

SIGMA COMPLEXES IN THE PYRIMIDINE SERIES.

5.* REACTION OF 5-NITROMETHOXYPYRIMIDINES WITH THE ANION OF MALONIC ACID DINITRILE

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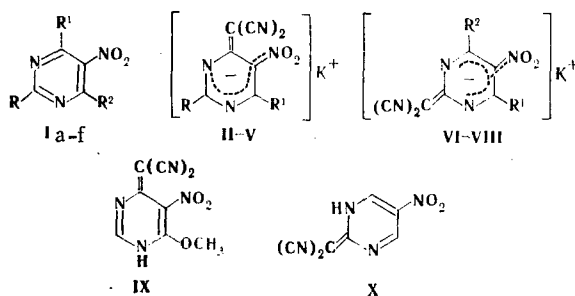
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The reaction of 5-nitromethoxypyrimidines with malonic acid dinitrile in the presence of potassium hydroxide was studied. It is shown that attack by the nucleophile is realized only in the positions of the pyrimidine ring occupied by methoxy groups and that potassium salts of the anions of 5-nitro-2(4)-dicyanomethylene-methoxypyrimidines are formed as a result of replacement of the methoxy groups.

In our previous research we established that stable anionic sigma complexes of the Meisenheimer type are formed in the reaction of 5-nitropyrimidines with the acetonide anion [2, 3]. Acetone is a weak CH acid (pK_a 20.0), while the acetonide anion is a strong nucleophile. In order to ascertain the effect of the strengths of CH acids on the formation and properties of the stable anionic σ complexes of the pyrimidine series, in the present research we studied the reaction of methoxy derivatives of 5-nitropyrimidine with the anion of malonic acid dinitrile — dicyanomethanide (the pK_a value of malonic acid dinitrile is 11.2).

The reaction of nitropyrimidines with malonic acid dinitriles was carried out in methanol solution in the presence of potassium hydroxide. Stable compounds, viz. the potassium salts of the anions of 5-nitro-2(4)-dicyanomethylenemethoxypyrimidines (II-VIII), were isolated in the form of colored crystalline saltlike substances.

In contrast to the reaction of acetonide anion with 5-nitromethoxypyrimidines [2, 3], in which the nucleophile added only to the most electron-deficient unsubstituted position, in this case splitting out of the readily removable methoxide anion and a proton from the malonic acid dinitrile residue evidently occur as a result of attack by the nucleophile, and the thermodynamically favorable potassium salts containing a dicyanomethylene group are formed. The existence of σ complexes of the Meisenheimer type was not detected in a single case by means of the UV and PMR spectra.



I a R=H, R¹=R²=OCH₃; b R=R¹=OCH₃, R²=H; c R=R¹=H, R²=OCH₃; d R=OCH₃, R¹=R²=H; e R=R¹=R²=OCH₃; f R=H, R¹=Cl, R²=OCH₃; II R=H, R¹=OCH₃, III R=OCH₃, R¹=H; IV R=R¹=H; V R=R¹=OCH₃; VI R¹=OCH₃, R²=H; VII R¹=R²=H; VIII R¹=R²=OCH₃

Replacement of the methoxy groups in the 2 and 4 positions to give mixtures of III and VI and V and VIII, respectively, are formed in each case in the reaction of pyrimidines Ib, e

*See [1] for communication 4.

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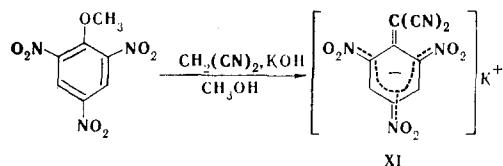
TABLE 1. Salts II-VIII and Dihydropyrimidines IX and X

