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ELECTROORGANIC SYNTHESES OF NITROGEN-HETEROCYCLES

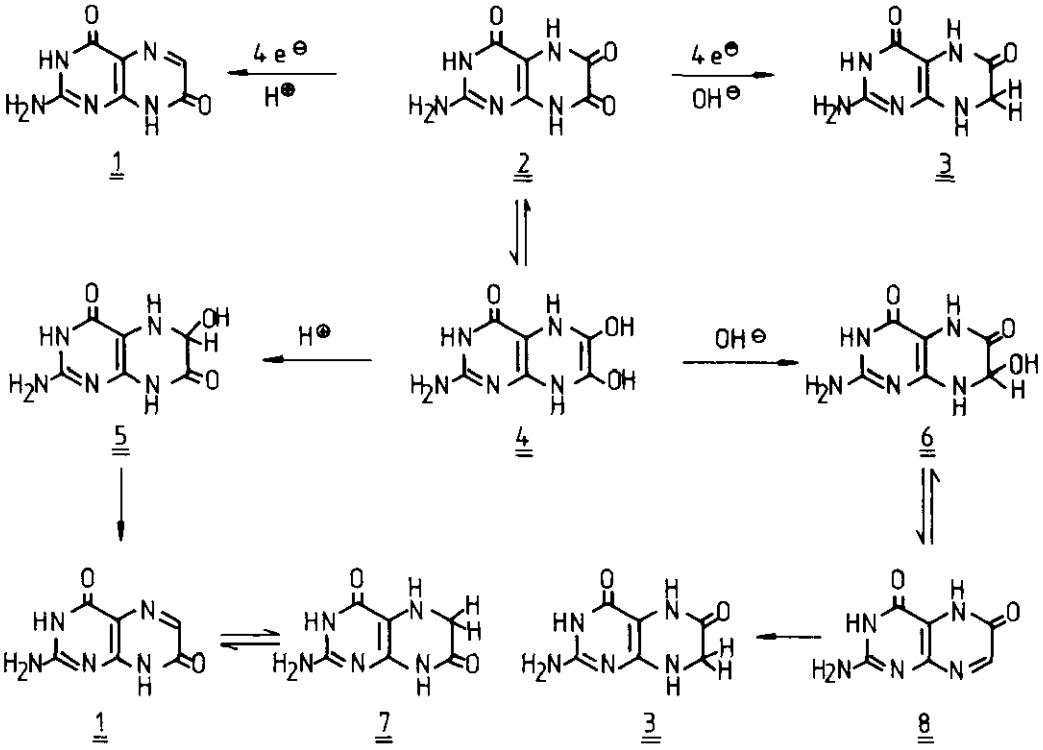
Wolfgang Pfleiderer(*) and Raphael Gottlieb
Fakultät für Chemie, Universität Konstanz
Postfach 5560, D-7750 Konstanz / West Germany

Electroorganic syntheses in the field of nitrogen heterocycles[1] reveal an interesting synthetic alternative to the purely chemical approach due to the fact that new and unexpected structures could be obtained under relatively mild conditions. The most obvious advantage of the electrolytic method is seen in the possibility of controlling over a wide range the activity of the reagent, the electron, by proper choice of the electrode potential. Another advantage includes the transfer of electrons at low temperature and a chosen pH, so that temperature- and acid- or base-sensitive compounds, such as many biologically active molecules, can be reduced or oxidized under mild and well-defined conditions.

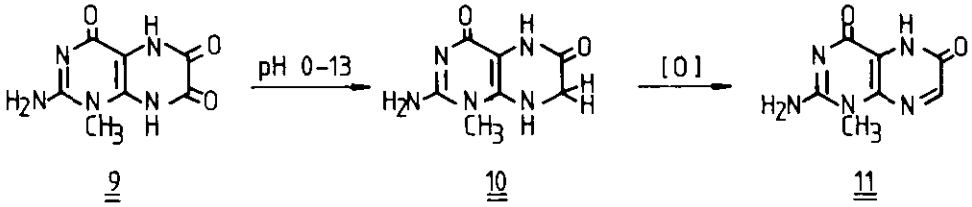
Our interest in electrochemical reductions of nitrogen-heterocycles traces back to the fact that the electrolysis of leucopterin (2) in strong acidic solution lead to isoxanthopterin (1)[2], whereas the chemical reduction with sodium amalgam in basic medium gave 7,8-dihydroxanthopterin (3)[3,4].

