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Studies on the Reactions of Pyrido[2,3-*d*]pyrimidine 3-Oxide with Ketones. The Transformation of Pyrido[2,3-*d*]pyrimidine 3-Oxide into 1,8-Naphthyridines*

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The direct reactions of pyrido[2,3-*d*]pyrimidine 3-oxide (III) with ketones without a base were carried out and resulted in the transformation of III into 1,8-naphthyridines (IV), although the yields of IV were poor.

Thus, acetophenone, propiophenone, butyrophenone, and valerophenone reacted with III yielding 2-phenyl- (IV-1), 3-methyl-2-phenyl- (IV-2), 3-ethyl-2-phenyl- (IV-3), and 3-propyl-2-phenyl-1,8-naphthyridine (IV-4), respectively, together with 2-aminonicotinaldehyde oxime (V) and 2-aminonicotinonitrile (VI). Similary acetone, 3-pentanone, 2-butanone, 2-pentanone, and 3-methyl-2-butanone resulted, respectively, in 2-methyl- (IV-5), 2-ethyl-3-methyl (IV-6), 2,3-dimethyl- (IV-7), 3-ethyl-2-methyl (IV-8), and 2-isopropyl-1,8-naphthyridine (IV-9) together with V and VI. Cyclopentanone, and cyclohexanone also gave 7,8-dihydro-6H-cyclopenta[*b*][1,8]naphthyridine (IV-10), and 6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridine (IV-11), respectively. Moreover III and 3,3-dimethyl-2-butanone did not lead to the expected 1,8-naphthyridines, but gave 3,3-dimethyl-1-(3-hydroxy-3,4-dihydro-4-pyrido[2,3-*d*]pyrimidinyl)-2-butanone (VIII).

These 1,8-naphthyridines, IV-1 to IV-12, were also prepared by the Friedlaender synthesis with 2-aminonicotinaldehyde (IX) and the corresponding ketone in the presence of sodium methoxide as a catalyst.

This study is one of our researches on the reactions of the condensed pyrimidine ring system with nucleophiles.[2] Recently an interest has been shown in the transformation of quinazoline 3-oxide (I) with ketones into quinolines (II).[3] For example, the reaction of I with acetophenone (VII-1) gave 2-phenylquinoline (II-1) as a main product.

With the expectation that a similar transformation takes place, we carried out the reactions described in this paper and found the desired transformation of pyrido[2,3-*d*]pyrimidine 3-oxide (III) into 1,8-naphthyridines (IV) in addition to the formation of 2-aminonicotinaldehyde oxime (V) and 2-aminonicotinonitrile (VI), although the yields of IV were very poor as shown in Table I.

Molar ratio of III to aromatic ketone was set 1: 6.25, that to cyclic ketone was 1: 14.0, and that to aliphatic ketone was 1: 60.0. A suitable reaction time and temperature for each case were shown in Table I.

Thus, acetophenone (VII-1), propiophenone (VII-2), butyrophenone (VII-3), and valerophenone (VII-4) reacted with III yielding, respectively, 2-phenyl-(IV-1), 3-methyl-2-phenyl-(IV-2), 3-ethyl-2-phenyl-(IV-3), and 3-propyl-2-phenyl-1,8-naphtyridine (IV-4) together with V and VI. Similarly acetone (VII-5), 3-pentanone (VII-6), 2-butanone (VII-7), 2-pentanone

* Dedicated to the memory of Prof. Eiji Ochiai.

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3) T. Higashino, K. Suzuki, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **23**, 746 (1975).

