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RECYCLIZATION OF SALTS OF ASYMMETRIC HANTZSCH PYRIDINES

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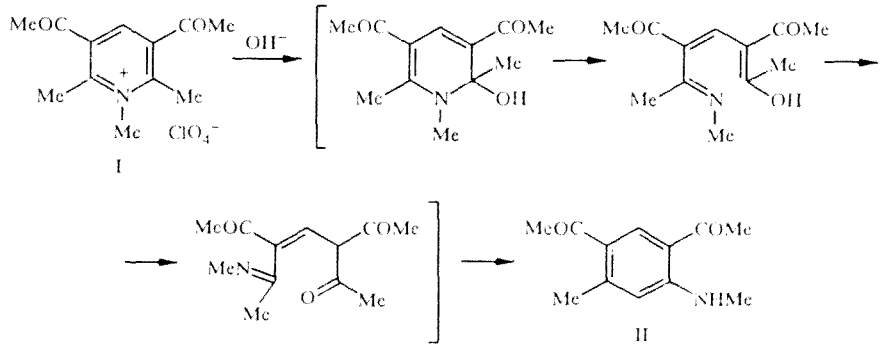
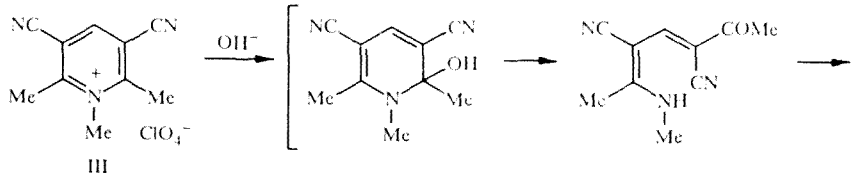
Some quaternary salts of asymmetric substituted pyridines with functional group at the 3- and 5-positions have been synthesized. It has been established that when there is an ester group present, the latter participates in the recyclization of the salts on treatment with alkali, resulting in the formation of pyridin-2-ones.

It was previously shown that the recyclization of quaternary 2,6-dimethyl-3,5-diacetylpyridinium salts I by aqueous alcoholic alkali occurs by a route involving isomerization to give 2,4-diacetyl-N,5-dimethylanilines II [1]. 2,6-Dimethyl-3,5-dicyanopyridinium salts III undergo a double rearrangement under similar conditions and form 2-methylamino-3-acetyl-5-cyanopyridines IV [1].



I

II



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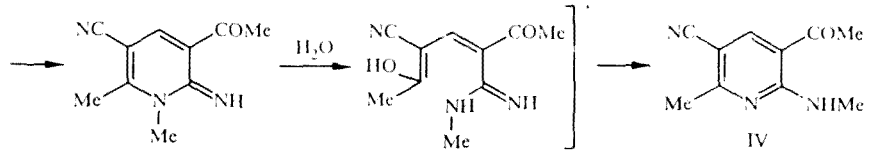

IV

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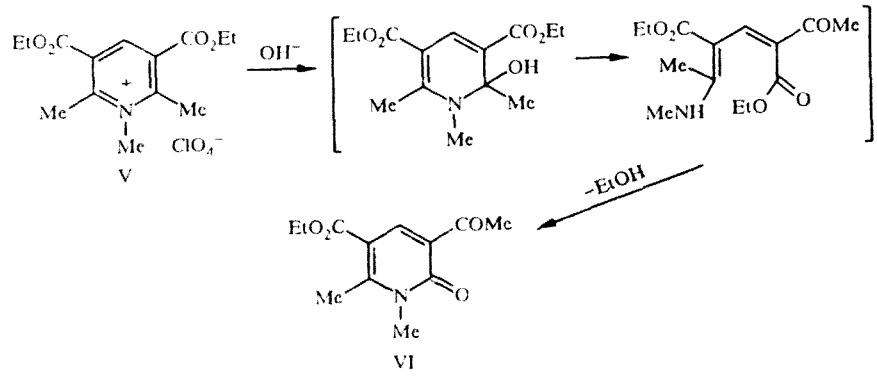
TABLE 1. Properties of Pyridinium Perchlorates

