in the 4 position reacts to give 2-amino-4-oxo-3,4-dihydro-sym-triazine-6-carboxylic acid (LI). The fact that acid L could not be isolated nor its presence proved is understandable, inasmuch as a strongly electrophilic double bond that is capable of again adding H_2O_2, after which CO_2 and H_2O are split out, is present in the 5,6 position. This mechanism makes it possible to understand why only ring opening rather than rearrangement occurs when the 1 position is blocked. It should be assumed that compounds of the XLII type are initially oxidized to trioxo derivative LIII, after which they are cleaved by hydrogen peroxide or peracids via the Baeyer–Villiger reaction scheme to give acid XLIII.



The formation of triazine XLVIb and a small amount of XLIII in the oxidation of XLIV is explained by the fact that the reaction goes in two directions.

Within the framework of an investigation of the N-oxidation of pteridines, we were also interested in the effect of strong electron-donor substituents in the pyrazine portion of the molecule on the course of the reaction. In order to clear up this problem, we treated various 7-hydroxy, 7-methoxy-, and 7-aminolumazines with hydrogen peroxide under the conditions that we usually employed.



7-Hydroxy-1,3-dimethyllumazine reacts very vigorously with hydrogen peroxide to give, ultimately, products of cleavage of the heteroring. However, when hydrogen peroxide is added slowly to prevent pronounced heating up of the reaction mixture, a high-melting substance that proved to be an isomer (LVI*a*) of the long-known 1,3-dimethyl-6,7-dioxotetrahydrolumazine [36] rather than 5-oxide LV*a*, could be isolated in ~50% yield.

The mechanism of this reaction apparently consists in simple dehydrogenation of covalent hydrate LVII, which is present in very low concentration, and, in this connection, it is not even detected in aqueous media. Initial formation of the 5-N-oxide with subsequent rearrangement should not be considered as an alternative possibility, inas-

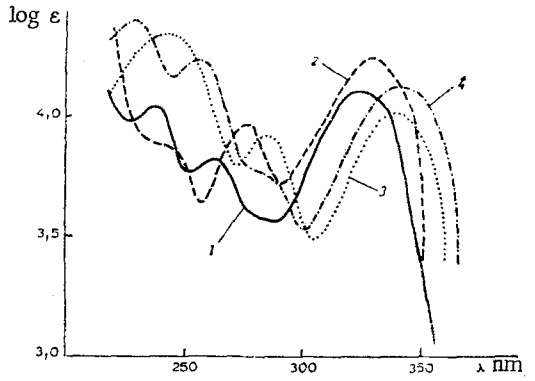


Fig. 7

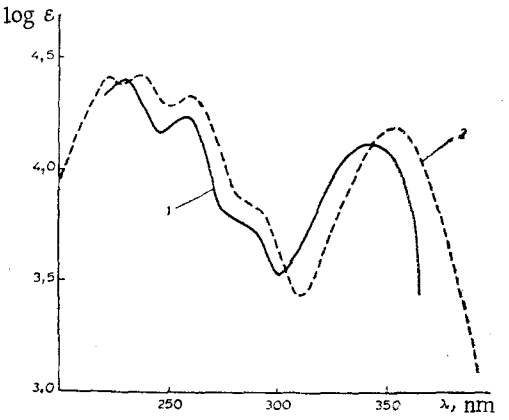


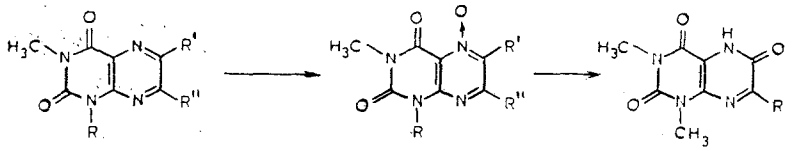
Fig. 8

Fig. 7. UV spectra of neutral molecules and monoanions of LIV*a* (1, pH 1.0; 2, pH 5.7) and LV*a* (3, pH 0.0; 4, pH 6.0).

Fig. 8. UV spectra of the monoanion of LV*a* (1, pH 6.0) and neutral LVg (2, pH 5.5) molecules.

much as 1,3-dimethyl-7-hydroxylumazine 5-oxide (LV*a*) prepared by a different method proved to be stable under the reaction conditions.

It is interesting that 7-methoxy-1,3-dimethyllumazine (LIV*a*) forms only the corresponding 5-oxide LVb during similar oxidation in connection with steric shielding of the 8 position by the substituent in the 1 peri position. 7-Hydroxy-1,3-dimethyllumazine 5-oxide (LV*a*) is formed in 48% yield from this oxide as a result of mild alkaline hydrolysis of the methoxy group.



