SIGMA COMPLEXES IN THE PYRIMIDINE SERIES

I. SIGMA COMPLEXES OF 5-NITRO-4,6-DIMETHOXYPYRIMIDINE

WITH ACETONYL AND PHENACYL ANIONS

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Complexes of the Meisenheimer type — potassium salts of 2H-5-nitro-4,6-dimethoxy-2-acetonyl- and 2-phenacylpyrimidines — were obtained for the first time by reaction of 5-nitro-4,6-dimethoxypyrimidine with acetone and acetophenone in the presence of potassium hydroxide. The structures of the complexes were proved by their oxidation to, respectively, 5-nitro-4,6-dimethoxy-2-acetonyl- and 2-phenacylpyrimidines and by means of their PMR and IR spectra.

The formation of σ complexes as intermediates in the pyrimidine series has been described in many cases in studies of nucleophilic substitution reactions [1-5]. Only the reaction of 5-nitro-, 5-nitro-2-methoxy-, and 5-nitro-4-methoxypyrimidines with potassium methoxide has been investigated in order to study the σ complexes [6]. The complexes were not isolated, and their structures were proved by their PMR spectra.

In the present research we obtained and isolated complexes in the reaction of 5-nitro-4,6-dimethoxypyrimidine (I) with acetone and acetophenone in the presence of potassium hydroxide; the complexes were isolated in the form of dark-red, infusible, crystalline substances.

It is known that nucleophilic attack on trinitroanisole by methoxide and ethoxide ions [6, 7] can occur at the carbon atom bonded to the methoxy group and that structures II or III are therefore possible for the σ complexes obtained from I.



II, III a $R = CH_3$; b $R = C_6H_5$

The PMR spectra of the complexes correspond to structure II (Table 1) rather than to III, since in the latter case one should observe a singlet from 2-H that is shifted 1-1.5 ppm relative to the signal of the starting compound to the strong-field region [6], and the nonequivalence of the protons of the OCH₃ groups in the 4 and 6 positions of the ring should be manifested. At the same time, a doublet (2H) and a triplet (1H) are observed in the spectra of the complexes. The considerable shift (more than 3 ppm) of the signal from 2-H to strong field relative to the signal of starting I is associated with a change in the hybridization of the 2-C atom from sp² to sp³. In addition, the equivalence of the methoxy groups in the 4 and 6 positions, which give a singlet (6H), indicates the presence of symmetrical anion II. Thus the reaction of $CH_3COCH_2^-$ and $C_6H_5COCH_2^-$ anions with 5-nitro-4,6-dimethoxypyrimidine (I) takes place in the 2 position.

This is apparently explained by steric factors during attack by the nucleophiles on the 4-C (6-C) atoms bonded to the CH₃O⁻ groups, by disruption of the conjugation of the methoxy

Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev 252660. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1389-1391, October, 1978. Original article submitted July 11, 1977; revision submitted February 27, 1978.

TABLE 1. PMR Spectra of Complexes IIa, b and 5-Nitro-4,6dimethoxypyrimidine (I)

Com- pound	Chemical shifts, ppm			J, HZ	Other signals
	2-H	H(CH₂)	H(CH₃O)	(2·H)- -H(CH ₂)	Ouler signals
I IIa IIb	8,50 (s) 5,16 (t) 5,25 (t)	2,84 (d) 3,31 (d)	3,98 (s) 3,70 (s) 3,65 (s)	6,8 7,2	$C(O) CH_3 2,43$ $C_6H_5 7,8; 8,1$

group with the ring in complexes III, and by the formation of the energetically more favorable symmetrical anion II.

5-Nitro-4,6-dimethoxy-2-acetonyl- and -2-phenacylpyrimidines (IVa, b), respectively, were obtained in the oxidation of complexes IIa, b with ferric chloride in aqueous solutions.



 H_{1} iv a R = CH₃; b R = C₆H₅

The structures of ketones IVa, b are confirmed by the results of elementary analysis, the IR spectral data, and the trend of the change in the PMR spectra (the disappearance of the triplet from 2-H in IIa, b). Complexes IIa, b are hydrolyzed to give starting I.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6 -DMSO (I and IIa, b) and CDCl₃ (IVa, b) were recorded at room temperature with a Tesla BS-487B spectrometer with hexamethyldisiloxane as the external standard. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer.

Potassium Salt (IIa) of the 2H-5-Nitro-4,6-dimethoxy-2-acetonylpyrimidine Anion. A 0.3-g (5.5 mmole) sample of finely ground KOH was added with stirring to a solution of 1 g (5.5 mmole) of I in 40 ml of acetone, during which the solution took on a red coloration that gradually became deeper. After 90 min, 0.15 g of KOH was added to the reaction mix-ture; another 0.15 g of KOH was added after 90 min. After 15 min, the mixture was filtered to remove the KOH, and the filtrate was concentrated to 7 ml. Absolute ether (20-30 ml) was added, and the crystalline red precipitate was removed by filtration, washed with ether (two 30-ml portions), and purified by reprecipitation from acetone. The yield of IIa was 1.3 g (86%). Found: C 38.4; H 4.4; K 13.7; N 14.8%. $C_9H_{12}KN_9O_5$. Calculated: C 38.4; H 4.3; K 13.9; N 14.9%.