Systematic electrochemical studies with leucopterin (2) and its 3- and 8-methyl derivatives over a wide pH-range indicated that there is an interesting pH-dependence of the reduction process leading to an isoxanthopterin derivative at low pH and a xanthopterin derivative at higher pH[5]. Since in both cases 4 electrons are consumed by the substrate we proposed as the important and initial step of a general mechanism a 2-electron up-take of the electrochemically active 6,7-dioxadiene system forming an endiol as the most likely first intermediate (4). This labile compound will then tautomerize according to the pH to two different covalent hydrates 5 and 6 which after loss of one mol of water to isoxanthopterin (1) and xanthopterin (8) will immediately be further reduced to the corresponding 5,6-(7) and 7,8-dihydro derivatives (3) respectively. On work-up the easily oxidizable 5,6-dihydroisoxanthopterins are converted to the quasi-aromatic analogs

whereas the more stable 7,8-dihydroxanthopterins could be isolated directly in this reduction stage.

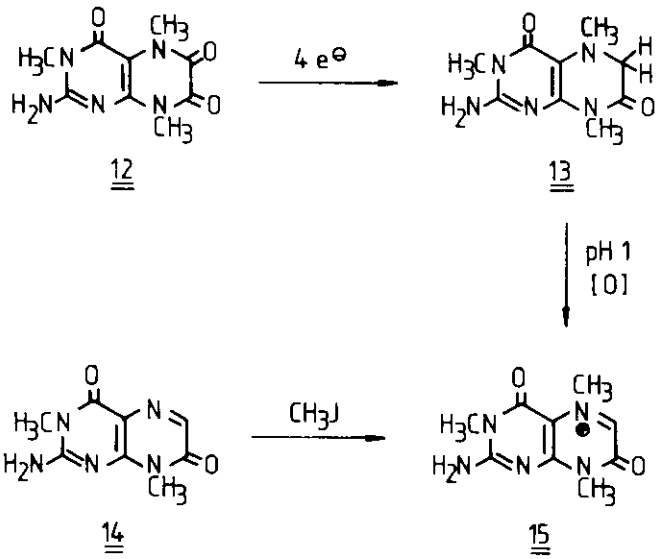


In order to prove the generality of this reaction 1-methyl-(9) and 3,5,8-trimethylleucopterin (12) have been treated analogously. Whereas 9 showed between pH 0 and 13 only one reaction product, 1-methyl-7,8-dihydroxanthopterin (10),



12 *did react solely to the other isomer* 3,5,8-trimethyl-5,6-dihydroisoxanthopterin (13) indicating that additional factors control the reaction pathways.

The structure of 10 was proven by oxidation to 1-methylxanthopterin (11) and 13 showed an easy air oxidation in acidic medium to the 3,5,8-trimethylisoxanthopteridinium cation (15) which was also obtained by quaternization of 3,8-dimethylisoxanthopterin (14) by methyl iodide showing a characteristic long wave absorption band at about 380 nm.