Com- pound	Time, h	IR spectrum, ν , cm^{-1}				UV spectrum, λ_{max} , nm	PMR spectrum, ppm				Found, %			Empirical formula	Calculated, %			Yield, %
							2-H	4-H (6-H)	OCH ₃	C	H	N	C		H	N		
		C \equiv N	C=C	NO ₂ ^s	NO ₂ ^{as}													
II ^a	5	2200—2210	1600	1280	1450	307, 417	8,36	—	4,05	37,2	1,6	27,1	C ₈ H ₄ KN ₅ O ₃	37,2	1,6	27,2	76	
III ^b	1	2200—2400	1590	1280	1450	330 405	—	8,80 8,96	4,06 4,15	37,2	2,0	27,2	C ₈ H ₄ KN ₅ O ₃	37,2	1,6	27,2	71	
VI		2195—2205	1600	1290	1470	335, 417 sh	8,61	8,80	—	37,4	1,2	30,3	C ₇ H ₅ KN ₅ O ₂	37,0	0,9	30,8	35	
IV	1,5	2180—2190	1600	1290	1470	417	—	9,15	—	37,1	1,1	30,9	C ₇ H ₅ KN ₅ O ₂	37,0	0,9	30,8	55	
VII	1	2195—2210	1595	1290	1460	311 400	—	—	4,01; 4,04 4,05	37,1	2,3	24,2	C ₉ H ₆ KN ₅ O ₄	37,6	2,1	24,4	77	
V	3,5	2205—2215	1640	1350	1520	308, 417	8,50	—	4,12	44,0	2,3	31,9	C ₈ H ₅ N ₅ O ₃	43,8	2,3	31,9	65 ^d	
IX ^c	—	2210—2220	1630	1350	1550	417	—	9,20	—	44,5	1,7	36,8	C ₇ H ₅ N ₅ O ₂	44,5	1,6	37,0	78	
X ^e	—																	

^aFound: OCH₃ 12.4%. Calculated: OCH₃ 12.1%. ^bFound: OCH₃ 12.2%. Calculated: OCH₃ 12.1%. ^cIR spectrum: 3200 cm⁻¹ (NH); PMR spectrum: 11.50 ppm (NH). ^dBy method A. ^eIR spectrum: 3100 cm⁻¹ (NH); PMR spectrum: 11.55 ppm (NH).

with dicyanomethanide. We were unable to separate these mixtures preparatively, and their presence was proved by the PMR and UV spectra.

One might have expected that an adduct with dicyanomethanide would be observed in the case of a more electron-deficient compound. We used 2,4,6-trinitroanisole as a model. We found that a product of replacement of the methoxy group by a dicyanomethylene group, viz., potassium 2-dicyanomethylene-1,3,5-trinitrocyclohexadienate, is also obtained in this case.



In analogy with the data in [4], protonation at the ring heteroatom occurs when salts II and VII are treated with sulfuric acid, and dihydropyrimidines IX and X with a pyrimidinylidene structure, which was proved by means of the PMR and UV spectra, are formed. This is in agreement with the data in [5], in which a pyrimidinylidene structure was proved for 1,4-dihydro-2,6-diphenyl-4-dicyanomethylenepyrimidine. Compound IX was also obtained from pyrimidine If and malonic acid dinitrile by the method in [6] for the synthesis of dicyanomethylenetriazine.

The structures of the salts obtained were proved by means of the PMR, IR, and UV spectra. All of the spectral changes that occur during their formation are typical for σ complexes. Signals in the region of ring protons (8.40–9.15 ppm) (except for V and VIII) and signals of protons of methoxy groups (4.00 ppm), which are absent in the spectra of salts IV and VII, are observed in the PMR spectra of all of the compounds. The signals of the protons of II–VIII are shifted to the strong-field region as compared with the signals of the protons of the starting pyrimidines. Signals of the ring protons of III (8.80 ppm) and of protons of a methoxy group (4.06 ppm, relative intensity 1:3) and, in the case of VI, signals at 8.96 and 4.15 ppm (1:3) are observed in the PMR spectrum of a mixture of III and VI. Similarly, signals of protons of methoxy groups for salt V at 4.01 and 4.04 ppm (relative intensity 1:1) and, in the case of VIII, a signal at 4.05 ppm are observed for a mixture of V and VIII. The spectrum of XI does not contain the signals of protons of methoxy groups of the starting trinitroanisole but does contain a distinct singlet (8.58 ppm) that characterizes the symmetrical character of the molecule. In the PMR spectra of IX and X the signals of the ring protons are shifted to the weak-field region relative to the signals of starting II and VII. The distinct signal at 11.50 ppm (NH) is evidence that IX and X have a pyrimidinylidene structure.

