FORMATION OF 1,3-DIMETHYLLUMAZINE-6-ALDOXIME BY A NOVEL CYCLIZATION REACTION

Herbert Fuchs and Wolfgang Pfleiderer*

Fachbereich Chemie, Universität Konstanz

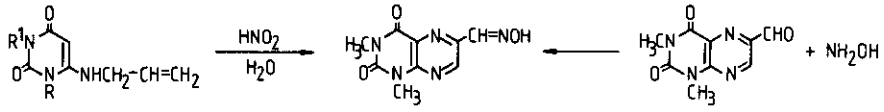
Postfach 7733, D-7750 Konstanz/West Germany

Nitrosation of 6-allylamino-1,3-dimethyluracil (1) in aqueous solution caused a novel ring closure forming 1,3-dimethyllumazine-6-aldoxime (5) whereas the reaction in aprotic solvents led to 8-vinyl-theophylline (11). 1,3-Diphenyl-(2), 1-methyl-(3) and 1-benzyl-6-allylaminouracil (4) react normally with nitrosation at C-5 followed by cyclization on heating to the corresponding 8-vinyl-xanthines 12 - 14.

6-Alkylamino- and 6-arylamino-5-nitrosouracils are an interesting group of compounds due to their high reactivity in cyclization reactions leading to xanthine[1,2,3,4], 7-hydroxy-xanthine[5,6], 8-aminoxanthine[7], 8-H-xanthine[8], 8-H-xanthine-7-oxide[6,8], pyrimido[5.4-e]1,2,5-oxadiazine[6,8], pyrimido[5.4-e]-as-triazine[9,10] and alloxazine[11,12,13] derivatives. Since 1,3-disubstituted 6-alkylamino-5-nitrosouracils are especially reactive intermediates[1,2] we extended our investigations to 1,3-dimethyl-(1)[14] and 1,3-diphenyl-6-allylaminouracil (2) in order to study their

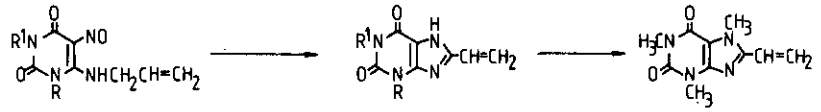
behaviour in nitrosation and cyclization reactions.

During treatment of 1 in water with an excess of sodium nitrite or isoamyl nitrite and acid at room temperature no deep coloration as usually found on nitrosations in this series was observed and neither the corresponding 5-nitroso derivative nor the cyclization product 8-vinyl-theophylline (11) was isolated, but instead a yellowish blue fluorescing compound of the empirical formula of $C_9H_9N_5O_3$ was found according to the mass spectrum. Its structure was concluded from the UV- and NMR-spectra as 1,3-dimethyllumazine-6-aldoxime (5) and could unambiguously be proven by synthesis from 1,3-dimethyllumazine-6-aldehyde (6)[15] and hydroxylamine.