12 13 14 15

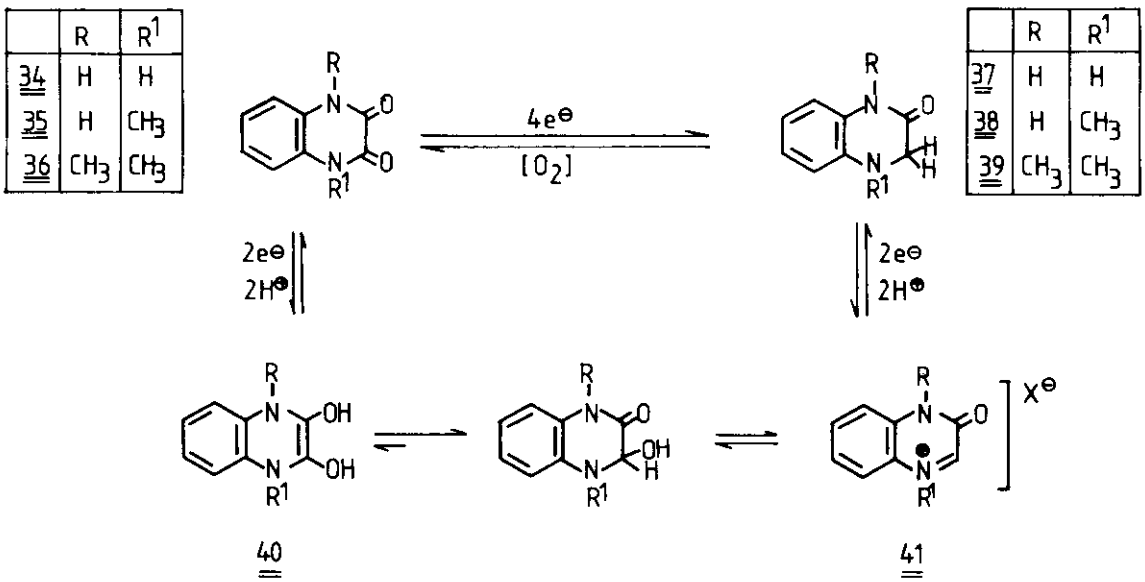
Further electrochemical reductions of various 2- and 4-substituted 6,7-dioxo-5,6,7,8-tetrahydropteridines (16-20)[6] revealed that the leucopterin case seems to be the exception in this series what the pH-dependence is concerned, since these compounds react in an identical manner to 7,8-dihydro derivatives (25-29). On presence of an N-8 substituent (21-24) the electrochemical reduction stops

	R	R^1	R^2
16	H	H	H
17	H	OH	H
18	H	OCH_3	H
19	H	NH_2	H
20	NH_2	NH_2	H
21	H	$N(CH_3)_2$	CH_3
22	OH	CH_3	CH_3
23	$NHCH_3$	H	CH_3
24	$N(CH_3)_2$	H	C_2H_5

	R	R^1	R^2	R^3
25	H	H	H	H
26	H	OH	H	H
27	H	OCH_3	H	H
28	H	NH_2	H	H
29	NH_2	NH_2	H	H
30	H	$N(CH_3)_2$	CH_3	OH
31	OH	CH_3	CH_3	OH
32	$NHCH_3$	H	CH_3	OH
33	$N(CH_3)_2$	H	C_2H_5	OH

after a $2e^-$ up-take forming stable pseudo-base-type molecules (30-33) with the hydroxy-function in 7-position.

The more simpler 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline system (34-36) is also reduced in acidic medium to the corresponding 2-oxo-1,2,3,4-tetrahydro derivatives (37-39) whereby the electron consumption is seen in an unusual $4e^-$ reduction wave on polarographic studies[7]. The mechanism of this transformation again will include a 1,2-endiol structure (40) as well as in the N-1 substituted cases a 1-methyl-2-oxo-3,4-dihydroquinoxalinium cation intermediate (41) according to the following scheme:



