Notes

[Chem. Pharm. Bull. 34(8)3431—3434(1986)]

Polycyclic *N*-Hetero Compounds. XXIV.[1] Reaction of Pyridine and Quinoline *N*-Oxides with *N*-Methylformamide

TAKASHI HIROTA,* TETSUTO NAMBA, and KENJI SASAKI

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima, Okayama 700, Japan

(Received December 16, 1985)

Reactions of pyridine and quinoline *N*-oxides with *N*-methylformamide are described. *N*-Methylcarbamoylation occurred at the C-2 or C-4 position of pyridine and quinoline derivatives.

Keywords——pyridine *N*-oxide; quinoline *N*-oxide; *N*-methylformamide; *N*-methylcarbamoylation; *N*-oxide; formamide; carbamoylation

In the earlier papers,[2] we reported a novel carbamoylation reaction that occurs on heating pyridine and quinoline *N*-oxides with formamide. To develop this carbamoylation reaction, *N*-methylformamide instead of formamide was used as a reagent to investigate whether or not *N*-methylcarbamoylation still occurs. Since the methyl group cyclized to a pyrimidine ring when 2,4,6-trimethylpyridine 1-oxide was heated with formamide,[2b] we were interested in the reactivity of the methyl group of heteroaromatic *N*-oxides with *N*-methylformamide.

As shown in Chart 1, reaction of pyridine 1-oxide (**1**) with *N*-methylformamide under reflux for 5 d afforded *N*-methylpyridine-2-carboxamide (**2**) and its 4-substituted isomer (**3**). Compounds **2** and **3** had been reported by Prijs *et al.*,[3] and instrumental data for our products also supported these structures. Compound **2** was a major product in this reaction. Analogously, *N*-methylcarbamoylation occurred at the α-position of the pyridine ring (**6**, **9**, and **12**) in the reactions of 2-, 3-, and 4-methylpyridine 1-oxides (**5**, **8**, and **11**) with *N*-methylformamide. Although two α-positions exist in compound **8**, *N*-methylcarbamoylation occurred at the sterically less hindered α-position as determined from the splitting pattern of the ^{1}H-NMR spectrum in the aromatic region. Similar reaction of 2, 6-dimethylpyridine 1-oxide (**14**) with *N*-methylformamide introduced an *N*-methylcarbamoyl group at the C-4 position (**15**). On the other hand, quinoline 1-oxide (**17**) was allowed to react with *N*-methylformamide to give 2- and 4-(*N*-methylcarbamoyl)quinolines (**18**, **19**).[4,5] In this reaction, *N*-methylformamide predominantly attacked the C-2 position, as in the case of **1**. In the reaction of 4-methylquinoline 1-oxide (**21**) with *N*-methylformamide, *N*-methylcarbamoylation occurred at the C-2 position (**22**),[6] as expected, and 4-methyl-2-quinolone (**23**)[7] was formed as a by-product.

Deoxygenated products of the starting *N*-oxides were detected by thin layer chromatography (TLC) in all reactions. *N*-Methylcarbamoylation of heteroaromatic *N*-oxides required a prolonged reaction time compared with that when formamide was used, but the yields in *N*-methylcarbamoylation were better than those in carbamoylation with formamide. One of the reasons for this difference seems to be the thermal stability of the amides. While formamide decomposes,[8] *N*-methylformamide is relatively stable at high temperature.

Similar *N*-methylcarbamoylation was reported for quinolines by Minisci *et al.*[9] and

