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ACTION OF NUCLEOPHILIC AGENTS ON THE PYRIMIDINE RING

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It is shown that 2-alkylpyrimidine methiodides in which the alkyl group is activated by electron-acceptor substituents undergo recyclization to the corresponding 2-methylaminopyridines in an alcohol solution of methylamine. Similar recyclization also takes place without quaternization of the pyrimidine ring when there is a strong electron-acceptor substituent (a nitro group) in the ring.

The pyrimidine ring is capable of adding the $\overline{N}H_2$ anion (potassium amide in liquid ammonia) to give a σ complex [1], while ammonia itself (as well as methylamine) requires heating (up to 190°C), during which the ring undergoes complete cleavage, and 2-methyl-5-ethylpyridine is formed from two molecules of pyrimidine [2]. Hydrazine hydrate, which is a strong nucleophile, also cleaves the pyrimidine ring to give pyrazole when the reaction mixture is heated to 130°C [3]. Even covalent addition of the elements of water, which may lead to hydrolytic opening of the pyrimidine ring [7], is known for pyrimidines, the ring of which is condensed with another aromatic ring or has a strong electron-acceptor substituent [4-6].

Pyrimidinium salts react with nucleophiles under mild conditions. In particular, the action of an alkaline agent leads to cleavage of the $N_{(1)}$–$C_{(6)}$ bond and solvolytic cleavage of the open form [8]. The open form sometimes closes again with the inclusion of a nucleophile molecule. Thus pyrimidine methiodide undergoes ring opening in liquid ammonia and recyclizes to give the nonalkylated pyrimidine. The scheme of this dealkylation through a step involving recyclization is confirmed by experiments with a labeled nitrogen atom [9], although this does not exclude the possibility of competitive direct dealkylation due to attack by the nucleophile on the methyl group. Instances of similar recyclizations in which the resulting ring includes a fragment of the attacking reagent [for example, the $\overline{C}H(CN)_2$ anion] are known [10, 11]. In addition to this, alkylpyrimidines and particularly their quaternary salts can react as CH acids under the influence of nucleophiles. Unstable anhydronium bases are formed from the quaternized structures in this case [7].

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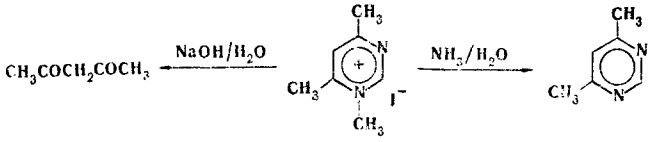
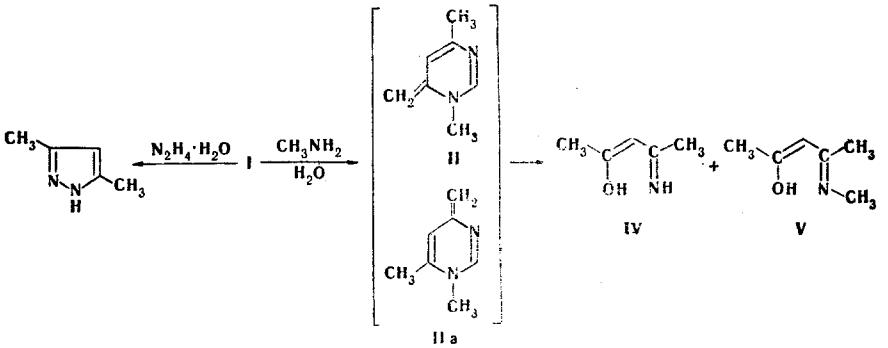
The rather high CH acidity of the side chain (i.e., the ease of formation of a carbanion) compelled us to assume that, in addition to the recyclizations described above, closing of the open ring to give an exocyclic fragment of the starting structure rather than the reagent is possible. We observed this sort of recyclization with conversion of the pyrimidine ring to a pyridine ring in the case of condensed systems — for example, in the isomerization of pyrimido[1,2-a]indoles to α-carbolines [12] and pyrazolo[1,5-a]pyrimidines to pyrazolo[3,4-b]pyridines [13].