As compared with the starting pyrimidines, the asymmetrical and symmetrical vibrations of the NO_2 group are shifted an average of 70 cm^{-1} to the lower-frequency region in the IR spectra of salts II–VIII. The reliability of the structure of the salts obtained is also confirmed by the appearance of an intense band at $1590\text{--}1600\text{ cm}^{-1}$, which corresponds to the stretching vibrations of the resulting $\text{C}=\text{C}$ bond. A band of medium intensity at 2200 cm^{-1} , the splitting of which is due to interaction between equivalent cyano groups [7], is also characteristic. In the case of dihydropyrimidines IX and X the vibrations of the nitro group are located in the normal-frequency range, while a weak band of stretching vibrations of the NH group is present at $3100\text{--}3200\text{ cm}^{-1}$.

The UV spectra of salts II–VIII contain a long-wave maximum ($\log \epsilon \approx 4$) that is usually interpreted as redistribution of the π -electron density between the pyrimidine ring and the nitro group. In this case one should evidently also assume interaction with the dicyanovinyl fragment, in connection with which the position of the absorption maximum in the hydrogenated molecules remains virtually unchanged.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6 -DMSO 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 spectrophotometer. The starting compounds were synthesized by known methods: 5-nitro-4,6-dimethoxypyrimidine (Ia) by the method in [8], 5-nitro-2,4-di-

methoxypyrimidine (Ib) by the method in [9], 5-nitro-2-methoxypyrimidine (Id) by the method in [10], and 5-nitro-4-methoxypyrimidine (Ic) by the method in [3].

5-Nitro-2,4,6-trimethoxypyrimidine (Ie). A solution of 0.3 g (0.013 mole) of sodium in 15 ml of methanol was added dropwise with vigorous stirring in the course of 30 min to a solution of 1 g (4.4 mmole) of 5-nitro-2,4,6-trichloropyrimidine [11] in 7 ml of methanol, and the mixture was stirred for 1 h. The precipitate was removed by filtration, the mother liquor was evaporated to half its original volume, and the resulting precipitate was combined with the initial precipitate to give 0.62 g (66%) of a product with mp 122-123°C (from hexane). PMR spectrum (CDCl₃): 4.43 (s, 2-OCH₃) and 4.41 ppm (s, OCH₃). Found: C 39.1; H 4.2; N 19.5%. C₇H₉N₃O₅. Calculated: C 39.1; H 4.3; N 19.3%.

General Method for the Preparation of II-VIII. A 1.5-mmol sample of finely ground potassium hydroxide was added with vigorous stirring to a mixture of 1.5 mmole of 5-nitro-methoxypyrimidine Ia-e and 1.5 mmole of malonic acid dinitrile in 5 ml of anhydrous methanol, during which the mixture took on a red coloration, which gradually became deeper. The reaction mixture was filtered, the solvent was removed, and the reaction product was precipitated with ether. In the case of nitropyrimidines Ia and Ie the reaction was carried out by refluxing methanol solutions of the reagents. Salt VII precipitated from the reaction mixture. The reaction times and the characteristics of the substances are presented in Table 1.

1,4-Dihydro-5-nitro-6-methoxy-4-dicyanomethylenepyrimidine (IX). A) A solution of 2 ml of 0.04 N H₂SO₄ was added dropwise to a solution of 0.4 g (1.5 mmole) of complex II in 5 ml of water, and the resulting brown precipitate was removed by filtration, washed with hexane, and dried. Crystallization from ethanol gave yellow needles.

B) A solution of 0.83 g (12.5 mmole) of malonic acid dinitrile in 5 ml of DMF was added with stirring in a stream of nitrogen to a suspension of 0.30 g (12.5 mmole) of sodium hydride in 5 ml of DMF. A 0.95-g (5.0 mmole) sample of chloropyrimidine If was added to the reaction mixture 20 min after hydrogen evolution was complete. After 1 h, the reaction mixture was evaporated to dryness, and 15 ml of dilute hydrochloric acid (1:1) was added. The red precipitate was removed by filtration and washed with water and hexane. The yield was 0.60 g (54%).

1,2-Dihydro-5-nitro-2-dicyanomethylenepyrimidine (X). A 5-ml sample of a 0.02 N solution of H₂SO₄ was added slowly with vigorous stirring to a solution of 0.5 g (2.2 mmole) of salt VII in 20 ml of water. The yellow precipitate was removed by filtration, washed with hexane, and crystallized from water. Dihydropyrimidines IX and X decomposed without melting when they were heated.

