A FACILE REARRANGEMENT OF PYRIDINECARBOHYDROXAMIC ACIDS IN FORMAMIDE [1]

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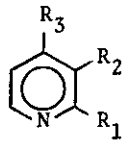
Abstract —— Five pyridinecarbohydroxamic acids were converted smoothly to the corresponding aminopyridines by means of the "amide modification" of the Lossen rearrangement.

In the Lossen rearrangement, a hydroxamic acid must first be acylated and the rearrangement and hydrolysis can be carried out by heating the isolated O-acyl derivative with alkali.[3] These preliminary steps make synthetic application of the Lossen rearrangement to achieving C-to-N migration in carboxyl derivatives less attractive than the related reactions.[3c] The "amide modification" of the rearrangement[4] appears to overcome these difficulties, since it does not require any prior treatment of hydroxamic acids. A short heating of hydroxamic acids RCONHOH in formamide converts them into amines RNH_2 accompanied by certain amounts of N-formylamines, ureas or heterocyclic compounds, depending on the nature of R. In the previous paper,[5] we reported a successful attempt of this modified method as applied to the rearrangement of anthranilohydroxamic acids and advocated the amide modification as a versatile method for the benzimidazol-2-one synthesis. In this paper we would like to report the rearrangement of pyridinecarbohydroxamic acids 1 ~ 5 by means of this modification.

A typical procedure for the reactions was as follows. A suspension of a hydroxamic acid (1 ~ 5)(10 ~ 20 mmol) in 5 ml of formamide was heated for 20 min at 130 ~ 150 °C. Aliquots were withdrawn and the consumption of the hydroxamic acid was confirmed by the ferric chloride test. The solution was cooled, poured into water, and the mixture was treated several times with chloroform. The combined extracts were evaporated to dryness on a rotary evaporator and the residue was recrystallized to give the results as summarized in Table 1.[6]

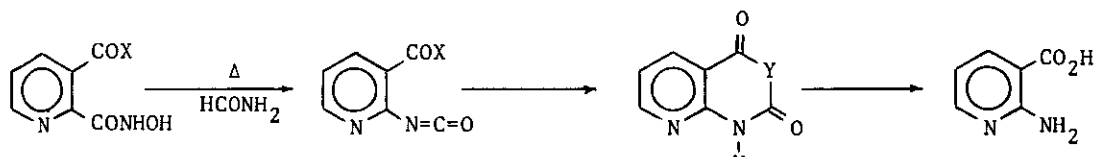
The rearrangement of pyridine-2- and 4-carbohydroxamic acids (1 and 3) took place smoothly to give the corresponding amines in good yields. In contrast to them,

Table 1. The modified Lossen rearrangement of pyridinecarbohydroxamic acids 1 ~ 5:[6]



No.	hydroxamic acid R_1	R_2	R_3	reaction product R_1	R_2	R_3	mp/°C	yield/%
1	CONHOH	H	H	NH_2	H	H	57	84
2	H	CONHOH	H	H	NH_2	H	64	24.5
				H	$NHCONH_2$	H	178	33.5
3	H	H	CONHOH	H	H	NH_2	159	79
4	CONHOH	COOH	H	NH_2	CO_2H	H	310	83.5
5	CONHOH	CONHOH	H	NH_2	CO_2H	H	310	80

pyridine-3-carbohydroxamic acid 2 underwent the Lossen rearrangement sluggishly and a mixture of 3-aminopyridine and 3-pyridylurea was obtained. Hydroxamic acids 4 and 5 derived from quinolinic acid gave 2-aminonicotinic acid 6 in good yield. Since the hydroxyamide group at the 2-position of the pyridine ring undergoes the Lossen rearrangement more readily than that in the 3-position, the formation of 6 from both 4 and 5 is interpreted as coming from the initial formation of 2-isocyanatonicotinic acids 7. Cyclization to give the Leuchs anhydride-type intermediates 8[7] followed by hydrolysis would lead to 6. The intermediacy of 8 (Y = NOH) is supported by the observation that this compound was isolated in 43 % yield when disodium 2,3-pyridinedicarbohydroxamate was heated with benzenesulfonyl chloride.[8]



4 (X = OH)
5 (X = NHOH)

7

8 (Y = O or NOH)

6

In the previously described attempt to carry out the classical Lossen rearrangement on 4, the monosodium salt of the O-benzoyl derivative was heated in water to give 6 in 54 % yield. A mixture of 8 (Y = O) (36 %) and 6 (40 % yield) was obtained when heated in dry toluene.[9]

In view of its simplicity and straightforwardness of the reaction, our method may safely be recommended to the rearrangement of pyridinecarbohydroxamic acids.[10]

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REFERENCES AND NOTES

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6) The pyridinecarbohydroxamic acids were prepared according to the literature method (B. E. Hackley, Jr., R. Plapinger, M. Stolberg, and T. Wagner-Jauregg, J. Am. Chem. Soc., 1955, 77, 3651. See also ref. 9). Satisfactory elemental analysis and IR and ^{1}H NMR spectral data were obtained for all the compounds. The reaction conditions were not optimized except for the following information. The use of formamide or N-methylformamide is essential to the present reaction (see also: E. Lipczyńska-Kochany, Wiadomości Chem., 1982, 36, 735). At lower temperatures (80 ~ 90°C), only hydrolysis of the hydroxamic acids took place.

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10) A mechanistic study of the reactions in formamide is in progress. The Lossen rearrangement of an O-formate or equivalent species is one of the candidates for the mechanism.

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