Dimerizations of π-Rich N-Heteroaromatic Compounds and Xanthine Derivatives[1)]

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Dimerization reactions of six π-rich N-heteroaromatic compounds (2—7) and five xanthine derivatives (8—12) in the presence of platinated palladium-carbon (Pd-Py/C) catalyst were investigated. *N*-Methylimidazole (2), benzimidazole (4) and *N*-methylbenzimidazole (5) condensed dehydrogenatively to afford the corresponding symmetric dimers when heated in the presence of Pd-Pt/C catalyst and pyridine *N*-oxide (1). On the other hand, imidazole (3), pyrazole (6) and *N*-methylpyrazole (7) did not dimerize under the same conditions. The same reactions using caffeine (10), 1,7-dimethylhypoxanthine (9) gave the corresponding dimers.

Keywords dehydrogenative dimerization; symmetric dimer; π-rich N-heteroaromatic; pyridine *N*-oxide; platinated palladium-carbon catalyst; synthesis; 8,8′-bicaffeine

In the previous paper, we have described the reactions of pyridine *N*-oxide (**1**) (PNO) with some hydroxypyrimidines in the presence of platinated palladium-carbon (Pd-Pt/C) catalyst.[2)] This reaction represents a dehydrogenative condensation in which the starting hydroxypyrimidines coupled to give mainly the corresponding dimers. We have also reported that more than forty N-heteroaromatic compounds dimerized to give the corresponding dimers under the same conditions. In these reactions the starting amines were pyridine and diazine derivatives. As only the α-carbon of the N-heteroaromatics was reactive in the dimerizations, the dimers had symmetrical structures. This reaction also seems interesting from a synthetic viewpoint for giving products which contain a ferroin system in the molecule.

As part of a series of studies on the reaction, we wish to describe in the present paper the dimerization of heterocycles which contain a π-rich five-membered ring (**2**—**7**) using pyridine *N*-oxide in the presence of Pd-Pt/C catalyst. Furthermore, we applied this reaction to a dimerization of xanthine and hypoxanthine derivatives (**8**—**12**).

First of all, the reaction of *N*-methylimidazole (**2**) with PNO was examined in the presence of Pd-Pt/C catalyst. Thus, a mixture of **2** and equimolar PNO was heated at 180—190 °C for 18 h in the presence of Pd-Pt/C catalyst under an N_2 atmosphere to give a dimer (**13**) and a 2-pyridyl derivative (**14**) (Chart 1). Based on the spectral data, the reactive site was C-2 between the two ring nitrogens. The structure of **13** was confirmed by comparison with an authentic sample prepared according to the reported procedure.[3)] Under the same conditions, imidazole (**3**) afforded a trace of product (**15**) which gave the molecular ion peak at *m/z* 134 in its mass spectrum (MS) presumably due to a dimer of **3** (Chart 1). However, the proton nuclear magnetic resonance (^{1}H-NMR) and the infrared (IR) spectra of **15** were not identical with those of authentic 2,2′-biimidazole (glycosine) prepared by the method of Kuhn *et al.*[4)] The reason why the reaction of **3** did not proceed is not clear.

