STUDIES ON NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS. SYNTHESIS OF BENZO[*b*][1,8]NAPHTHYRIDINE AND ITS OXIDATION REACTIONS WITH PEROXY ACID

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Abstract - A new method for the synthesis of benzo[*b*][1,8]naphthyridine (**4**) was established through the dehydrogenation of 5,6,7,8-tetrahydro-1,9-diazaanthracene. Oxidation reactions of **4** with peroxy acid afforded seven-membered 1,4-oxazepine derivatives (**5**-**8**).

Nitrogen-containing heterocyclic compounds have extensive pharmaceutical applications and *m*-Amsacrin (*m*-AMSA),[1] an acridine derivative, has been produced as an antitumor agent. In basic research on nitrogen-containing heterocyclic compounds such as acridine, the present authors have sought new methods for the synthesis of naphthonaphthyridines such as 7,8-, 7,11-, and 11,12-diazabenz[*a*]anthracenes.[2]
When naphtho[1,2-*b* and 2,1-*b*][1,8]naphthyridines was oxidized with peroxy acid in the usual procedure, a ring expansion was previously noted to form seven-membered 1,4-oxazepine ring.[2c] In the present paper, a modified method for the synthesis of benzo[*b*][1,8]naphthyridine (1,9-diazaanthracene) and the oxidation of benzo[*b*][1,8]naphthyridine are described.

RESULTS AND DISCUSSION

Benzo[*b*][1,8]naphthyridine[3] was previously synthesized by the Skraup reaction of 2-aminoquinoline. However, the yield was poor, and a new method to improve this was sought. The dehydrogenation of 5,6,7,8-tetrahydro-1,9-diazaanthracene (**1**)[4] has not been reported to date without an 8-methyl derivative, and 8-methyl-1,9-diazaanthracene has been obtained.[5]
Compound (**1**) was dehydrogenated using 20 % palladium on charcoal in *p*-cymene, at 180 ℃ for 15 h. The desired 1,9-diazaanthracene was not obtained. Instead compounds (**2**), (47 %) and (**3**), (24 %) were produced. Compound (**2**) was considered to be 1,2,3,4-tetrahydro-1,9-diazaanthracene on the basis of its ^{1}H-NMR spectrum. Compound (**3**) was obtained by the dehydrogenation of **2** under the same conditions, suggesting **2** to be an intermediate of **3**. Compound (**3**) showed aromatic proton at 2-8 positions and

methylene and NH proton signals at δ 4.10 and at δ 7.20, respectively. The structure of **3** was therefore determined as 9,10-dihydro-1,9-diazaanthracene. Reaction conditions are summarized in Table 1.

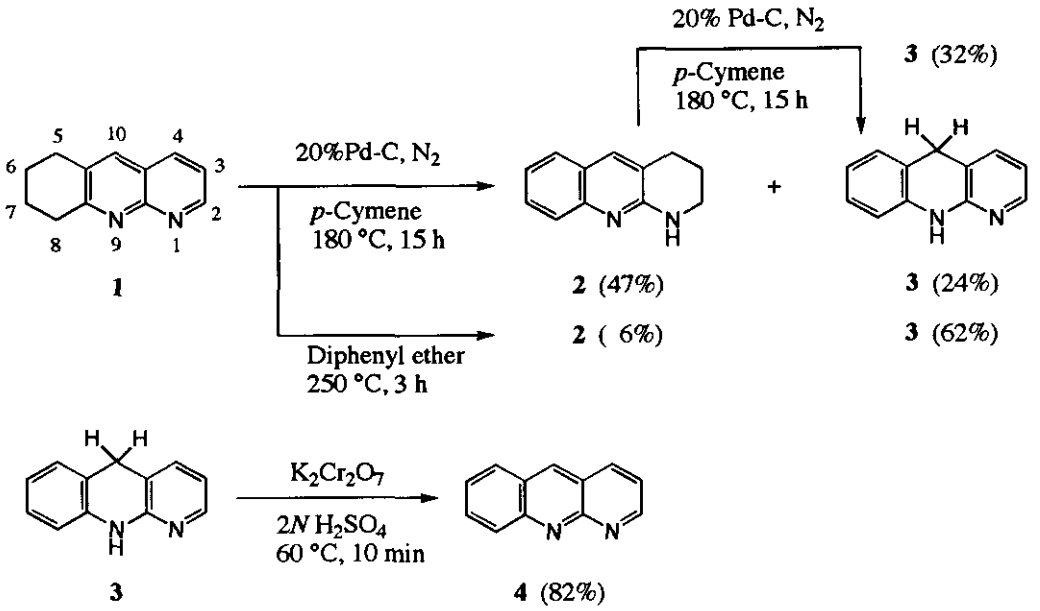
Heating at 250 ℃ for 3 h in diphenyl ether gave in 56% yield of **3**, which was further improved by using a larger amount of solvent, (62 %). On oxidation of **2** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), the starting material was recovered and polymerization occurred at high temperatures such as 250 ° C for 1 h. Compound (**3**) was oxidized with potassium dichromate in dilute sulfuric acid to produce 1,9-diazaanthracene (**4**) in a high yield of 82 %.

