SIGMA COMPLEXES IN THE PYRIMIDINE SERIES.

6.* REACTION OF 5-NITRO-2-METHOXY- AND 5-NITRO-4,6-DIMETHOXYPYRIMIDINES WITH THE ACETYLACETONE CARBANION

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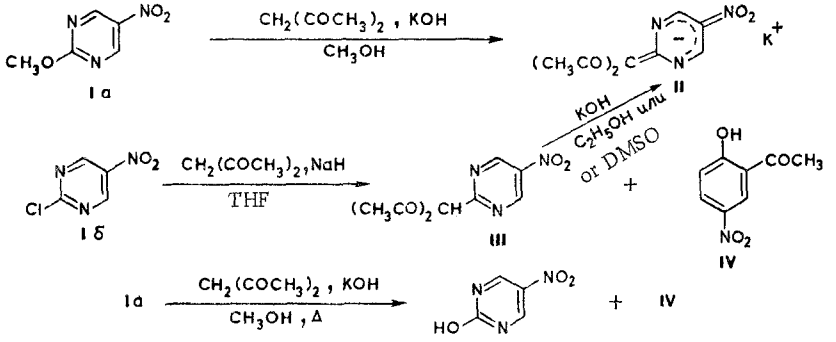
Depending on the reaction conditions, the reaction of 5-nitro-2-methoxy- and 5-nitro-4,6-dimethoxypyrimidines with the acetylacetone carbanion gives potassium salts of 5-nitrodiacetylmethylenepyrimidines or, as a result of recyclization of the pyrimidine ring, 5-nitro-2-hydroxyacetophenone.

It has been shown [1] that replacement of the methoxy group to give stable potassium salts of 5-nitro-2(4)-dicyanomethylenepyrimidine anions occurs in the reaction of 5-nitromethoxypyrimidines with the malonic acid dinitrile carbanion.

In order to ascertain the possibility of the formation of anionic σ complexes with a weaker nucleophile than dicyanomethanide, in the present research we investigated the reaction of 5-nitro-2-methoxy- and 5-nitro-4,6-dimethoxypyrimidines with acetylacetone in alkaline media (the pK_a of acetylacetone is 8.9 [2]).

A substance (in 3% yield), which, according to the UV and PMR spectral data, was identical to the potassium salt (II) of the 5-nitro-2-diacetylmethylenepyrimidine anion, which was also obtained from 5-nitro-2-diacetylmethylpyrimidine (III) and potassium hyroxide, was isolated in the reaction of 5-nitro-2-methoxypyrimidine (Ia) with acetylacetone in methanol in the presence of an equimolar amount of potassium hydroxide.



As in the case of the malonic acid dinitrile carbanion, nucleophilic attack by the acetylacetone carbanion is not realized at the free position of the pyrimidine ring but rather at the carbon atom that contains the methoxy group (a good leaving group) to give the thermodynamically stable salt II.

When we carried out this reaction in refluxing methanol, we obtained products of hydrolysis of the starting pyrimidine, viz., 5-nitro-2-hydroxypyrimidine and 5-nitro-2-hydroxyacetophenone (IV). Only acetophenone IV was isolated in 34% yield when pyrimidine Ia was refluxed in acetylacetone in the presence of triethylamine (see the experimental section). The same compound was also obtained as a side product in the synthesis of pyrimidine III from 5-nitro-2-chloropyrimidine (Ib) and acetylacetone in the presence of sodium hydride. The formation of acetophenone IV was proved by the PMR spectrum, the results of elementary analysis, and the absence of a melting-point depression for a mixture of a sample of this product with a genuine sample synthesized by the method in [3].

*See [1] for communication 5.

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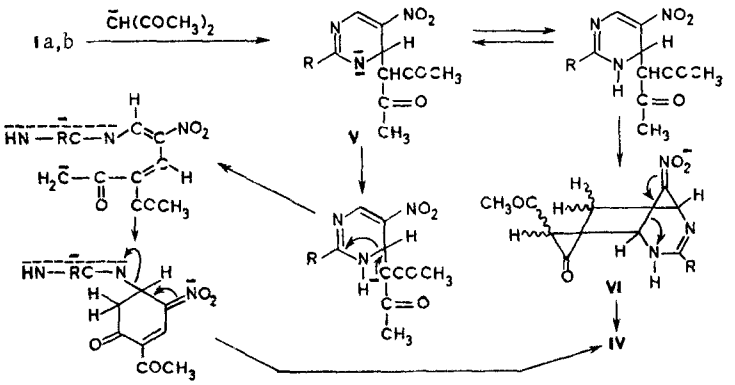
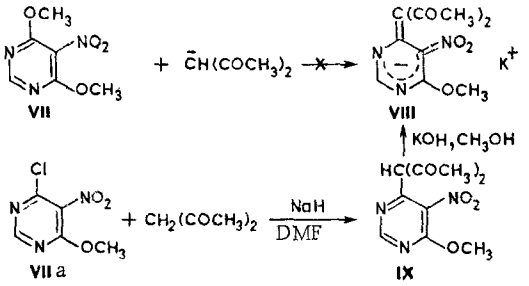
In analogy with studies in which recyclization of the pyrimidine ring under the influence of strong nucleophiles to give compounds of the pyridine series was described, it may be assumed that the conversion of 5-nitro-2-substituted pyrimidines to acetophenone IV takes place with the liberation of isourea derivatives from the intermediate anionic σ complex V or via a "meta-bonding" mechanism (VI) [4, 5].