LIV b-g LV a-g LVI a-d

LIV b R=CH_3, R′=H, R″=OCH_3; c R=R′=CH_3, R″=OH; d R=R′=CH_3, R″=OCH_3; e R=C_6H_5, R′=CH_3, R″=OH; f R=C_6H_5, R′=CH_3, R″=OCH_3; g R=CH_3, R′=H, R″=NH_2; LV a R=CH_3, R′=H, R″=OH; b R=CH_3, R′=H, R″=OCH_3; c R=R′=CH_3, R″=OH; d R=R′=CH_3, R″=OCH_3; e R=C_6H_5, R′=CH_3, R″=OH; f R=C_6H_5, R′=CH_3, R″=OCH_3; g R=R′=CH_3, R″=NH_2; LVI a R=OH; b R=OCH_3; c R=NHAc; d R=NH_2

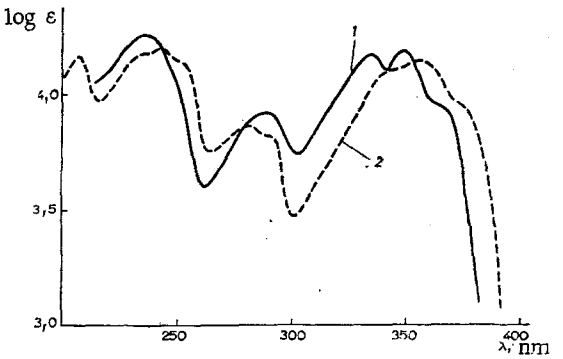


Fig. 9. UV spectra of the monoanion LVI*a* (1, pH 7.0) and neutral LVId (2, pH 3.15) molecules.

It is natural that when a substituent is present in the 6 position, oxidation proceeds normally, such that 7-hydroxylumazines LIVc,e, like the corresponding 7-methoxy derivatives LIVd,*f*, are readily oxidized to 5-oxides LVc-*f* by 85% hydrogen peroxide in trifluoroacetic acid and by 30% hydrogen peroxide in formic acid. 7-Amino-1,3-dimethyllumazine (LIVg) behaves like methoxy derivative LIV*a* and is oxidized by hydrogen peroxide in trifluoroacetic acid to give oxide LVg. However, 1,3-dimethyl-6-7-dioxotetrahydrolumazine (LVI*a*) is formed as a result of rearrangement of the 5-N-oxide to a 6-oxo group during an attempt to saponify the 7-amino group in order to obtain LV*a*. 5-Hy-

TABLE 4. Physical Properties of 7-Substituted Lumazines

Compound	pK_a (H_2O, 20°)	λ_{max}, nm*				log ε				pH	Molecular characteristics†
7-Hydroxy-1,3-dimethyllumazine (LIVa)	3,47	238	263		325	4,04	3,81		4,10	1,0	0
		[240]	277		329	[3,86]	3,96		4,23	5,7	—
7-Methoxy-1,3-dimethyllumazine (LIVb)		239	262		322	4,09	3,84		4,13	5,0	0
7-Hydroxy-1,3,6-trimethyllumazine (LIVc)	3,80		269	284	327		3,82	3,79	4,09	1,5	0
				279	329			3,91	4,23	6,0	—
7-Methoxy-1,3,6-trimethyllumazine (LIVd)		[235]	265		324	[3,98]	3,86		4,07	5,0	0
7-Hydroxy-3,6-dimethyl-1-phenyllumazine (LIVe)	3,86			280	325			4,03	4,11	1,0	0
				278	328			4,01	4,24	6,0	—
7-Methoxy-3,6-dimethyl-1-phenyllumazine (LIVf)		[225]	262		322	[4,16]	4,04		4,08	CH_3OH	0
7-Amino-1,3-dimethyllumazine (LIVg)	−1,05	227	261		365	4,50	4,07		4,17	−3,0	+
		215	247	275	336	4,46	3,84	3,98	4,23	5,0	0
7-Hydroxyl-1,3-dimethyllumazine 5-oxide (LVa)	2,30		243	285	339		4,34	3,91	4,01	0,0	0
		230	257	[280]	342	4,40	4,24	[3,78]	4,12	6,0	—
7-Methoxy-1,3-dimethyllumazine 5-oxide (LVb)			250	287	340		4,39	3,84	3,94	CH_3OH	0
7-Hydroxy-1,3,6-trimethyllumazine 5-oxide (LVc)	2,57		250	284	339		4,25	3,76	4,01	0,0	0
		228	258		337	4,36	4,18		4,13	6,0	—
7-Methoxy-1,3,6-trimethyllumazine 5-oxide (LVd)			246	[287]	342		4,41	[3,72]	3,96	CH_3OH	0
7-Hydroxy-3,6-dimethyl-1-phenyllumazine 5-oxide (LVe)	2,84		252	[285]	334		4,26	[3,83]	3,98	0,0	0
		229	260		337	4,33	4,24		4,12	6,0	—
7-Methoxy-3,6-dimethyl-1-phenyllumazine 5-oxide (LVf)			248	[285]	340		4,35	[3,81]	3,92	CH_3OH	0
7-Amino-1,3-dimethyllumazine 5-oxide (LVg)	−1,59	230	255		353	4,52	3,95		4,18	−4,0	+
		237	261	[288]	354	4,42	4,32	[3,84]	4,18	5,5	0
1,3-Dimethyl-6,7-dioxotetrahydrolumazine (LVIa)	3,63			292	330			4,03	3,98	1,0	0
		235		289	334	4,25		3,92	4,17		
				348	[365]			4,19	[3,95]	7,0	—
7-Amino-1,3-dimethyl-6-oxodihydrolumazine (LVId)	−2,59	224	283	357	[368]	4,19	3,92	3,93	[3,92]	−5,5	+
	8,09	243	[250]	280	342	4,20	[4,15]	3,88	4,09		
				355	[370]			4,14	[3,97]	3,15	0
		238		285	[341]	4,30		3,85	[4,11]		
				353	[367]			4,19	[4,06]	11,0	—

