with stirring. The resulting solution was cooled immediately, and the precipitate was removed by filtration, washed with ether, and dried to give 1.27 g (87%) of a product with mp 137-138°C (from ethyl acetate). IR spectrum (in CCl_4): 1670, 1770 cm^{-1} (2 C=O). UV spectrum, λ_{max} (log ε): 241 (4.41), 248 (4.39), 268 (4.23), and 330 nm (4.85). PMR spectrum (in d_7-DMF): 2.22, 2.30 (2 s, 2 $COCH_3$); 5.02 (s, CH_2); 7.00-8.40 ppm (m, aromatic protons). Found: C 62.2; H 5.3; N 12.1%. $C_{12}H_{12}N_2O_3$. Calculated: C 62.1; H 5.2; N 12.1%.

1,3-Diacetyl-3-acetamidooxindole (IV). A 0.4-g (1.46 mmole) sample of N-acetyl-2-acetoxy-3-acetamidoindole was heated on a Wood's metal bath at 180-190°C for 1-2 min, 2-3 ml of methanol was added to the melt, and the mixture was cooled. The precipitate was removed by filtration, washed with methanol, and dried to give 0.26 g (64%) of a product with mp 176.5-178°C (from methanol). IR spectrum: 1670, 1710, 1720, 1750 (4 C=O); 3350 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 240 nm (3.90) sh. PMR spectrum (in $CDCl_3$): 1.95, 2.04, 2.72 (3 s, 3 $COCH_3$); 7.00-8.35 (m, aromatic protons); 7.45 ppm (broad s, NH). Found: C 61.4; H 5.2; N 10.3%. $C_{14}H_{14}N_2O_4$. Calculated: C 61.3; H 5.2; N 10.2%.

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TRANSFORMATIONS OF 1,2-DIMETHYLPYRIDINIUM IODIDE UNDER THE INFLUENCE OF SULFITES OF CYCLIC AMINES

A. N. Kost,* T. V. Stupnikova,
V. N. Kalafat, R. S. Sagitullin,
and V. P. Marshtupa

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The transformations of 1,2-dimethylpyridinium iodide under the influence of sulfites of morpholine, piperidine, and piperazine were investigated. It was established that it undergoes demethylation and recyclization both with and without exchange of an amino group when it is heated with aqueous solutions of the cyclic amines.

Several reaction pathways that depend on the structures of the reagents are possible in the reaction of nucleophiles with 1-alkylpyridinium salts. The data from deuterium exchange and NMR spectroscopy indicate that the CH acidity of the N-methyl group in the 1-methylpyridinium salts is negligible, that deuterium exchange through the CH_2 group in the 1-benzylpyridinium salt proceeds slowly, and that the principal process under the influence of alkoxide ion is deprotonation in the α position of the pyridine ring [1, 2]. The process appears to be somewhat different under the influence of the NH_2^- ion, which adds to the C_2 atom to give a dihydropyridine structure [3]. A similar capacity for addition was noted for $NO_2CH_2^-$ and $C_2H_5S^-$ ions, but in this case addition occurred at both the C_2 atom and the C_4 atom in the case of 3-substituted 1-alkylpyridinium salts [4]. The cyanide ion adds virtually only to the C_4 atom, and the process is reversible [5]. It is known [6] that attack by the hydroxide ion takes place preferably at the C_2 atom and leads to hydrolytic ring opening. In the case of the 1-(2,4-dinitrophenyl)pyridinium salt this opening process is observed even under the influence of piperidine. Finally, one should take into account the possibility of attack by the nucleophile on the carbon atom of the alkyl group bonded to the ring nitrogen atom, which leads to dealkylation [7]. The same final result can be observed in the case of ring opening with subsequent replacement of the methylamine fragment by an amine fragment and

*Deceased.

Donetsk State University, Donetsk 340055. M. V. Lomonosov Moscow State University, Moscow 117234.

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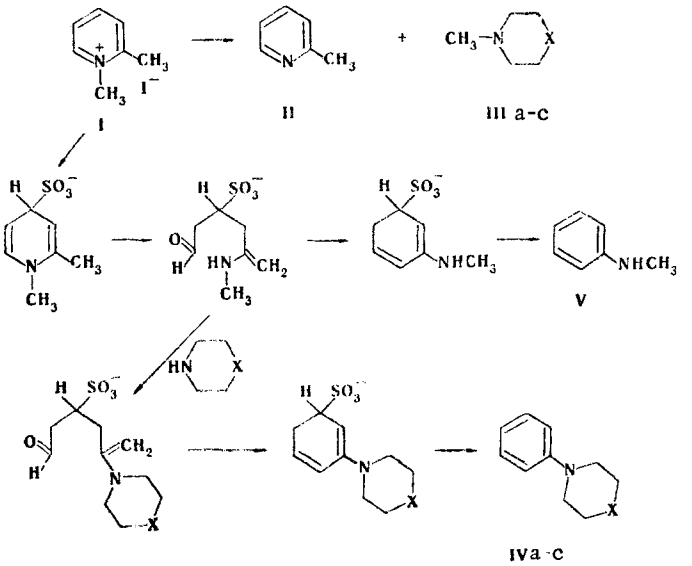
the formation of a nonquaternized pyridine ring, as described in [8].

