Reactions of Pyridine *N*-Oxide with Some Hydroxypyrimidines in the Presence of Platinated Palladium-Carbon Catalyst[1)]

Isamu MURAKOSHI, Toshikazu SEKINE,* Yoshihiro HIGUCHI, Nobuyuki OHYAMA and Tomoko YAMADA

Faculty of Pharmaceutical Sciences, Chiba University, 1–33 Yayoi-cho, Chiba 260, Japan. *Received November 30, 1988*

The reactions of pyridine *N*-oxide (1) with hydroxypyrimidine derivatives (2—7) in the presence of platinated palladium-carbon (Pd-Pt/C) catalyst were studied. 5-Hydroxypyrimidine (2), 4-hydroxypyrimidines (3 and 4) and 1-methyl-2-pyrimidinone (6) gave the corresponding dimers and 2-pyridyl derivatives by this condensation with high regioselectivity at the dehydrogenative position, while 2-hydroxypyrimidine (5) gave only the 2-pyridyl derivative. 2,4-Dihydroxypyrimidine (7) did not react under similar reaction conditions. All the products obtained in these reactions are new compounds.

These dimerization reactions may be useful for the synthesis of the dimers of N-heteroaromatic compounds.

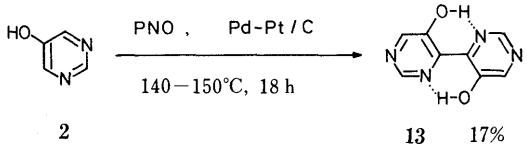
Keywords pyridine *N*-oxide; hydroxypyrimidine; platinated palladium-carbon catalyst; bipyrimidine; dimer; dehydrogenative dimerization; regioselectivity

We have previously reported that the dehydrogenative coupling reaction of pyridine *N*-oxide (PNO) (**1**) with pyridine (**8**) in the presence of Pd-Pt/C gave bipyridyl (**9**) and terpyridyl (**10**),[2a)] and also the reaction of PNO with pyrimidine (**11**) under the same conditions gave bipyrimidyl (**12**) as a main product and 2-pyridyl derivatives.[2b)] This reaction was further applied to other N-heteroaromatic compounds to give the corresponding dimers and 2-pyridyl derivatives.[2a,3a,b)] An important feature of the reaction is that the coupling occuerred at the α and α′ positions of the heterocyclic rings without exception. In order to establish the regioselectivity we carried out the reaction using hydroxypyrimidine derivatives (**2**—**7**).

Heating 5-hydroxypyrimidine (**2**) at 140—150 °C with equimolar PNO in pyridine in the presence of Pd-Pt/C under an N_2 atmosphere gave a reaction product, 5,5′-dihydroxy-4,4′-bipyrimidyl (**13**) (Chart 1). In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **13**, the hydroxyl protons resonated at lower field (δ 12.85 ppm) than that of the corresponding monomer (**2**) (δ 10.20 ppm). This low-field shift suggests that two hydroxy groups in **13** form hydrogen bonds to the ring nitrogens of the adjacent rings. The structure of **13** was confirmed by spectroscopic and elemental analyses.

When the reaction with PNO was carried out using 4(3*H*)-pyrimidinone (**3**) under the same conditions, three products (**14**—**16**) were formed (Chart 2). The dimeric product was a mixture consisting of two isomers (**14** and **15**). Although a small amount of pure **14** could be separated by recrystallization from EtOH, isolation of **15** was unsuccessful because of the insolubility of the compound. In order to determine the structures and the product ratio of **14** and **15**, the mixture was derived into the methoxy compounds without further separation.[4)]