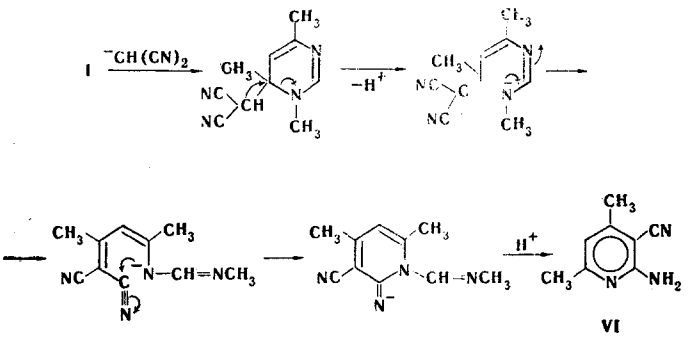
Our experiments showed that 1,4,6-trimethylpyrimidinium iodide (I) readily undergoes hydrolysis when it is heated with aqueous alkali to give acetylacetone. The action of ammonium hydroxide leads to demethylation to give 4,6-dimethylpyrimidine (III).



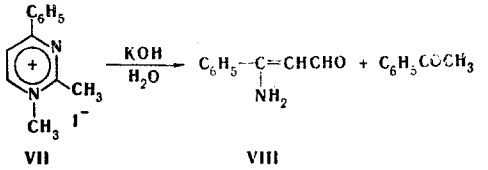
A stronger base — an aqueous solution of methylamine — initially gives rise to the development of a crimson coloration (λ_{max} 350-360 nm), which corresponds to the formation of anhydronium base II or IIa, after which it leads to a mixture of imines IV and V, which were identified by means of the PMR and mass spectra and by comparison of their chromatographic mobilities with the mobilities of samples with known structures. Finally, hydrazinolysis, as reported by van der Plas [3], gives 3,5-dimethylpyrazole.



In acetonitrile in the presence of triethylamine salt I reacts with malononitrile to give 2-amino-3-cyano-4,6-dimethylpyridine (VI) in 52% yield. In this case the absence of a protic solvent excluded the simultaneous solvolysis processes, as a result of which recyclization occurred but was attended by the incorporation of the reagent in the resulting ring and elimination of a portion of the atoms of starting I. The formation of VI indicates that the nucleophile preferentially attacks the $C_{(6)}$ atom, in agreement with the literature data (for example, see [9, 10]).



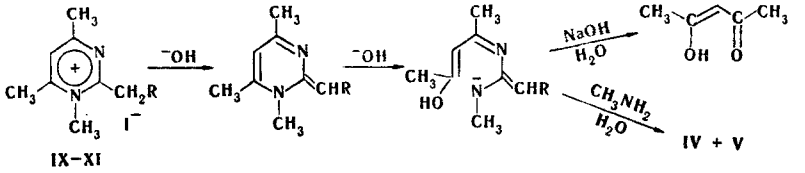
On the basis of this (although it is difficult to assert a priori that the orientation of the nucleophilic attack is retained on passing to the anhydronium base) we set up a series of experiments with pyrimidinium salts containing a methyl or substituted methylene group in the 2 position rather than in the 6 position.



VII VIII

It was found that salt VII readily undergoes hydrolysis when it is refluxed briefly in aqueous KOH solution (acetophenone was isolated). Under milder conditions (without refluxing), in addition to acetophenone we were able to identify β-aminocinnamaldehyde (VIII). Amine VIII and acetophenone were also isolated in 16 and 36% yields, respectively, when salt VII was refluxed with 30% aqueous methylamine solution for 3 h.

Methiodides IX-XI behave in the same way in aqueous solutions of alkali and methylamine. Acetylacetone (in sodium hydroxic lution) or a mixture of imines IV and V (in aqueous methylamine solution) were detected.



IX-XI

IX R=H; X R=C_6H_5; XI R=$COOC_2H_5$

The formation of an anhydronium base (absorption at 340-400 nm) was noted initially.

All of the investigated models (VII and IX-XI) are readily demethylated in ammonium hydroxide. It is possible that demethylation proceeds through a step involving cleavage of the $N_{(1)}$—$C_{(6)}$ bond and recyclization under these conditions (as in the reaction with liquid ammonia [9]).

However, when salt X is heated with an anhydrous alcohol solution of methylamine, it forms the expected 2-methylamino-3-phenyl-4,6-dimethylpyridine (XII) and the demethylation product, i.e., 2-benzyl-4,6-dimethylpyrimidine (XIII).