	R	R^1
34	H	H
35	H	CH_3
36	CH_3	CH_3

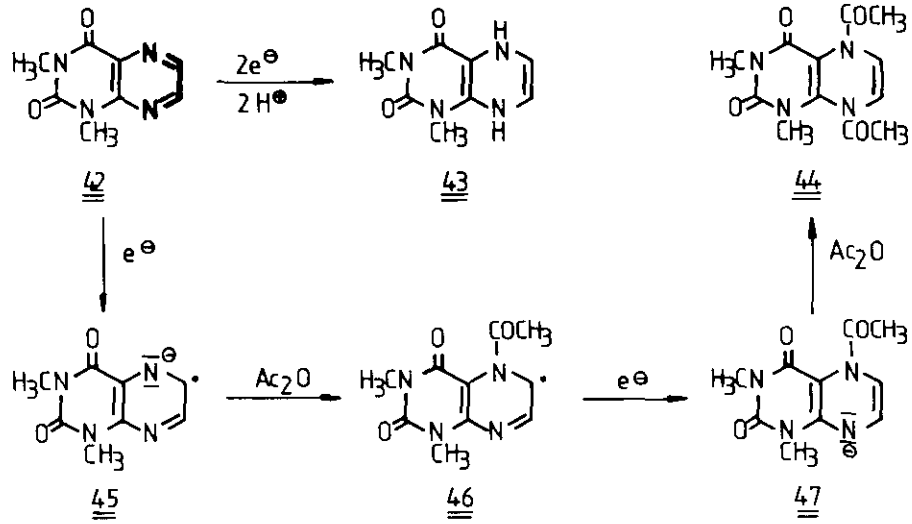
	R	R^1
37	H	H
38	H	CH_3
39	CH_3	CH_3

On air oxidation 38 and 39 are converted back to the starting materials 35 and 36 respectively via an intermediate quinoxalinium cation formation as noticed from the time-dependent changes of the UV-spectra[7].

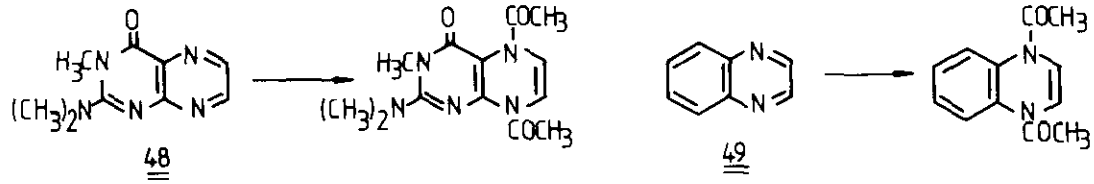
The above presented heterocyclic compounds have in common that the electroactive part in these di-amides are bounded by the adjacent carbonyl functions representing an 1,4-dioxadiene system. Extension of these findings to other 1,4-diheterodiene combinations in particular in the pteridine field offers therefore an interesting principle for a broad variety of potentially electrochemically active pteridine derivatives prone to cathodic reductions.

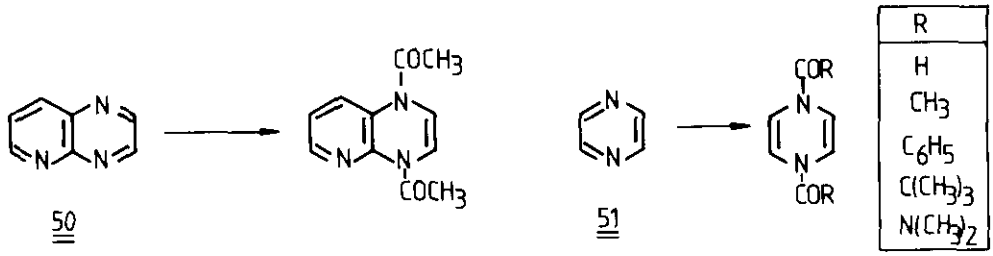
The electroactive part in 1,3-dimethyllumazine (42) is localized in the pyrazine moiety of the molecule revealing a 1,4-diazadiene system which is conver-

ted by a $2e^-/2H^+$ reduction step into the corresponding 5,8-dihydro derivative (43). This form is thermodynamically unstable due to the antiaromatic 8π -character and could therefore not be isolated. The formation of the 5,8-dihydropteridine structure as an intermediate was proven however by trapping experiments with acetic anhydride yielding 5,8-diacetyl-1,3-dimethyl-5,8-dihydrolumazine (44), the constitution of which has unequivocally been elucidated by an X-ray analysis[8].



