PYRIMIDINE σ-COMPLEXES. 10.* FIRST FUROXANO[3,4-d]PYRIMIDINE ANION σ-COMPLEXES

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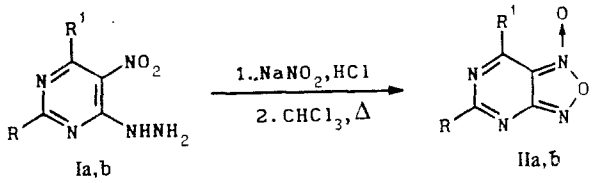
Preparations are reported for anionic σ-complexes derived from 5- and 7-methoxyfuroxano[3,4-d]pyrimidines. The 5-methoxy derivatives add alcohols and water to form covalent σ-adducts.

5-Nitropyrimidine derivatives have sufficient π-electron deficiency for the formation of anionic σ-complexes with stability dependent on the nature of the nucleophile. Thus, anionic Meisenheimer σ-complexes were detected by spectral methods in the reaction of 5-nitropyrimidine and its methoxy derivatives with O- and N-nucleophiles [2, 3], while these complexes were isolated in the case of carbanions [4, 5].

Numerous examples have been reported for the formation of anionic σ-complexes derived from benzofuroxanes [6, 9] and furoxano[3,4-d]pyridine [10]. We thus assumed that fusion of a 1,2,5-oxadiazole ring to a pyrimidine ring would significantly increase the electron deficiency of the pyrimidine ring, which would permit preparation of previously unreported anionic furoxano[3,4-d]pyrimidine σ-complexes. This question was studied in this work.

5-Methoxyfuroxano[3,4-d]pyrimidine (IIa), which had previously not been described, and 7-methoxyfuroxano[3,4-d]pyrimidine (IIb), which has been reported by Binder et al. [11], were used as the starting reagents. These compounds were selected since they encompass the two possible combinations of substituted and unsubstituted pyrimidine ring positions. This permitted us to elucidate which positions are most favorable for nucleophilic attack.

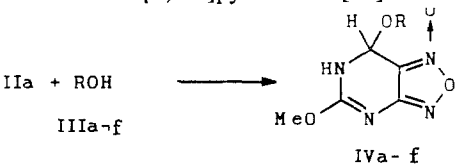
Furoxano[3,4-d]pyrimidines (IIa) and (IIb) were obtained by the diazotization of the corresponding 2- and 4-methoxy-5-nitro-6-hydrazinopyrimidines (Ia) and (Ib).



Ia,b IIa,b

I, II a R=OMe, R'=H; b R=H, R'=OMe

7-Alkoxyfuroxano[3,4,-d]-6,7-dihydropyrimidines (IVa)-(IVf) are formed upon dissolving 5-methoxyfuroxano[3,4-d]pyrimidine (IIa) in primary, secondary, and tertiary alcohols and water. Analogous products of the addition of primary alcohols were described for 5-diethylaminofuroxano[3,4-d]pyrimidine [12].



IVa- f

III, IV a R=Me, bR=Et, c R=Bu, dR=i-Pr, eR=t-Bu, fR=H

*For Communication 9, see [1].

