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DIRECT HYDROXYLATION OF N-SUBSTITUTED [4,5-b]PYRIDINES AND IMIDAZO[4,5-c]PYRIDINES

Yu. M. Yutilov and I. A. Svertilova

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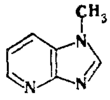
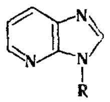
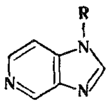
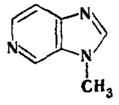
It is shown that when N-methyl (or benzyl) derivatives of imidazo[4,5-b]pyridine and N-methyl-substituted derivatives of imidazo[4,5-c]pyridine are heated with alkalis, the imidazole ring is always hydroxylated to give the corresponding 2-imidazolones.

It is known [1, 2] that quinoline and N-alkylbenzimidazoles are readily hydroxylated when they are fused with alkalis. This provides a basis for the assumption that in the case of hydroxylation of N-substituted imidazo[4,5-b]pyridines (I, (II) and imidazo[4,5-c]pyridines (III, IV) the reaction center may be found both in the pyridine and the imidazole fragments of the molecules.


I

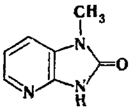

II a-c

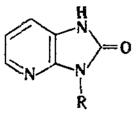

III a-c

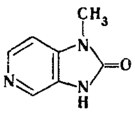

IV

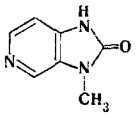
II, III a R=CH_3; b R=$CH_2C_6H_5$; c R=C_6H_5

When I, IIa,b, IIIa, and IV are heated with excess anhydrous potassium hydroxide to 150-190°C one observes a vigorous reaction with hydrogen evolution to give imidazo[4,5-b]-pyridin-2-ones (V, VIa, b) and imidazo[4,5-c] pyridin-2-ones (VII and VIII) [3].


V


VI a, b


VII


VIII

VI a R=CH_3; b R=$CH_2C_6H_5$

The success of this transformation depends decisively on both the mutual orientation of the imidazole and pyridine rings in I-IV and on the nature of the N-substituent. Particularly high yields of imidazopyridin-2-ones are obtained in the imidazo[4,5-b]pyridine series. In this connection one should note that the least basic of the examined compounds (IIa [4]) is hydroxylated under the mildest conditions in almost quantitative yield, whereas this transformation is less characteristic for the more basic imidazo[4,5-c]pyridines (IIIa

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Institute of Physical-Organic Chemistry and Carbon Chemistry, Academy of Sciences of the Ukrainian SSR, Donetsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1252-1254, September, 1976. Original article submitted October 28, 1975.

TABLE 1. Hydroxylation of Imidazopyridines I-IV

Starting compound	Reaction conditions		Imidazolone	mp, °C*	Yield, %
	temp., °C	time, min			
I	150—155	15	V	200—201	70
IIa	175—180	20	VIa	235—236	98
IIb	160—170	30	VIb	175—176	65
IIIa	165—170	30	VII	271—272	27
IV	180—190	20	VIII	259—260	44

*The compounds were purified by crystallization: V from benzene, VIa and VIII from ethanol, VIb from water—ethanol, and VIIa from dioxane. The melting points of all of the compounds were in agreement with those described in [3].

and IV), and the yields of imidazolones (VII and VIII) are low; however, in contrast to the isomeric IIb, we were unable to subject N-benzyl-substituted IIIb to this reaction. After fusing imidazopyridine IIIb with potassium hydroxide at 185-190°, we isolated ∿75% of the starting compound, and raising the temperature of the reaction mixture to 200-210° led to complete resinification of the compound. This sort of behavior is particularly characteristic for N-phenyl derivatives of imidazo[4,5-b]pyridine (IIc) and imidazo[4,5-c]pyridine (IIIc), which undergo resinification at 180-190°, although from 85 to 100% of the starting compounds can be recovered after heating with alkali at 160-170°.

In contrast to the results obtained for N-substituted benzimidazoles [2], replacement of potassium hydroxide by sodium hydroxide in the reaction with bases I-IV does not affect the yields of imidazolones V-VIII.

EXPERIMENTAL

Imidazopyridines I, IIa, IIIa,b, and IV. These compounds were obtained by the method in [5].

2-Mercapto-3-benzyl-3H-imidazo[4,5-b]pyridine. A mixture of 1.60 g (8 mmole) of 3-amino-2-benzylaminopyridine [3], 6.42 g (40 mmole) of potassium ethylxanthate, and 30 ml of pyridine was refluxed for 5 h, after which the pyridine was removed by distillation, and the residue was dissolved in a small amount of 5% NaOH solution. The alkaline solution was heated with charcoal and filtered, and the filtrate was acidified to pH 5 and 10% hydrochloric acid. The resulting precipitate was removed by filtration and washed with water to give 1.65 (87%) of colorless prisms with mp 210-211° (from aqueous alcohol). Found: C 64.5; H 4.8; S 13.3%. $C_{13}H_{11}N_3S$. Calculated: C 64.7; H 4.6; S 13.3%.