We obtained a mixture of methoxy derivatives (**17** and **18**) in a ratio of 50 : 1 and separated them chromatographically. In the mass spectrum (MS) of the dimer (**17**) the *m/z* 110 (1/2 $M^+ + 1$) ion is the base peak, whereas in the case of the dimer (**18**) the base peak is the *m/z* 217 ($M^+ - 1$) ion. In the aromatic region of the ^{1}H-NMR spectrum of **17** only two doublets (δ 8.86 and 6.83 ppm, $J = 5.6$ Hz) are observed, but in the case of **18** two more signals (singlets, 8.98 and 7.82 ppm) are present in the region. Furthermore, **17** and **18** each formed a stable chelate with Fe^{2+}, showing the presence of a ferroin group in the molecule.[5)] These results show that **3** dimerized in a symmetric form to give **14** and dimerized in an asymmetric form to give **15** in the ratio of 50 : 1. A small amount of a 2-pyridyl derivative (**16**) was also obtained and its structure was confirmed by spectroscopic and elemental analyses. Therefore, all the products obtained in this reaction have reacted at the α-positions to the ring nitrogens of the starting materials and the main product obtained was the dimer (**14**) which is bonded at C-2 in the pyrimidinone ring.



2 13 17%

Chart 1

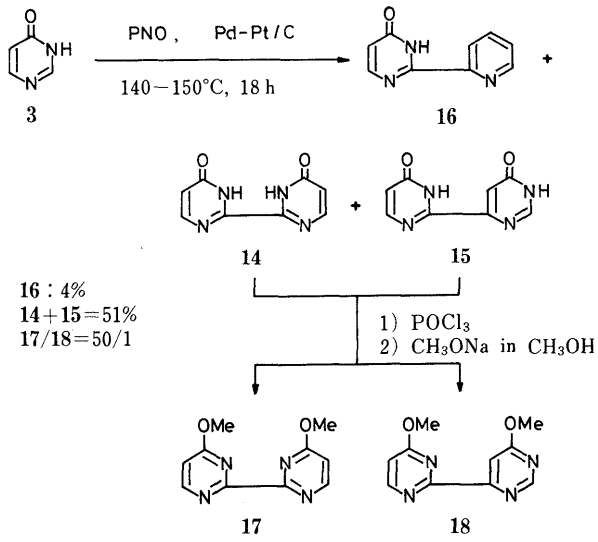


Chart 2

It was anticipated that this type of reaction using the N-methyl derivative of **3** (**4**) would proceed with dimerization at C-6 rather than at C-2 since the latter is sterically more hindered by the N-methyl group than C-6. In a subsequent reaction using 3-methyl-4-pyrimidinone (**4**) under the same conditions, the major products were the dimer (**19**) and a 2-

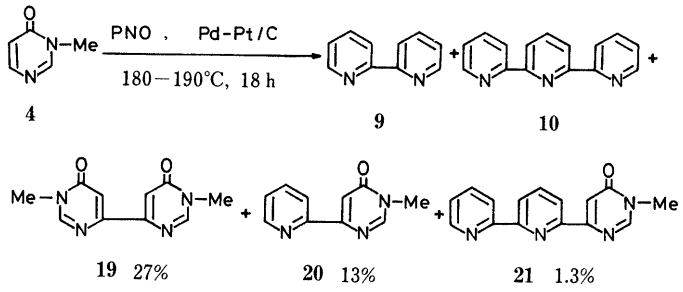


Chart 3

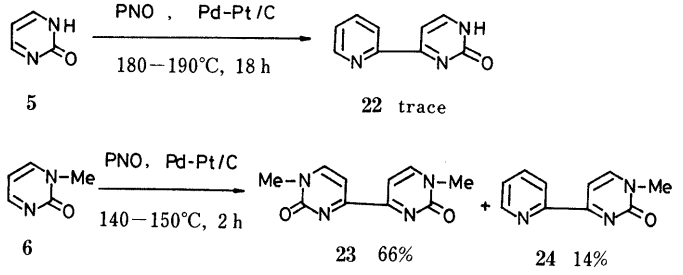


Chart 4

pyridyl derivative (**20**) which were both bonded at C-6 in the pyrimidinone ring. During this reactions, small amounts of **21**, bipyridyl (**9**) and terpyridyl (**10**) were also obtained (Chart 3). No product bonded at the 2-position of the pyrimidinone ring was obtained. These results indicate that these dimerization reactions using PNO as an oxidant and Pd-Pt/C catalyst are sensitive to this steric factor. The structures of **19**—**21** were determined by spectroscopic and elemental analyses.