	R	R^1
1	CH_3	CH_3
2	C_6H_5	C_6H_5
3	H	CH_3
4	H	$C_6H_5CH_2$

5 6

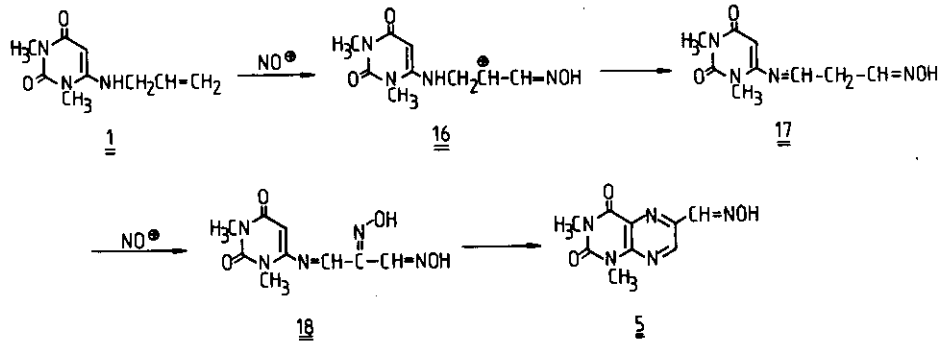


	R	R^1
7	CH_3	CH_3
8	C_6H_5	C_6H_5
9	H	CH_3
10	H	$C_6H_5CH_2$

	R	R^1
11	CH_3	CH_3
12	C_6H_5	C_6H_5
13	H	CH_3
14	H	$C_6H_5CH_2$

15

If the nitrosation of 1 was performed in an aprotic solvent such as ethyl acetate with isoamyl nitrite/p-toluenesulfonic acid on boiling under reflux an intermediary violet colour is noticed for a short time followed by decoloration and separation of a colourless precipitate. This product was identified as 8-vinyl-theophylline (11) by elementary analysis and physical means and led on methylation to 8-vinyl-caffein (15). An attempt to isolate the alleged intermediate 6-allylamino-1,3-dimethyl-5-nitrosouracil (7) has so far been unsuccessful even on working at -70°C in concentrated solution. The different reaction pathways seem to be dependent on the polarity of the reaction medium since nitrosation in methanol and ethanol respectively led to a mixture of 1,3-dimethyllumazine-6-aldoxime (5) and 8-vinyl-theophylline (11).



We therefore propose for the formation of 5 a mechanism which involves in protic polar solvents a primary electrophilic attack at the allyl function (16), 1,2-shift in the side chain to a malondialdehyde derivative (17), which is then again nitrosated at the active methylene group (18) followed by acid catalysed ring closure to 5.

Furthermore the solubility of the 1,3-disubstituted 6-allylaminouracil may also have some influence on the product formation since 6-allylamino-1,3-diphenyluracil (2) did form the red 5-nitroso derivative 8 on nitrosation in water at 0°C in the usual manner. This compound cyclizes easily to 1,3-diphenyl-8-vinylxanthine (12) on heating to 160°C or 15 min. boiling in acetone.

It was also of interest to know whether the terminal vinyl group of the allyl function shows enough activation on the adjacent CH_2-group in the cyclization process if the N-1 substituent is missing, since simple 6-alkylamino-5-nitrosouracils of this type refuse to cyclize[2]. 6-Allylamino-3-methyl-(3) and 6-allylamino-3-benzyluracil (4) respectively have been nitrosated in the usual manner to the corresponding 5-nitroso derivatives 9 and 10 which both on heating in DMF cyclized to 1-methyl-(13) and 1-benzyl-8-vinyl-xanthine (14) respectively in good yields indicating a similar activation by the vinyl group as found earlier with the benzyl substituent[2].

Table - Physical Data of Uracil and Xanthine Derivatives

Reaction	Yield %	mp (°C)	Empirical Formula	Elementary Analysis	C	H	N
2	73	234-236	$C_{19}H_{17}N_3O_2$	Calc.:	71.45	5.37	13.16
				Found:	71.55	5.34	12.67
3	55	252-255	$C_8H_{11}N_3O_2$	Calc.:	53.03	6.12	23.19
				Found:	52.98	5.93	23.74
4	39	234-236	$C_{14}H_{15}N_3O_2$	Calc.:	65.35	5.88	16.33
				Found:	65.73	5.89	16.09
1 → 5	33	280-283	$C_9H_9N_5O_3$	Calc.:	45.96	3.86	29.78
				Found:	45.56	3.87	29.33
6 → 5	70	280-283					
2 → 8	90	310	$C_{19}H_{16}N_4O_3$	Calc.:	65.51	4.63	16.08
				Found:	65.38	4.58	16.05
3 → 9	45	190	$C_8H_{10}N_4O_3$	Calc.:	45.71	4.80	26.66
				Found:	45.66	4.72	26.31
4 → 10	76	162-165	$C_{14}H_{14}N_4O_3$	Calc.:	58.73	4.93	19.57
				Found:	59.03	4.92	19.27
1 → 11	54	340-350	$C_9H_{10}N_4O_2$	Calc.:	52.42	4.89	27.17
				Found:	52.17	4.75	27.56
8 → 12	71	>300	$C_{19}H_{14}N_4O_2$	Calc.:	69.08	4.27	16.96
				Found:	68.73	4.24	16.92
9 → 13	75	>350	$C_8H_8N_4O_2$	Calc.:	49.99	4.20	29.16
				Found:	50.10	4.25	29.10
10 → 14	62	>225 decomp.	$C_{14}H_{12}N_4O_2$	Calc.:	62.68	4.51	20.89
				Found:	62.35	4.56	20.65
14 → 15	85	214-215	$C_{10}H_{12}N_4O_2$	Calc.:	54.54	5.49	25.44
				Found:	54.51	5.21	25.31

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