Compound (**4**) was treated with *m*-chloroperbenzoic acid (*m*-CPBA) at 20 ℃ for 3 h to produce the expected seven-membered 1,4-oxazepine compounds (**5**, 47 %) and (**6**, 24 %). When heated at 60 ℃ for 3 h, the yield of **5** decreased to 21 % and that of **6** increased to 33 %. The structure of **5** was confirmed by the 2D HMBC NMR spectrum shown in Figure 1. This structure was also supported by the similarity between the NMR spectrum patterns of **5** and **6** and those of 12-acetyloxy-7,12-dihydronaphtho[1,2-*b*]-pyrido[2,3-*e*][1,4]oxazepine, whose structure was previously determined by X-Ray crystallography.[2c]

Reactions of compound (**4**) with peracetic acid were as follows. Peracetic acid was prepared by reaction of acetic acid with 30 % hydrogen peroxide at 60 °C for 4 h. Compound (**4**) was added to the reaction mixture containing peracetic acid and reacted at 20 ℃ for 1 h to afford compounds (**7**) to (**10**). Compound (**7**) was found to be an 1,4-oxazepine derivative (11 %) and **8** to be an *N*-oxide (20 %). Compound (**9**) corresponded to the molecular formula $C_{12}H_8N_2O_2$ on the basis of the analytical data and the MS spectrum with *m/z*: 212 (M^+). ^{1}H-NMR spectrum showed a hydrogen bonded proton signal of NH---ON at δ 10.33. The proton at the 10-position vanished and signals of protons at 2, 3, and 4-positions of the pyridine ring appeared as double doublets. The structure of **9** was considered to be 1-oxy-1-azaacridone by the comparison of the proton chemical shifts with those of 1-azaacridone (**11**).[6] The chemical shifts of protons at positions 2, 3, and 4 (δ: 8.72, 7.28, and 8.78) of **11** appeared in higher magnetic fields than those of **9** (δ: 8.60, 7.19, and 8.35) due to the effect of the *N*-oxide group[7] in **9**. The structure of **9** was supported by the finding that oxidation of **11** with *m*-CPBA gave **9** as the sole product. (Scheme 1).

Compound (**10**) was considered to be a ring-opened compound similar to that of the product obtained from acridine[8] based on the ^{1}H-NMR spectrum showing signals corresponding to the CHO group at δ 9.91, NH---OC and OH---OC hydrogen bond at δ 10.50 and 10.64. To determine whether CHO or OH group of **10** was bound to the pyridine or benzene ring, the comparison of the proton NMR chemical shifts was made with the chemical shifts of 2-anilinopyridine. Structure of **10** was confirmed by the finding that when the CHO group was bound to the pyridine ring, the ring proton signals shifted to a lower field through the electron-withdrawing effect of this group and when the OH group was bound to the benzene ring, shifts to a higher magnetic field due to the electron-donating effect of the OH group were noted. Comparison of its proton NMR chemical shifts with that of 2-anilinopyridine, indicated that the CHO group was bound to the pyridine ring and the OH group was bound to the benzene ring.