I, V, VI a R=OCH_3; b R=Cl

5-Nitro-4,6-dimethoxypyrimidine (VII) does not react with the acetylacetone carbanion, although we were able to isolate the corresponding potassium salt VIII from 5-nitro-4-diacetylmethyl-6-methoxypyrimidine (IX).



This is probably due to the relatively low nucleophilicity of the acetylacetone carbanion or to the steric hindrance created by the nitro group in the ortho position relative to one of the possible centers of nucleophilic attack by a bulky nucleophile such as diacetylmethanide.

According to the data in [6], the lower limit of the pK_a values of conjugated acids, the anions of which are capable of giving σ complexes with 1,3,5-trinitrobenzene, is 5-7 pK_a units. In fact, in contrast to acetone, acetophenone, and malonic acid dinitrile anions, the acetylacetone carbanion is a weak nucleophile and does not form σ complexes with 5-nitromethoxypyrimidines at room temperature.

On the basis of the PMR (Table 1) and IR spectra a pyrimidinylidene structure can be assigned to III and IX. The absence of a signal of the proton of a methylidyne carbon atom in the PMR spectrum and the presence of an absorption band of an NH group in the IR spectrum constitute evidence in favor of this. However, a more detailed study of the problems of the tautomerism of III and IX requires further research.

Compound XII, which has a similar structure and contains an acetonylidene residue (a salt of the Zimmermann type [7, 8]), was obtained by the reaction of 5-nitro-4,6-dimethoxy-2-acetonylpyrimidine (XI) [9] with potassium methoxide in methanol.

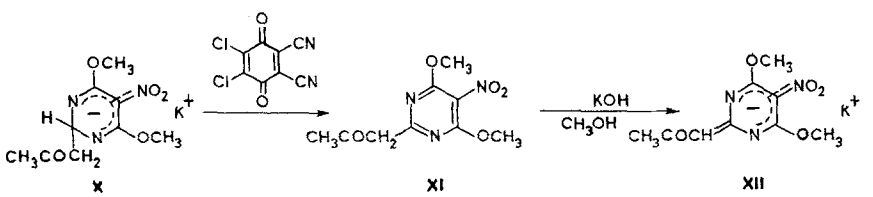


TABLE 1. PMR (in d_6-DMSO) and UV (in Methanol) Spectra of II, III, VIII, and IX

Compound	PMR spectrum, δ, ppm (relative intensity)				UV spectrum, λ_{max}, nm
	2-H	4(6)-H	OCH_3	CH_3	
II	—	8,52 (1)	—	1,88 (3)	448[a]
VIII	8,74 (1)	—	4,12 (3)	2,17 (6)	328 435 sh.
III[a]	—	9,75 (1)	—	2,60 (6)	
III	—	9,65 (1)	—	2,46 (6)	284, 334[c]
IX[b]	9,26 (1)	—	4,48 (3)	2,19 (6)	
IX	9,20 (1)	—	4,26 (3)	2,03 (6)	282

[a]In ethanol. [b]In deuterochloroform. [c]In chloroform.

TABLE 2. UV spectra (λ_{max}, nm) of X and XII

Compound	Solvent				
	methanol	acetone	DMSO	DMF	water
X	330	351	348	352	330
XII	—	440	440	440	440

The UV spectrum of salt XII contains a longer-wave absorption band as compared with the complex of the Meisenheimer type (X); this is evidently determined by an increase in the length of the π-electron conjugation chain, which also includes a keto component, in contrast to σ complex X. It is apparent from Table 2 that the absorption maximum of potassium salt XII does not depend on the nature of the solvent. Under the influence of mineral acids or a large excess of methanol salt XII is converted to starting acetonylpyrimidine XI as a consequence of protonation of the methylidyne carbon atom.

The IR spectra of II, VIII, and XII at 1520-1610 cm^{-1} contain a complex structured band with three principal maxima at 1520, 1580, and 1610 cm^{-1}, which were assigned to the asymmetric vibration of the nitro group, the stretching vibration of the C=C bond, and the vibration of the carbonyl group, respectively. The significant shift of the stretching vibration of the C=O group to the low-frequency region (∼50 cm^{-1}) as compared with the vibration of the carbonyl group in σ complex X serves as additional evidence for the formation of a lengthened chromophore chain in II, VIII, and XII, which have a pyrimidinylidene structure.