3-Benzyl-3H-imidazo[4,5-b]pyridine (IIb). A mixture of 2.40 g (10 mmole) of 2-mercapto-3-benzyl-3H-imidazo[4,5-b]pyridine and 60 ml of 10% nitric acid was heated at 50-55° for 2 h, after which it was cooled and made alkaline to pH 10 with 40% NaOH solution. The resulting precipitate was removed by filtration to give 2 g (95%) of colorless prisms with mp 80° (from n-hexane). Found: C 74.4; H 5.4; N 19.8%. $C_{13}H_{11}N_3$. Calculated: C 74.6; H 5.3; N 20.1%.

2-Mercapto-3-phenyl-3H-imidazo[4,5b]pyridine. This compound was obtained in 89% yield from 3-amino-2-phenylaminopyridine [3] by the method used to prepare 2-mercapto derivative IIb. The product was obtained as prisms with mp 293-295° (from aqueous alcohol). Found: C 63.0; H 4.3; S 13.9%. $C_{12}H_9N_2S$. Calculated: C 63.4; H 4.0; S 14.1%.

3-Phenyl-3H-imidazo[4,5-b]pyridine (IIc). A mixture of 1.50 g (6.6 mmole) of 2-mercapto-3-phenyl-3H-imidazo[4,5-b]pyridine and 30 ml of 10% nitric acid was heated carefully on a water bath. At 70° the mixture began to effervesce with the evolution of nitrogen oxides, after which it was allowed to stand at the same temperature for 30 min. It was then heated on a boiling-water bath for 1.5 h. The solution was evaporated to one-third of its original volume and made strongly alkaline with 40% NaOH. The reaction product was extracted with hot benzene. The benzene extract was dried with solid alkali, and the solvent was removed by distillation to give 1.17 g (90%) of an oil, which crystallized on prolonged standing to give colorless needles with mp 31-32° (after slow sublimation). The picrate was obtained as light-yellow prisms with mp 171-172° (from alcohol). Found: C 51.2; H 2.9; N 19.6%. $C_{12}H_9N_3 \cdot C_6H_3N_3O_7$. Calculated: C 51.0; H 2.9; N 19.8%.

2-Mercapto-1-phenyl-1H-imidazo[4,5-c]pyridine. This compound was obtained in 90% yield from 3-amino-4-phenylaminopyridine [3] by the method used to prepare 2-mercapto derivative IIb. The product was obtained as prisms with mp 310° (from aqueous alcohol). Found: C 62.9; H 4.1; S 14.0%. $C_{12}H_9N_3S$. Calculated: C 63.4; H 4.0; S 14.1%.

1-Phenyl-1H-imidazo[4,5]pyridine (IIIc). This compound was obtained in 88% yield by oxidation of the corresponding mercapto derivative as in the preparation of IIc. The product was obtained as colorless needles with mp 105-106° (from benzene–hexane). Found: C 73.5; H 4.4; N 21.4%. $C_{12}H_9N_3$. Calculated: C 73.8; H 4.6; N 21.5%.

General Method for Hydroxylation of Imidazopyridines (Table 1). A mixture of 10 mmole of imidazopyridine and 50 mmole of anhydrous KOH or NaOH was heated at 150-190°. At the end of hydrogen evolution, the fused mixture was cooled and dissolved in 2-3 ml of water. The aqueous solution was acidified to pH 5-6 with hydrochloric acid, and the resulting precipitate was removed by filtration, washed with a small amount of cold water, dried, and crystallized from a suitable solvent.

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SYNTHESIS AND PROPERTIES OF SUBSTITUTED 2-IMIDAZOLIDINONES

T. G. Kharlamova, Yu. G. Putsykin,
and Yu. A. Baskakov

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4-Hydroxy- and 4-hydroxylamino-1-hydroxy-3-aryl-5,5-dimethyl-2-imidazolidinones, respectively, were obtained by treatment of N-arylcarbamoyl derivatives of N-(1-oximino-2-methyl-2-porpyl)hydroxylamine with acids and alkalis. 4-Hydroxylaminoimidazolidinones react with p-nitrobenzaldehyde to give nitrones and are converted in acidic media to 4-hydroxy derivatives, which by the action of methanol in the presence of p-toluenesulfonic acid give 4-methoxy-2-imidazolidinones. Acylation and alkylation of 4-hydroxy- and 4-methoxy-2-imidazolidinones take place at the hydroxy group attached to $N_{(1)}$.

In the present research we have studied the behavior of the previously obtained N-arylcarbamoyl derivatives of N-(1-oximino-2-methyl-2-propyl)hydroxylamine [1] (I) in acidic and alkaline media. It was established that dissolving of I in aqueous NaOH solution and subsequent neutralization lead to the isolation of white crystalline II, the results of the elementary analysis of which are in agreement with the data for starting I.

The absorption band of a carbonyl group at 1715 and 1720 cm^{-1}, shifted to the high-frequency region by 50-60 cm^{-1} as compared with the same band in the spectra of starting I,

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