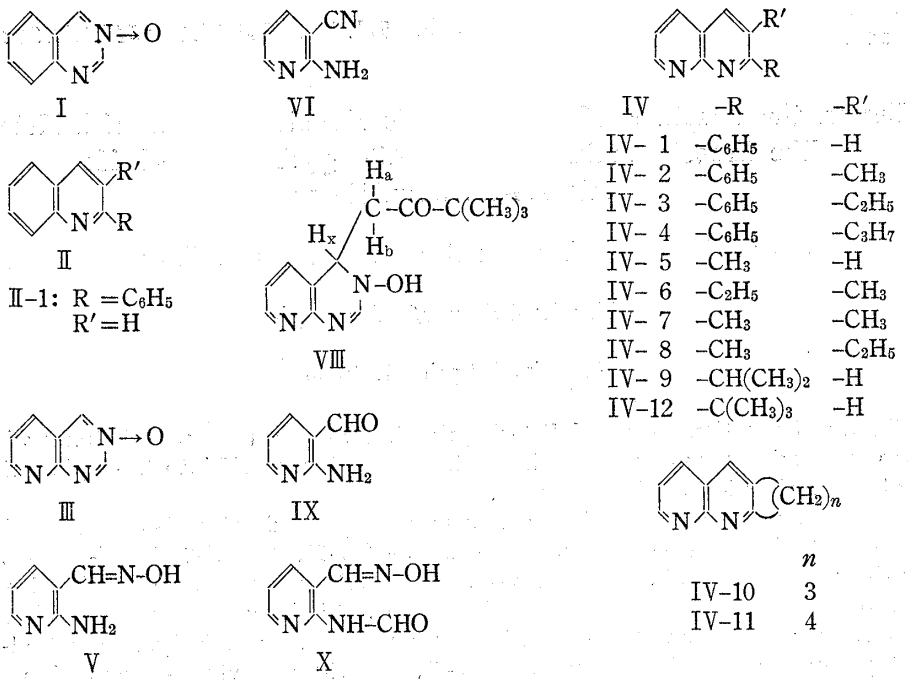

Chart 1

TABLE I. Reactions of III with Ketones (VII)

Products / Ketones	Reaction time (hr)	Reaction temperature (°C)	IV	(%)	Melting point of IV (°C)[a]	V (%)	VI (%)	VIII (%)
VII-1	4.5	140—150	IV-1	2.6	104—105	trace	4.8	—
VII-2	4.5	150—160	IV-2	5.3	113—114	1.4	4.6	—
VII-3	4.5	150—160	IV-3	4.0	125—126	1.1	5.8	—
VII-4	4.5	150—160	IV-4	1.7	95— 96	1.7	3.4	—
VII-5	4.5	175—180	IV-5	1.6	99	6.7	1.0	—
VII-6	6.0	175—180	IV-6	1.1	93— 94	1.4	1.1	—
VII-7	4.5	170—175	IV-7	3.2	139—140	4.4	trace	—
VII-8	4.5	175—180	IV-8	2.7	93— 94	8.5	3.9	—
VII-9	4.5	175—180	IV-9	1.0	65— 66	trace	trace	—
VII-10	3.0	140—145	IV-10	6.5	140—141	—	—	—
VII-11	4.0	140—145	IV-11	18.5	108—109	—	—	—
VII-12	4.5	175—180	—	—	—	—	—	9.8

a) colourless needles

(VII-8), and 3-methyl-2-butanone (VII-9) resulted, respectively, in 2-methyl- (IV-5), 2-ethyl-3-methyl- (IV-6), 2,3-dimethyl- (IV-7), 3-ethyl-2-methyl- (IV-8), and 2-isopropyl-1,8-naphthyridine (IV-9) together with V and VI. Cyclopentanone (VII-10), and cyclohexanone (VII-11) also gave 7,8-dihydro-6H-cyclopenta[*b*][1,8]naphthyridine (IV-10), and 6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridine (IV-11), respectively. Moreover III and 3,3-dimethyl-2-butanone (VII-12) did not lead to the expected 1,8-naphthyridines, but gave 3,3-dimethyl-1-(3-hydroxy-3,4-dihydro-4-pyrido[2,3-*d*]pyrimidinyl)-2-butanone (VIII).

The structures of IV-1, IV-5, V, and VI were respectively determined by mixed melting point test with the corresponding authentic specimens prepared from other routes.[2g,4] The compounds IV-1 to IV-12 were also prepared by the Friedlaender synthesis with 2-amino-nicotinaldehyde (IX) and VII in the presence of sodium methoxide as a catalyst. The struc-

4) *a*) E.M. Hawes and D.G. Wibberley, *J. Chem. Soc.* (*C*), **1966**, 315; *b*) *Idem*, *ibid.*, **1967**, 1564.