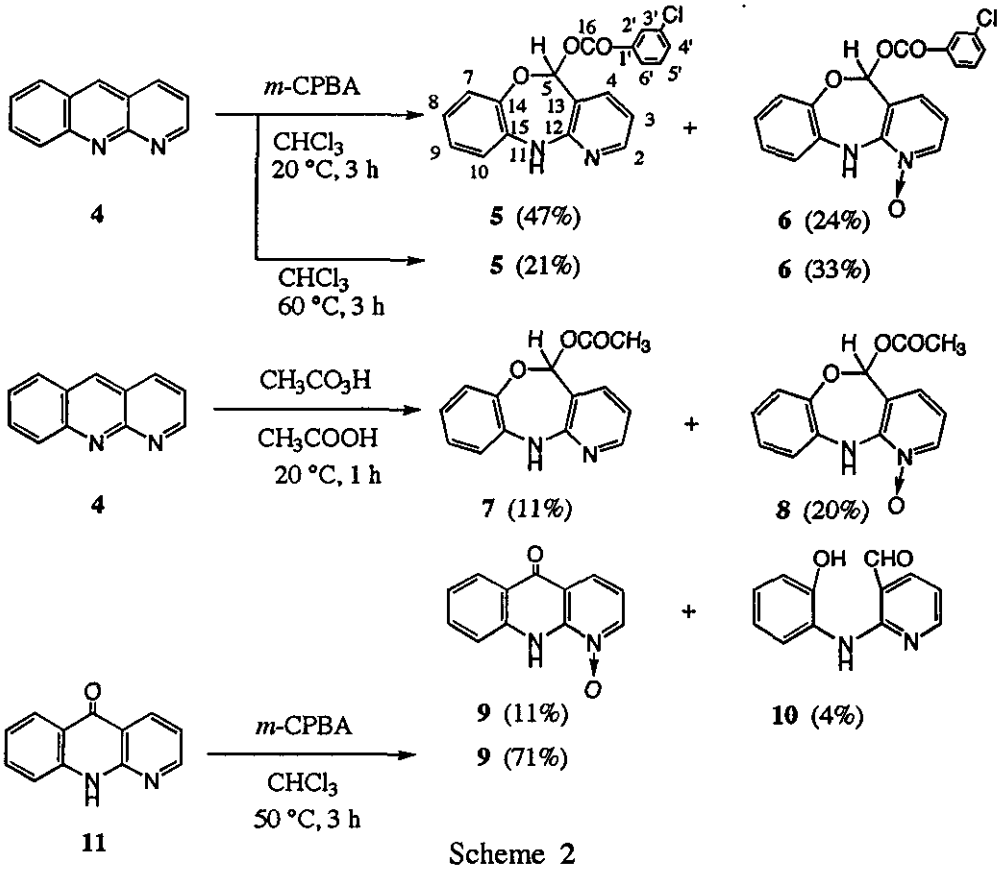
CONCLUSION



Scheme 1

Table 1. Dehydrogenation of **1** and **2** with 20% Pd-C

Compd (No.)	(mmol)	20% Pd-C (g)	Solvent	(mL)	Temp (°C)	Time (h)	Product (**2**) (%)	Product (**3**) (%)
1	10	1.0	*p*-Cymene	20	180	15	47	24
1	10	0.5	Ph-O-Ph	30	250	1	23	36
1	10	0.5	Ph-O-Ph	30	250	3	17	56
1	10	0.5	Ph-O-Ph	30	250	6	12	44
1	10	0.5	Ph-O-Ph	5	250	3	25	50
1	10	1.0	Ph-O-Ph	30	250	6	7	40
1	10	2.0	Ph-O-Ph	30	250	3	-	36
1	10	1.0	Ph-O-Ph	60	250	3	6	62
1	10	1.0	Diethylene glycol	30	250	3	7	54
2	10	1.0	*p*-Cymene	20	180	15	35	32
2	10	1.0	Diethylene glycol	30	250	3	21	43
2	1	DDQ 2 mmol	Diethylene glycol	15	250	1	polymerized	