The reaction of 2(1*H*)-pyrimidinone (**5**) with PNO under the same conditions gave a trace of the product (**22**) (Chart 4). Although in order to improve the yield of **22** the reaction conditions were examined (see Experimental section), a major product was not obtained.

On the other hand, in the case of 1-methyl-2-pyrimidinone (**6**), the reaction proceeded smoothly and a dimer (**23**) and a 2-pyridyl derivative (**24**) were obtained (Chart 4). Confirmation that both **23** and **24** were bonded at C-4 in the pyrimidinone ring was obtained from spectral and elemental analyses. For example, **23** gave the molecular ion peak at *m/z* 218 in its MS, and an elemental analysis suggested the molecular formula, $C_{10}H_{10}N_4O_2$. The infrared (IR) spectrum of **23** showed a band due to an amide group (1655 cm^{-1}). The ^{1}H-NMR spectrum of **23** indicated a symmetrical structure with two doublets (δ 8.95 and 7.70 ppm, J=6.1 Hz) and a singlet (δ 4.03 ppm) of relative intensity 1 : 1 : 3. No peak due to the proton at C-4 in the pyrimidinone ring was observed. From these results, the structure of **23** was determined as 4,4′-bi-1-methylpyrimidinone. It is suggested that the reason why the reaction with 1-methyl-2-pyrimidinone (**6**) proceeded whereas the reaction with 2(1*H*)-pyrimidinone (**5**) did not proceed was that tautomerism is present in the pyrimidinone ring.

When the reaction of 2,4(1*H*,3*H*)-pyrimidinedione (uracil) (**7**) was tried, no product was obtained and the starting material was recovered quantitatively. It was considered that since uracil (**7**) has no pyridine-type (sp^2-hybridized) nitrogen but only amide (sp^3-hybridized) nitrogen in its ring, the reaction did not proceed. This hypothesis is supported by the fact that 2(1*H*)-pyridone which possesses only amide nitrogen in its ring did not dimerize under the same conditions. Therefore, it is considered that a pyridine-type nitrogen in the hetero ring is necessary for this dehydrogenative coupling reaction.

When these reactions were tried in the absence of PNO or Pd-Pt/C, dimerization did not occur and in all cases the starting material was recovered quantitatively. Furthermore, when pyridine was absent as a solvent in these reactions, the yields of 2-pyridyl derivatives decreased, as has been reported previously.[6]

In all experiments, the products obtained were the dimers of the starting amines or 2-pyridyl derivatives with the bond at the α-position to the nitrogen in the pyrimidine (pyrimidinone) ring. This dimerization reaction using Pd-Pt/C catalyst and PNO as an oxidizing agent is therefore a useful method of synthesis of symmetric dimers of N-heteroaromatics such as pyridine because the reaction is simple and has high regioselectivity at the dehydrogenative position.

Experimental

Melting points were measured with a Yanagimoto micro melting point apparatus, and are uncorrected. IR spectra were recorded with a Hitachi 260 spectrophotometer in KBr disks. MS were recorded with Hitachi M-60 mass spectrometers. ^{1}H-NMR spectra were obtained with JEOL MH-100 and FX-270 spectrometers. Chemical shifts for the ^{1}H-NMR spectra are reported as δ values from $SiMe_4$ as an internal standard. Abbreviations used are: singlet = s; doublet = d; broad = br. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. Chromatography was performed on silica gel (Kieselgel 60, 70—230 mesh, Merck). Thin layer chromatography (TLC) was performed on Silica gel $60F_{254}$ plates (Merck). The spots were visualized by exposing the plate to ultraviolet (UV) light (254 nm) or by spraying them with 1% $FeSO_4$ solution. The following compounds were prepared according to the reported procedures: 5-hydroxypyrimidine[7a]; 4(3*H*)-pyrimidinone[7b]; 3-methyl-4-pyrimidinone[7c]; 2(1*H*)-pyrimidinone[7d]; 1-methyl-2-pyrimidinone.[7e]

General Methods A mixture of hydroxypyrimidine, PNO (equimolar) and pyridine (half equimolar) was heated in an oil bath at 140—150 °C (180—190 °C) for 2—18 h in the presence of Pd-Pt/C[8] (0.2 g/1 g of hydroxypyrimidine) under an N_2 atmosphere.