Potassium 2-Dicyanomethylene-1,3,5-trinitrocyclohexadienate (XI). A mixture of 0.18 g (0.70 mmole) of 2,4,6-trinitroanisole, 0.05 g (0.7 mmole) of malonic acid dinitrile, and 7 ml of methanol was stirred for 1 h, after which the solvent was removed, and the residue was precipitated with ether to give 0.18 g (78%) of blood-red crystals. IR spectrum: 2200-2220 (C≡N); 1310, 1480 cm⁻¹ (NO₂). UV spectrum, λ_{max}: 420 nm. PMR spectrum: 8.58 ppm (s). Found: C 34.4; H 0.6; N 22.2%. C₉H₂KN₅O₆. Calculated: C 34.3; H 0.6; N 22.2%.

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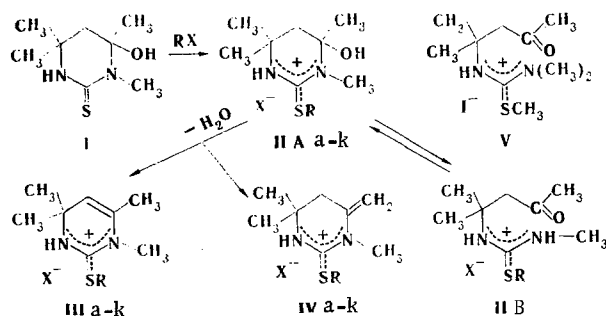
STRUCTURE OF SALTS OF SUBSTITUTED 2-ALKYLTHIOTETRAHYDOPYRIMIDINES

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The structure and ring-chain tautomerism of 2-alkylthio-3,4,6,6-tetramethyl-4-hydroxy-3,4,5,6-tetrahydropyrimidine hydrohalides (Alk = CH₃, C₂H₅, n-C₃H₇, n-C₄H₉, iso-C₄H₉, CH₂C₆H₅, Hal = Cl, Br, I) were analyzed by means of UV, IR, and PMR spectroscopy. It is shown that the cations of the salts in the crystalline state and in solutions exist primarily in the cyclic form.

In [1] we reported the synthesis of 2-alkylthio-3,4,6,6-tetramethyl-4-hydroxy-3,4,5,6-tetrahydropyrimidine hydrohalides, the structure of which is discussed in the present communication.



II-IV a R=CH₃, X=I; b R=CH₃, X=Cl; c R=C₂H₅, X=Br; d R=C₂H₅, X=Cl;
e R=n-C₃H₇, X=Br; f R=p-C₃H₇, X=Cl; g R=n-C₄H₉, X=Br; h R=n-C₄H₉, X=Cl;
i R=iso-C₄H₉, X=I; j R=iso-C₄H₉, X=Cl; k R=CH₂C₆H₅, X=Cl

Compounds IIa-k were obtained by the reaction of 3,4,6,6-tetramethyl-4-hydroxyhexahydropyrimidine-2-thione (I) with alkyl halides in acetone at 20°C. The spectral characteristics of the synthesized compounds are presented in Tables 1 and 2.

The cations of salts IIa-k can exist in two tautomeric forms, viz., the acyclic oxoalkylisothiuronium form (IIB) and the cyclic substituted 2-alkylthio-4-hydroxytetrahydropyrimidinium form (IIA). We have previously observed ring-chain tautomerism in the substituted 4-hydroxyhexahydropyrimidine-2-thione series [2].

The IR spectra of IIa-k in mineral oil do not contain a band corresponding to the stretching vibrations of the C=O group, and this indicates the existence of the cations of the salts in the crystalline state in cyclic form IIA. Broad absorption bands corresponding to the stretching vibrations of N-H and O-H groups connected by intermolecular hydrogen bonds are observed in the 3000-3600 cm⁻¹ region.

The cyclic structure of the cations of salts II is also retained in solutions in chloroform, in the IR spectra of which a ν_{C=O} band is also absent. Slow dehydration of II occurs when the chloroform solutions are allowed to stand, as evidenced by the appearance of absorption bands at 1690 and 1647 cm⁻¹. The first band can be assigned to the stretching vibrations of the C=C bond in 2-alkylthio-3,4,6,6-tetramethyl-3,6-dihydropyrimidine hydrohalides (III), while the second band can be assigned to the ν_{C=C} band of the isomeric products, viz., 2-alkylthio-3,6,6-trimethyl-4-methylene-3,4,5,6-tetrahydropyrimidine hydro-

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