When an alkyl chain is present, particularly in the α position relative to the pyridine ring, the process is complicated by the possibility of splitting out of a proton from this hydrocarbon chain with the formation of an unstable anhydro base [9]. The opening of the pyridine ring (through the anhydro base or with initial attack on the C_2 atom) in such structures may lead to hydrolysis with subsequent cyclization, this time with the participation of the side chain, i.e., with the formation of a benzene ring rather than a pyridine ring. In fact, Lukes and Jizba [10] have found that when 1,2-dimethylpyridinium bromide is heated with alkali, it splits out a molecule of methylamine and gives phenol in 4-5% yield, while 1-ethyl-2,6-dimethylpyridinium bromide was similarly converted to m-cresol in 48-69% yield. The substantial increase in the yield in the second case makes it possible to imagine that the decisive factor is not the reactivity of the starting ring, the introduction of a second methyl group in which decreases the electrophilicity and creates steric hindrance, but rather the ability of the open form to undergo hydrolysis with splitting out of ethylamine and ring formation. The same authors used ammonium sulfite as the reagent but established only N-dealkylation in the case of a number of models [8].

It has been shown that 1,2-dialkylpyridinium salts and even 2-methylpyridines themselves can be converted to the corresponding alkylanilines, i.e., they can undergo recyclization with the participation of the side chain without the loss of an amine fragment [11, 12]. The use of an alkylamine or an alkylammonium sulfite as the reagent suppresses hydrolysis of the open form but may also lead to exchange of the amine fragment [13]. Recyclization by means of an amine sulfite possibly takes place in the first step of the process somewhat differently than in the case of the action of hydroxide ion or a primary amine, since one should assume primary attack on the C_4 atom of the pyridine ring, which also determines the relatively facile ring opening. The subsequent steps evidently proceed in a complex manner [12].

In the present research we made a systematic study of the transformations of 1,2-dimethylpyridinium iodide (I) under the influence of sulfites of cyclic amines. We selected morpholine, piperidine, and piperazine, the p pairs of electrons of the nitrogen atoms of which are sterically accessible and the basicities of which are high (the pK_a values are, respectively, 8.43, 10.60, and 11.70). In addition, these amines undergo the Bucherer reaction poorly [14]. This is important in connection with the fact that one should have excluded the possibility of the occurrence of the reaction through a step involving the phenol with the subsequent replacement of the hydroxy group by an amino group.

It was found that heating iodide I with an aqueous solution of morpholine sulfite (at 150°C for 30 h) leads to demethylation and the formation of 1-methylmorpholine (IIIa) and α-picoline (II). In addition, the proposed recyclization takes place with and without exchange of the amino group, as a result of which 1-phenylmorpholine (IVa) and N-methylaniline (V) are formed:



III–IVa X=O; b X=CH_2; c X=NH

TABLE 1. Recyclization of 1,2-Dimethylpyridinium Iodide under the Influence of Sulfites of Cyclic Amines

Reagent and amine: amine bisulfite ratio	Reagent pH	Yields of reaction products, %			
		II	V	IIIa–c	IVa, b
Morpholine[a]					
1 : 2	8,3	22	11	10	4
1 : 1	8,3	25	13	12	3
2 : 1	8,8	26	15	11	2
4 : 1	9,6	18	43	20	6
Piperidine[b]					
1 : 2	10,6	12	13	12	8
2 : 1	11,4	22	16	17	15
Piperazine[c]					
1 : 2	6,7	14	64	17	—
1 : 1	7,6	12	53	13	—
2 : 1	9,8	18	83	20	—

[a]The reaction products are IIIa and IVa. [b]The reaction products are IIIb and IVb. [c]The reaction product is IIIc.