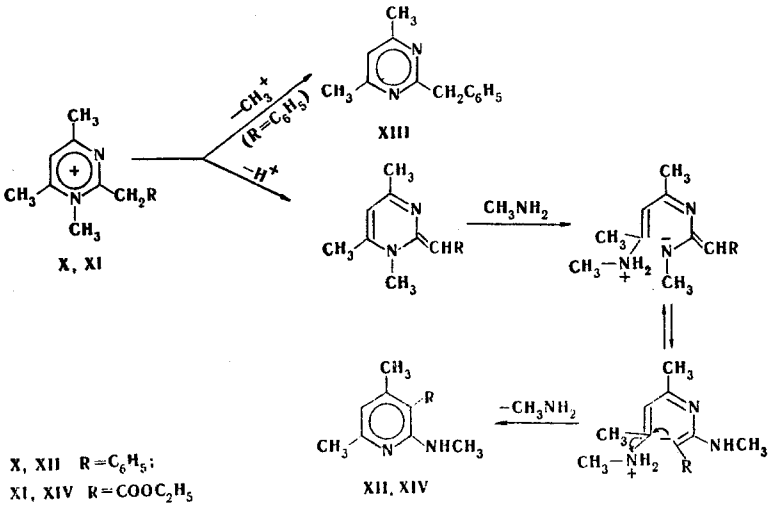
Recyclization also takes place when methiodide XI is refluxed under the same conditions, and 2-methylamino-3-carbethoxy-4,6-dimethylpyridine (XIV) is formed in 69% yield. A demethylation product was not detected. The PMR spectrum of XIV (in CCl_4) contains three singlets of methyl groups at 2.27, 2.31, and 2.94 ppm, a singlet of an aromatic proton (6.0 ppm), and a triplet and quartet of an ethyl group. The UV spectrum (in alcohol) contains absorption maxima at 215 (4.19), 257 (3.89), and 341 nm (3.75); this is characteristic for such pyridines. Under the same conditions methiodide VII does not undergo rearrangement but gives only a demethylation product.

Thus under identical conditions XI forms only a recyclization product, X undergoes both rearrangement and partial demethylation, and salt VII forms only a demethylation product, and recyclization is not observed in this case.

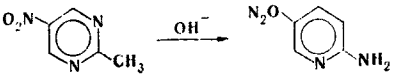
The demethylation of salts VII and X under the influence of methylamine (in contrast to demethylation with ammonia) cannot occur through transamination (via the ANRORC scheme) but only through direct nucleophilic attack on the methyl group bonded to the nitrogen atom of the pyrimidinium salt.

Thus, if one excludes solvolysis processes, competition between demethylation and recyclization nevertheless remains. The CH acidity of the alkyl group in the 2 position is of decisive significance here. Thus the presence of an electron-acceptor group ($COOC_2H_5$) in the side chain of salt XI increases the CH acidity, and this ensures recyclization. However, if the alkyl group is not activated by an acceptor substituent (salt VII), only demethylation occurs.

We were consequently able to show that 1,2-dialkylpyrimidinium salts are capable of undergoing recyclization to the corresponding 2-aminopyridines (evidently through a step involving the anhydronium bases) under the influence of a nucleophilic agent. A review of previously known transformations of such salts was recently published [14].



It is apparent that sufficient CH acidity of the side chain can be created not only by quaternization but also by the introduction of a strong electron acceptor in the pyrimidine ring. In fact, 2-amino-5-nitropyridine (XVI), with mp 183-184°C, was isolated in 7-8% yield after heating 2-methyl-5-nitropyrimidine (XV) in aqueous alkali.



XV XVI

Let us note that a substance with mp 186-187°C, to which pyrimidine structure XV was erroneously assigned [15, 16], was obtained in the reaction of nitromalonic dialdehyde with acetamidine (in alkaline media). In fact, aminopyridine XVI is formed via this pathway, as proved by the independent synthesis of Biffin and co-workers [4]. It may be assumed that isomerization of pyrimidine XV to pyridine XVI takes place during the synthesis (in alkaline media), but a special study is required for this.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Varian T-60 spectrometer with tetramethylsilane as the standard. The mass spectra were recorded with an MKh-1303 spectrometer with introduction of the substances into the ionization region at 50 eV. The UV spectra of alcohol solutions of the compounds were recorded with a Cary-15 spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were obtained with a UR-10 spectrometer. The substances obtained were separated with a column filled with L-40/100μ silica gel in a benzene–acetone system (3:1).