Scheme 2

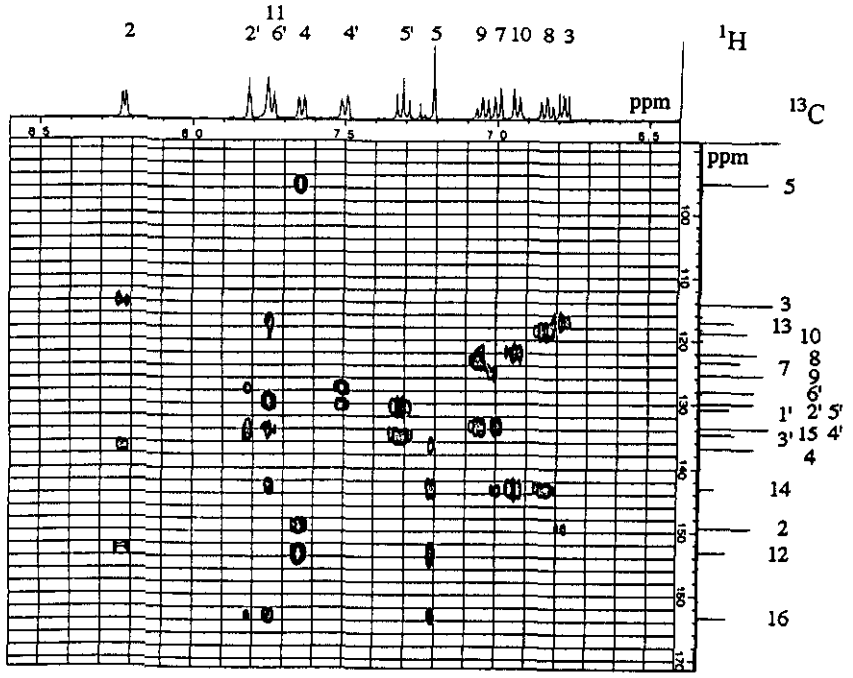


Figure 1. HMBC spectrum of compound (**5**) in $CDCl_3$

Since the right hand side pyridine ring in **1** undergoes reduction more easily than the benzene ring in quinoline and benzoquinoline, isomerized **2** was obtained through the dehydrogenation and hydrogenation of **1** with Pd-C. But this type's reaction was observed only for the 5,6,7,8-tetrahydro-1,9-diazaanthracene. Ring expansion occurred during the oxidation of **4** by *m*-CPBA. Such reactions do not occur in bicyclic 1,8-naphthyridine[9] and tricyclic acridine.[8] Thus, the ring expansion may be considered characteristic of nitrogen-containing heterocycles having a benzo[*b*][1,8]naphthyridine ring. Reactions of **4** with peroxy acids gave 1,4-oxazepine in a better yield than previously noted with the naphthonaphthyridine ring.[2c] The productions of compound (**9**) and ring-opened compound (**10**) indicate that **4** also has acridine-like characteristics not observed in the naphthonaphthyridine ring.

EXPERIMENTAL

^{1}H-NMR spectra were recorded with a JEOL JNM GX-270 spectrometer with tetramethylsilane (TMS) as the internal standard. Chemical shifts are given on a δ scale (ppm). The MS spectrum was taken with a Hitachi GC-MS M-80 spectrometer. IR and UV-VIS spectra were recorded on a JASCO IRA-I and Shimadzu UV-240 spectrophotometer, respectively.

9,10-Dihydro-1,9-diazaanthracene (3)

A mixture of **1** (0.92 g, 5 mmol) and 20% palladium on charcoal (Pd-C) (0.5 g) in diphenyl ether (or *p*-cymene) (30 mL) was heated under reflux at 250 ℃ (or 180 ℃), with stirring for 3 h (or 15 h). Following the removal of the catalyst (Pd-C) by filtration, $CHCl_3$ (30 mL) was added to the filtrate and the mixture was then extracted with 10% HCl. The extracts were washed with $CHCl_3$, and basified with 10% NaOH. The solution was extracted 3 times with $CHCl_3$. The extracts were washed with water, dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed over silica gel [eluted with $CHCl_3$-acetone (10 : 1)] to give compounds (**2**, **3**). The first elution gave 1.13 g (62%) of **3**.

3: pale yellow needles (cyclohexane), mp 163-165 ℃; MS *m/z*: 182 (M^+). IR ($CHCl_3$) cm^{-1}: 3420 (NH), 1602, 1584, 1490, 1443. UV-VIS (cyclohexane) λmax nm (log ε)=287 (4.04), 384 (2.69). ^{1}H-NMR ($CDCl_3$) δ: 4.10 (s, 2H, H-10), 6.71 (m, 1H, H-5), 6.77 (dd, 1H, J=7.4, 5.0 Hz, H-3), 6.88 (m, 1H, H-6), 7.09 (m, 1H, H-8), 7.10 (m, 1H, H-7), 7.29 (br s, NH), 7.34 (dd, 1H, J=7.4, 1.0 Hz, H-4), 8.02 (dd, 1H, J=5.0, 1.0 Hz, H-2). *Anal.* Calcd for $C_{12}H_{10}N_2$: C, 79.10; H, 5.53; N, 15.37. Found: C, 79.24; H, 5.32; N, 15.20. The second elution gave 0.11g (6%) of **2**.