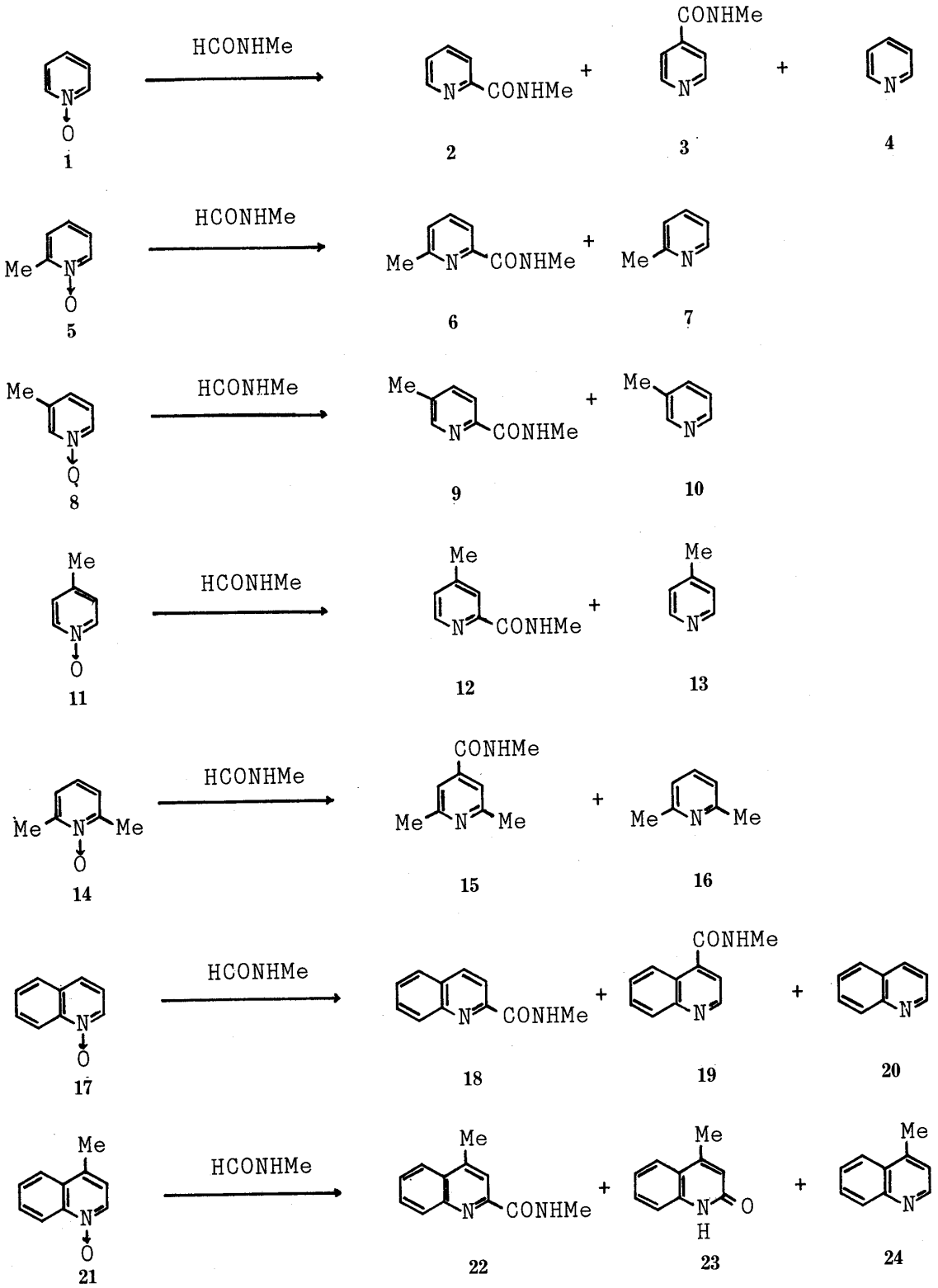

Chart 1

Dziembowska and Szafran,[10] and for pyrimidines by Sakamoto *et al.*[11] including the homolytic substitution of *N*-heteroaromatic compounds with *N*-methylformamide. The reaction mechanism of carbamoylation with formamide was proposed in the earlier papers,[2] and a similar mechanism may be considered for *N*-methylcarbamoylation at an anionic site of *N*-heteroaromatic *N*-oxides with *N*-methylformamide.