*The characteristics of the inflections are given in parentheses.

†A zero denotes a neutral molecule, a minus sign indicates a monoanion, and a plus sign indicates a monocation.

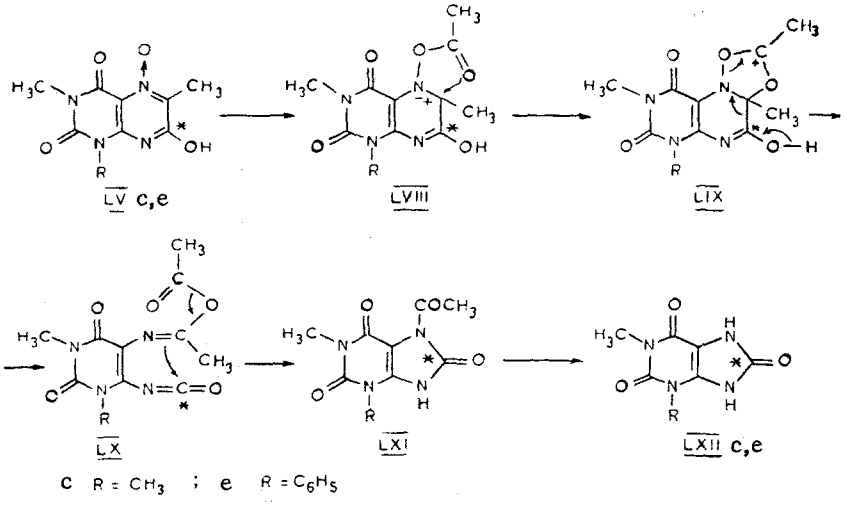
droxide LV*a* reacts similarly to give the same LVI*a* by refluxing with 2 N hydrochloric acid or as a result of a true Katada rearrangement by refluxing with acetic anhydride. In the case of acetic anhydride and N-oxides LVb,g, the reaction proceeds similarly, such that 7-methoxy- (LVIb) and 7-acetamido-1,3-dimethy-6-oxodihydrolumazine (LVIc) were isolated, and LVIc is deacylated to give amine LVId in alkaline media.

The structures of the synthesized compounds are most reliably established by determination of the pK_α values and by means of the UV spectra of solutions with different pH values (Table 4).

A comparison of the physical properties of the 5-N-oxides and the starting compounds shows, as expected, that the acidity of the 7-hydroxy group increases by 1-1.2 pK units when an N-oxide function is introduced, while the long-wave absorption maximum is shifted bathochromically in both neutral molecules and in the monoanions (Fig. 7).

The similarity of the structures of LV*a* and LVg or LVI*a* and LVId is established unambiguously on the basis of the Jones rule [37], i.e., by comparison of the monoanions of the first compound with the neutral 7-amino-substituted lumazines (Figs. 8 and 9).

Intending to obtain 6-methyllumazine 5-oxides by the Kobayashi-Boekelheide rearrangement, we used LVD,*f*, but only starting materials LIVd,*f* are formed when these compounds are refluxed in acetic anhydride as a result of removal of the oxide group. The corresponding 7-hydroxy-6-methyllumazine 5-oxides (LVc,e), on the other hand, react quite unusually, and the disappearance of the fluorescence characteristic for pteridines indicates profound rearrangement of the skeleton. The reaction products were identified as 1,3-dimethyl- (LXIIc) and 1-methyl-3-phenyluric acid (LXIIe). The mechanism of this ring contraction was ascertained by means of labeled atoms. Radioactive uric acid LXIIc is formed only when there is a ^{14}C label in the 7 position of 5-oxide LVc, while 6-^{14}C derivative LVc or unlabeled LVc react with 1-^{14}C-acetic anhydride to give a nonradioactive purine derivative. The mechanism that best satisfies the experimental data consists in acetylation of the N-oxide to give LVIII, which, by Grob rearrangement through a step involving LIX, is converted to isocyanate LX, which then cyclizes to 7-acetyluric acid derivative LXI. Saponification of the latter gives uric acids LXIIc,e.



The results presented here were the subject of detailed publications [38-41] in which all of the experimental details can be found.

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