Ring-opening Reaction of 6,8-Di-t-butyl-1,2,3,4-tetrahydro-9aH-pyrido [2,1-b] benzoxazole

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Ring-opening Reaction of 6, 8-Di-t-butyl-1, 2, 3, 4-tetrahydro-9aH-pyrido [2, 1-b] benzoxazole

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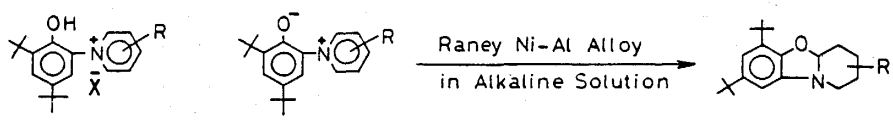
Dedicated to Professor Otohiko Tsuge on the occasion of his retirement

Treatment of 6,8-di-t-butyl-1,2,3,4-tetrahydro-9aH-pyrido[2,1-b]benzoxazole (**3a**) with conc. hydrochloric acid gave 2,4-di-t-butyl-6-piperidinophenol (**4**) and 2,4-di-t-butyl-6-(2-oxopiperidino)phenol (**5**) in 26 and 25% yields. Reaction of **3a** with acetic anhydride afforded 2,4-di-t-butyl-6-[1-(1,2,3,4-tetrahydro-5-acetylpyridyl)]phenyl acetate (**6**) and 6,8-di-t-butyl-1-acetyl-2,3,4,4a-tetrahydropyrido[2,1-b]benzoxazole (**7**) in 41 and 25% yields. Hofmann degradation of the quarternary salts of **3a** with methyl and ethyl iodide gave the expected ring-opend [1,4]oxazonines, **10a** and **10b**, in 43 and 10% yields, respectively.

Recently, we have reported[1,2] the reductive cyclization of 1-(3,5-di-t-butyl-2-hydroxyphenyl)pyridinium halide **1** and their inner salt **2** by treatment with Raney Ni-Al alloy in an alkaline solution, giving 6,8-di-t-butyl-1,2,3,4-tetrahydro-9aH-pyrido[2,1-b]benzoxazole **3**.



1 2 3

Compound **3** is pharmacologically interesting because its skeleton resembles a part of the structure of vomicine which has a strychnine-like biological activity. In fact, we experienced numbness in an oral cavity though **3** was handled with an extreme care. Therefore, it is of interest to investigate the chemical reactivity of **3**.

We now report the ring-opening reaction of **3a** (R=H) with hydrochloric acid and acetic anhydride and Hofmann degradation of quarternary salt of **3a**.

Results and Discussion

(1) Reaction with conc. hydrochloric acid and acetic anhydride

Treatment of **3a** with conc. hydrochloric acid in methanol at reflux for 16 h gave piperidino-

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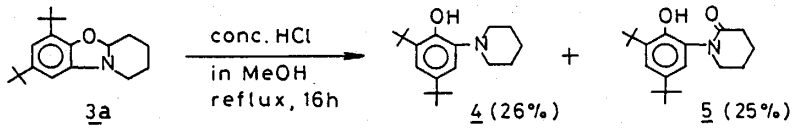
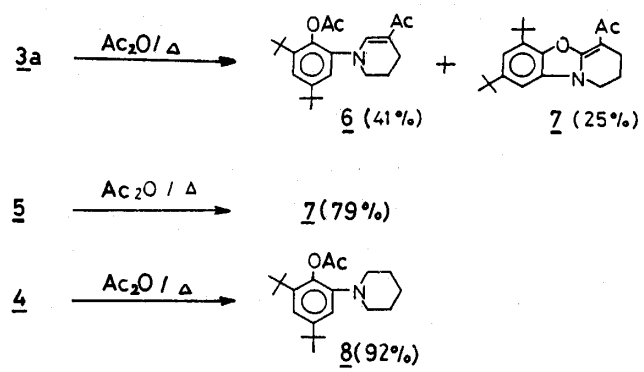
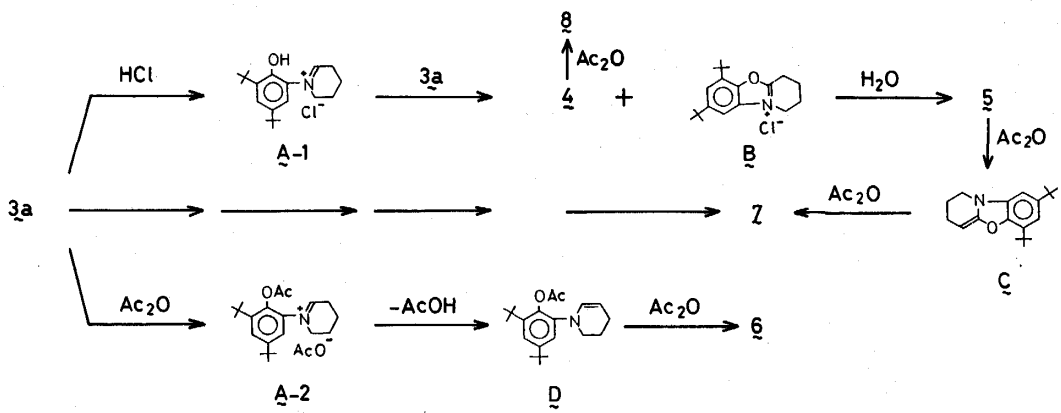
phenol **4** [3] and (2-oxopiperidino)phenol **5** in 26 and 25% yields, respectively. The structures of **4** and **5** were deduced from their spectral data; in IR spectrum of **5**, carbonyl absorption band was observed at 1635 cm^{-1}, thus suggesting the presence of amide-skeleton. Compound **4** corresponds to the reductively ring-opened product of **3a**, while **5** to the oxidatively ring-opened one.