The initial step in such an electrochemical reduction is in principle a one-electron transfer giving rise to a radical anion (45) which could be detected in the present case by ESR during electrolysis in dry DMF with tetra-n-butylammonium iodide as electrolyte. 45 is a strong nucleophile reacting with acetic anhydride to 46 which will accept another electron to the en-amide anion 47 reacting finally

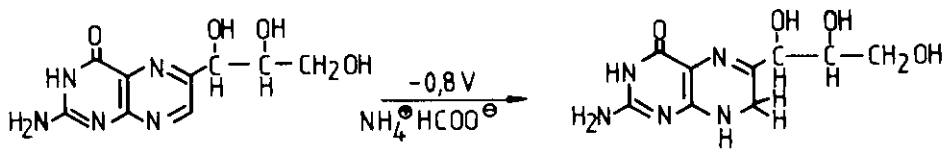




to the reaction product 44.

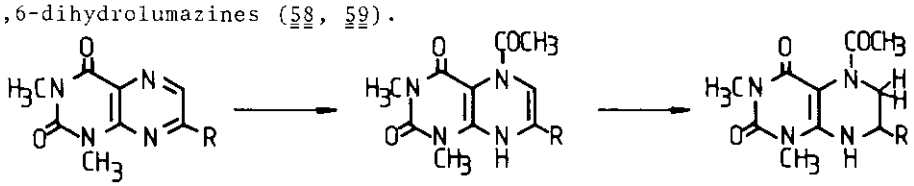
The electrochemical reductive acylation process could be applied also to pterins (48) as well as to other 1,4-diazine systems[9,10] such as quinoxalines (49), pyrido-pyrazines (50) and pyrazines (51) forming stable 1,4-diacyl-1,4-dihydro derivatives in high yields.

A practical use of the potential controlled selective reduction can be seen from the conversion of neopterin (52) to 7,8-dihydroneopterin (53) in 55 % yield or from the formation of various 7,8-dihydropterins as intermediates in drosopterin synthesis[11]. The reactions proceed presumably via the 5,8-dihydro derivatives which tautomerize to the thermodynamically more stable 7,8-dihydro isomers.



52 53

Starting from 7-dimethylamino-(54) and 7-hydroxy-1,3-dimethyllumazine (55) respectively the electrochemical reduction in presence of acetic anhydride takes place in a similar manner but forming from steric and electronic reasons only N-5 monoacetyl derivatives (56, 57) which immediately tautomerize to 5-acetyl-5,6-dihydrolumazines (58, 59).



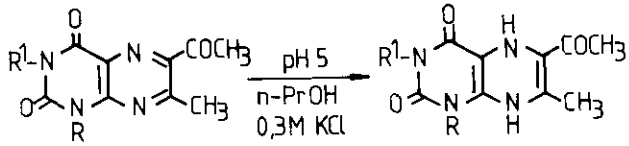
	R
54	$N(CH_3)_2$
55	OH

	R
56	$N(CH_3)_2$
57	OH

	R
58	$N(CH_3)_2$
59	OH

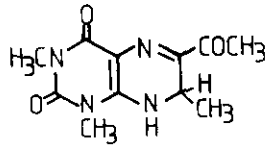
An extension of the partial reductions to 6-acyllumazines offers a series of additional possibilities due to the potentially selective reactivity of the built-in electroactive 1,4-diaza- and 1,4-oxazadiene system respectively in these molecules. 6-Acetyl-7-methyllumazines (60-62) are electrochemically reduced at pH 5 in n-propanol/0.3 M KCl solution to the corresponding 5,8-dihydro derivatives (63-65) which are stable enough under anaerobic conditions to be isolated due to the fact that the 6-acyl group counteracts the 8π -system by its electro-attrac-

ting power and mesomeric interaction. The long wave absorption band of lox extinction at 480-490 nm is very characteristic for such types of compounds[12] and can be regarded as a structural proof.



