SYNTHESIS AND PROPERTIES OF UNUSUALLY STABLE, HETEROCYCLIC NITRILIUM-YLIDES

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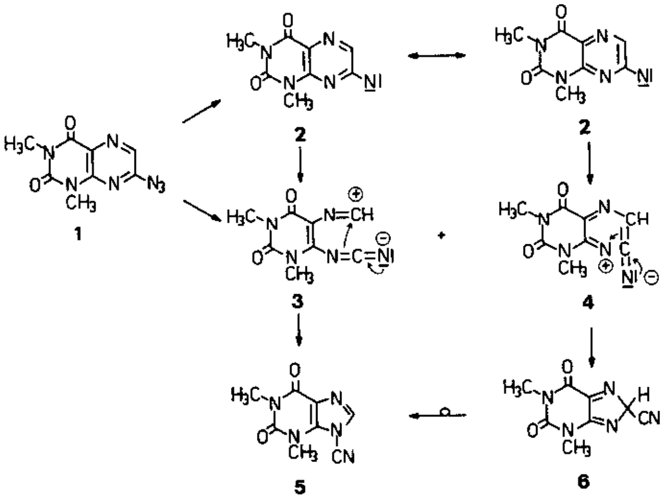
Sir Derek Barton dedicated to his 70th birthday and in admiration of his many important contributions to chemistry.

Abstract - 7-Azido-1,3-disubstituted lumazines show at elevated temperatures two new ring contractions leading to 9-cyanoxanthines and a new type of stable purin-8-yl nitrilium ylides. This high stability is due to a strong resonance stabilization of the negatively charged purinyl anion moiety, which does not even afford a bulky substituent at the nitrilium C-atom to counteract secondary reactions. The structures of the new nitrilium ylides have been proven by spectral means and comparisons with model substances.

The chemistry of nitrilium ylides[1] is under investigation for more than 25 years and revealed numerous syntheses, which generate this reactive function under a variety of conditions[2-5]. It is generally agreed that only in special cases a stable isolable nitrilium ylide can be expected due to the high reactivity of this functionality in 1,3-dipolar cycloaddition reactions and towards nucleophiles. Only recently the synthesis of the first stable nitrilium ylide could be achieved by the photolysis of diazotetrakis(trifluoromethyl)cyclopentadiene in presence of 1-adamantyl nitrile to form 1-adamantyl nitrilium N-tetrakis(trifluoromethyl)cyclopentadienylide[6], which was crystallized and its structure proven unequivocally by X-ray structure determination[7]. This result is not unexpected in view of the anion stabilizing ability of the tetrakis(trifluoromethyl)cyclopentadienylide moiety as well as the steric bulk of the adamantyl residue. The first example of a thermally generated nitrilium ylide is derived from 5-tert.-butyl-3,3-bis(trifluoromethyl)-2,3-dihydro-1,4,λ^5-oxazaphosphol by vacuum flash pyrolysis at 400°/10^{-3} Torr and matrix isolation at -196°C[8].

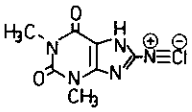
Our interest in nitrilium ylides arose more or less accidentally during studies of various relatively unstable 7-azidolumazine derivatives. We noticed that 7-azido-

1,3-dimethyllumazine (1) converts on drying at 100°C in the oven in a solid state reaction without change of its habitus into a new product, which was identified as 9-cyano-1,3-dimethylxanthine (5). We assume that this new pteridine → purine ring-contraction proceeds either via the intermediary nitrene 2 or directly in a zwittazido cleavage[9,10] to the intermediates 3 and 4 respectively, which cyclize directly to 9-cyano-1,3-dimethylxanthine (5) or via the 8-cyano isomer 6 followed by a 1,5-sigmatropic shift of the functional group.



There are already some precedences in literature of analogous ring contractions of 2-azidopyrazines into N-cyanoimidazoles[11,12].

In a second experiment we heated 1 in xylene and obtained a relatively insoluble material isomeric with 5 according to elemental analysis and the distinct differences of their uv and ir spectra. Treatment of this product in H_2O or n-BuOH led to 8-aminotheophylline indicating that another pyrazine ring contraction has taken place on heating of 1 in an aprotic solvent. From the nmr spectrum in D_6-DMSO can be concluded that the structure of theophyllin-8-yl isocyanide (7) has to be excluded as a sensible possibility due to the presence of a singlet at 8.58 ppm, which is rather a C-H than a N-H signal from its stability in a D_2O exchange experiment. Since heterocyclic azides[13-17] show a broad variety of reactions the structures of a cyclic carbodiimide (8), a condensed 1,3-diazeto[1,2-f]purine derivative (9), a spiro-compound (10) or a resonance stabilized nitrilium ylide (11) cannot a priori be eliminated.