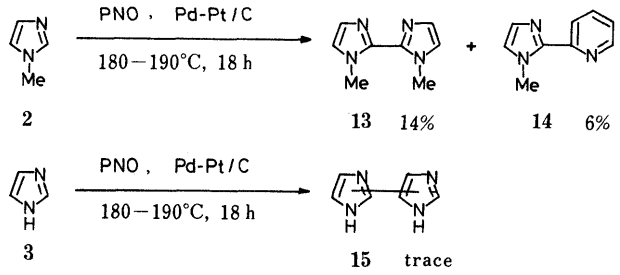


Chart 1

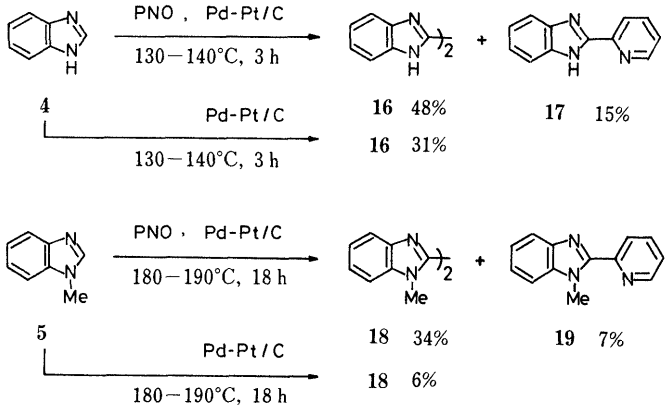


Chart 2

We attempted the reaction of benzimidazole (**4**) with PNO to give a dimer (**16**) and a 2-pyridyl derivative (**17**) (Chart 2). *N*-Methylbenzimidazole (**5**) also reacted with PNO to give a dimer (**18**) and a 2-pyridyl derivative (**19**), as expected (Chart 2). These dimerizations depended on the presence of Pd-Pt/C catalyst as in the case of the reactions with the pyridine series, whereas in the absence of PNO, **4** and **5** dimerized in 31% and 6% yields, respectively. This indicated that these benzimidazoles could easily dehydrogenate on the surface of Pd-Pt/C catalyst in the absence of PNO. There are many reports on the dimer of **4**, but a direct coupling reaction of **4** to give the dimer has not been reported. The structures of **16**—**18** were determined by comparison with authentic specimens prepared accoring to the methods reported in the literature.[5−7)]

The same dimerization reactions of another type of diazoles, pyrazole (**6**) and *N*-methylpyrazole (**7**), were attempt-

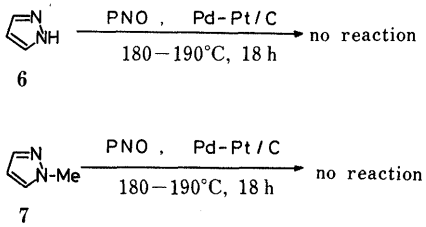


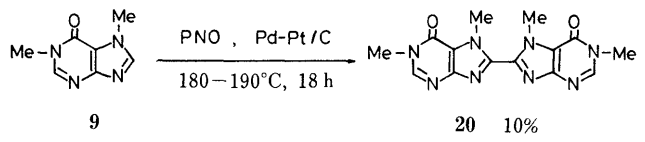
Chart 3

ed (Chart 3). However, no product was obtained and the starting materials were recovered quantitatively even under the modified reaction conditions described in the experimental section. It is an interesting coincidence that pyridazines[8] and pyrazoles, in both of which the two nitrogens are adjacent to each other, did not dimerize under similar reaction conditions.

The findings that some of these π-rich N-heteroaromatics dimerized as in the case of the π-deficient series prompted us to apply these dimerization reactions to fused N-heteroaromatic compounds which have five- and six-membered N-hetero rings in the molecule.

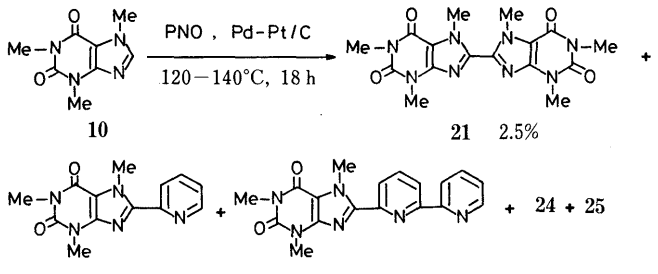
1,7-Dimethylhypoxanthine (**9**) when heated with PNO in the presence of Pd-Pt/C catalyst afforded a dimer (**20**), whereas hypoxanthine (**8**) did not dimerize under the same conditions (Chart 4). The dimeric product of **9** which bonded at C-2, between the two nitrogens in the pyrimidinone ring, was not obtained. This indicates that the imidazole ring was more reactive than the pyrimidinone ring in this dimerization. The structure of **20** was proved by analysis of the spectral data.