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Chemical formula	T_{mp}, °C	UV spectrum, λ_{max}, nm (log ε)*	PMR spectrum, δ, ppm (coupling constant, J, Hz)**					Yield, %
				5-H,	7-H (J,Hz)	OCH_3, s	NH, br.s	other signals	
IIa	$C_5H_4N_4O_3$	85...87 (dec.)	263 (3,67), 273 301 (3,76), 314 (3,71), 333	—	9,41	4,05	—		32
IIb***	$C_5H_4N_4O_3$	120	244 (3,54), 352 (3,27)	8,59	—	4,10	—		23
IVa	$C_6H_8N_4O_4$	138...140 (dec.)	232 (4,02), 256 (3,95)	—	6,02 br.s	3,86	8,34	3,29 (s, OCH_3)	97
IVb	$C_7H_{10}N_4O_4$	114...115	232 (3,55), 255 (3,49)	—	6,04 (d, J = 3,2)	3,85	8,29	3,59 (q, OCH_2); 1,09 (t, CH_3)	98
IVc	$C_9H_{14}N_4O_4$	Oil	232 (3,94), 256 (3,89)	—	6,07 (d, J = 3,0)	3,88	8,33	3,48 (t, OCH_2); 1,48...1,25 (m CH_2); 0,82 (t, CH_3)	96
IVd	$C_8H_{12}N_4O_4$	Oil	233 (3,73), 256 (3,55)	—	6,07 (d, J = 2,9)	3,84	8,28	4,00 (m, OCH); 1,09 (t, CH_3)	91
IVe	$C_9H_{14}N_4O_4$	Oil	232 (4,02), 256 (3,98)	—	6,23 (d, J = 3,2)	3,83	7,86	1,26 (s CH_3)	91
IVf	$C_4H_6N_4O_4$	144...146 (dec.)	232 (3,91), 256 (3,88)	—	6,15 (d, J = 2,5; $^3J_{H\,OH}$ = 8,8)	3,87	8,75	6,24 (d, OH)	99
V	$C_6H_7N_4NaO_4$	—	353	—	5,81 br.s	3,60	—	3,11 (s, OCH_3)	54
VI	$C_6H_7N_4NaO_4$	—	365	7,39	—	2,98	—		52

*The UV spectra of IIb and IVa-IVf were taken in methanol. The UV spectrum of IIb was taken in methylene chloride, while the UV spectra of V and VI were taken in tetrahydrofuran.

**The PMR spectra of IIa, IIb, and IVa-IVf were taken in acetone-d_6, while the PMR spectra of V and VI were taken in DMSO-d_6.

***Obtained according to Binder [11].

TABLE 2. ^{13}C NMR Spectra of Compounds Synthesized

Compound	Chemical shifts, δ, ppm (in DMSO-d_6)					
	$C_{(5)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	OCH_3	other carbon atoms
IIa	166,39	156,77	105,77	159,93	56,51	
IVa	160,86	75,71 75,48	102,28	158,42	55,11	53,38 (OCH_3)
IVb	160,44	74,22	102,37	158,02	54,82	61,98 (OCH_2); 14,78 (CH_3)
IVc	160,46	74,35	102,23	158,04	54,80	13,37 (CH_3); 38,57, 30,97 (CH_2); 65,86 (OCH_2)
IVd	160,32	73,07	102,80	157,94	54,78	69,87 (OCH); 22,90, 22,17 (CH_3)
IVe	160,38	73,58	102,57	158,15	55,05	83,7 (OC); 34,1 (CH_3)
IVf	160,20	68,59	104,39	158,17	54,77	

Covalent σ-adducts IVa-IVf were isolated as stable, colorless crystalline solids or oils. Prolonged heating of IVa-IVe at reflux in water leads to the formation of IVf as the result of hydrolysis.

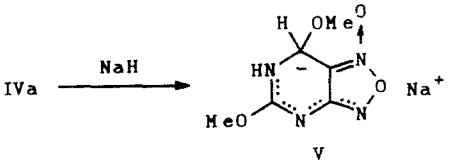
The formation of the ortho-quinoid structure of the pyrimidine fragment in IIa results from the fusion of its 1,2,5-oxadiazole ring. The addition of alcohols and water at the activated double bond is attributed to the presence of a 1,3-azadiene fragment in this compound.

The structures of these compounds were supported by their UV, PMR, and ^{13}C NMR spectra. The PMR spectra for all σ-adducts IVa-IVf have signals for the geminal proton of the pyrimidine ring in the vicinity of 6.0 ppm, signals for the methoxy proton in the vicinity of 3.8 ppm, signals for the NH group in the vicinity of 8.3 ppm, and signals for the hydrocarbon residues of the alkoxyl groups. The significant upfield shift of the geminal proton ($\Delta\delta$ = 3.18-3.39 ppm) in comparison with the signal for the ring proton in starting furoxano[3,4-d]pyrimidine IIa (Table 1) indicates breakdown of the aromaticity of the pyrimidine ring. The existence of σ-adducts IVa-IVf as furoxano[3,4-d]-6,7-dihydropyrimidines is supported by the doublet structure for the signal of the geminal proton (J ~ 3 Hz).