Reaction of 5-Hydroxypyrimidine (2) with PNO (1) After cooling of the mixture (1 g of **2**, 140—150 °C, 18 h), EtOH (300 ml) was added and the reaction mixture was refluxed. Then Pd-Pt/C catalyst was filtered off, the filtrate was evaporated to dryness and the residue was chromatographed on silica gel with $CHCl_3$–EtOH (9 : 1, v/v) as an eluent, to give the dimer (**13**) (0.17 g, 17%) with recovered starting material (2) (0.58 g, 58%). Compound **13** was recrystallized from EtOH; yellow needles, mp 265—267 °C (dec.). IR γ_{max} cm^{-1}: 3400, 1400, 1290. MS *m/z*: 190 (M^+). ^{1}H-NMR (DMSO-d_6): 12.85 (2H, br, 5-, 5′-OH), 8.93 (2H, s, 2-, 2′-H), 8.80 (2H, s, 6-, 6′-H). *Anal.* Calcd for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.47. Found: C, 50.54; H, 3.26; N, 29.30.

Reaction of 4(3*H*)-Pyrimidinone (3) with PNO (1) After cooling, the reaction mixture (5.0 g of **3**, 140—150 °C, 18 h) was diluted with a large amount of EtOH, and the Pd-Pt/C catalyst was filtered off. The filtrate was concentrated until crystals commenced to form. A mixture of **14** and **15** was collected by filtration (2.57 g, 51%). A small amount of **14** was purified by repeated crystallizations of a portion of the mixture of **14** and **15** from EtOH; colorless needles, mp > 300 °C. IR γ_{max} cm^{-1}: 1645 (CONH). MS *m/z*: 190 (M^+). ^{1}H-NMR (CF_3COOD): 8.66 (2H, d, J=6.7 Hz, 5-, 5′-H), 7.31 (2H, d, J=6.7 Hz, 4-, 4′-H). *Anal.* Calcd for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.47. Found: C, 50.53; H, 3.27; N, 29.36. Then the filtrate was evaporated to dryness and the residue was chromatographed on silica gel with $CHCl_3$–EtOH (9.5 : 0.5, v/v) as an eluent, to give **16** (0.4 g, 4%) and the starting material (1.45 g, 29%). Compound **16** was recrystallized from *n*-hexane; colorless needles, mp 150.5—151 °C. IR γ_{max} cm^{-1}: 1690 (CONH). MS *m/z*: 173 (M^+). ^{1}H-NMR ($CDCl_3$): 11.14 (1H, br, NH), 8.05 (1H, d, J=6.7 Hz, 6-H), 6.49 (1H, d, J=6.7 Hz, 5-H). *Anal.* Calcd for $C_9H_7N_3O$: C, 62.47; H, 4.07; N, 24.27. Found: C, 62.40; H, 4.13; N, 24.12.

