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Polycyclic N-Hetero Compounds. XIII.[1] Reactions of Pyridine N-Oxides with Formamide

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Reactions of pyridine (I, IV, X, XIII) or condensed pyridine (VII, XVI, XVIII) N-oxides with formamide were described. Although pyrimidinyl cyclization of active methyl group was unsuccessful, introduction of carbamoyl group at pyridine ring carbon adjacent to nitrogen atom was successful, *i.e.*, 6-methylpyridine-2-(II), 4-methylpyridine-2-(V), 4-methylquinoline-2-(VIII), 5-methylpyridine-2-(XI), pyridine-2-(XIV), quinoline-2-(XVII), and isoquinoline-1-(XIX) carboxyamides were obtained.

Keywords——pyridine N-oxides; formamide; active methyl group; carbon-carbon bond formation; electrophilic substitution; N-heteroaromatic amides;

The previous paper[3] described that 4-methylpyrimidines were converted to 4-(5-pyrimidinyl)pyrimidines by heating with formamide in the presence of phosphoryl chloride or with trisformylaminomethane in formamide. Since the authors were interested in the activity of methyl group of their N-oxides, the reactions of N-heteroaromatic N-oxides containing active methyl group with formamide were investigated. However, carbamoylation was resulted at α-position of pyridine ring without pyrimidinyl cyclization of methyl group. Moreover same results were successful in pyridine N-oxides without active methyl group. The present paper describes a novel facile carbamoylation reaction of pyridine and condensed pyridine N-oxides.

As shown in Chart 1, at first, pyridine and condensed pyridine N-oxides with methyl group in activated position were used as starting materials and these N-oxides were heated with formamide without catalyst. The reaction of 2-methylpyridine 1-oxide (I) with formamide at 180—190° for 28 hr gave colorless needles, mp 116°. The molecular formula of the substance agreed with $C_7H_8ON_2$ and the infrared (IR) absorption and proton magnetic resonance (PMR) spectral data suggested the structure of the product as 6-methylpyridine-2-carboxyamide (II), which was identified with the authentic sample prepared by Meyer's method.[4] 2-Methylpyridine (III), deoxygenated product of I, was also obtained in our reaction mixture.

Analogously, the reaction of 4-methylpyridine 1-oxide (IV) with formamide gave 4-methylpyridine-2-carboxyamide (V) and deoxygenated 4-methylpyridine (VI). The similar reaction of 4-methylquinoline 1-oxide (VII) with formamide afforded 4-methylquinoline-2-carboxyamide (VIII)[5] and 4-methylquinoline (IX). The PMR spectrum of VIII exhibited one-proton singlet at δ 8.12 attributable to C-3-H, consequently the position of carboxyamide group was determined at C–2.

1) Part XII: T. Koyama, T. Mozai, T. Hirota, Y. Ishino, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **24**, 2585 (1976).
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4) H. Meyer, *Rec. Trav. Chem.*, **44**, 328 (1925).
5) M. Szafran and T. Driembowska, *Rocz. Chem.*, **44**, 1805 (1970).