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 obtained with a Specord IR-71 spectrometer. The electronic spectra of solutions of the compounds in methanol (10^{-4} mole/liter) were recorded with a Specord UV-vis spectrophotometer.

Potassium Salt (II) of the 5-Nitro-2-diacetylmethylenepyrimidine Anion. A) A 0.08-g (1.4 mmole) sample of potassium hydroxide was added with vigorous stirring to a mixture of 0.2 g (1.3 mmole) of 5-nitro-2-methoxypyrimidine (Ia) [10] and 0.14 ml (1.4 mmole) of acetylacetone in 6 ml of methanol, during which the mixture became slightly red. After 5 h, the mother liquor was evaporated to dryness, and the residue was treated with diethyl ether (three 50-ml portions). The resulting precipitate was dissolved in acetone (5 ml), and the solution was filtered rapidly. The acetone was removed, and salt II was precipitated by means of ether. The yield was 0.01 g (3%).

B) A 0.013-g (0.22 mmole) sample of potassium hydroxide was added to a solution of 0.05 g (0.22 mmole) of 5-nitro-2-(diacetylmethyl)pyrimidine (III) in 0.5 ml of deuterated dimethyl sulfoxide (DMSO), and the solution was investigated by PMR spectroscopy.

5-Nitro-2-hydroxyacetophenone (IV). A) A mixture of 0.95 g (6.1 mmole) of pyrimidine Ia, 12 ml (12.0 mmole) of acetylacetone, and 0.8 ml (5.8 mmole) of triethylamine was re-

fluxed for 4 h, after which it was evaporated to dryness, and the residue was chromatographed with a column packed with LSL-254 silica gel (20 g) by elution with chloroform to give 0.37 g (34%) of a product with mp 101-102°C (from hexane) [3]. PMR spectrum (d_6-acetone): 12.46 (broad s, OH); 8.40 (broad s, 6-H); 8.00, 6.73 (dd, 3-H and 4-H); 2.30 ppm (s, CH_3). Found: C 52.8; H 3.9; N 7.7%. $C_8H_7NO_4$. Calculated: C 53.0; H 4.2; N 7.6%.

B) A mixture of 1.0 g (6.4 mmole) of pyrimidine Ia, 0.7 ml (7.0 mmole) of acetylacetone, and 0.4 g (7.1 mmole) of potassium hydroxide was refluxed in 30 ml of methanol for 8 h, after which it was cooled, and the resulting precipitate was separated. The filtrate was evaporated to dryness, and the residue was treated with 15 ml of acetone. The undissolved residue was mixed with the initial precipitate to give a total of 1.05 g of product. After crystallization from methanol, it was dissolved in 10 ml of water, and the aqueous solution was neutralized with 0.6 N sulfuric acid solution, as a result of which 0.13 g (14%) of 5-nitro-2-hydroxypyrimidine precipitated. A second reaction product (0.40 g), which dissolved in acetone, was precipitated by means of ether and dissolved in water. The aqueous solution was neutralized with sulfuric acid, as a result of which 5-nitro-2-hydroxyacetophenone, which was identified by means of a mixed-melting point determination with a sample obtained by method A, precipitated. The yield was 0.15 g (13%).

5-Nitro-2-(diacetylmethyl)pyrimidine (III). A solution of 1.1 ml (10.8 mmole) of acetylacetone was added with stirring and cooling (with cold water) in a stream of nitrogen to a suspension of 0.26 g (10.8 mmole) of sodium hydride in 30 ml of dry tetrahydrofuran (THF). A solution of 1.42 g (8.9 mmole) of chloropyrimidine Ib [11] in 5 ml of THF was added slowly 30 min after complete liberation of hydrogen, and the resulting solution became dark-red. After 1.5 h, the reaction mixture was evaporated to dryness, and the residue (2.15 g) was chromatographed with a column packed with silica gel (20 g) by elution with benzene to give 0.17 g (9%) of 5-nitro-2-hydroxyacetophenone. The residual substance (1.32 g) was eluted with a large amount of chloroform. Three recrystallizations from hexane gave 0.13 g (6%) of III with mp 106-108°C. Found: C 48.8; H 4.0; N 18.5%. $C_9H_9N_3O_4$. Calculated: C 48.8; H 4.1; N 18.8%.