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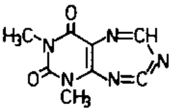

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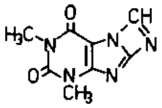

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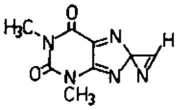

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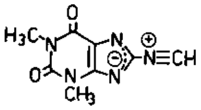

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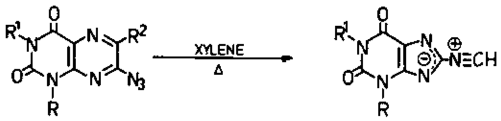
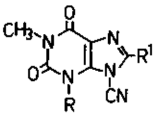
It is obvious that the solution of the difficult structural problem will arise from spectral data and comparisons with model substances. From the ir spectrum, which exhibits a characteristic band at 2180 cm^{-1} we can conclude that the cyclic carbodiimid 8, the tricyclic ring system 9, and the spiro-structure 10 respectively are very much unlikely, whereas the existence of a stable nitrilium ylide (11) is in favour. The uv spectrum in methanol shows two strong bands at 234 and 295 nm and a shoulder at 250 nm, which resembles best with 8-ethinyltheophylline[18] as the closest structural analog (Table). Very similar spectral features are also found for the reaction products derived from 7-azido-1-isopropyl-3-methyllumazine (12) and its 1-neopentyl- (13) and 1-neopentyl-3-n-octyl analog (14) in a similar manner and leading to better soluble nitrilium ylides (18-20). The presence of an additional alkyl substituent in 6-position (15, 16) or the removal of the N-1 substituent (17) does not favour the nitrilium ylide formation but leads to the 9-cyano-xanthines 21-23.



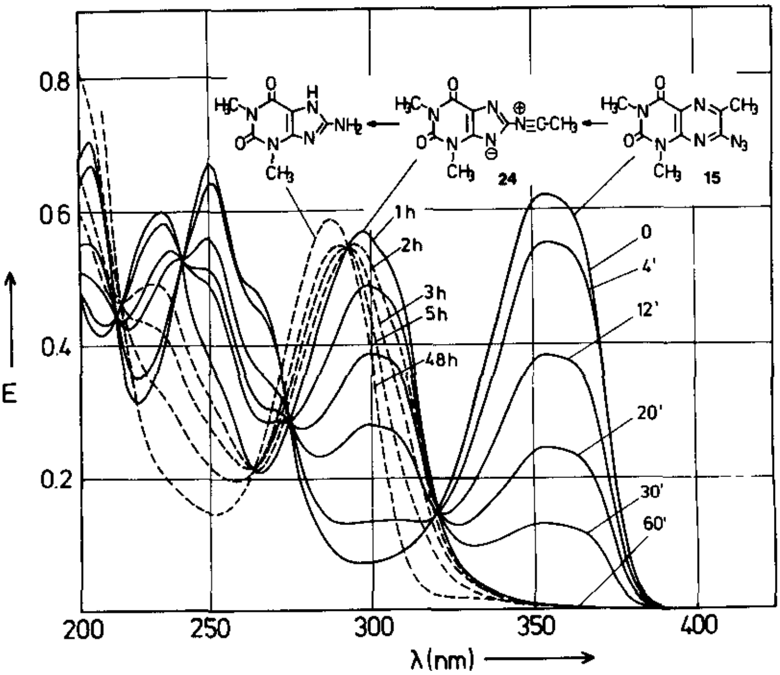
	R	R¹	R²
12	$CH(CH_3)_2$	CH_3	H
13	$CH_2C(CH_3)_3$	CH_3	H
14	$CH_2C(CH_3)_3$	C_8H_{17}	H
15	CH_3	CH_3	CH_3
16	CH_3	CH_3	$CH(CH_3)_2$
17	H	CH_3	H