Methoxylation of the Mixture of 14 and 15[4] $POCl_3$ (81 g) and PCl_5 (0.5 g) were added to the mixture of **14** and **15** (0.16 g), and the whole was refluxed for 18 h. After cooling, $POCl_3$ was removed *in vacuo*. The residue was poured onto ice, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and $CHCl_3$ was evaporated off. The residue was dissolved in a solution of CH_3ONa, prepared by dissolving metallic Na (0.5 g) in absolute MeOH (300 ml), and the mixture was refluxed for 2 h. After cooling, the precipitated NaCl was filtered off, the filtrate was evaporated to dryness, and the residue was taken up in water and extracted with ether. The ether extract was dried over Na_2SO_4. After removal of the ether, the residue (mixture of **17** and **18**, 0.11 g, 71%) was chromatographed on silica gel with $CHCl_3$–EtOH (9.5 : 0.5, v/v) as an eluent, to give pure **17** and **18**. Compound **17** was recrystallized from *n*-hexane; colorless needles, mp 126—128 °C. IR γ_{max} cm^{-1}: 1020. MS *m/z*: 218 (M^+), 110 (base, $1/2M^+ + 1$). ^{1}H-NMR ($CDCl_3$): 8.86 (2H, d, J=5.6 Hz, 6-, 6′-H), 6.83 (2H, d, J=5.6 Hz, 5-, 5′-H), 4.14 (6H, s, 2 × OCH_3). *Anal.* Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.05; H, 4.65; N, 25.59. Compound **18** was also recrystallized from *n*-hexane; colorless needles, mp 131—133 °C. IR γ_{max} cm^{-1}: 1030. MS *m/z*: 218 (M^+), 217 (base, $M^+ - 1$). ^{1}H-NMR ($CDCl_3$): 8.98 (1H, s, 2-H) 7.82 (1H, s, 5-H), 8.65 (1H, d, J=5.6 Hz, 6′-H), 6.81 (1H, d, J=5.6 Hz, 5′-H), 4.11, 4.07 (each 3H, s, 2 × OCH_3). *Anal.* Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.05; H, 4.70; N, 25.54.

The mixture of **17** and **18** was gas chromatographed[9]; the ratio of **17** : **18** was 50 : 1.

Reaction of 3-Methyl-4-pyrimidinone (4) with PNO (1) After cooling, the reaction mixture (2.0 g of **4**, 140—150 °C, 18 h) was refluxed with $CHCl_3$ (50 ml) and filtrated. The filtrated was digested with $CHCl_3$ (250 ml), and the Pd-Pt/C catalyst was filtered off. On cooling, colorless crystals separated were collected (**19**, 0.54 g, 27%). Compound **19** was recrystallized from MeOH; colorless needles, mp > 300 °C. IR γ_{max} cm^{-1}: 1615 (CONH). MS *m/z*: 218 (M^+). ^{1}H-NMR (CF_3COOD): 9.13 (2H, s, 2-, 2′-H), 7.61 (2H, s, 5-, 5′-H), 3.89 (6H, s, 2 × N-CH_3). *Anal.* Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 54.85; H, 4.54; N, 25.65. The $CHCl_3$ filtrate was evaporated to dryness, and the residue was chromatographed on silica gel with $CHCl_3$ as an eluent, to give 2,2′-bipyridyl (**9**) and 2,2′; 6,2″-terpyridyl (**10**) which were identified by comparison with authentic samples.[2a] Other fractions were collected, and chromatographed on silica gel with C_6H_6–EtOH (8 : 2, v/v) as an eluent, and subjected to preparative TLC on silica gel[10] with $CHCl_3$–EtOH (9.5 : 0.5, v/v) as an eluent, to give **20** (0.45 g, 13%) and **21** (20 mg). Compound **20** was recrystallized from C_6H_6; colorless needles, mp 162.5—163 °C. IR γ_{max} cm^{-1}: 1665 (CONH). MS *m/z*: 187 (M^+). ^{1}H-NMR ($CDCl_3$): 8.20 (1H, s, 2-H), 7.51 (1H, s, 5-H), 3.57 (3H, s, N-CH_3). *Anal.* Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.13; H, 4.74; N, 22.46. Compound **21** was recrystallized from EtOH; colorless needles, mp 253—256 °C. IR γ_{max} cm^{-1}: 1680. MS *m/z*: 264 (M^+). ^{1}H-NMR ($CDCl_3$): 8.22 (1H, s, 2-H), 7.77 (1H, s, 5-H), 3.60 (3H, s, N-CH_3). *Anal.* Calcd for $C_{14}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 67.95; H, 4.56; N, 21.00.