Experimental

Melting points were recorded on a Yanagimoto micro melting point apparatus. All melting points and boiling points are uncorrected. Analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The infrared (IR) spectra were obtained with a Nihon Bunko DS-301 spectrometer and the frequencies are expressed in cm^{-1}. The ^{1}H-NMR spectra were measured with a Hitachi R-22 spectrometer (90 MHz) with tetramethylsilane as an internal standard (δ value). The mass spectra (MS) were taken with a Shimadzu LKB-9000 instrument at 70 eV.

General Procedure for the Reaction of Heteroaromatic *N*-Oxides with *N*-Methylformamide——A mixture of 0.03 mol of heteroaromatic *N*-oxide and 0.3 mol of *N*-methylformamide was refluxed with stirring until the starting *N*-oxide was no longer detectable on TLC, except for the reaction of **8**. Excess *N*-methylformamide was distilled off under reduced pressure. Deoxygenated products of the starting *N*-oxides were confirmed to be present in the distillate by TLC in all reactions, and compounds **16**, **20**, and **24** could be isolated. In the case of pyridine *N*-oxides (**1**, **5**, **8**, and **11**), *N*-methylcarbamoylated compounds (**2**, **6**, **9**, and **12**) were contained in the distillate, and were collected by fractional distillation under reduced pressure. In other cases, the distillation residue was extracted with $CHCl_3$. Each extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (Wakogel C-200) with mixtures of benzene–$CHCl_3$ and $CHCl_3$–acetone.

Reaction of Pyridine 1-Oxide (1) with *N*-Methylformamide——Reflux time: 5 d. Fractional distillation of the first distillate gave *N*-methylpyridine-2-carboxamide (**2**) in 17% yield as a colorless oil, bp 143—146 °C/25 mm (lit.[3] bp 128 °C/12 mm). IR (neat): 3375, 3340, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.97 (3H, d, J=5 Hz, $NHCH_3$, changed to a singlet with D_2O), 7.30 (1H, ddd, J=8, 5, 2 Hz, H-5), 7.74 (1H, dd, J=8, 2 Hz, H-4), 8.10 (1H, dd, J=8, 2 Hz, H-3), 8.39 (1H, dd, J=5, 2 Hz, H-6), 7.0—8.7 (1H, br, CONH, disappeared with D_2O). MS *m/e*: 136 (M^+). *Anal.* Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.57; H, 6.08; N, 20.42. The $CHCl_3$ extract of the first distillation residue was chromatographed on silica gel. The $CHCl_3$ eluate was recrystallized from benzene to give *N*-methylpyridine-4-carboxamide (**3**) in 2% yield as colorless prisms, mp 113—114 °C (lit.[3] mp 115 °C). IR (KBr): 3365, 3327, 1646 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.93 (3H, d, J=5 Hz, $NHCH_3$, changed to a singlet with D_2O), 6.2—6.9 (1H, br, CONH, disappeared with D_2O), 7.50 (2H, dd, J=6, 2 Hz, H-3 and 5), 8.61 (2H, dd, J=6, 2 Hz, H-2 and 6). MS *m/e*: 136 (M^+). *Anal.* Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.92; H, 5.81; N. 20.63.

Reaction of 2-Methylpyridine 1-Oxide (5) with *N*-Methylformamide——Reflux time: 57 h. Fractional distillation of the first distillate gave *N*, 6-dimethylpyridine-2-carboxamide (**6**) in 11% yield as a colorless oil, bp 150—155 °C/25 mm. IR (neat): 3390, 3340, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s, 6-CH_3), 2.97 (3H, d, J=5 Hz, $NHCH_3$, changed to a singlet with D_2O), 7.24 (1H, dd, J=7, 1.5 Hz, H-5), 7.4—8.4 (1H, br, CONH, disappeared with D_2O), 7.68 (1H, t, J=7 Hz, H-4), 7.96 (1H, dd, J=7, 1.5 Hz, H-3). MS *m/e*: 150 (M^+). *Anal.* Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.71; H, 6.91; N, 18.49.