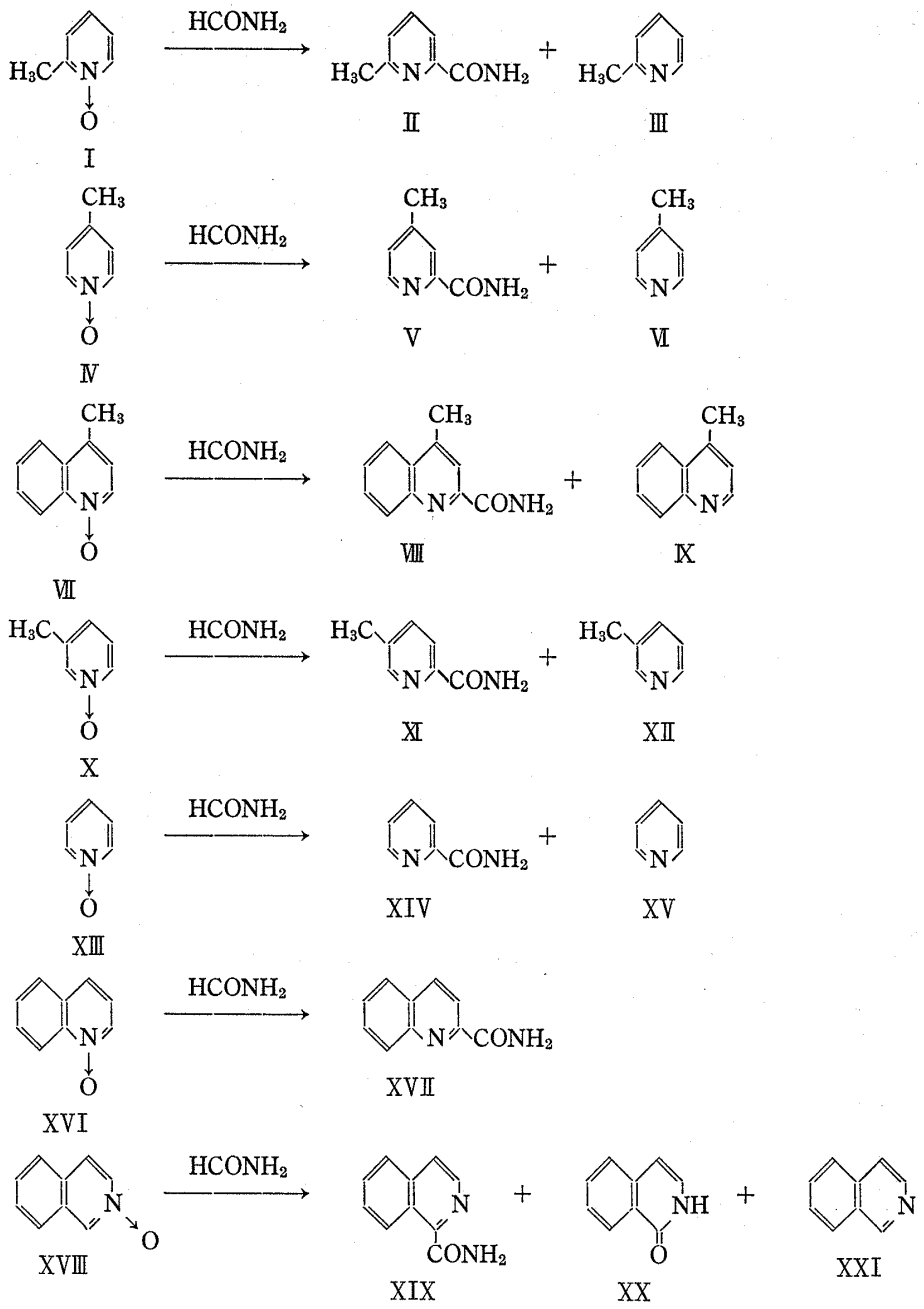

Chart 1

Since the above methylpyridine N-oxides gave 2-carbamoylpyridines without pyrimidinyl cyclization, pyridine N-oxides without active methyl group were subjected to the similar reaction with formamide to generalize this carbamoylation reaction. The reaction of 3-methylpyridine 1-oxide (X) with formamide gave 5-methylpyridine-2-carboxyamide (XI)[6] and 3-methylpyridine (XII). The position of carbamoyl group was determined by PMR spectrum (refer to experimental part). The analogous reaction of pyridine 1-oxide (XIII) afforded pyridine 2-carboxyamide (XIV)[7] and pyridine (XV). XIV was identified with authentic sample. Similarly, quinoline 1-oxide(XVI) gave quinoline-2-carboxyamide(XVII).[8] The PMR spectrum of XVII exhibited two-proton AB quartet at low field attributable to

6) N. Kucharczyk and A. Zvakova, *Collect. Czeoh. Chem. Commun.*, **28**, 55 (1963).
7) C. Engler, *Chem. Ber.*, **27**, 1784 (1894).
8) T. Takahashi and Y. Hamada, *Yakugaku Zasshi*, **75**, 755 (1955).

C–3 and C–4 protons, consequently the position of carboxyamide group was determined at C–2. The reaction of isoquinoline 2-oxide (XVIII) with formamide gave isoquinoline-1-carboxyamide (XIX)[9] and isocarbostyril (XX).[10] The position of carboxyamide group of XIX was determined at C–1 similar to XVII, and XX was identified with authentic sample.