2: colorless needles (AcOEt), mp 180-182 ℃; MS *m/z*: 184 (M^+), 183 (M^+-1). IR ($CHCl_3$) cm^{-1}: 3425 (NH), 1628, 1500, 1444. ^{1}H-NMR ($CDCl_3$) δ: 1.98 (m, 2H, H-3), 2.90 (m, 2H, H-4), 3.52 (t, 2H, J=5.4 Hz, H-2), 5.58 (br s, 1H, NH) 7.15 (m, 1H, H-6), 7.45 (m, 1H, H-7), 7.52 (m, 1H, H-5), 7.54 (s, 1H, H-10), 7.56 (m, 1H, H-8). *Anal.* Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.56; N, 15.20. Found: C, 78.17; H, 5.32; N, 15.24.

Benzo[*b*][1.8]naphthyridine (4)

A solution of **3** (0.91 g, 5 mmol) in 2*N*-H_2SO_4 (30 mL) was added to a solution of $K_2Cr_2O_7$ (1.8 g, 6.1

mmol) in water (60 mL) at 60 ℃ and the mixture was stirred for 10 min. The reaction mixture was made alkaline with NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was recrystallized from AcOEt to give 0.74g (82%) of **4** as yellow prisms, mp 197-199 ℃ (lit.,[3] mp 190-192 ℃). MS *m/z*: 180 (M^+). IR (KBr) cm^{-1}: 3020, 1619, 1604, 1547, 1507, 740. UV-VIS (H_2O) λmax nm (log ε)=227 (4.45), 247 (4.80), 354 (4.10). ^{1}H-NMR ($CDCl_3$) δ: 7.47 (dd, 1H, J=8.4, 3.7 Hz, H-3), 7.60 (m, 1H, H-6), 7.85 (m, 1H, H-7), 8.03 (m, 1H, H-5), 8.36 (dd, 1H, J=8.4, 2.0 Hz, H-4), 8.37 (m, 1H, H-8), 8.80 (s, 1H, H-10), 9.28 (dd, 1H, J=3.7, 2.0 Hz, H-2). *Anal.* Calcd for $C_{12}H_8N_2$: C, 79.98; H, 4.47; N, 15.54. Found: C, 80.04; H, 4.53; N, 15.36.

Oxidation of 4 with *m*-CPBA

A solution of **4** (0.9 g, 5 mmol) and *m*-CPBA (*ca.* 70% purity) (2.47 g, 12 mmol) in $CHCl_3$ (50 mL) was stirred at 20 ℃ for 3 h. A solution of 5% Na_2CO_3 (100 mL) was added to the reaction mixture and the whole was extracted with $CHCl_3$. The extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed over silica gel [eluted with $CHCl_3$] to give compounds (**5**, **6**). The first elution gave 0.82 g (47%) of **5**.

5: pale yellow needles (MeCN), mp 156-158 ℃; MS *m/z*: 352 (M^+), 323, 213, 197 (M^+-$OCOC_6H_4Cl$). IR ($CHCl_3$) cm^{-1}: 3400 (NH), 1733 (C=O). UV-VIS (cyclohexane) λmax nm (log ε)=203 (4.66), 283 (4.15). ^{1}H-NMR ($CDCl_3$) δ: 6.79 (dd, 1H, J=7.4, 5.0 Hz, H-3), 6.84 (m, 1H, H-8), 6.94 (m, 1H, H-10), 7.01 (m, 1H, H-7), 7.06 (m, 1H, H-9), 7.21 (s, 1H, H-5), 7.32 (t, 1H, J=8.1 Hz, H-5'), 7.51 (m, 1H, H-4'), 7.65 (dd, 1H, J=7.4, 1.7 Hz, H-4), 7.73 (br s, 1H, NH), 7.75 (m, 1H, H-6'), 7.82 (m, 1H, H-2'), 8.23 (dd, 1H, J=5.0, 1.7 Hz, H-2); ^{13}C-NMR ($CDCl_3$) δ: 95.2 (C-5), 114.2 (C-3), 117.1 (C-13), 118.7 (C-10), 122.0 (C-8), 123.3 (C-7), 125.3 (C-9), 127.9 (C-6'), 129.8 (C-2'), 129.9 (C-5'), 130.7 (C-1'), 133.7 (C-4', 15), 134.7 (C-3'), 136,8 (C-4), 143.0 (C-14), 149.3 (C-2), 163.3 (C-16). *Anal.* Calcd for $C_{19}H_{13}N_2O_3Cl$: C, 65.06; H, 3.99; N, 8.12. Found: C, 64.68; H,3.69; N, 7.94. The second elution gave 0.45 g (24%) of **6**.