Reaction of 3-Methylpyridine 1-Oxide (8) with *N*-Methylformamide——Reflux time: 7 d. Fractional distillation of the first distillate gave a mixture of *N*, 5-dimethylpyridine-2-carboxamide (**9**) and **8**, bp 92—99 °C/2 mm, which was subjected to silica gel chromatography with a gradient of $CHCl_3$–acetone. The $CHCl_3$ eluate gave **9** in 21% yield as a pale yellow oil. IR (neat): 3400, 3350, 1658 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s, 5-CH_3), 3.02 (3H, d, J=5 Hz, $NHCH_3$, changed to a singlet with D_2O), 7.61 (1H, br d, J=7 Hz, H-4), 7.9 (1H, br, CONH, disappeared with D_2O), 8.09 (1H, d, J=7 Hz, H-3), 8.33 (1H, br s, H-6). MS *m/e*: 150 (M^+). *Anal.* Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.91; H, 6.88; N, 18.74. The eluate with $CHCl_3$–acetone (4 : 1) gave unreacted **8** in 10% yield.

Reaction of 4-Methylpyridine 1-Oxide (11) with *N*-Methylformamide——Reflux time: 32 h. Fractional distillation of the first distillate gave *N*, 4-dimethylpyridine-2-carboxamide (**12**) in 38% yield as a colorless oil, bp 157—160 °C/25 mm. IR (neat): 3420, 3360, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, 4-CH_3), 2.94 (3H, d, J=5 Hz, $NHCH_3$, changed to a singlet with D_2O), 7.04 (1H, dd, J=5, 2 Hz, H-5), 7.84 (1H, d, J=2 Hz, H-3), 8.19 (1H, d, J=5 Hz, H-6), 7.5—8.5 (1H, br, CONH, disappeared with D_2O). MS *m/e*: 150 (M^+). *Anal.* Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.89; H, 6.76; N, 18.52.

Reaction of 2,6-Dimethylpyridine 1-Oxide (14) with *N*-Methylformamide——Reflux time: 29 h. Fractional distillation of the first distillate gave 2, 6-dimethylpyridine (**16**) in 32% yield as a colorless oil, bp 57—61 °C/46 mm. The $CHCl_3$ extract of the first distillation residue was chromatographed on silica gel. The eluate with $CHCl_3$–acetone (19 : 1) was recrystallized from benzene to give *N*, 2, 6-trimethylpyridine-4-carboxamide (**15**) in 8% yield as colorless needles, mp 151—153 °C. IR (KBr): 3300, 1658 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.47 (6H, s, 2-CH_3 and 6-CH_3), 2.92 (3H, d, J=5 Hz, $NHCH_3$, changed to a singlet with D_2O), 6.33 (1H, br, CONH, disappeared with D_2O), 7.17 (2H, s, H-3 and 5). MS *m/e*: 164 (M^+). *Anal.* Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.71; H, 7.41; N, 17.11.

Reaction of Quinoline 1-Oxide (17) with *N*-Methylformamide——Reflux time: 9 h. Fractional distillation of the first distillate gave quinoline (**20**) in 23% yield, bp 120—125 °C/25 mm. The $CHCl_3$ extract of the first distillation residue was chromatographed on silica gel. The $CHCl_3$ eluate was recrystallized from benzene to give *N*-methylquinoline-2-carboxamide (**18**) in 9% yield as colorless needles, mp 116—116.5 °C (lit.[4] mp 117—118 °C). IR (KBr): 3450, 3374, 1679 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.03 (3H, d, J=5 Hz, $NHCH_3$, changed to a singlet with D_2O), 7.28—8.02 (4H, m. H-5, 6, 7, and 8), 8.20 (2H, s, H-3 and 4; this signal appeared at 8.16 and 8.56 as an AB quartet in