As the result, pyrimidinyl cyclization product of methyl groups at 2- or 4-position of pyridine N-oxides was not isolated, but introduction of carboxyamide group to pyridine ring carbon was occurred and the new carbon-carbon linkage was formed.

As the representative carbon-carbon bond formation at pyridine 1-oxide ring carbon, reactions of pyridine 1-oxides with cyanide ion (introduction of CN group, Reissert reaction), active methylene compounds, enamines or enol ethers, and organometalic compounds were described.[11] Referred to these reactions, the presumable reaction mechanism is shown in Chart 2.

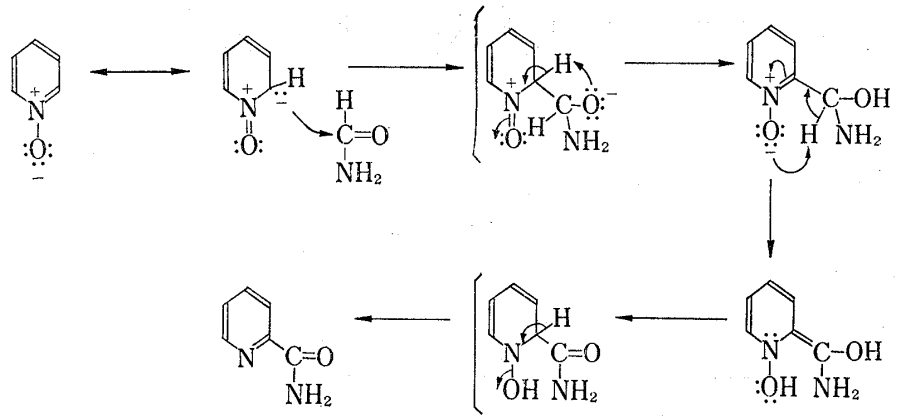

Chart 2

Okamoto and Yamada[12] obtained purine by heating formamide at 170—180°. Since our reaction condition was similar to that of them, formation of purine was confirmed in the above all reactions on thin-layer chromatography (TLC).

Experimental

Melting points were determined with Yanagimoto micro melting point apparatus and uncorrected. IR spectra were recorded on Nippon Bunko DS-301 spectrometer. PMR spectra were taken with Hitachi R-22 spectrometer (90 MHz) in $CDCl_3$ with tetramethylsilane as an internal standard (δ value), s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Mass Spectra were obtained with Shimadzu LKB-9000 instrument at 70 eV ionization potential.

General——A mixture of 0.03 mole of N-heteroaromatic N-oxide and 0.3 mole of $HCONH_2$ was heated at 180—205° until disappearance of the starting material (except for X) on TLC. After cooled, 30 ml of H_2O was added into the reaction mixture and then extracted with cyclohexane, benzene, and $CHCl_3$ successively. Each extract was washed with H_2O, dried over Na_2SO_4, and evaporated. Each residue was extracted several times with boiling cyclohexane. The cyclohexane-soluble fractions were cooled and deposited crystals were collected. Evaporation of the filtrate of carbamoylpyridines gave crude deoxygenated pyridines, identical with the authentic sample on TLC.

Reaction of 2-Methylpyridine 1-Oxide(I) with $HCONH_2$——A mixture of 3.27 g of I and 13.5 g of $HCONH_2$ was heated at 180—190° for 28 hr and the reaction mixture was worked up as described above. 0.11 g (2.7%) of 6-methylpyridine-2-carboxyamide (II) was obtained as colorless needles, mp 116° (reported mp 116°[4]). *Anal.* Calcd. for $C_7H_8ON_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.72; H, 5.89; N, 20.41. Mass Spectrum *m/e* (M^+): 136. IR ν_{max}^{KBr} cm^{-1}: 3420, 3130, 1650 (N–H), 1672 (C=O). PMR: 2.53 (3H, s, CH_3), 7.29 (1H, bd,

9) J.M. Wefer, A. Catala, and F.D. Popp, *J. Org. Chem.*, **30**, 3075 (1965).
10) E. Bamberger and W. Frew, *Chem. Ber.*, **27**, 208 (1894).
11) A.R. Katritzky and J.M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, London and New York, 1971, p. 299.
12) T. Okamoto and H. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 623 (1972).

