SIGMA COMPLEXES IN THE PYRIMIDINE SERIES. 2.* σ COMPLEXES OF 5-NITROPYRIMIDINE AND METHOXY-SUBSTITUTED 5-NITROPYRIMIDINES WITH THE ACETONE ANION

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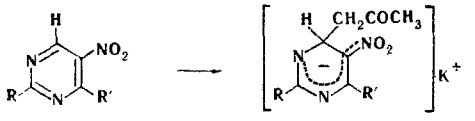
The corresponding σ complexes of the Meisenheimer type, viz., anions of the potassium salts of 6H-5-nitro-6-acetonylpyrimidines, were obtained and isolated in the reaction of 5-nitro-, 5-nitro-4-methoxy-, 5-nitro-2-methoxy-, and 5-nitro-2,4-dimethoxypyrimidines with acetone in the presence of potassium hydroxide. The structures of the complexes were proved by means of the PMR, IR, and UV spectra. It is shown that the acetone anion in all cases adds to the methoxy-unsubstituted position of the pyrimidine ring, whereas nucleophilic attack takes place at the C_4 atom when the 2 and 4 positions are free.

We have previously shown [1] that stable σ complexes are formed in the reaction of 5-nitro-4,6-dimethoxypyrimidine with acetone and acetophenone anions and that nucleophilic attack occurs at the C_2 atom.

In the present research we studied the reaction of 5-nitropyrimidine and methoxy-substituted 5-nitropyrimidines with the acetone anion. The model 5-nitropyrimidines were selected in such a way as to make it possible to ascertain which positions in the pyrimidine ring (methoxy-substituted or methoxy-unsubstituted) are most favorable for nucleophilic attack by the acetone anion. In all cases we obtained and isolated stable σ complexes, viz., the potassium salts (IIa-d) of 6H-5-nitro-5-acetonyl-pyrimidines. The structures of the σ



I a-d IIa-d

I, IIa R=R′=H; b R=H, R′=OCH$_3$; c R=OCH$_3$, R′=H; d R=R′=OCH$_3$

complexes were proved by the PMR, IR, and UV spectra. Absorption in the region of the aromatic protons (7-10 ppm), of a proton attached to a saturated carbon atom (5 ppm), and of protons of methoxy, methylene, and methyl groups (2-5 ppm) is observed in the PMR spectra of all of the σ complexes. The signals in the case of formation of complexes are shifted to strong field as compared with the signals in the spectra of the starting compounds because of disruption of the aromatic character.

Nucleophilic attack on Ia, b may be realized at the 2 or 4 (6) position of the pyrimidine ring; two singlets (each with an intensity of one proton), which are shifted 2.1 and 1.3 ppm to strong field relative to the signals of starting pyrimidine Ia, are observed along with the appearance of a triplet at 5 ppm in the spectrum of σ complex IIa. A 1.8 ppm shift of the proton of the pyrimidine ring to strong field is observed in the case of σ complex IIb.

The signals in the spectrum of complex IIc can be assigned unambiguously, and this makes it possible to make the assignments in the spectra of complexes IIa and IIb and to determine the point of attack by the acetone anion. Nucleophilic attack occurs at the unsubstituted 6 position of the ring in the formation of σ complex IId.

*See [1] for communication 1.

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TABLE 1. PMR Spectra of I and II

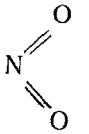
Compound	Solvent	δ, ppm (J, Hz)			
		2-H	4-H	6-H	other signals
Ia	DMSO	9,68 s	9,70 s	9,70 s	—
Ib	The same	9,20 s	—	9,45 s	4,27 s OCH_3
Ic	$CDCl_3$	—	9,62 s	9,62 s	4,46 s OCH_3
Id	The same	—	—	9,35 s	4,32 s 4,39 s, OCH_3
IIa	d_6-DMSO	7,60 s	8,43 s	5,37 t (7)	2,73 d CH_2 (7) 2,33 s CH_3
IIb	The same	7,42 s	—	5,42 t (7)	2,68 d CH_2 (7) 2,30 s CH_3 3,86 s OCH_3
IIc	The same	—	8,52 s	5,25 t (7)	2,71 d CH_2 (7) 2,33 s CH_3 3,68 s OCH_3
IId	The same	—	—	5,36 t (7)	2,79 d CH_2 (7) 2,37 s CH_3 3,71 s 3,93 s OCH_3

Splitting of the central component of the triplet into two symmetrical parts is characteristic for the absorption of the geminal proton (∿5 ppm) in complexes IIa-c. The magnitude of this splitting is ∿3 Hz, which is considerably greater than the constant of spin–spin coupling with the aromatic ring proton [2]. At the same time, the presence of a mixture of complexes that are substituted in the 2 and 4 positions (IIa-b) is excluded as a consequence of the absence of signals of the aromatic proton in the 4 position of the ring and the absence of the complex structure for the long-wave absorption band at 400 nm that is characteristic for the investigated σ complexes (see the information given below).