6: pale yellow prisms (AcOEt), mp 167-168 ℃; MS *m/z*: 368 (M^+), 352 (M^+-O), 213 (M^+-$OCOC_6H_4Cl$), 197. IR ($CHCl_3$) cm^{-1}: 3225 (hydrogen bonding in NH---ON), 1736 (C=O). UV-VIS (cyclohexane) λmax nm (log ε)=205 (4.29), 258 (3.96), 278 (3.73). ^{1}H-NMR ($CDCl_3$) δ: 6.74 (dd, 1H, J=7.7, 6.7 Hz, H-3), 6.96 (m, 1H, H-9), 7.05 (m, 1H, H-8), 7.15 (m, 2H, H-7, H-10), 7.24 (s, 1H, H-5), 7.34 (t, 1H, J=8.1 Hz, H-5'), 7.35 (dd, 1H, J=7.7, 1.0 Hz, H-4), 7.54 (m, 1H, H-4'), 7.73 (m, 1H, H-6'), 7.81 (m, 1H, 2'H), 8.28 (dd, 1H, J=6.7, 1.0 Hz, H-2), 9.83 (br s, 1H, NH). *Anal.* Calcd for $C_{19}H_{13}N_2O_4Cl$: C, 61.87; H, 3.56; N, 7.61. Found: C, 61.87; H,3.53; N, 7.60.

Oxidation of 4 with Peracetic Acid

Peracetic acid was prepared as follows: a solution of 30% H_2O_2 (13.6 mL) in AcOH (34 mL) was stirred at 55-60 ℃ for 4 h, cooled to 20 ℃, to which was added **4** (11.08 g, 6 mmol) and the mixture was stirred at 20 ℃ for 1 h. $NaHSO_3$ (*ca.* 12 g) was added to cause the decomposition of H_2O_2. The reaction mixture

was treated in the same manner as the oxidation mixture of **4** with *m*-CPBA. The first elution gave 0.05 g (4%) of **10**.

10: pale brown plates (CCl_4), mp 129-131 ℃; MS *m/z*: 214 (M^+), 197 (M^+-OH), 196 (M^+-H_2O), 185 (M^+-CHO), 168 (196 -CO). IR (KBr) cm^{-1}: 3445 (OH), 3400 (NH), 1645 (CHO), 1610, 1572, 1520, 1450, 760. ^{1}H-NMR ($CDCl_3$) δ: 6.85 (dd, 1H, J=7.4, 5.0 Hz, H-3), 6.89 (m, 1H, H-4'), 7.08 (m, 2H, H-3', 6'), 7.14 (m, 1H, H-5'), 7.96 (dd, 1H, J=7.4, 2.0 Hz, H-4), 8.30 (dd, 1H, J=5.0, 2.0 Hz, H-2), 9.91 (s, 1H, CHO), 10.50 (br s, 1H, NH), 10.66 (s, 1H, OH). *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.21; H,4.72; N, 13.01. The second elution gave 0.164 g (11%) of **7**.

7: pale yellow prisms (hexane), mp 124-126 ℃; MS *m/z*: 256 (M^+), 213 (M^+-$COCH_3$), 197 (M^+-$OCOCH_3$). IR ($CHCl_3$) cm^{-1}: 3398 (NH), 1752 (C=O). UV-VIS (cyclohexane) λmax nm (log ε)=284 (4.32). ^{1}H-NMR ($CDCl_3$) δ: 2.06 (s, 3H, $OCOCH_3$), 6.76 (dd, 1H, J=7.4, 5.0 Hz, H-3), 6.87 (m, 1H, H-10), 6.89 (m, 1H, H-9), 6.94 (s, 1H, H-5), 7.01 (m, 1H, H-7), 7.06 (m, 1H, H-8), 7.33 (br s, 1H, NH), 7.56 (dd, 1H, J=7.4, 1.7 Hz, H-4), 8.19 (dd, 1H, J=5.0, 1.7 Hz, H-2). *Anal.* Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.83; H, 4.86; N, 10.82. The third elution gave 0.33 g (20%) of **8**.