	R	R¹
18	$CH(CH_3)_2$	CH_3
19	$CH_2C(CH_3)_3$	CH_3
20	$CH_2C(CH_3)_3$	C_8H_{17}



	R	R¹
21	CH_3	CH_3
22	CH_3	$CH(CH_3)_2$
23	H	H

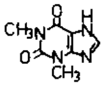
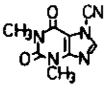
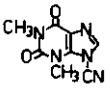
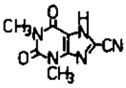
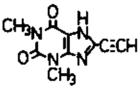
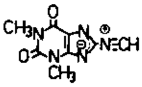
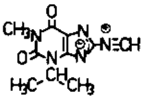
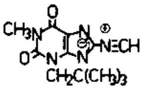
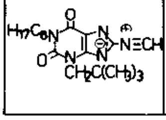
In the case of 7-azido-1,3,6-trimethyllumazine (15) the formation of the corresponding nitrilium ylide (24) could only be detected on photolysis in methanol as an intermediate which is further hydrolysed to give 8-aminotheophylline.



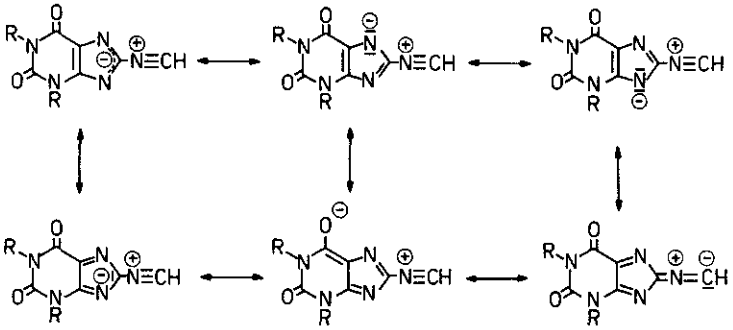
More information was finally obtained from ^{13}C-nmr spectra, which are in excellent agreement with the proposed stable nitrilium ylide structures 11, 18-20.

It was found with the well-soluble nitrilium ylide 20 in a gated decoupling experiment in $CDCl_3$ a ^1H-^{13}C coupling of 246 Hz at 145.5 ppm, which is due to the nitrilium moiety of the molecule proving directly this unusual structure. There was also observed another long-range coupling of 10 Hz of the signal at 109.5 ppm, which has to be assigned logically to the C-8 atom. Comparing the ^{13}C-nmr spectra of the purinium-betaine structures with those of the other xanthine derivatives (table) it is obvious that the different electron distributions in both systems show similarities only at C-6, C-2 and C-4, whereas in the zwitter-ion molecules the chemical shifts of C-5 are moved down-field to some extent and C-8 is altered tremendously up-field indicating a relatively high electron density at this center.

Regarding the mechanism of formation of the nitrilium ylides we assume first cleavage to the intermediate 3, which shows an electrocyclization to 8 followed by a valence tautomerism to 9 and finally ring opening to 11.

	Uv Spectra IN MeOH		Ir	^{13}C-Nmr Spectra IN DMSO-d_6					
	λ_{MAX}	lg ε	cm^{-1}	C-6	C-2	C-4	C-8	C-5	-X≡C-
	270	4.02		154 0	150 9	147 5	139 9	106 1	
	[230] 283	[3.85] 3.84	2258	152.7	150.7	147.3	146.0	103.0	105 8
	245 [260]	4 00 [3.94]	2260	155.7	149 9	137.2	140.0	103.0	114.6
	218 296	4.38 4.12	2220	154 0	150 6	146 5	121.1	110.3	111.4
	222 [246] 294	4.40 [3.63] 4.25	2140	153 7	150 9	147 0	131 8	107 2	84 0 73.5
	234 [250] 295	4 22 [3 95] 4.21	2180	156.9	154 0	148 5	109 4	114 4	146 5
	237 [250] 296	4.19 [3.97] 4.19	2200	156 9	154.9	147 8	109 4	114 2	146 6
	237 [250] 297	4.19 [3.98] 4.19	2190	157 6	154.1	149.1	109 5	114 3	146 8
	238 [250] 297	4 22 [3 98] 4 25	2180	157 7	152 7	148 8	110 1	114 5	145 5

The unusual high thermodynamical stability of the new type of heterocyclic nitrilium ylides is due to a strong resonance stabilization of the negatively charged anion moiety of the molecule. We have isolated with this type of compounds the first case of a stable nitrilium ylide, which does not afford a further bulky substituent at the nitrilium ylide C-atom to counteract secondary reactions.



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