Although the difference in the pK_a values of the morpholine sulfites used is slight, it has an appreciable effect on the yields of all four reaction products (Table 1). The contribution of dealkylation and recyclization processes without exchange of an amine fragment and, consequently, the yields of α-picoline and the corresponding N-methylmorpholine and N-methylaniline increase as the pH of the solution of the amine sulfite increases (i.e., as the percentage of the free base increases). However, the contribution of recyclization with exchange of an amine fragment (i.e., the yield of N-phenylmorpholine) decreases to a small extent and becomes extremely insignificant (within the limits of 2-4%) but increases somewhat (up to 6%) when the percentage of free morpholine in the reaction mixture is increased significantly. The contribituion of dealkylation (i.e., the yield of α-picoline) is approximately constant (~20%), but the yield of the corresponding N-methylmorpholine is usually halved, except in the case of a high percentage of morpholine in the mixture, for which the yields are comparable. This may be a consequence of the fact that the dealkylation proceeds not only by means of attack by morpholine on the $N-CH_3$ group of the picolinium salt but also with the participation of another nucleophile such as the OH^- ion, which gives methanol. The yield of N-methylaniline, i.e., the product of "pure" recyclization, increases as the percentage of morpholine in the reaction mixture increases and reaches a maximum value (43%) at a morpholine:morpholine bisulfite ratio of 4:1 at the maximum pH of the solution of the sulfite reagent.

Demethylation takes place to a lesser extent when morpholine is replaced by piperidine, and the yields of α-picoline and N-methylpiperidine are comparable, i.e., the CH_3 group is transferred only to piperidine. The processes with and without exchange of a methylamine fragment take place to virtually the same extent (in ~15% yield).

Demethylation with the formation of α-picoline and N-methylpiperazine was observed to a slight extent in experiments with piperazine, and the principal reaction product was N-methylaniline (up to 83%). The yields of all three substances increased as the pH of the medium was increased. In this case the presence of a second basic nitrogen atom in the ring of the reagent changes the ratio of the competitive reactions. In all of the cases presented above one might have assumed that IVa-c are formed in a secondary process via the scheme of the Bucherer reaction due to conversion of the initially formed phenol. However, not even traces of phenol were detected in an analysis of the reactive mixture by thin-layer chromatography (TLC), whereas a special experiment showed that phenols are not converted to IVa-c upon reaction with aqueous solutions of sulfites of cyclic amines under similar conditions.

EXPERIMENTAL

Chromatography was realized in a loose thin layer of aluminum oxide (activity II) in chloroform–benzene–hexane (30:6:1) (system A) and benzene–hexane (30:6) (system B). The pH values were determined with a pH-340 apparatus.

Reaction of 1,2-Dimethylpyridinium Iodide with Sulfites of Cyclic Amines (General Method). A mixture of 5 mmole of 1,2-dimethylpyridinium iodide and 20 ml of an aqueous solution of the amine sulfite was heated in a sealed ampul at 150°C for 30 h, after which the mixture was extracted with chloroform, and the chloroform extracts were dried over K_2CO_3 and concentrated. The mixture of pyridine and amines was separated with a column filled with Al_2O_3 by

successive elution with systems A and B to give the following compounds: α-picoline (bp 128-130°C; picrate mp 149-150°C), N-methylaniline (bp 195-196°C; picrate mp 144-145°C), N-methylmorpholine (bp 116-117°C; picrate mp 225-226°C), N-phenylmorpholine [mp 59-60°C (from hexane); picrate mp 162-164°C], N-methylpiperidine (bp 106-107°C; picrate mp 148°C), N-phenylpiperidine (bp 245-250°C; picrate mp 148°C), and N-methylpiperazine (bp 134-136°C; picrate mp 272-273°C). The purity of the α-picoline and amines obtained was monitored by chromatography. The compounds were identified by comparison of the bases and picrates with genuine samples.

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REACTION OF N-PHENYLMALEINIMIDE WITH 2- AND 4-VINYLPYRIDINES

P. B. Terent'ev, V. G.Kartsev, and A. N. Kost*

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The reaction of 2- and 4-vinylpyridines with N-phenylmaleinimide in acetic anhydride proceeds via the scheme of the diene synthesis and leads to pyrrolo[3,4-f]-quinoline and pyrrolo[3,4-i]isoquinoline derivatives.

We have previously shown that the reaction of 2- and 4-vinylpyridines (I, II) with azadienophiles proceeds via a 1,4-cycloaddition scheme with the participation of a pseudodiene system (the vinyl group plus the C_2—C_3 multiple bond of the pyridine ring) [1, 2]. In addition, Wagner-Jauregg and co-workers have found that in neutral media (butanol and acetonitrile) the reaction of vinylpyridines I and II with N-substituted maleinimides proceeds via a 1,3-dipolar cycloaddition scheme with the participation of the pyridine nitrogen atom and leads to complex polycyclic compounds [3, 4].

We have established that they react with N-phenylmaleinimide via the usual scheme of the diene synthesis in acetic anhydride, in which the nucleophilic properties of vinylpyridines are markedly suppressed. Thus, we obtained diadducts IVa-d (Table 1), the formation of which can be explained by reaction of the initially formed adducts III with a second molecule of dienophile via the previously proposed scheme [1], when we refluxed mixtures of vinylpyridines Ia-d with N-phenylmaleinimide in acetic anhydride for many hours: (Scheme, top, following page.)

*Deceased.

M. V. Lomonosov Moscow State University, Moscow 117234.

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