The utility of our method was also demonstrated by the dimerization of caffeine (**10**) to 8,8′-bicaffeine (**21**) under the same conditions. When the reaction was carried out in pyridine, the reaction products **21**—**25** were obtained (Chart 5). Compounds **24** and **25** were identified by comparison with the authentic samples[9] to be 2,2′-bipyridyl and 2,2′:6′,2″-terpyridyl, respectively. The structures of α-pyridyl and α,α'-dipyridyl derivatives were also confirmed by spectroscopic and elemental analyses. Priewe and Polik[10] reported that the reaction of 8-hydrazinocaffeine with Fe^{3+} gave a red substance together with caffeine. They suggested the product to be a dimer of caffeine from the IR spectrum and elemental analysis but details were not reported. Compound **21** was obtained as colorless needles and had a melting point above 300°C. Compound **21** was confirmed to be 8,8′-bicaffeine by spectroscopic and elemental analyses. This is the first synthesis and characterization of 8,8′-bicaffeine. Furthermore, the reaction conditions for this dimerization were examined as shown in Table I, and the yield was optimized by use of 2,6-lutidine



9 20 10%

Chart 4



10 21 2.5%

22 33% 23 trace + 24 + 25

Chart 5

TABLE I. Formation of **21** under Various Conditions

Run	Amine *N*-oxide	Solvent	Reaction conditions Temperature (°C)	Time (h)	Yield of **21** (%)
1	PNO	Pyridine	120—140	18	2.5
2	PNO	—	180—190	18	23
3	2,6-Lutidine *N*-oxide	Pyridine	120—140	18	31
4	2,6-Lutidine *N*-oxide	2,6-Lutidine	180—190	3	50
5	2,6-Lutidine *N*-oxide	—	180—190	3	90
6	—	—	180—190	18	0

N-oxide (LNO) at 180—190 °C for 18 h (90%). Generally, PNO deoxygenates in this reaction to give pyridine, which can dimerize easily. On the other hand, LNO can not afford its dimer as a by-product because 2,6-lutidine has no α-hydrogen as a reactive site. Thus LNO is a better reagent for this dimerization.

Similar reactions of theobromine (**11**) and theophylline (**12**) were attempted but no product was obtained under the same conditions. Some different conditions were tried, but none were successful. The observed difficulty in the reactions of **8**, **11** and **12** is probably due to the insolubility of the starting materials in the reaction solvents.

In conclusion, it would seem that these reactions with PNO in the presence of Pd-Pt/C catalyst provide a new and convenient method for preparation of symmetrical dimers of π-rich N-heteroaromatic compounds.

Experimental

All melting points were recorded with a Yanagimoto micromelting point apparatus and are uncorrected. Spectral data were obtained as follows: IR with a Hitachi 260-10 spectrophotometer; MS with a Hitachi M-60 mass spectrometer; ^{1}H-NMR with a JEOL FX-270 spectrometer (using tetramethylsilane as an internal standard). Chemical shifts are given in δ values (ppm) and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; dd, double doublet. Elemental analyses were carried out with a Perkin-Elmer 240 analyzer. Thin layer chromatography was carried out on Silica gel 60 F_{254} plates (Merck). For column chromatography, Silica gel 60 (70—230 mesh, Merck) and aluminum oxide 90 (70—230 mesh, Merck) were used. The following compounds were prepared according to the reported procedures; *N*-methylpyrazole[11a]; *N*-methylbenzimidazole[11b]; hypoxanthine and 1,7-dimethylhypoxanthine.[11c]

Dimerization Reaction of *N*-Methylimidazole (2) A mixture of **2** (1 g) and equimolar PNO (1.2 g) was heated at 180—190°C in the presence of Pd-Pt/C catalyst (0.2 g) for 18 h under an N_2 atmosphere. After cooling, the reaction mixture was filtered and the residue was washed with $CHCl_3$. The filtrate and the washing were combined and evaporated to dryness, and the residue was chromatographed on silica gel with $CHCl_3$–EtOH (10:0.3, v/v) as an eluent, to give **13** (0.13 g, 13%). Compound **13** was recrystallized from cyclohexane, mp 115—116°C. Lit.[3] mp 113—114 °C. The other fractions were mixed and chromatographed on aluminum oxide with C_6H_6 as an eluent to give **14** (0.13 g, 6%) and recover **2** (0.6 g, 60%). Compound **14** was a colorless oil. MS *m/z*: 159 (M^+). ^{1}H-NMR ($CDCl_3$): 7.11 (1H, d, J=1 Hz, 5-H), 6.97 (1H, d, J=1 Hz, 4-H), 4.13 (3H, s, N-CH_3). Picrate; $C_9H_9N_3 \cdot C_6H_3N_3O_7$, yellow needles (EtOH), mp 194—195°C. *Anal.* Calcd for $C_{15}H_{12}N_6O_7$: C, 46.40; H. 3.12; N, 21.65. Found: C, 46.25; H, 3.04; N, 21.67.