Compound	Empirical formula	mp, °C	PMR spectrum, (DMSO-d_6), δ, ppm							Reaction temp., °C	Reaction time, h	Yield, %
			1-CH_3 (s, 3H)	2-CH_3 (s, 3H)	6-CH_3 (s, 3H)	5-$COOCH_2CH_3$ (J = 7Hz)		R	4-Ph (m, 5H)			
						CH_3 (t, 3H)	CH_2 (q, 2H)					
IXa	$C_{18}H_{19}ClN_2O_6$	118...120	4,19	2,85	3,05	0,84	4,07	–	7,63...7,43	90	12	81
IXb	$C_{24}H_{24}ClNO_7$	187...188	4,20	2,88	2,65	0,85	4,06	7,73...7,33 (10H, m, 4-Ph, 5-CO-Ph)		65	14	85
IXc	$C_{19}H_{22}ClNO_7$	161...162	4,11	2,77	2,68	0,81	4,03	2,06 (3H, s, $COCH_3$)	7,54...7,17	65	16	85

TABLE 2. Properties of Pyridin-2-ones

Compound	Empirical formula	mp, °C	PMR spectrum ($CDCl_3$), δ, ppm					IR spectrum, ν, cm^{-1}	Yield, %
			1-CH_3 (s, 3H)	6-CH_3 (s, 3H)	$COCH_3$ (s, 3H)	5-R	4-Ph (m, 5H)		
Xa	$C_{16}H_{14}N_2O_2$	163...164	3,57	2,66	2,11	–	7,40...7,20	1650, 1715 (C=O), 2240 (C ≡ N)	80
Xb	$C_{22}H_{19}NO_3$	191...192	3,60	2,27	2,08	7,49...6,92 (10H, m, 4-Ph, 5-COPh)		1640, 1705 (C=O)	88
Xc	$C_{17}H_{17}NO_3$	136...137	3,56	2,32	2,10	1,69 (3H, s, $COCH_3$)	7,35...7,13	1640, 1700 (C=O)	70
Xd	$C_{22}H_{20}N_2O_3$	248...250	3,57	2,44	2,15	8,30 (1H, br.s, NH); 7,25...7,01 (10H, m, 4-Ph, 5-CONHPh)		1630, 1680 (C=O), 3420 (NH)	80

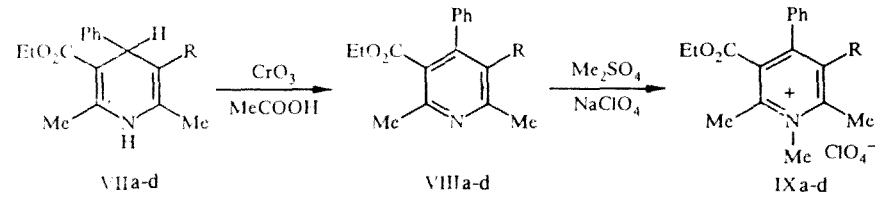
In the case of the 2,6-dimethyl-3,5-diethoxycarbonylpyridinium salt V, reaction involves an ester group in the formation of a new ring, yielding the pyridin-2-one VI [2].



In salts of asymmetric Hantzsch pyridines it is not possible to predict *a priori* the recyclization route from the presence of different functional groups on the $C_{(3)}$ and $C_{(5)}$ atoms.

In order to shed light on this question we synthesized asymmetric 2,6-dimethyl-1,4-dihydropyridines VII by a known method [3-5]. 3-Cyano-5-ethoxycarbonyl-1,4-dihydropyridine VIIa was obtained by condensation of 3-aminocrotononitrile with the benzylidene derivative of ethyl acetoacetate in 72% yield. Compound VIIb was obtained by condensation of ethyl β-aminocrotonate with the benzylidene derivative of benzoylacetone. Reaction of acetylacetone imine with the benzylidene derivative of ethyl acetoacetate yielded the 1,4-dihydropyridine VIIc. The synthesis of compounds VIId-IXd has been reported in [6].