It is apparent from the data in Table 1 that the nucleophile in all cases adds to the unsubstituted position of the ring, whereas it adds to the more electrophilic C_4 atom when there are free positions (2 and 4 in Ia-b) in the ring, and this leads to a change in its hybridization from sp^2 to sp^3.

An analysis of the frequencies of the absorption bands of the NO_2 group is extremely revealing in the interpretation of the IR spectra of the anionic σ complexes. The position of the frequencies of the symmetrical and symmetrical vibrations of the nitro group is widely known [3, 4]. The high degree of typical character with respect to the frequency for the asymmetrical vibration [5] is also demonstrated from the results of calculations of the frequencies and forms of the normal vibrations, and this makes it possible to compare the frequency of this band with the force constant of the bond and, qualitatively, with its electron population.

Since the formation of a σ complex is accompanied by redistribution of the electron density between the pyridine ring and the nitro group and by delocalization of the electron density, a shift of the corresponding bands to lower frequencies should occur in the IR spectra.

Whereas the maximum shift with respect to the starting nitrobenzenes is observed for the symmetrical vibration of the NO_2 group for the σ complexes of polynitrobenzenes with acetone [6], as is apparent (Table 2) in the formation of complexes from 5-nitropyrimidines, the band of the asymmetrical valence vibrations of the nitro group experiences a greater shift (120-140 cm^{-1}), although the frequency of the symmetrical vibration also undergoes an average shift of 100 cm^{-1}. Considering the high degree of typical character of the asymmetric vibration, one should state that the force constant of the  bonds and, correspondingly, the polarization of the bonds change substantially. An intense band at 1650 cm^{-1}, which was assigned to the stretching vibrations of the C=O bond, also appears in the spectra of the complexes.

Characteristic changes also occur in the electronic spectra of the examined σ complexes (Table 2). A long-wave maximum at 380–450 nm is observed for them. The coefficient of

TABLE 2. IR and UV Spectra of Starting 5-Nitropyrimidines Ia-d and σ Complexes IIa-d

Compound	IR spectrum		UV spectrum	Compound	IR spectrum		UV spectrum,
	$\nu_{NO_2}^{s}$, cm^{-1}	$\nu_{NO_2}^{as}$, cm^{-1}	λ_{max}, nm		$\nu_{NO_2}^{s}$, cm^{-1}	$\nu_{NO_2}^{as}$, cm^{-1}	λ_{max}, nm
Ia	1370	1520	238	IIa	1270	1430	360; 454
Ib	1360	1550	233; 279	IIb	1250	1410	251; 405
Ic	1340	1580	272	IIc	1240	1440	234; 397
Id	1330	1570	254; 285	IId	1280	1450	249; 385

TABLE 3. Results of Elementary Analysis of σ-Complexes IIa-d

Compound	Found, %				Empirical formula	Calc., %				Yield, %
	C	H	K	N		C	H	K	N	
IIa	38,3	4,7	17,4	18,8	$C_7H_8KN_3O_3$	38,0	3,6	17,7	19,0	25
IIb	38,3	4,5	15,2	16,7	$C_8H_{10}KN_3O_4$	38,2	4,0	15,6	16,7	20
IIc	38,3	4,3	15,4	16,4	$C_8H_{10}KN_3O_4$	38,2	4,0	15,6	16,7	68
IId	38,6	4,6	13,7	14,7	$C_9H_{12}KN_3O_5$	38,4	4,3	13,9	14,9	79

extinction of this absorption band is on the order of 10^4 liters-mole^{-1}-cm^{-1}, i.e., it is much larger than for the bands associated with charge transfer in aromatic π-complexes.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane as the external standard. The IR spectra of KBr pellets of the compounds were recorded with a Specord IR-71 spectrometer. The electronic spectra of ∿ 10^{-4} mole/liter solutions of the compounds in methanol were recorded with a Specord UV-vis spectrometer. The starting 5-nitro- (Ia) [7], 5-nitro-2-methoxy- (Ib) [8], and 5-nitro-2,4-dimethoxypyrimidine (Id) [9] were obtained by known methods.

5-Nitro-4-methoxypyrimidine (Ib). This compound was obtained by a modification of the method in [10]. A 2-g (0.012 mole) sample of freshly prepared silver acetate was added with stirring to a suspension of 0.5 g (2.7 mmole) of 5-nitro-4-methoxy-6-hydrazinopyrimidine [10] in 7 ml of water. After 2 h, a small portion of potassium carbonate was added, and the reaction mixture was filtered. The mother liquor was extracted with chloroform (50 ml) and dried over $MgSO_4$. The solvent was removed, and the residue was crystallized from petroleum ether (40-60°C) to give 0.25 g (65%) of white needles with mp 39-40°C (mp 39-40°C [10]).