Reaction of the Pyrimidinium Salts with Aqueous Alkali. A) A 2.5-ml sample of a 2 N solution of sodium hydroxide was added to a solution of 0.25 g (1.0 mmole) of 1,4,6-trimethylpyrimidinium iodide in 2.5 ml of water, and the mixture was refluxed for 30 min. It was then extracted with chloroform, and the extract was dried with Na_2SO_4. Removal of the solvent by distillation gave 0.055 g (65%) of acetylacetone, which was identified by conversion to the known 3,5-dimethylpyrazole by reaction with hydrazine hydrate. Similarly, the reaction of 0.264 g (1.0 mmole) of salt IX, 0.34 g (1.0 mmole) of salt X, and 0.336 g (1.0 mmole) of XI gave, respectively, 0.057 (57%), 0.054 (54%), and 0.068 g (68%) of acetylacetone.

B) Similar refluxing of 0.95 g (3.0 mmole) of iodide VII with 10 ml of 1 N sodium hydroxide solution gave 0.23 g (64%) of acetophenone.

Demethylation of Pyrimidinium Salts. A solution of 2 mmole of pyrimidine methiodide (I, VII, or IX-XI) in 10 ml of 20% ammonium hydroxide was refluxed for 15-20 min, after which the mixture was extracted with benzene. The extract was dried with calcium chloride, and the solvent was removed by distillation to give the corresponding pyrimidines. The yield of 4,6-dimethylpyrimidine from iodide I was 48%, the yield of 2,4,6-trimethylpyrimidine from salt IX was 56%, the yield of 2-methyl-4-phenylpyrimidine from methiodide VII was 67%, the yield of 2-benzyl-4,6-dimethylpyrimidine from iodide X was 44%, and the yield of

ethyl 4,6-dimethyl-2-pyrimidinylacetate from salt XI was 52%. All of the pyrimidines obtained were identical to genuine samples according to the PMR and mass spectra and the chromatographic mobilities.

Reaction of 1,4,6-Trimethylpyrimidinium Iodide with Hydrazine Hydrate. A 92% solution of hydrazine hydrate was added dropwise with stirring to 0.5 g (2.0 mmole) of iodide I in 5 ml of alcohol until the pyrimidinium salt dissolved completely, and the solution was heated at 80°C for 15 min. It was then cooled and diluted with water, and the precipitate was removed by filtration to give 0.13 g (68%) of 3,5-dimethylpyrazole with mp 103-104°C, in agreement with the literature value. The product had a molecular weight of 96 according to its mass spectrum.

Reaction of 1,4,6-Trimethylpyrimidinium Iodide with Malononitrile. A 0.75-ml sample of triethylamine was added dropwise to a mixture of 1.25 g (5.0 mmole) of 1,4,6-trimethylpyrimidinium iodide, 0.4 g (6.0 mmole) of malononitrile, and 25 ml of dry acetonitrile. After 30 min, a white substance began to precipitate from the solution. The precipitate was removed by filtration and recrystallized from acetonitrile to give 0.38 g (52%) of 2-amino-3-cyano-4,6-dimethylpyridine with mp 160-162°C. PMR spectrum (CCl_4), δ: 2.62 and 2.67 (s, 4- and 6-CH_3), 6.63 (s, 5-H), and 6.83 ppm (broad s, NH_2). UV spectrum (in alcohol), λ_{max} (log ε): 218 (4.17), 247 (3.80), 320 nm (3.60). IR spectrum: 2222 (C≡N) and 3400 cm^{-1} (NH_2). Found: C 65.1; H 6.0; N 28.7%; M (by mass spectrometry) 147. $C_8H_9N_3$. Calculated: C 65.3; H 6.1; N 28.6%; M 147.

Reaction of Pyrimidinium Salts with Aqueous Methylamine Solution. A) A mixture of 0.5 g (2 mmole) of 1,4,6-trimethylpyrimidinium iodide (I) and 5 ml of a 25% aqueous solution of methylamine was refluxed for 1 h, after which it was extracted with benzene, and the products were separated with a column to give 24 mg (14%) of acetylacetone imine (IV) and 38 mg (17%) of acetylacetone methylimine (V). According to the mass spectra and chromatographic mobilities, the products were identical to genuine samples obtained by independent methods [17, 18].