	R	R^1
60	CH_3	CH_3
61	CH_3	H
62	H	CH_3

	R	R^1	λ max.
63	CH_3	CH_3	488
64	CH_3	H	488
65	H	CH_3	485



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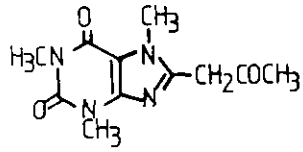

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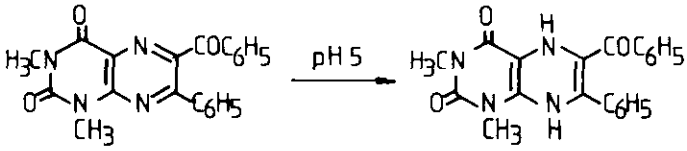
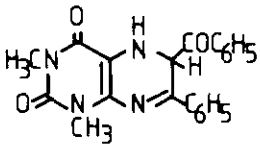
Reduction of 60 in acidic medium (0.5 N HCl/n-propanol) lead to 6-acetyl-1,3,7-trimethyl-7,8-dihydrolumazine (66) may-be by an acid catalysed tautomerism from 63. Reaction of 60 at pH 7 in formamide and in presence of Robinson-Britton-puffer afforded a more severe structural change with a mechanistically unknown ring-contraction to a 8-acetonyl-coffein (67).

Another interesting substrate for electrochemical reductions was found in 6-benzoyl-1,3-dimethyl-7-phenyllumazine (68) which showed a series of reactions depending on the various reaction conditions. At pH 5 again the 5,8-dihydro derivative (69) is formed whereas treatment at pH 8 in DMF and ammonium formiate



68 69



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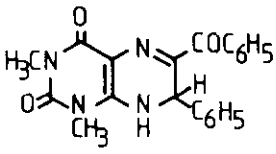

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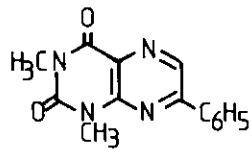
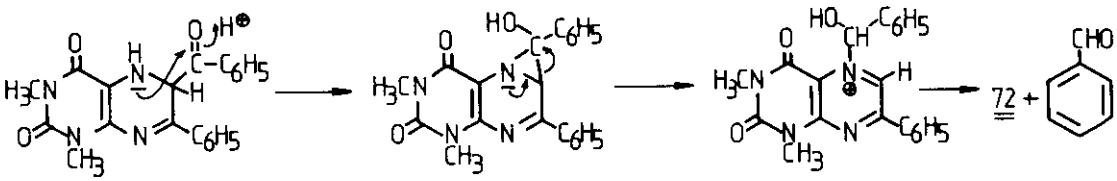


72

solution gave rise to a mixture of 70 % of 6-benzoyl-1,3-dimethyl-7-phenyl-5,6- (70) and 22 % of 7,8-dihydrolumazine (71). If the reduction is performed in n-propanol/0.3 M KCl solution at pH 8 deacylation became the main reaction pathway yielding 73 % of 1,3-dimethyl-7-phenyllumazine (72) besides 15 % of 71.

This unusual deacylation may be based on a homolytic cleavage reaction of a radical intermediate or is derived from the 5,6-dihydro derivative, the conversion of which to 72 and benzaldehyde could spectrophotometrically be followed at pH 1 under anaerobic conditions favouring the following mechanism:



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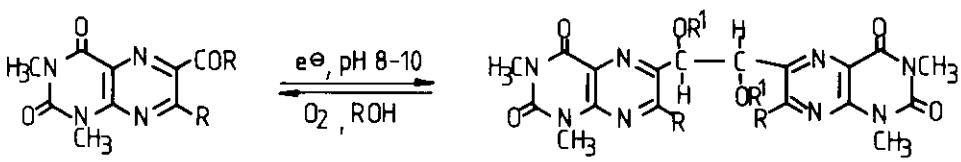
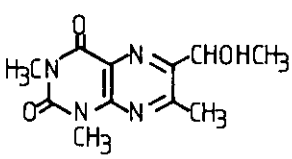
An entirely different reaction pathway took place with 6-acetyl-1,3,7-trimethyllumazine (60) during cathodic reduction in n-propanol/0.3 M KCl solution at pH 8-10 forming the threo-pinacol 73 in an one-electron reduction process and a highly stereospecific dimerization[13-15] in 84 % yield. 73 of which an X-ray



