SYNTHESIS OF NITROSOPYRIDINOLS BY CYCLOCONDENSATION OF ISONITROSO β-DICARBONYL COMPOUNDS WITH CYANOACETAMIDE

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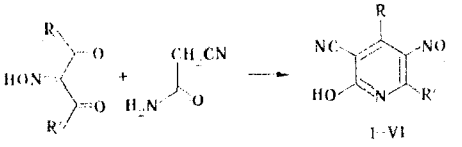
UDC 547.823

The cyclocondensation of isonitroso β-dicarbonyl compounds with cyanoacetamide leads to nitroso derivatives of the pyridine series. The corresponding nitrosopyridinols are formed when isonitroso β-diketones participate in the cyclization, while nitrosopyridinediols are formed from isonitroso derivatives of β-oxo carboxylic acid esters.

We have previously reported the condensation of isonitroso β-dicarbonyl compounds with ketones in the presence of alkali metal alkoxides [1] and with enamines [2], which leads, respectively, to nitrosophenols and nitrosoanilines. One might have assumed that if cyanoacetamide were used in the reaction with isonitroso β-diketones the formation of the corresponding nitrosopyridines would be possible. The fact that cyanoacetamide undergoes cyclization with β-diketones and β-oxo carboxylic acid esters with the formation of a pyridine ring [3] constitutes evidence in favor of this.

The successful occurrence of this reaction would make it possible to synthesize nitrosopyridines, which have been obtained by the reduction of nitropyridines and nitrosation of derivatives that contain no less than two hydroxy groups or a hydroxy group and an amino group simultaneously [4].

In fact, compounds, the IR and UV spectra and results of elementary analysis of which were in agreement with the hypothetical nitrosopyridinols (I-IV), were obtained in the reaction of cyanoacetamide with isonitroso β-dicarbonyl compounds in the presence of bases (alcoholic alkali and piperidine).



I-VI

I $R=R'=CH_3$; II* $R=CH_3$, $R'=C_6H_5$; III* $R=4\text{-}ClC_6H_4$, $R'=CH_3$; IV* $R=4\text{-}CH_3C_6H_4$, $R'=CH_3$; V $R=CH_3$, $R'=OH$; VI $R=C_6H_5$, $R'=OH$

The reaction of isonitroso derivatives of β-oxo carboxylic acid esters with cyanoacetamide leads to nitrosopyridinediols V and VI.

The structure of nitrosopyridinol I was proved by alternative synthesis. For this we studied 2,4-dimethyl-5-cyano-6-pyridinol by cyclization of acetylacetone with cyanoacetamide [6], and the product was nitrated in the 3 position by the method in [7] and reduced to the corresponding amine. Pyridinol I, which we synthesized by the method above, was reduced by the same method. The UV and IR spectra and the melting points of the aminopyridinols synthesized by the two methods were in agreement.

Thus the investigated cyclocondensation of isonitroso β-dicarbonyl compounds with cyanoacetamide opens up a new route to the synthesis of nitroso derivatives of the pyridine series.

*An alternative structure with a different orientation of the substituents is possible.

Siberian Technological Institute, Krasnoyarsk 660049. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 514-515, April, 1983. Original article submitted June 14, 1982.

 0009-3122/83/1904-0420$07.50

TABLE 1. Nitrosopyridinols I-VI

Compound	Synthesis time	Dec. temp., °C	N found, %	Empirical formula	N calc., %	Yield, %
I	2 h	115	23,7	$C_8H_7N_2O_2$	23,4	60
II*	7 days	270	17,5	$C_{13}H_9N_2O_2$	17,0	74
III*	10 days	280	15,3	$C_{13}H_8ClN_2O_2$	15,5	54
IV*	7 days	254	16,6	$C_{14}H_{11}N_2O_2$	16,1	55
V	2 h	310	23,4	$C_7H_5N_2O_3$	23,1	34
VI	10 min	126	17,4	$C_{12}H_7N_2O_3$	17,3	27

*An alternative structure with a different orientation of the groups is possible. The regiospecificity has not yet been investigated.

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded with a UR-20 spectrometer. The UV spectra were recorded with an SF-16 spectrophotometer.

2,4-Dimethyl-3-nitroso-5-cyano-6-pyridinol (I). A 0.5-g sample of piperidine was added to a solution of 1.26 g (0.01 mole) of isonitrosoacetylacetone and 0.84 g (0.01 mole) of cyanoacetamide in 10 ml of ethanol, and the mixture was maintained at room temperature for 30 min. It was then diluted with diethyl ether, and the resulting green substance was removed by filtration, washed with ether, and dried to give a product with mp 115°C (dec.) in 60% yield. Compounds II-IV were similarly obtained.

4-Methyl-3-nitroso-5-cyanopyridine-2,6-diol (V). A solution of 0.84 g (0.01 mole) of cyanoacetamide in 20 ml of alcoholic KOH (1.68 g of KOH) was added to 1.51 g (0.01 mole) of isonitrosoacetoacetic ester, and the mixture was maintained at room temperature for 2 h. During this time, green crystals of the potassium salt of the desired product precipitated. Workup gave a product with mp 280°C (dec.) in 96% yield [from aqueous alcohol (1:1)]. For the isolation of the nitrosopyridinediol in free form the salt was dissolved in 5 ml of water, and the solution was cooled and neutralized with dilute HCl (1:1). The resulting brown precipitate was removed by filtration and recrystallized from water to give a product with mp 310°C (dec.) in 34% yield.

3-Nitroso-4-phenyl-5-cyanopyridine-2,6-diol (VI). A solution of 0.84 g (0.01 mole) of cyanoacetamide in 20 ml of alcoholic KOH (2.24 g) was added to 2.21 g (0.01 mole) of isonitrosobenzoylacetic ester, and the mixture was maintained at room temperature for 30 min. It was then diluted with diethyl ether, and the liberated potassium salt (in the form of an oil) was washed with petroleum ether until a solid precipitate formed. Workup gave a product with mp 250°C (dec.) in 84% yield. The reaction product was isolated in free form by the method described above to give a product with mp 126°C (from water) in 27% yield.

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