J=7.5 Hz, C-5-H), 7.71 (1H, t, J=7.5 Hz, C-4-H), 7.99 (1H, bd, J=7.5 Hz, C-3-H), 5.8 and 7.8 (each 1H, b, NH_2, disappeared with D_2O). Evaporation of the filtrate of II gave 0.12 g (5%) of crude 2-methylpyridine (III).

Reaction of 4-Methylpyridine 1-Oxide(IV) with $HCONH_2$——A mixture of 3.27 g of IV and 13.5 g of $HCONH_2$ was heated at 185—190° for 3 hr and the reaction mixture was worked up as described above. 0.17 g (4.1%) of 4-methylpyridine-2-carboxyamide (V) was obtained as colorless prisms, mp 130—131°. *Anal.* Calcd. for $C_7H_8ON_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.74; H, 6.02; N, 20.50. Mass Spectrum *m/e* (M^+): 136. IR ν_{max}^{KBr} cm^{-1}: 3370, 3230, 1660 (N–H), 1685 (C=O). PMR: 2.40 (3H, s, CH_3), 7.25 (1H, dd, J=6 Hz, 2 Hz, C-5-H), 8.05 (1H, d, J=2 Hz, C-3-H), 8.40 (1H, d, J=6 Hz, C-6-H), 6.6—7.6 (2H, b, NH_2, disappeared with D_2O). Evaporation of the filtrate of V gave 0.15 g (6%) of 4-methylpyridine (VI).

Reaction of 4-Methylquinoline 1-Oxide(VII) with $HCONH_2$——A mixture of 4.77 g of VII and 13.5 g of $HCONH_2$ was heated at 190° for 4 hr and the reaction mixture was worked up usually. 0.72 g (13.7%) of 4-methylquinoline-2-carboxyamide (VIII)[5] was obtained as colorless needles, after sublimation at 134—148° on slide glass to colorless feathers, mp 139.5—140.5°. *Anal.* Calcd. for $C_{11}H_{10}ON_2$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.23; H, 5.60; N, 14.81. Mass Spectrum *m/e* (M^+): 186. IR ν_{max}^{KBr} cm^{-1}: 3420, 3240, 1664 (N–H), 1708 (C=O). PMR: 2.72 (3H, s, CH_3), 7.55—7.85 (2H, m, C-6, 7-H), 7.87—8.10 (2H, m, C-5, 8-H), 8.10 (1H, s, C-3-H), 5.8, 7.9 (each 1H, b, NH_2, disappeared with D_2O). Evaporation of the filtrate of VIII gave 0.04 g (1%) of 4-methylquinoline (IX) as crude oil.

Reaction of 3-Methylpyridine 1-Oxide(X) with $HCONH_2$——A mixture of 3.27 g of X and 13.5 g of $HCONH_2$ was heated at 185—195° for 28 hr and the reaction mixture was worked up usually. The hot cyclohexane-soluble fraction was fractionated with preparative TLC (Merck, alumina PF_{254}; $CHCl_3$: acetone=1: 1). a) The fraction of *Rf* value *ca.* 0.6—0.7 was collected and recrystallized from cyclohexane to give 0.06 g (1.5%) of 5-methylpyridine-2-carboxyamide (XI) as colorless prisms, after sublimation at 130—148° on slide glass to colorless prisms, mp 180°. *Anal.* Calcd. for $C_7H_8ON_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.69; 5.98; N, 20.70. Mass Spectrum *m/e* (M^+): 136. IR ν_{max}^{KBr} cm^{-1}: 3410, 3280, 1650 (N–H), 1670 (C=O). PMR: 2.34 (3H, s, CH_3), 7.58 (1H, dd, J=7 Hz, 2 Hz, C-4-H), 8.04 (1H, d, J=7 Hz, C-3-H), 8.31 (1H, d, J=2 Hz, C-6-H), 5.5, 7.8 (each 1H, b, NH_2, disappeared with D_2O). b) The fraction of *Rf* value *ca.* 0.9—1 gave 0.25 g (10%) of crude 3-methylpyridine (XII). c) The fraction of *Rf* value *ca.* 0.1—0.2 gave 0.2 g of X. The hot cyclohexane-insoluble fraction of the $CHCl_3$ extract in the general method was subjected to vacuum distillation to give 0.9 g of X, bp 154—157°/16 mmHg, combined yield 1.1 g (37%).