DMSO-d_6, $J=8$ Hz), 7.1—8.6 (1H, br, CONH, disappeared with D_2O). MS *m/e*: 186 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H. 5.41; N, 15.05. Found: C, 70.86; H, 5.32; N, 15.02. The eluate with $CHCl_3$–acetate (9 : 1) was recrystallized from benzene to give *N*-methylquinoline-4-carboxamide (**19**) in 3% yield as colorless needles, mp 109—110 °C (lit.[5] mp 111 °C). IR (KBr): 3420, 3240, 1638 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ: 2.92 (3H, d, $J=5$ Hz, $NHCH_3$, changed to a singlet with D_2O), 7.37 (1H, d, $J=4.5$ Hz, H-3), 7.40—7.76 (2H, m, H-6 and 7), 7.96 (1H, dd, $J=8$, 1.5 Hz, H-5 or 8), 8.17 (1H, dd, $J=7.5$, 2 Hz, H-5 or 8), 7.1—8.4 (1H, br, CONH, disappeared with D_2O), 8.76 (1H, d, $J=4.5$ Hz, H-2). MS *m/e*: 186 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.11; H, 5.28; N, 15.11.

Reaction of 4-Methylquinoline 1-Oxide (21) with *N*-Methylformamide——Reflux time: 15 h. Fractional distillation of the first distillate gave 4-methylquinoline (**24**) in 2% yield, bp 130—135 °C/25 mm. The $CHCl_3$ extract of the first distillation residue was chromatographed on silica gel. The $CHCl_3$ eluate was recrystallized from cyclohexane to give *N*, 4-dimethylquinoline-2-carboxamide (**22**) in 7% yield as pale yellow needles, mp 112—113 °C (lit.[6] mp 109 °C). IR (KBr): 3360, 1662 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (3H, s, 4-CH_3), 2.96 (3H, d, $J=5$ Hz, $NHCH_3$, changed to a singlet with D_2O), 7.38—7.71 (2H, m, H-6 and 7), 7.83—8.01 (2H, m, H-5 and 8), 8.04 (1H, s, H-3), 7.1—8.4 (1H, br, CONH, disappeared with D_2O). MS *m/e*: 200 (M^+). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.94; H, 6.07; N, 13.82. The eluate with $CHCl_3$–acetone (9 : 1) was recrystallized from benzene to give 4-methyl-2-quinolone (**23**) in 2% yield as colorless prisms, mp 219—220 °C (lit.[7] mp 219—221 °C). IR (KBr): 3411, 1662 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.46 (3H, s, 4-CH_3), 6.50 (1H, s, H-3), 7.02—7.61 (4H, m, H-5, 6, 7, and 8), 12.45 (1H, br, NH, disappeared with D_2O). MS *m/e*: 159 (M^+). *Anal.* Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.31: H, 5.77; N, 8.91.

Acknowledgement The authors are grateful to Mr. A. Iwadoh for microanalyses and mass spectral measurements.

References and Notes

1) Part XXIII: T. Hirota, K. Kawanishi, K. Sasaki, and T. Namba, *Chem. Pharm. Bull.*, **34**, 3011 (1986).
2) *a*) T. Koyama, T. Namba, T. Hirota, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.*, **25**, 964 (1977); *b*) T. Hirota, T. Namba, and K. Sasaki, *J. Heterocyclic Chem.*, "submitted."
3) B. Prijs, R. Gall, R. Hinderling, and H. Erlenmeyer, *Helv. Chim. Acta*, **37**, 90 (1954).
4) R. R. Arndt, A. Jordaan, and V. P. Joynt, *J. Chem. Soc., Supplement*, **1964**, 5969.
5) T. S. Work, *J. Chem. Soc.*, **1942**, 429.
6) I. Ono and N. Hata, *Bull. Chem. Soc. Jpn.*, **56**, 3667 (1983).
7) W. M. Lauer and C. E. Kaslow, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, John Wiley & Sons, Inc., New York, 1955, p. 580.
8) H. Yamada and T. Okamoto, *Yakugaku Zasshi*, **95**, 493 (1975).
9) F. Minisci, A. Arnone, M. Cerere, R. Galli, G. P. Gardini, M. Perchinunno, and O. Porta, *Gazz. Chim. Ital.*, **103**, 13 (1973).
10) T. Dziembowska and M. Szafran, *Rocz. Chem.*, **48**, 2293 (1973).
11) T. Sakamoto, T. Sasaki, and H. Yamanaka, *Chem. Pharm. Bull.*, **28**, 571 (1980).