σ Complexes IIa-d. A 5-mmole sample of ground KOH was added with vigorous stirring to a solution of 5 mmole of 5-nitropyrimidines Ia-d in 40 ml of acetone, and the resulting red solution gradually became deeper red. After 1.5-2 h, 5 mmole of KOH was added, and the mixture was stirred for another hour. It was then filtered, and the mother liquor was concentrated to 5 ml. Complexes IIa-d were precipitated with absolute ether (100 ml) in the form of red crystalline substances with a characteristic metallic luster, which decomposed when they were heated above 200°C. For purification, the reaction products were dissolved in acetone and precipitated by the addition of ether.

LITERATURE CITED

1. V. M. Cherkasov, G. Ya. Remennikov, and E. A. Romanenko, Khim. Geterotsikl. Soedin., No. 10, 1389 (1978).
2. M. Kimura, N. Obi, and M. Kawazai, Chem. Pharm. Bull., 17, 299 (1969).
3. L. Bellamy, Infrared Spectra of Complex Molecules, Methuen, London (1958).
4. A. V. Iogansen and G. D. Litovchenko, Zh. Prikl. Spektrosk., 3, 539 (1965).
5. M. Strauss, Chem. Rev., 70, 667 (1970).
6. É. G. Kaminskaya, S. S. Gitis, and A. Ya. Kaminskii, Zh. Prikl. Spektrosk., 23, 243 (1975).

7. H. C. van der Plas, H. Jogejan, and A. Koudijs, J. Heterocycl. Chem., 15, 485 (1978).
8. D. J. Brown and R. V. Foster, Austr. J. Chem., 19, 2321 (1966).
9. D. M. Besly and A. A. Goldberg, J. Chem. Soc., 4997 (1957).
10. M. E. C. Biffin, D. J. Brown, and T. C. Lee, Austr. J. Chem., 20, 1041 (1967).

CHEMICAL TRANSFORMATIONS OF TRISUBSTITUTED PYRAZOLO[3,4-d]PYRIMIDINES AND THEIR 1-RIBOSIDES

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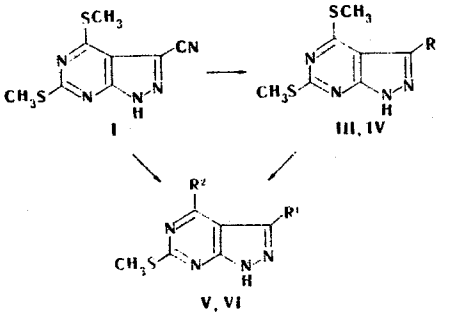
A number of 3,4,6-trisubstituted pyrazolo[3,4-d]pyrimidines and their 1-ribosides were synthesized from 3-cyano-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidine. The cyano group was converted to thiocarbamoyl, imido ester, carboxamidoximno, carboxamidrazono, carboxy, and amidino groups. The 4-methylmercapto group was replaced by mercapto, methoxy, amino, and hydrazino groups. The reactivities of methylmercapto and 3-cyano groups in substituted pyrazolo[3,4-d]pyrimidines and the corresponding nucleosides with respect to nucleophilic agents were compared. The introduction of a ribose residue in the 1 position facilitates nucleophilic addition to the 3-cyano group and replacement of the 4-methylmercapto group. High resistance of the 6-methylmercapto group to the action of nucleophilic agents and higher reactivity of the cyano groups as compared with methylmercapto groups were observed.

In connection with the fact that compounds that have high antitumorigenic activity are found among 3,4-disubstituted pyrazolo[3,4-d]pyrimidines and their 1-ribosides [1], the preparation of various 3,4,6-trisubstituted pyrazolo[3,4-d]pyrimidines and their 1-ribosides seems of interest. We used 3-cyano-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidine (I) and 1-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)3-cyano-4,6-dimethylmercaptopyrazolo[3,4-d] pyrimidine (II), the synthesis of which was developed in [2], as the key compounds in these synthesis.

The chemical conversions of 3-cyano-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidine (I) were accomplished via the scheme:



III $R=CSNH_2$; IV $R=C(=NOH)NH_2$; V $R^1=CSNH_2$, $R^2=NH_2$ (from III); VI $R^1=C(=NH)NHNH_2$, $R^2=NHNH_2$ (from I)

3-Thiocarbamoyl-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidine (III) is formed when hydrogen sulfide is passed through a solution of heterocycle I in ethanol in the presence of triethylamine. 4,6-Dimethylmercaptopyrazolo[3,4-d]pyrimidine-3-carboxylic acid amidoxime (IV) was synthesized by refluxing I with hydroxylamine hydrochloride in ethanol in the presence of triethylamine. Replacement of the 4-methylmercapto group to give 4-hydrazino-6-

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