Table II. The Friedlaender Synthesis of IX with VII

Products / Ketones	IV	(%)	Formula	Analysis Calcd. C	H	N	Found C	H	N
VII-1	IV-1	81	$C_{14}H_{10}N_2$	81.53	4.89	13.58	—	—	—
VII-2	IV-2	72	$C_{15}H_{12}N_2$	81.79	5.49	12.72	81.79	5.77	12.70
VII-3	IV-3	55	$C_{16}H_{14}N_2$	82.02	6.02	11.96	82.45	6.23	11.87
VII-4	IV-4	75	$C_{17}H_{16}N_2$	82.22	6.50	11.28	81.80	6.58	11.15
VII-5	IV-5	64	$C_9H_8N_2$	74.97	5.59	19.43	—	—	—
VII-6	IV-6	74	$C_{11}H_{12}N_2$	76.71	7.02	16.27	76.82	7.03	16.13
VII-7	IV-7	32	$C_{10}H_{10}N_2$	75.92	6.37	17.71	76.09	6.17	17.66
VII-8	IV-8	45	$C_{11}H_{12}N_2$	76.71	7.02	16.27	76.30	7.04	16.19
VII-9	IV-9	15	$C_{11}H_{12}N_2$	76.71	7.02	16.27	77.06	7.03	16.36
VII-10	IV-10	52	$C_{11}H_{10}N_2$	77.62	5.92	16.46	77.18	5.87	16.46
VII-11	IV-11	39	$C_{12}H_{12}N_2$	78.23	6.57	15.21	78.34	6.58	15.19
VII-12[a]	IV-12	46	$C_{12}H_{14}N_2$	77.38	7.58	15.04	77.40	7.55	15.12

a) mp 78—79°

Table III. NMR Spectra of IV

	Chemical shift (τ) in $CDCl_3$ 3-H	4-H	5-H	6-H	7-H	Other	Coupling constant (cps) $J_{3,4}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
IV-2	—	2.07[s]	1.95[q]	2.30–	1.06[q]	2.30– ($2\text{-}C_6H_5$), 7.52[s] ($3\text{-}CH_3$)	—	7.8	2.2	4.0
IV-3	—	1.99[s]	1.87[q]	2.30–	1.02[q]	2.30– ($2\text{-}C_6H_5$), 7.12[q] 8.81[t] ($3\text{-}C_2H_5$)	—	7.7	1.8	4.1
IV-4	—	2.09[s]	1.96[q]	2.30–	1.06[q]	2.30– ($2\text{-}C_6H_5$), 7.22[t] 8.50[m] 9.17[t] ($3\text{-}C_3H_7$)	—	8.0	1.9	3.9
IV-6	—	2.29[s]	2.03[q]	2.73[q]	1.15[q]	6.47[q] 8.54[t] ($2\text{-}C_2H_5$), 7.64[s] ($3\text{-}CH_3$)	—	7.9	1.8	4.1
IV-7	—	2.29[s]	2.05[q]	2.73[q]	1.14[q]	7.30[s] ($2\text{-}CH_3$), 7.61[s] ($3\text{-}CH_3$)	—	8.0	1.9	4.0
IV-8	—	2.27[s]	2.00[q]	2.72[q]	1.13[q]	7.29[s] ($2\text{-}CH_3$), 7.23[q] 8.69[t] ($3\text{-}C_2H_5$)	—	8.1	2.0	4.2
IV-9	2.73[d]	2.08[d]	2.00[q]	2.75[q]	1.10[q]	6.72[se] 8.59[d] ($2\text{-}CH(CH_3)_2$)	8.3	7.7	1.9	4.0
IV-10	—	2.29[s]	2.07[q]	2.75[q]	1.17[q]	6.86[t] 6.97[t] 7.85[qu] ($(CH_2)_3$)	—	7.7	1.9	4.1
IV-11	—	2.25[s]	2.00[q]	2.69[q]	1.06[q]	6.6—8.5[m] ($(CH_2)_4$)	—	7.8	1.9	3.9
IV-12	2.51[d]	2.05[d]	2.00[q]	2.70[q]	1.07[q]	8.53[s] ($2\text{-}C(CH_3)_3$)	8.5	7.8	2.0	4.1

s: singlet, d: doublet, q: quartet, qu: quintet, m: multiplet, t: triplet, se: septet

tures of these 1,8-naphthyridines were assigned on the bases of elemental analyses and nuclear magnetic resonance (NMR) spectra shown in Table II and III.

Assignment of VIII was made by the following bases. Elemental analysis showed that III had combined with VII-12 in a 1:1 ratio, and its NMR spectrum showed the characteristic eight peaks (AB portion), the four peaks (X portion) of ABX pattern (τ=7.72, H_a; 7.46, H_b; 5.44, H_x; $J_{a,b}$=10.0 cps; $J_{a,x}$=9.0 cps; $J_{b,x}$=6.0 cps), and the three singlets of the nonequivalence of the three methyl groups (τ=8.53, 8.70, 8.94). The nonequivalence of the methylene protons and that of the three methyl groups might be due to the presence of three different substituents on the assymetric ring carbon atom at the 4-position or to restricted rotation (see Chart 1).