The ^{13}C NMR spectrum of methoxy[3,4-d]pyrimidine IIa (Table 2) corresponds to the parameters given by Terrier et al. [13] for 4,6-dinitrobenzofuroxane and is characterized by three downfield signals for the carbon atoms of the azomethine bonds and the quaternary carbon atom attached to the N-oxide fragment (105.77 ppm). Comparison of the ^{13}C NMR spectra of starting IIa and covalent adducts IVa-IVf shows that the signal for $C_{(7)}$ is shifted upfield upon the formation of these adducts ($\Delta\delta$ = 81.06-88.18 ppm) which indicates a change in the hybridization of this atom from sp^2 to sp^3.

The electronic spectra of σ-adducts IVa-IVf (Table 1) indicate an identical conjugation chain. The absorption maxima of these compounds are shifted bathochromically relative to starting IIa. Thus, the spectral data unequivocally indicate 6,7-dihydropyrimidine structure for IVa-IVf.

The action of sodium hydride on covalent σ-adduct IVa in tetrahydrofuran gives anionic Meisenheimer complex V, which was isolated as an orange crystalline solid with a characteristic metallic shine, which is readily hydrolyzed in the air and decomposes explosively upon trituration.

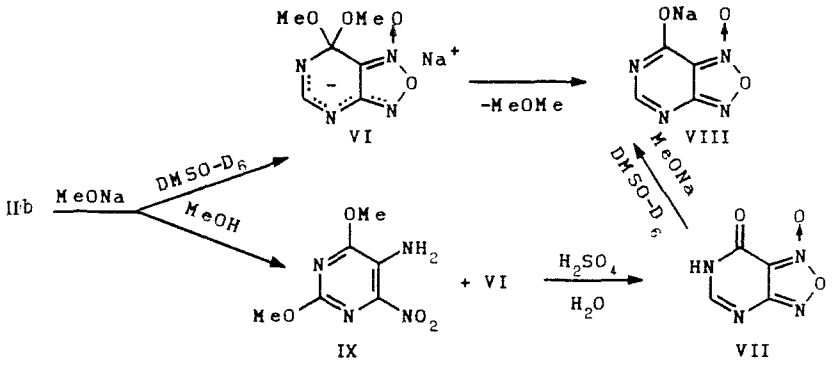


V

The PMR spectrum of σ-complex V shows an upfield shift of the signal for the geminal hydrogen atom ($\Delta\delta$ = 0.2 ppm) in comparison with the analogous signal of the starting σ-adduct, possibly as a consequence of delocalization of electron density in the pyrimidine ring.

The substituent in furoxano[3,4-d]pyrimidine IIb is in the most electron-deficient position of the ring. A gradual disappearance of the signals of the starting compound and appearance of a singlet at 7.39 ppm are observed upon mixing equimolar amounts of IIb and sodium methylate in DMSO-d_6 in an NMR tube. Such an upfield shift ($\Delta\delta$ = 1.20 ppm) of the pyrimidine ring proton indicates breakdown in the aromaticity of the ring and is characteristic for the formation of anionic σ-complex VI. A decrease in the intensity of the signal at 7.39 ppm is observed 55 min after the reaction onset accompanied

by the appearance of a singlet at 7.94 ppm, which becomes the only downfield signal over time. This new singlet is apparently related to the ring proton of salt VIII.



When this reaction is carried out in methanol, anionic hemiacetal σ-complex VI and 5-amino-2,4-dimethoxy-6-nitropyrimidine (IX) were isolated 55 min after mixing the reagents by precipitation upon adding ether. Product IX was described in our previous work [14]. The PMR spectrum of σ-complex VI has two singlets corresponding to the protons of the pyrimidine ring and methoxy groups with 1:6 intensity ratio.