The oxidation of 1,4-dihydropyridines VII with chromium trioxide in acetic acid gave pyridines VIII in 60-70% yield.

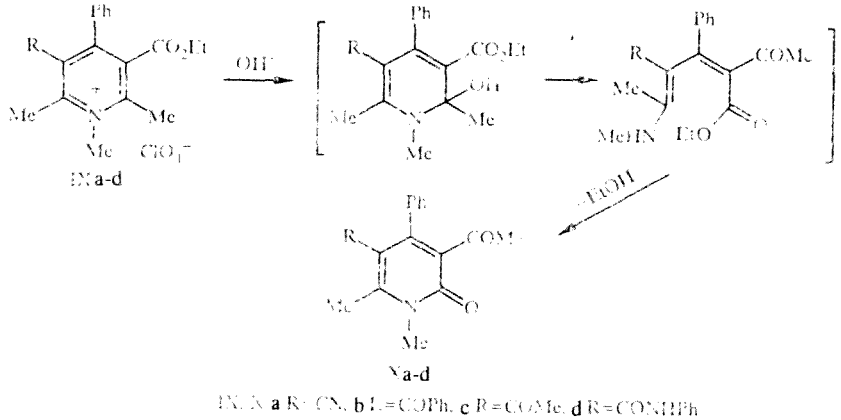


VII–IX a R=CN, b R=COPh, c R=COMe, d R=CONHPh

The PMR spectra of the quaternary pyridinium salts IX are listed in Table 1.

We have established that the recyclization of pyridinium salts IX by aqueous alcoholic alkali at room temperature results in the formation of the functionally substituted pyridin-2-ones X in 79-88% yield. Their structures have been confirmed from their PMR and IR spectra (see Table 2) and from elemental analysis.

The first stage of the reaction is the addition of hydroxyl ion to the 6-position of the ring and the formation of a pseudobase. This is followed by scission of the pyridine ring at the C–N bond and the formation of a new ring via the ester group with elimination of a molecule of ethanol.



No other compounds were detected. This indicates that the alternative recyclization route with attack by hydroxyl ion at the 2-position, which could result in an aminopyridine an substituted anilines, does not occur.

Thus, it has been established that attack by hydroxyl ion occurs at the 6-position of the ring, regardless of what substituent is at the 3-position, and this dictates the course of the reaction.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) in $CDCl_3$ and DMSO-d_6 solution, with HMDS as the internal standard. The IR spectra were recorded on a Specord IR-71 instrument in $CHCl_3$. The course of the reaction and the purity of the compounds were monitored by TLC on Silufol UV-254 plates in chloroform–ethyl acetate (9:1). The properties of the compounds synthesized are listed in Tables 1 and 2.

The results of elemental analysis for C and H in the compounds prepared corresponded to the calculated values.

3-Substituted 1,2,6-trimethyl-4-phenyl-5-ethoxycarbonylpyridinium Perchlorates (IXa-c) (general method). The respective pyridine (VIIIa-c, 5 mmole) [3-5] was heated with 1.9 ml (20 mmole) of freshly prepared dimethyl sulfate (reaction time and temperature are indicated in Table 1). The mixture was cooled and washed with ether (3 × 10 ml), the residue was dissolved in 5 ml of water, and a saturated aqueous solution of 1.5 g of sodium perchlorate was added. The precipitate that formed was filtered off, dried, and recrystallized from ethanol.

5-Substituted 3-Acetyl-1,6-dimethyl-4-phenylpyridine-2-ones (Xa-d) (general method). To a solution of 1 mmole of the respective pyridinium perchlorate IX in 7 ml of 50% ethanol was added a solution of 0.2 g (5 mmole) of NaOH in 2 ml of 50% ethanol. The reaction mixture was left for 1 h at room temperature. The crystals that precipitated were filtered off, washed with water until a neutral reaction was given by the water, and dried. The product was recrystallized from ethanol.

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