It is clear that both V and VI are the ring opening products of III, and VII is not concerned with the formation of V and VI. During the extraction of the reaction mixture with 2N hydrochloric acid, V may be produced by hydrolysis of 2-formamidonicotinaldehyde oxime (X), formed through addition of water to unchanged III and resulting ring cleavage between the 2- and 3-positions, as shown in Chart 2. In fact when a solution of III dissolved in 2N hydrochloric acid was allowed to stand at ordinary temperature for 10 min, V was obtained in 20% yield together with X. But it can not be explained as yet what specific processes contribute to the formation of VI.

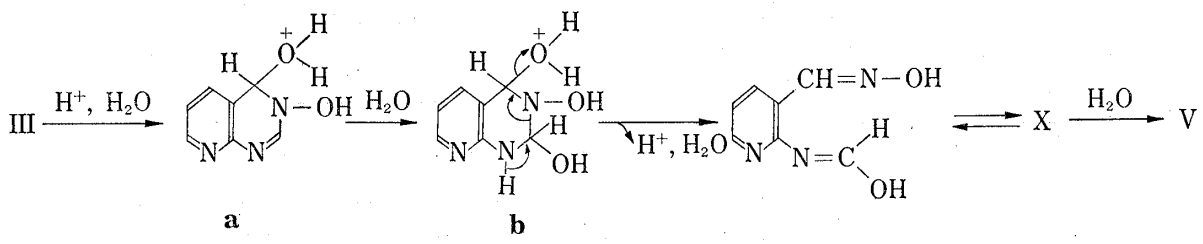

Chart 2

The possible reaction mechanism of the formation of 1,8-naphthyridines (IV) is probably similar to that of the transformation of quinazoline and its 3-oxide (I) into quinolines (II) reported previously,[2e-f,3] and may be written as shown in Chart 3. The first step is the formation of a 3,4-dihydropyrido[2,3-*d*]pyrimidine derivative (**c**) by attack of VII at the most reactive 4-position of III. Then another molecule of VII adds to **c** to form a 1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine intermediate (**d**). Subsequent ring cleavage of **d** between the 2- and 3-positions followed by elimination of hydroxylamine molecule give **f** *via* **e**. Finally IV is formed from **f** through **g** and **h**; that is to say, ring closure of **f** accompanied by elimination of a carbonium ion (**i**)[2e] give **g**, and loss of hydroxide ion from **g** or its tautomer **h** leads to IV. And according to the above mechanism, VIII corresponds to an intermediate (**c**).

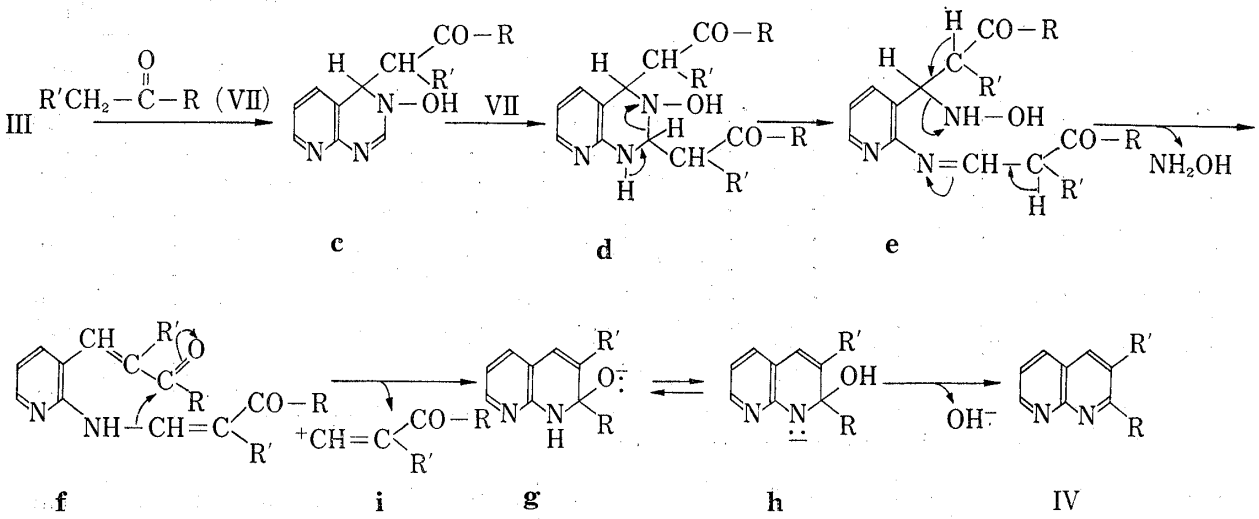

Chart 3

Experimental[5]

Infrared (IR) spectra were recorded with a Jasco Grating Infrared Spectrophotometer Model IRA-1.