Furoxano[3,4-d]-6,7-dihydropyrimidin-7-one (VII) is formed upon acidification of the aqueous solution of σ-complex VI to pH 2. The structure of VII was in accord with the data of Temple et al. [15]. The conversion of VII into sodium salt VIII indicates that this salt is formed as the result of elimination of dimethyl ether from σ-complex VI in the PMR study of this reaction.

Thus, independently of the position of the substituent in the pyrimidine ring, the attack of the O-nucleophiles is accomplished at the most electron-deficient position of the ring.

EXPERIMENTAL

The UV spectra were taken on an M-40 spectrometer. The NMR spectra were taken on a Bruker WP-200 spectrometer with HMDS as the internal standard. The purity of the compounds was monitored by thin-layer chromatography on Silufol UV-254 plates in chloroform.

The elemental analysis data for IIa and IVa-IVf for C, H, and N correspond to the calculated values.

Hydrazinopyrimidines Ia and Ib and 7-methoxyfuroxano[3,4-d]pyrimidine (IIb) were obtained according to Brown [16, 17] and Binder [11], respectively.

5-Methoxyfuroxano[3,4-d]pyrimidine (IIa, $C_5H_4N_4O_3$). A solution of 2.71 g (39.3 mmoles) sodium nitrite in 15 ml water was added dropwise with stirring to a solution of 4.27 g (23.1 mmoles) hydrazinopyrimidine Ia in 55 ml 0.6 N hydrochloric acid at 0°C. The reaction mixture was maintained for 2 h at 25°C and neutralized by the addition of aqueous $KHCO_3$. The orange solution was extracted with three 100-ml portions of dry, ethanol-free methylene chloride and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was heated in 30 ml dry, ethanol-free chloroform at reflux for 6 h. The residue was crystallized from absolute hexane to give 1.23 g (32%) IIa.

5,7-Dimethoxyfuroxano[3,4-d]-6,7-dihydropyrimidine (IVa, $C_6H_8N_4O_4$). A sample of 1.0 g (5.95 mmoles) IIa was dissolved in 20 ml absolute methanol. After 5 h, the solvent was removed at reduced pressure. The residue was crystallized from benzene.

Covalent σ-adducts IVb-IVf were synthesized analogously.

Anionic σ-Complex V. A solution of 0.4 g (2.0 mmole) σ-adduct IVa in 5 ml tetrahydrofuran was added dropwise with rapid stirring in an argon stream into a suspension of 0.05 g (2.1 mmoles) sodium hydride in 10 ml tetrahydrofuran. Two hours after no further hydrogen was released, the reaction mixture was filtered. The mother liquor was evaporated to 1-2 ml and an orange-red precipitate with a characteristic metallic shine was precipitated by the addition of three 15-ml ether portions.

Reaction of 7-methoxyfuroxano[3,4-d]pyrimidine (IIb) with Sodium Methylate. A sample of 0.13 g (2.41 mmoles) sodium methylate was added with stirring to a suspension of 0.39 g (2.32 mmoles) IIb in 8 ml methanol. After 55 min, the reaction mixture was evaporated to 2 ml and anionic σ-complex VI was precipitated as an orange-red solid by the addition of four 50-ml ether portions. The yield of VI was 0.34 g (52%). Ether was removed from the mother liquor at reduced pressure.

The residue contained 0.04 g (8.7%) 5-amino-2,4-dimethoxy-6-nitropyrimidine (IX), mp 170-171°C (from methanol). This product was identified by comparison with an authentic sample described in our previous work [14].

Acid Hydrolysis of Anionic σ-Complex VI. A solution of 0.34 g (1.53 mmole) σ-complex VI in 3 ml water was treated with stirring with 0.6 N sulfuric acid to pH 2. A white precipitate of VII with the consistency of cottage cheese precipitated out, mp 199-201°C. The yield of VII was 0.15 g (55%). This product was identified by comparison with an authentic sample described by Temple [15].

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