	R
60	CH_3
73	H

	R	R^1
74	CH_3	H
75	H	H
76	CH_3	Ac



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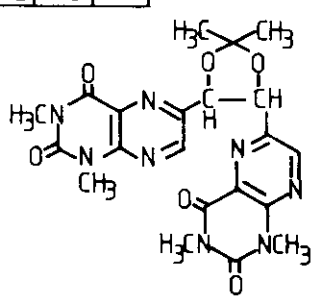

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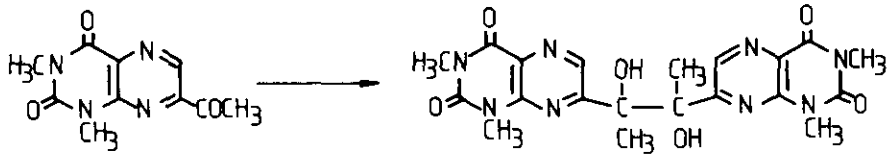
analysis[16] has proven the structure turned out to be a relatively labile compound presumably due to some internal strain by crowding and its abnormal long central C-C-bond of 1.589 Å.

Treatment of 74 in alcohol in presence of oxygen led back to starting material 60 which was furthermore obtained on attempted acetylation with acetic anhydride. Heating above the melting point effected disproportionation of 74 to a 1/1-mixture of 60 and 6-(1-hydroxyethyl)-1,3,7-trimethyllumazine (77).

If 1,3-dimethyllumazine-6-aldehyde (73) is reduced analogously to the pinacol 75 the internal steric strain obviously is minimized to a large extent since 75 turned out to possess normal stability. Acetylation afforded the diacetyl derivative 76 and treatment with 2,2-dimethoxypropane under acid catalysis gave the corresponding isopropylidene derivative 78.

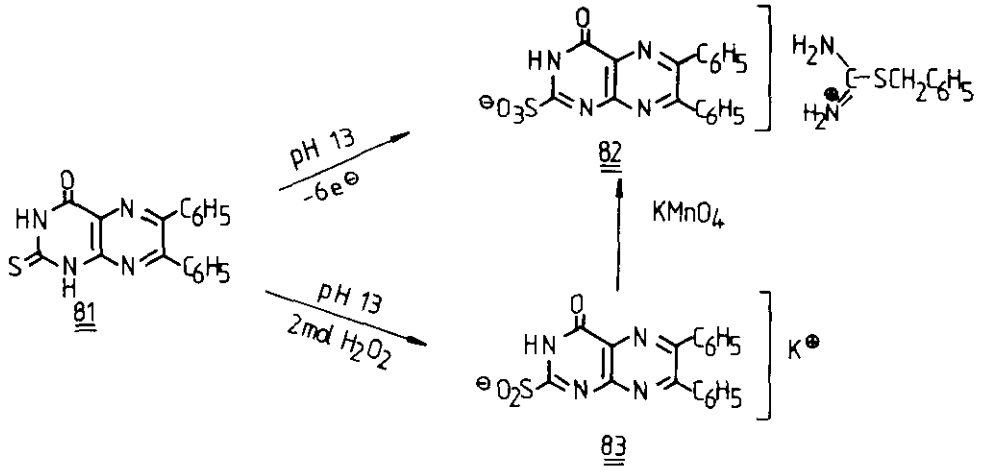
7-Acetyl-1,3-dimethyllumazine (79) however formed another labile pinacol 80 indicating a further crowding effect localized at the alcoholic C-atoms.



79 80

Finally we turned our attention also to anodic oxidation processes and investigated recently the electrochemical behaviour of 2-thiolumazines in basic medium. It was found that 6,7-diphenyl-2-thiolumazine (81) is anodically oxidized in a $6e^-$-process to 4-oxo-6,7-diphenyl-3,4-dihydropteridine-2-sulfonic acid which has been isolated as a benzylisothiuronium salt (82). The same compound could also chemically be obtained by direct permanganate oxidation or via the corresponding pteridine-2-sulfinic acid (83) a reaction product of 81 on treatment with 2 mol of dilute hydrogen peroxide.

Further experiments in this field will prove whether selective anodic oxidations will directly lead to disulfides, sulfenic, sulfinic, and sulfonic acids respectively, which seem to be valuable synthetic intermediates in pteridine transformations.



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