NMR spectra were measured at 60 Mc and 23° on a Hitachi High Resolution NMR Spectrometer Model R-24. Tetramethylsilane was used an internal standard.

Reaction of III with VII——i) Reaction with Aliphatic Ketone: A mixture of 0.003 mole (440 mg) of III and 0.18 mole of aliphatic ketone in a sealed tube was heated under the condition described in Table I. After aliphatic ketone was removed under reduced pressure, the residue was dissolved in benzene and extracted with 2N HCl. The HCl solution was neutralized with K_2CO_3 and extracted with $CHCl_3$–benzene mixture (1: 1). After drying over anhyd. Na_2SO_4, solvent was removed under reduced pressure. The residue thus obtained was passed through a column of alumina by changing eluate as follows; benzene, benzene–$CHCl_3$ mixture (9: 1), $CHCl_3$, and MeOH. The first elution with benzene–$CHCl_3$ mixture gave IV (colourless needles from benzene–petr. ether mixture), and the second elution afforded VI, mp 131° (slightly yellow plate from petr, ether). The elution with MeOH gave V, mp 165° (colourless needles from H_2O).

In the case of VII-12, VIII, mp 158° (colourless plate from petr. ether), was obtained in 9.8% yield (72 mg) from the elution with benzene–$CHCl_3$ mixture. *Anal.* Calcd. for $C_{13}H_{17}O_2N_3$ (3,3-dimethyl-1-(3-

5) All melting points were not corrected.

hydroxy-3,4-dihydropyrido[2,3-*d*]pyrimidinyl)-2-butanone): C, 63.14; H, 6.93; N, 16.99. Found: C, 62.73; H, 6.75; N, 17.04. IR ν_{max}^{KBr} cm^{-1}: 1620 (C=O). NMR (in $CDCl_3$) τ=2.08 (1H, quartet, 7-H, $J_{5,7}$=2.0 cps, $J_{6,7}$=4.1 cps), 2.77 (1H, quartet, 5-H, $J_{5,6}$=7.5 cps), 3.35 (1H, quartet, 6-H), 3.7—4.2 (1H, broading, -OH), 4.24 (1H, singlet, 2-H), 5.44 (1H, quartet, 4-H, $J_{a,x}$=9.0 cps, $J_{b,x}$=6.0 cps), 7.72 (1H, quartet, H_a, $J_{a,b}$=10.0 cps), 7.46 (1H, quartet, H_b), 8.53, 8.70, 8.94 (9H, singlet, $-CH_3$).

ii) Reaction with Aromatic or Cyclic Ketone: A mixture of 0.003 mole (440 mg) of III and 0.02 mole of aromatic ketone or 0.042 mole of cyclic ketone was heated under the reaction condition descrived in Table I. The reaction mixture was treated as the same manner described in i) to separate IV, V and VI.

Yields of reaction products were listed in Table I.

Preparation of IV——A mixture of 0.003 mole (366 mg) of IX, 0.004 mole of VII, and 4 drops of 2% MeONa solution was heated at 100° for 30 min. The reaction mixture was dissolved in benzene, and the benzene solution was extracted with 2N HCl. The HCl solution was neutralized with K_2CO_3 and extracted with benzene. After drying over anhyd. Na_2SO_4, the extract was passed through a column of silicic acid to remove impurities. Recrystallization from petr. ether gave IV.

Yields and elemental analyses of IV were listed in Table II, and NMR spectra were shown in Table III.

Reaction of III with 2N HCl——A solution of 300 mg of III dissolved in 5 ml of 2N HCl was allowed to stand at room-temperature for 10 min. The reaction mixture was neutralized with K_2CO_3, and the separated crystals was collected by suction and recrystallized from MeOH to give X, mp 167° (decomp.) (slightly yellow crystals), in 28% yield (94 mg). MeOH was removed under reduced pressure from the filtrate to give V, mp 165° from H_2O (colourless needles), in 20% yield (56 mg).

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