Reaction of **3a** with acetic anhydride at reflux for 1 h afforded two products, **6** and **7**, in 41 and 25% yields, respectively. In IR spectrum of **6**, a broad band was observed at 1610-1580 cm^{-1}, which is ascribed to β-ketoenamine-type carbonyl absorption. ^{1}H-NMR spectrum of **6** showed a singlet at 7.30 ppm. Thus, the structure of **6** was deduced as [1-(1,2,3,4-tetrahydro-5-acetylpyridyl)]phenyl acetate. Compound **7** was elucidated as 2,3,4,4a-tetrahydropyrido[2,1-b]-benzoxazole from its spectral data and from the fact that **7** was obtained in 79% yield when **5** was treated with refluxing acetic anhydride.



Compound **6** is not a precursor of **7** and vice versa as both **6** and **7** are stable in refluxing acetic anhydride. Compound **4** gave **8** in 92% yield, but not **6**. Thus, tentative formation pathway of **4**–**7** is proposed in Scheme 1. Protonation of **3a** might give **A**–**1** which oxidize **3a**

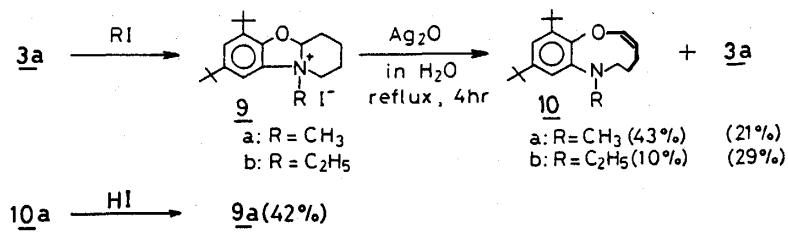


(Scheme 1)

to give **4** and **B**. Hydrolysis of **B** gives **5**. Compound **5** is cyclized to **C** by acetic anhydride. As the C=C double bond of **C** is considered to have a combined nature of those of enamine and vinyl ether, it is acetylated to give **7**. On the other hand, treatment of **3a** with acetic anhydride afforded **A–2** which gives enamine **D**. Acetylation of enamine **D** gives **6**. But, formation pathway of **7** in the reaction of **3a** with acetic anhyclride is not konwn.

(2) Hofmann degradation

Hofmann degradation of quaternary salts, **9a** and **9b**, in the presence of silver oxide afforded the expected 9-membered heterocycles, **10a** and **10b**, in 43 and 10% yields, respectively, together with free base **3a**. Stereochemistry of olefinic part in **10** is cis from ^{1}H-NMR. Treatment of **10a** with hydroiodic acid gave recyclized **9a** in 42% yield.



Experimental

All melting points are uncorrected. IR spectra were measured on a JASCO A-102 spectrophotometer as KBr pellet or liquid films on NaCl. ^{1}H- and ^{13}C-NMR spectra were determined in $CDCl_3$ at 100 MHz on a JEOL FX-100 spectrometer with Me_4Si as an internal standard. Mass spectra were obtained on a JEOL JMS-O1SG-2 spectrometer at 75 eV using a direct inlet system. Column chromatography was carried out on silica gel (Wako gel, C-300).

Reaction of 3a with conc. hydrochloric acid.

After a mixture of **3a** (1.00g) and conc. hydrochloric acid (0.2mL) in methanol (100mL) was refluxed for 16 h, the solvent was evaporated in vacuo. The residue was dissolved in benzene (100mL) and the benzene solution was washed with aqueous 10% $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated in vacuo and the residue was chromatographed. Compound **4** [3] (0.26g, 26%) was eluted with a 1:2-mixture of benzene and hexane and **5** (0.26g, 25%) with a 3:1-mixture of benzene and ethyl acetate. 2,4-Di-t-butyl-6-(2-oxo-piperidino)phenol (**5**): colorless needles, mp 195–200°C (decomp.) (a mixture of methanol and water); IR 3175 and 1635cm^{-1}; ^{1}H-NMR δ=1.28 and 1.44 (each 9H, s), 1.80–2.08 (4H, m), 2.50–2.72 (2H, m), 3.60–3.82 (2H, m), 6.92 (1H, s, exchanged with D_2O), and 7.00 and 7.26 (each 1H, d, J=2.5 Hz); mass, m/e 303 (M^+). Found: C, 75.34; H, 9.74; N, 4.46%. Calcd for $C_{29}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62%.