Potassium Salt (VIII) of the 5-Nitro-4-diacetylmethylene-6-methoxypyrimidine Anion. A mixture of 0.1 g (0.4 mmole) of 5-nitro-4-(diacetylmethyl)-6-methoxypyrimidine (IX) and 0.02 g (0.4 mmole) of ground potassium hydroxide was stirred in 5 ml of methanol for 45 min, after which the reaction mixture was filtered, and the mother liquor was evaporated. Salt VIII was precipitated by means of absolute ether. The yield was 0.07 g (63%). Found: C 41.0; H 3.8; N 14.2%. $C_{10}H_{10}KN_3O_5$. Calculated: C 41.2; H 3.5; N 14.4%.

5-Nitro-6-methoxy-4-(diacetylmethyl)pyrimidine (IX). A 2.6-ml (26.0 mmole) sample of acetylacetone was added slowly with vigorous stirring in a stream of nitrogen to a suspension of 0.6 g (25.0 mmole) of sodium hydride in 10 ml of dimethylformamide (DMF). A 1.9-g (10.0 mmole) sample of 5-nitro-4-chloro-6-methoxypyrimidine (VIIa) [12] was added 30 min after liberation of hydrogen was complete, and the solution became dark-red. After 1 h, the reaction mixture was evaporated to dryness, and the residue was treated with dilute (1:1) hydrochloric acid. The mixture was cooled, and the resulting precipitate was dissolved in diethyl ether. The undissolved part was separated, and the mother liquor was evaporated to dryness to give 1.1 g (43%) of a product with mp 93-94°C (from hexane). Found: C 47.3; H 4.4; N 16.5%. $C_{10}H_{11}N_3O_5$. Calculated: C 47.4; H 4.4; N 16.6%.

Potassium Salt (XII) of the 5-Nitro-2-acetylmethylene-4,6-dimethoxypyrimidine Anion. A mixture of 0.1 g (0.4 mmole) of 5-nitro-2-acetonyl-4,6-dimethoxypyrimidine (XI) and 0.023 g (0.4 mmole) of ground potassium hydroxide was stirred in 5 ml of methanol for 30 min, after which the mixture was filtered, and salt XII was precipitated with absolute ether (50 ml). The yield was 0.09 g (82%). PMR spectrum (d_6-DMSO): 2.48 (s, CH_3), 4.00 (s, OCH_3), and 5.10 ppm (s, CH). Found: C 38.3; H 4.1; N 14.5%. $C_9H_{10}KN_3O_5$. Calculated: C 38.7; H 3.6; N 15.0%.

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SYNTHESIS OF 4-CHLORO-1,2,3-TRIAZOLE DERIVATIVES BY DIAZOTIZATION OF 6-SUBSTITUTED 5-AMINO-4-CHLOROPYRIMIDINES

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It is shown that 4-cyano- and 4-carbalkoxy-5-chloro-1,2,3-triazoles, respectively, are formed in the diazotization of 4,6-dichloro- and 4-chloro-6-alkoxy-5-aminopyrimidines. It was observed that a methyl group in the 2 position of the starting pyrimidine derivative does not affect the structures of the reaction products under the described conditions.

Despite the extensive use of reactions involving the transformation of heterocyclic systems in synthetic organic chemistry [1], they occupy an insignificant position among the methods for the preparation of 1,2,3-triazole derivatives [2]. In particular, the conversion of 5-diazouracils to 1,2,3-triazoles was reported only in 1976 [3].

We have previously shown that sulfides of 4-methoxy-5-amino-6-mercaptopyrimidine are converted by diazotization to methyl 1,2,3-triazole-4-carboxylate derivatives [4]. In a continuation of this research we studied the behavior of 6-substituted 5-amino-4-chloropyrimidines under similar conditions.

It is known that the structures of the products of diazotization of 5-aminopyrimidines depend on the character of the substituents in the pyrimidine ring [5]. The substituents in the 2, 4, or 6 position of the 5-aminopyrimidine molecule often undergo various transformations during diazotization. For example, 2,4-dichloro-5-aminopyrimidine forms a diazouracil [6]. 4,6-Dichloro-5-aminopyrimidine (Ia) and its 6-substituted derivatives such as 6-alkoxy-5-amino-4-chloropyrimidines, which are converted by diazotization to 4-chloro-1,2,3-triazole-5-carboxylic acid derivatives, behave differently. Thus treatment of 4,6-dichloro-5-aminopyrimidine with sodium nitrite in aqueous HCl leads to the production of 4-chloro-5-cyano-1,2,3-triazole (IIa), whereas 5-carbomethoxy- and 5-carbethoxy-4-chloro-1,2,3-triazoles (IIb, c) are formed from 4-methoxy- and 4-ethoxy-5-amino-6-chloropyrimidines (Ib, c), respectively.

With respect to both its melting point and its spectral characteristics, IIc corresponds to the 4-chloro-5-carbethoxy-1,2,3-triazole recently obtained by other methods [7, 8] (see the experimental section).

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