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The Transformation of Pyrido[2,3-*d*]pyrimidine into 1,8-Naphthyridine

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The reaction of pyrido[2,3-*d*]pyrimidine (**1**) with active methylene compounds and ketones (NuH) were carried out, and resulted in the formation of 1,8-naphthyridines.

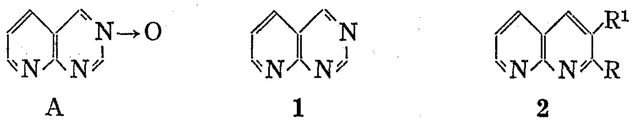
Thus, the reaction with acetophenone (NuH-1), propiophenone (NuH-2), butyrophenone (NuH-3), cyclopentanone (NuH-4), cyclohexanone (NuH-5), malononitrile (NuH-6), and ethyl cyanoacetate (NuH-7) gave 2-phenyl- (**2-1**), 3-methyl-2-phenyl- (**2-2**), 3-ethyl-2-phenyl-1,8-naphthyridine (**2-3**), 7,8-dihydro-6*H*-cyclopenta[*b*][1,8]naphthyridine (**2-4**), 6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridine (**2-5**), 2-amino-1,8-naphthyridine-3-carbonitrile (**2-6**), and ethyl 2-amino-1,8-naphthyridine-3-carboxylate (**2-7**), respectively.

And the possible reaction mechanism was proposed.

Keywords——pyridopyrimidine; active methylene compounds; ketones; naphthyridines; ring transformation; mechanism

Recently an interest has been shown in the transformation of pyrido[2,3-*d*]pyrimidine 3-oxide (A) with active methylene compounds and ketones (NuH) into 1,8-naphthyridines (**2**).[2] For example, the reaction of A with acetophenone (NuH-1) without solvent and catalyst gave 2-phenyl-1,8-naphthyridine (**2-1**).[2b]

With the expectation that a similar transformation takes place, we carried out the reaction of pyrido[2,3-*d*]pyrimidine (**1**)[3] with NuH and found the desired transformation of **1** into **2**, although the yields of **2** were not so good as shown in Table I.



	-R	-R^1
2-1	-C_6H_5	-H
2-2	-C_6H_5	-CH_3
2-3	-C_6H_5	-C_2H_5
2-4	-$(CH_2)_3$-	
2-5	-$(CH_2)_4$-	
2-6	-NH_2	-CN
2-7	-NH_2	-$COOC_2H_5$

Chart 1

Molar ratio of **1** to NuH was set 1: 2.5. A suitable reaction time and temperature for each case were shown in Table I. Thus, NuH-1, propiophenone (NuH-2), and butyrophenone (NuH-3) reacted with **1** yielding **2-1**,[2b] 3-methyl-2-phenyl- (**2-2**)[2b], and 3-ethyl-2-phenyl-1,8-naphthyridine (**2-3**),[2b] respectively. Similarly, the reaction with cyclopentanone (NuH-4), and cyclohexanone (NuH-5) resulted in the formation of 7,8-dihydro-6*H*-cyclopenta[*b*][1,8]naphthyridine (**2-4**),[2b] and 6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridine (**2—5**),[2b] respectively. Malononitrile (NuH-6), and ethyl cyanoacetate (NuH-7) in methanol also gave 2-amino-1,8-naphthyridine-3-carbonitrile (**2-6**),[2a] and ethyl 2-amino-1,8-naphthyridine-3-carboxylate (**2-7**),[2a] respectively. But the reaction with aliphatic ketone such as 3-pentanone (NuH-8) and 2-butanone (NuH-9) did not give any of **2**, and resulted in the recovery

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[1] Location: *2-2-1 Oshika, Shizuoka-shi.*

[2] *a*) T. Higashino and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), 21, 2643 (1973); *b*) T. Higashino, K. Suzuki, and E. Hayashi, *ibid.*, 23, 2939 (1975).

[3] T. Higashino and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **18**, 1457 (1970).

of the starting material (**1**). The identification of each of 1,8-naphthyridines (**2-1** to **2-7**) was made by the mixed melting point test using the corresponding authentic specimen prepared by each specific route.[2a,b)]

Table I. Reaction of **1** with NuH

NuH	Reaction time (hr)	Reaction temp. (°C)	Product 2	%	mp (°C)	Recovery of **1** %
NuH-1	12	140—150	**2-1**	17.9	104—105	12.6
NuH-2	12	140—150	**2-2**	30.0	113—114	18.3
NuH-3	12	140—150	**2-3**	31.6	125—126	13.0
NuH-4	12	130—140	**2-4**	28.2	140—141	—
NuH-5	12	130—140	**2-5**	16.6	108—109	—
NuH-6[a)]	21	Room temp.	**2-6**	73.2	260—265 (dec.)	—
NuH-7[b)]	38	Room temp.	**2-7**	7.7	187—189 (dec.)	23.9
NuH-8	21	170—180	—			66.0
NuH-9	24	180—200	—			80.2

a) In MeOH. *b*) In EtOH.

The possible reaction mechanism is similar to that of the transformation of A into 2 reported previously,[2b)] and may be written as in Chart 2 involving addition—ring opening between the 2- and 3-position—ring closure.

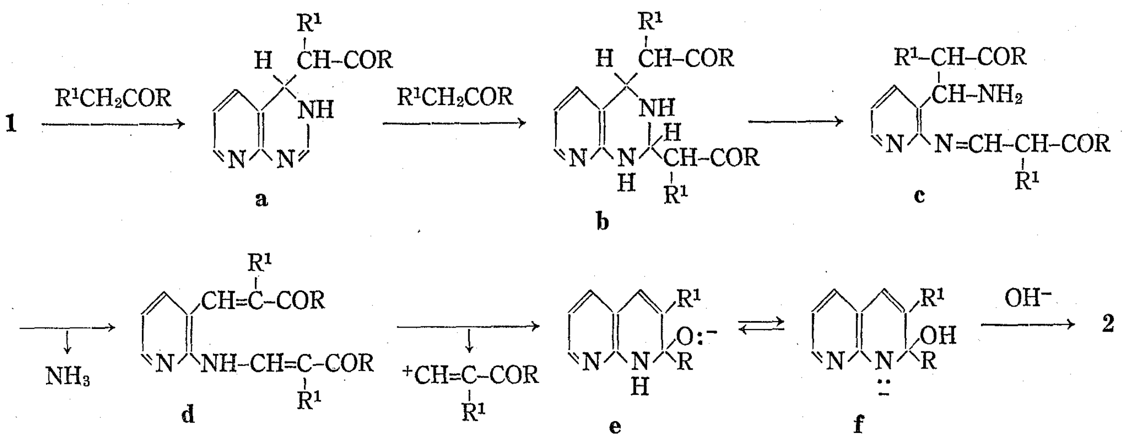

Chart 2

Experimental

Reaction of 1 with NuH——In a sealed tube a mixture of **1** (262 mg, 2.0 mmol) and NuH (5.0 mmol) was heated under the condition shown in Table I. The reaction mixture was extracted with 2 N HCl, and the HCl layer was neutralized with K_2CO_3. The separated oily substance was extracted with $CHCl_3$ and dried over Na_2SO_4. The extract was chromatographed on a column of silica gel by changing eluent as follows; benzene, benzene–$CHCl_3$ (1 : 1), $CHCl_3$, and MeOH. The elution with benzene–$CHCl_3$ gave **2** as white needles from petr. ether. The elution with $CHCl_3$ recovered **1**, mp 107—108° as colorless needles from petr. ether. The yields of **2** were shown in Table I.

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