Reaction of Pyridine 1-Oxide (XIII) with $HCONH_2$——A mixture of 2.85 g of XIII and 13.5 g of $HCONH_2$ was heated at 195—205° for 2.5 hr and the reaction mixture was worked up usually. 0.26 g (7.0%) of pyridine-2-carboxyamide (XIV) was obtained as colorless needles, mp 107.5° (reported mp 107°[7]). *Anal.* Calcd. for $C_6H_6ON_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.25; H, 5.09; N, 22.70. Mass Spectrum *m/e* (M^+): 122. IR ν_{max}^{KBr} cm^{-1}: 3430, 3170, 1610 (N–H), 1660 (C=O). PMR: 7.38 (1H, ddd, J=6 Hz, 5 Hz, 2 Hz, C-5-H), 7.80 (1H, ddd, J=7 Hz, 6 Hz, 2 Hz, C-4-H), 8.11 (1H, dd, J=7 Hz, 2 Hz, C-3-H), 8.50 (1H, dd, J=5 Hz, 2 Hz, C-6-H), 5.65, 7.95 (each 1H, b, NH_2, disappeared with D_2O). Evaporation of the filtrate of XIV gave 0.04 g (2%) of pyridine (XV).

Reaction of Quinoline 1-Oxide (XVI) with $HCONH_2$——A mixture of 4.41 g of XVI and 13.5 g of $HCONH_2$ was heated at 195—205° for 2.5 hr and the reaction mixture was worked up usually. 0.38 g (7.4%) of quinoline-2-carboxyamide (XVII) was obtained as colorless needles, mp 132.5—133° (reported mp 133°[8]). *Anal.* Calcd. for $C_{10}H_8ON_2$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.61; H, 4.80; N, 16.15. Mass Spectrum *m/e* (M^+): 172. IR ν_{max}^{KBr} cm^{-1}: 3420, 3110, 1612 (N–H), 1695 (C=O). PMR: 7.48—8.15 (4H, m, C-5,6,7,8-H), 8.25 (2H, s, C-3,4-H, this signal appeared at 8.03 and 8.38 as AB quartet in DMSO-d_6, J=8 Hz), 5.8, 7.8 (each 1H, b, NH_2, disappeared with D_2O).

Reaction of Isoquinoline 2-Oxide (XVIII) with $HCONH_2$——A mixture of 4.41 g of XVIII and 13.5 g of $HCONH_2$ was heated at 190—200° for 4 hr and the reaction mixture was worked up usually, but crystallization of hot cyclohexane-soluble fraction was unsuccessful. Therefore, the cyclohexane, benzene, and $CHCl_3$ extracts were combined and then chromatographed over silica gel. The benzene eluate gave 0.11 g (3%) of isoquinoline (XXI). The benzene–$CHCl_3$ (1: 1) eluate was recrystallized from cyclohexane to give 0.43 g (8.3%) of isoquinoline-1-carboxyamide (XIX) as colorless prisms, mp 170—171° (reported np 168—170°[9]). *Anal.* Calcd. for $C_{10}H_8ON_2$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.82; H, 4.59; N, 16.38. Mass Spectrum *m/e* (M^+): 172. IR ν_{max}^{KBr} cm^{-1}: 3410, 3155, 1620 (N–H), 1678 (C=O). PMR: 7.63—7.97 (3H, m, C-5,6,7-H), 7.82, 8.48 (each 1H, AB q, J=5 Hz, C-3,4-H), 9.58 (1H, m, C-8-H), 5.7, 7.8 (each 1H, b, NH_2, disappeared with D_2O). The $CHCl_3$–acetone (3: 1) eluate was recrystallized from H_2O to give 0.05 g (1%) of isocarbostyril (XX) as colorless needles, mp 209—210°, identical with the authentic sample[10] (mixed mp, IR, and PMR).

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