Potassium Salt (IIb) of the 2H-5-Nitro-4,6-dimethoxy-2-phenacylpyrimidine Anion. This compound was similarly obtained in 62% yield. Found: C 48.8; H 4.0; K 11.4; N 12.0%. C₁₄H₁₄KN₉O₅. Calculated: C 48.9; H 4.1; K 11.3; N 12.2%. Compounds IIa, b are infusible and are insoluble in water, acetone, and alcohol.

<u>5-Nitro-4,6-dimethoxy-2-acetonylpyrimidine (IVa)</u>. A solution of 1.8 g of ferric chloride in 15 ml of water was added dropwise with stirring to a solution of 1.6 g (5.7 mmole) of IIa in 40 ml of water, and the liberated oily substance was extracted with ehter (three 75-ml portions). The ether extract was dried with MgSO₄, the ether was removed by distillation, and the residue was crystallized to give 0.92 g (67%) of product. The product was recrystallized from hexane to give IVa with mp 99-100°C. IR spectrum: 1720 (C=0); 1340 and 1580 cm⁻¹ (NO₂). Found: C 44.7; H 4.4; N 17.3%. C₉H₁₁N₃O₅. Calculated: C 44.8; H 4.6; N 17.4%.

5-Nitro-4,6-dimethoxy-2-phenacylpyrimidine (IVb). A 1.6-g (4.6 mmole) sample of IIb was oxidized with 1.4 g of ferric chloride by the procedure used to oxidize IIa. Removal of the ether by distillation gave a dark-red viscous oil (0.75 g), which we were unable to crystallize. The product was isolated by chromatography with a column filled with LSL-254 silica gel (elution with benzene). Removal of the benzene by distillation gave yellow-green

crystals, with mp 157-158°C (from hexane), in 5% yield. IR spectrum: 1630 (C=0); 1380 and 1540 cm⁻¹ (NO₂). Found: C 55.2; H 4.2; N 13.6%. $C_{14}H_{13}N_{3}O_{5}$. Calculated: C 55.4; H 4.3; N 13.8%. Compounds IIa, b were oxidized by the method in [8].

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PYRIMIDINES

LXVI.* BROMINATION OF SUBSTITUTED 4-PHENYLPYRIMIDINE 1-OXIDES

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It is shown that the bromination of 4-phenylpyrimidine l-oxide takes place in the 5 position of the pyrimidine ring. When there is a methyl group in the pyrimidine N-oxide molecule, it also undergoes bromination. The direction of the reaction depends on the bromination conditions. A bromine atom in the 5 position of pyrimidine N-oxide is readily exchanged by a methoxy group.

The chemical properties of azines are changed substantially when an N-oxide group, which is capable of displaying both acceptor and donor properties [2], is introduced. Of the N-oxides of azines, little study has been devoted to pyrimidine derivatives [2], although a number of papers involving the study of the chemical properties of pyrimidine N-oxides have recently appeared [3-6]. Continuing our research on pyrimidine derivatives [1] we became interested in the possibility of using pyrimidine N-oxides for the synthesis of some difficult-to-obtain compounds, particularly alkyl- and aryl-substituted 5-halopyrimidines [7, 8]. No information on the halogenation of pyrimidine N-oxides is available in the literature. We studied the reactions of some pyrimidine N-oxides with brominating agents such as bromine and N-bromosuccinimide (NBS), taking into account the fact that the bromine-containing compounds are the most interesting of the halo derivatives because of the high lability of the bromine atom.

We used 4-phenylpyrimidine 1-oxide (Ia) and 6-methyl- (Ib) and 2-methyl-4-phenylpyrimidine 1-oxide (Ic), which we obtained in 40-80% yields by oxidation of the corresponding pyrimidines with hydrogen peroxide in the presence of sodium tungstate in analogy with [9], as the starting compounds. We were unable to obtain 2,4-diphenylpyrimidine 1-oxide by this method or by oxidation of 2,4-diphenylpyrimidine with hydrogen peroxide in acetic acid. The difficulty involved in the oxidation of 2-phenylpyrimidines to N-oxides has already been previously noted [10], and compounds of this type have not yet been obtained. On the basis of the literature data on steric hindrance in the oxidation of the nitrogen atom of a heteroring adjacent to a phenyl group and the easier oxidation of a nitrogen atom

*See [1] for communication LXV.

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