Attempted Dimerization Reaction of Imidazole (3) A similar reaction of **3** (1.0 g) was carried out and 2 mg of **15** was isolated from the reaction mixture by column chromatography on aluminum oxide with $CHCl_3$ as an eluent. Compound **15** was obtained as colorless needles, mp >300 °C. MS *m/z*: 134 (M^+). ^{1}H-NMR ($CDCl_3$): 6.85 (1H, d, J=1.3 Hz), 7.00 (1H, d, J=1.3 Hz), 7.44 (1H, s), 7.46 (1H, d, J=1.3 Hz). ^{1}H-NMR of 2,2′-biimidazole.[12]

Dimerization Reaction of Benzimidazole (4) (A) A mixture of **4** (1.0 g) and equimolar PNO (0.8 g) was heated at 130—140°C in the presence of Pd-Pt/C catalyst (0.2 g) for 3 h under an N_2 atmosphere. After cooling of the reaction mixture, EtOH (150 ml) was added and the whole was refluxed. Then Pd-Pt/C was filtered off, and the filtrate was concentrated to 50 ml. Precipitated crystals (**16**, 0.48 g, 48%) were collected and recrystallized from EtOH; colorless needles, mp >300 °C. Lit.[5] mp >300 °C. 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 recover **4** (0.33 g, 33%) and to give **17** (0.24 g, 15%). Compound **17** was recrystallized from EtOH, colorless needles, mp 228—230 °C. Lit.[6] mp 216—219 °C (B) The same reaction of **4** in the absence of PNO resulted in formation of **16** (0.31 g, 31%) and recovery of **4** (0.66 g, 66%). (C) The same reaction of **4** in the absence of Pd-Pt/C catalyst resulted in quantitative (97%) recovery of **4**.

Dimerization Reaction of *N*-Methylbenzimidazole (5) (A) A mixture of **5** (2.0 g) and equimolar PNO (0.4 g) was heated at 180—190 °C in the presence of Pd-Pt/C catalyst (0.4 g) for 18 h under an N_2 atmosphere. After cooling, the reaction mixture was digested with EtOH, and Pd-Pt/C was filtered off. The filtrate was evaporated to dryness and the residue was chromatographed on silica gel with $CHCl_3$–EtOH (9.8:0.2, v/v) as an eluent to give **18** (0.67 g, 34%) and **19** (0.11 g, 7%). Compound **18** was recrystallized from EtOH; colorless needles, mp 216—217 °C. Lit.[13] mp 211—212 °C. Compound **19** was colorless oil. MS *m/z*: 209 (M^+). Picrate; yellow needles (EtOH), mp 181—182 °C.

(B) The same reaction of **5** in the absence of PNO resulted in formation of **18** (0.12 g, 6%) and recovery of **5** (1.78 g, 88%).

(C) The same reaction of **5** in the absence of Pd-Pt/C catalyst resulted in quantitative (96%) recovery of **5**.

Attempted Dimerization Reactions of Pyrazoles (6 and 7) Similar reactions of pyrazoles (**6** and **7**) were tried under the following conditions.

(A) pyrazole (1.0 g), PNO (1.4 g), Pd-Pt/C (0.2 g), 120—140 °C, 18 h.

(B) pyrazole (1.0 g), PNO (2.8 g), Pd-Pt/C (0.2 g), 120—140 °C, 18 h.

(C) pyrazole (1.0 g), PNO (1.4 g), Pd-Pt/C (0.2 g), 180—190 °C, 18 h.

(D) pyrazole (1.0 g), PNO (1.4 g), Pd-Pt/C (0.5 g), 180—190 °C, 18 h.

No product was observed on TLC and the pyrazoles were recovered quantitatively under these modified conditions and in the absence of PNO or Pd-Pt/C catalyst.