8: colorless needles [benzene-ligroin (1:3)], mp 142-144 ℃; MS *m/z*: 272 (M^+), 256 (M^+-O), 229 (M^+-$COCH_3$), 213 (M^+-$OCOCH_3$). IR ($CHCl_3$) cm^{-1}: 3220 (hydrogen bonding in NH---ON), 1762 (C=O). UV-VIS (cyclohexane) λmax nm (log ε)=210 (4.37), 261 (4.39), 304 (4.42), 349 (3.73). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (s, 3H, $COCH_3$), 6.71 (dd, 1H, J=6.8, 5.4 Hz, H-3), 6.96 (s, 1H, H-5), 7.03 (m, 2H, H-8, 9), 7.12 (m, 2H, H-7, 10), 7.28 (dd, 1H, J=6.8, 1.0 Hz, H-4), 8.23 (dd, 1H, J=5.4, 1.0 Hz, H-2), 9.71 (br s, 1H, NH). *Anal.* Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.77; H, 4.49; N, 10.34. The fourth elution gave 0.145 g (11%) of **9**.

9: yellow needles (EtOH), mp > 300 ℃; MS *m/z*: 212 (M^+), 196 (M^+-O), 168 (196 -CO). IR (KBr) cm^{-1}: 3050 (NH), 2790, 1645 (C=O), 1614, 1208 (N-O), 750. ^{1}H-NMR ($CDCl_3$) δ: 7.19 (dd, 1H, J=8.1, 6.4 Hz, H-3), 7.42 (m, 1H, H-7), 7.53 (m, 1H, H-8), 7.79 (m, 1H, H-6), 8.35 (dd, 1H, J=8.1, 1.4 Hz, H-4), 8.45 (m, 1H, H-5), 8.60 (dd, 1H, J=6.4, 1.4 Hz, H-2), 10.33 (br s, 1H, NH). *Anal.* Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.90; H, 3.80; N, 13.01.

Oxidation of 11 with *m*-CPBA

A solution of **11** (0.1 g, 0.5 mmol) and *m*-CPBA (*ca.* 70% purity) (0.27 g, 1.1 mmol) in $CHCl_3$ (100 mL) was stirred at 50 °C for 3 h. The reaction mixture was treated in the same manner as the oxidation mixture of **4** with *m*-CPBA. The elution gave 0.075 g (71%) of **9** as yellow needles (EtOH), mp > 300 ℃. The product was identical to **9**, previously synthesized by the oxidation of **4** with peracetic acid, by the comparison of their IR and ^{1}H-NMR spectra.

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REFERENCES

1. G. J. Atwell, B. C. Baguley, G. J. Finlay, G. W. Rewcastle, and W. A. Denny, *J. Med. Chem.*, 1986, **29**, 1769.
2. a) I. Takeuchi, Y. Hamada, and M. Hirota, *Chem. Pharm. Bull.*, 1993, **41**, 747; b) Y. Terada, I. Takeuchi, K. Koyasu, and Y. Hamada, *Heterocyclic Commun.*, 1996, **2**, 447; c) I. Takeuchi, K. Asai, Y. Hamada, K. Masuda, H. Suezawa, M. Hirota, Y. Kurono, and K. Hatano, *Heterocycles*, 1996, **43**, 2139.
3. Y. Hamada, I. Takeuchi, and M. Hirota, *Chem. Pharm. Bull.*, 1974, **22**, 485.
4. R. P. Thummel and D. K. Kohli, *J. Heterocycl. Chem.*, 1977, **14**, 685.
5. Q. Chen and L. W. Deady, *J. Heterocycl. Chem.*, 1992, **29**, 1197.
6. A. I. Mikhalev and M. E. Konshin, *Khim. Geterotsikl. Soedin.*, 1977, 1241 (*Chem. Abstr.*, 1978, **88**, 22701y).
7. A. R. Katritzky and J. M. Lagowsky, *J. Chem. Soc.*, 1961, 43.
8. R. M. Acheson and B. Adcock, *J. Chem. Soc.* (C), 1968, 1045.
9. W. W. Paudler, D. J. Pokorny, and S. J. Cornrich, *J. Heterocycl. Chem.*, 1970, **7**, 291.

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