Similarly, mixtures of imines IV and V in 27 and 18%, 20 and 22%, and 25 and 24% yields, respectively, were isolated when 2-mmole samples of salts IX-XI were refluxed under the same conditions.

B) A 0.62-g (2 mmole) sample of 1,2-dimethyl-4-phenylpyrimidinium iodide (VII) was heated in a sealed ampul with 8 ml of a 25% aqueous solution of methylamine for 3 h, after which the mixture was extracted with benzene and separated on a plate with aluminum oxide in a benzene—acetone system (4:1) to give 0.085 g (36%) of acetophenone and 0.084 g (30%) of β-aminocinnamaldehyde (VIII). PMR spectrum of VIII (CCl_4), δ: 5.33 (d, =CH—, J = 2.5-3 Hz), 6.5 (broad s, NH_2), 7.1-7.6 (m, C_6H_5), and 9.05 ppm (d, CHO, J = 2.5-3 Hz). Compound VIII had a molecular weight of 147 according to the mass spectrum.

Reaction of Pyrimidine Salts with an Alcohol Solution of Methylamine. 1. Rearrangement of Ethyl 1,4,6-Trimethyl-2-pyrimidinylacetate Iodide (XI) to 2-Methylamino-3-carbethoxy-4,6-dimethylpyridine (XIV). A mixture of 0.2 g (0.6 mmole) of salt XI and 10 ml of a 20% alcohol solution of methylamine was heated in a sealed ampul at 85-90°C for 30 h. At the end of the heating period, the mixture was evaporated in vacuo, and the residue was separated with a column to give 0.085 g (69%) of pyridine XIV with mp 39-40°C. PMR spectrum (CCl_4), δ: 1.31 (t, CH_3, J = 8 Hz), 2.27 and 2.31 (s, 4- and 6-CH_3), 2.94 (s, NCH_3), 4.18 (q, CH_2, J = 8 Hz), and 6.0 ppm (s, 5-H). UV spectrum (in alcohol), λ_{max} (log ε): 215 (4.19), 257 (3.89), and 341 nm (3.75). The product had a molecular weight of 208 according to the mass spectrum.

2. Rearrangement of 1,4,6-Trimethyl-2-benzylpyrimidinium Iodide (X) to 2-Methylamino-3-phenyl-4,6-dimethylpyridine (XII). A mixture of aminopyridine XII and 2-benzyl-4,6-dimethylpyrimidine (XIII) was obtained under the same conditions from 0.2 g (0.6 mmole) of iodide X and 6 ml of a 25% alcohol solution of methylamine. The mixture was separated with a column to give 0.042 g (34%) of pyridine XII and 0.033 g (29%) of pyrimidine XIII. PMR spectrum of XII (CCl_4), δ: 2.52 and 2.58 (s, 4- and 6-CH_3), 3.32 (s, NCH_3), and 6.9-7.1 ppm (broad s, 5H, C_6H_5). UV spectrum (in alcohol), λ_{max} (log ε): 259 (3.59) and 310 nm (3.0). Compound XII had a molecular weight of 212 according to the mass spectrum. Pyrimidine XIII had mp 39-40°C and was identical to a genuine sample according to its chromatographic mobility and mass spectrum.

3. Demethylation of 1,2-Dimethyl-4-phenylpyrimidinium Iodide. A 0.22-g (65%) sample of 2-methyl-4-phenylpyrimidine was obtained under similar conditions from a mixture of 0.62 g (2 mmole) of salt VII and 10 ml of a 25% alcohol solution of methylamine.

Rearrangement of 2-Methyl-5-nitropyrimidine (XV) to 2-Amino-5-nitropyridine (XVI). A mixture of 0.1 g (0.67 mmole) of 2-methyl-5-nitropyrimidine and 10 ml of 50% aqueous alcohol containing 1 g of potassium hydroxide was refluxed for 3 h, after which it was extracted with chloroform, and the products were separated with a column to give 8 mg (8%) of 2-amino-5-nitropyridine with mp 183-184°C (mp 184-186°C [19]).

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