Dimerization Reactions of Hypoxanthines (8 and 9) (A) 1,7-Dimethylhypoxanthine (**9**): A mixture of **9** (0.4 g) and equimolar PNO (0.32 g) was heated at 180—190 °C in the presence of Pd-Pt/C catalyst (0.1 g) for 18 h under an N_2 atmosphere. After cooling, the reaction mixture was digested with $CHCl_3$ and Pd-Pt/C was filtered off. The filtrate was concentrated until crystals commenced to form. The precipitate was collected, giving **20** (40 mg, 10%), colorless needles, mp >300 °C. IR ν_{max} cm^{-1}: 1690. MS *m/z*: 326 (M^+). ^{1}H-NMR ($CDCl_3$): 8.08 (2H, s, 2,2′-H), 4.61, 3.46 (each 6H, s, 2 × N-CH_3). And **9** was recovered (0.32 g, 80%).

(B) Hypoxanthine (**8**): Similar reaction of **8** under the same conditions resulted in recovery of **8** (89%) and no product was observed on TLC. The use of other reaction solvents (2,6-lutidine, H_2O, and CH_3COOH) was examined but no product was observed.

Dimerization Reactions of Xanthines (10—12) (A) Caffeine (**10**): A mixture of **10** (2.0 g), equimolar PNO (1.0 g) and pyridine (0.4 g) was heated at 120—140 °C in the presence of Pd-Pt/C catalyst (0.4 g) for 18 h under an N_2 atmosphere. After cooling, the reaction mixture was digested with $CHCl_3$ (100 ml). The $CHCl_3$-insolubles were refluxed with DMSO (100 ml) and Pd-Pt/C was filtered off. The filtrate was concentrated until crystals commenced to form (15 ml). The precipitate was collected, giving **21** (50 mg, 2.5%), colorless needles, mp >300°C. IR ν_{max} cm^{-1}: 1700, 1655. MS *m/z*: 386 (M^+). ^{1}H-NMR (CF_3COOD): 4.40, 3.85, 3.65 (each 6H, s, 2 × N-CH_3). *Anal.* Calcd for $C_{16}H_{18}N_8O_4$: C, 49.73; H, 4.70; N, 29.00. Found: C, 49.52; H, 4.71; N, 28.68. The $CHCl_3$-solubles were shaken with H_2O. From the aqueous layer, **10** was recovered (1.14 g, 57%). The $CHCl_3$ layer was evaporated to dryness and the residue was refluxed with benzene. The benzene-solubles were chromatographed on aluminum oxide with benzene as an eluent to give 2,2′-bipyridyl (**24**) (33 mg) and 2,2′;6′,2″-terpyridyl (**25**) (17 mg). Then the benzene-insolubles were chromatographed on silica gel with $CHCl_3$ as an eluent to give **22** (0.67 g, 33%) and **23** (11 mg). Compound **22** was recrystallized from C_6H_6, colorless needles; mp 248—249 °C. IR ν_{max} cm^{-1}: 1700, 1655. MS *m/z*: 271 (M^+). ^{1}H-NMR ($CDCl_3$): 8.68 (1H, d, J=5 Hz, 6-H), 8.22 (1H, d, J=7.6 Hz, 3-H), 7.84 (1H, td, J=7.6, 1.7 Hz, 4-H), 7.36 (1H, m, 5-H), 4.48, 3.64, 3.44 (each 3H, s, N-CH_3). *Anal.* Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.50; H, 4.88; N, 25.57. Compound **23** was recrystallized from C_6H_6; colorless needles, mp 262—264°C. IR ν_{max} cm^{-1}: 1700, 1655. MS *m/z*: 348 (M^+). ^{1}H-NMR ($CDCl_3$): 8.52 (1H, dd, J=7.9, 1 Hz, 5-H), 8.27 (1H, dd, J=7.9, 1 Hz, 3-H), 7.98 (1H, dd, J=7.9, 7.9 Hz, 4-H), 4.61, 3.66, 3.46 (each 3H, s, N-CH_3).

(B) Theobromine (**11**) and Theophylline (**12**): Similar reactions of **11** and **12** under the reaction conditions modified as described for hypoxanthine (**8**) resulted in recovery of the starting materials.

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References and Notes

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