Reaction of 2(1*H*)-Pyrimidinone (5) with PNO (1) After cooling of the reaction mixture (1.0 g of **5**, 140—150 °C, 18 h), $CHCl_3$ (150 ml) was added and the whole was refluxed. The Pd-Pt/C catalyst was filtered off, the filtrate was evaporated to dryness, and the residue was chromatographed on silica gel with $CHCl_3$–EtOH (9.5 : 0.5, v/v) as an eluent, to give **22** (8 mg), as colorless crystals (sublimation, 80 °C/18 mmHg), mp 251—252 °C. IR γ_{max} cm^{-1}: 1665 (CONH). MS *m/z*: 178 (M^+). ^{1}H-NMR (CF_3COOD): 8.97 (1H, d, J=6.1 Hz, 6-H), 7.81 (1H, d, J=6.1 Hz, 5-H). Some starting material was recovered (0.81 g, 81%).

Then the reaction conditions were modified as follows (a—c), but in all cases only a trace of **22** was obtained and no other product was observed on TLC. a) **22** (1.0 g), PNO (0.94 g), pyridine (1.2 g), 180—190 °C, 18 h. b) **22** (1.0 g), PNO (2.8 g), pyridine (0.41 g), 140—150 °C, 18 h. c) **22** (1.0 g), PNO (3.7 g), 140—150 °C, 18 h.

Reaction of 1-Methyl-2-pyrimidinone (6) with PNO (1) After cooling, the reaction mixture (1.0 g of **6**, 140—150 °C, 2 h) was digested with $CHCl_3$ (100 ml) and filtered. The filtrate was evaporated to dryness and the residue was chromatographed on silica gel with $CHCl_3$–EtOH (9.7 : 0.3, v/v) as an eluent, to give **24** (0.24 g, 14%). Compound **24** was recrystallized from CH_3COOEt; colorless needles, mp 213—214 °C. IR γ_{max} cm^{-1}: 1650 (CONH). MS *m/z*: 187 (M^+). ^{1}H-NMR ($CDCl_3$): 7.78 (1H, d, J=6.9 Hz, 6-H), 7.50 (1H, d, J=6.9 Hz, 5-H), 3.64 (3H, s, N-CH_3). *Anal.* Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 63.95; H, 4.88; N, 22.45. Then the filtrated was diluted with CH_3COOH, and the Pd-Pt/C catalyst was filtered off. The filtrate was evaporated until crystals commenced to form. The precipitate was collected, giving **23** (0.66 g, 66%); colorless needles, mp > 300 °C. IR γ_{max} cm^{-1}: 1655 (CONH). MS *m/z*: 218 (M^+). ^{1}H-NMR (CF_3COOD): 8.95 (2H, d, J=6.1 Hz, 6-, 6′-H), 7.70 (2H, d, J=6.1 Hz, 5-, 5′-H), 4.03 (6H, s, 2 × N-CH_3). *Anal.* Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.02; H, 4.65; N, 25.60.

Reaction of 2,4(1*H*,3*H*)-Pyrimidinedione (7) with PNO (1) After cooling, the mixture (1.0 g of **7**, 140—150 °C, 18 h) was digested with $CHCl_3$ (30 ml) and filtered. From this filtrate, only PNO was recovered. The filtrated was then digested with H_2O and Pd-Pt/C catalyst was filtered off. The filtrate was concentrated until crystals commenced to form. Then the precipitate was collected, and the starting material was recovered (0.95 g, 95%).

Even when **7** was heated at 180—190 °C with PNO, no product was obtained and the starting material was recovered (96%).

Reaction of 2(1*H*)-Pyridone with PNO (1) A similar reaction of 2(1*H*)-pyridone under the same conditions was tried but the starting material was recovered (90%) and no reaction product was observed on TLC.

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References and Notes

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8) Pd-Pt/C catalyst was prepared as reported previously; J. Haginiwa and Y. Higuchi, *Yakugaku Zasshi*, **93**, 140 (1973).
9) Gas chromatography (GC) was run on a Hitachi 164 unit equipped with a flame ionization detector; column, stainless steel 3 mm × 1 m (SE-30 10%); carrier gas, N_2; column temperature, 140 °C.
10) Kiesel gel 60 F_{254} (Merck).