Reaction of 3a with acetic anhydride.

A mixture of **3a** (1.00g) in acetic anhydride (15mL) was refluxed for 1 h. After being cooled to room temperature, it was extracted with benzene (100mL×3). The benzene solution was washed with aqueous 10% $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated in vacuo to leave a residue which was chromatographed. Compound **6** (0.53g, 41%) was eluted with ethyl acetate and **7** (0.29g, 25%) with a 95: 5-mixture of ethyl acetate and methanol.

2,4-Di-t-butyl-6-[1-(1,2,3,4-tetrahydro-5-acetyl)pyridyl)]phenyl acetate **(6)**: pale yellow prisms, mp 163–165°C (petr. ether); IR 1765 and 1610–1580cm^{-1}; ^{1}H-NMR δ=1.30 and 1.34 (each 9H, s), 1.86 (2H, t, J=6 Hz), 2.15 and 2.24 (each 3H, d, J=2 Hz), 2.38 (2H, t, J=6 Hz), 3.20–3.60 (2H, m), 7.02 and 7.28 (each 1H, d, J=2 Hz), 7.30 (1H, s). Found: C, 74.58; H, 9.06; N, 3.46%. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.46%.

1-Acetyl-6,8-di-t-butyl-2,3,4-trihydropyridino[2,1-b]benzoxazole **(7)**: pale yellow prisms, mp 207–209°C (petr. ether); IR 1640, 1620, and 1580–1540cm^{-1}; ^{1}H-NMR δ=1.32 and 1.44 (each 9H, s), 1.96 (2H, q, J=6 Hz), 2.50 (3H, s), 2.62 and 3.76 (each 2H, t, J=6 Hz), and 6.76 and 6.97 (each 1H, d, J=2 Hz). Found: C, 76.95; H, 9.04; N, 3.99%. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28%.

Reaction of 4 with acetic anhydride.

After a mixture of **4** (0.20g) in acetic anhydride (3mL) was refluxed for 1h, it was worked up as described above, giving 2,4-di-t-butyl-6-piperidinophenyl acetate **(8)** (0.21g): colorless viscous oil; IR 1770cm^{-1}; ^{1}H-NMR δ=1.30 and 1.35 (each 9H, s), 1.45–1.76 (6H, m), 2.30 (3H, s), 2.60–3.00 (4H, m), and 7.04 and 7.13 (each 1H, d, J=2 Hz); mass m/e 331 (M^+). Found: C, 76.26; H, 10.30; N, 4.50%. Calcd for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.22%.

Reaction of 5 with acetic anhydride.

After a mixture of **5** (0.50g) in acetic anhydride (15mL) was refluxed for 1 h, it was worked up as decribed above to give **7** (0.43g, 79%).

Preparation of quarternary salt 9.

(i) Preparation of 9a. A mixture of **3a** (5.00g) and methyl iodide (20mL) in ether (40mL) was kept to stand at room temperature for 24 h and precipitated **9a** was filtered. The filtrate was evaporated and the residue was triturated with petr. ether and cold ether, giving another crop of **9a.** N-Methyl-6,8-di-t-butyl-1,2,3,4-tetrahydro-9aH-pyrido[2,1-b]benzoxazolium iodide **(9a)**: colorless needles (7.10g, 95%), mp 201–203 (decomp.) (water); ^{1}H-NMR δ=1.36 (18H, s), 1.52–2.32 (5H, m), 2.52–2.82 (1H, m), 3.60–3.92 (1H, m), 4.00 (3H, s), 4.40–4.76 (1H, m), 5.86–6.04 (1H, m), and 7.36 and 7.82 (each 1H, d, J=2Hz). Found: C, 55.93; H, 7.55; N, 3.00 %. Calcd for $C_{20}H_{32}NOI$: C, 55.94; H, 7.51; N, 3.26%.

(ii) Preparation of 9b. A mixture of **3a** (5.00g) in ethyl iodide (50mL) was refluxed for 24 h and treated as described above, giving N-ethyl-6,8-di-t-butyl-1,2,3,4-tetrahydro-9aH-pyrido

[2,1−b]benzoxazolium iodide **(9b)** (5.50g, 71%): colorless plates, mp 171−174 (decomp.) (water); ^{1}H-NMR δ=1.28 (3H, t, J=8 Hz), 1.36 and 1.37 (each 9H, s), 1.44−2.40 (5H, m), 2.42−2.84(1H, m), 4.50−4.75 (4H, m), 6.38−6.56 (1H, m), and 7.38 and 7.66 (each 1H, d, J=2 Hz). Found: C, 56.68; H, 7.73; N, 2.85%. Calcd for $C_{21}H_{34}NOI$: C, 56.88; H, 7.73; N, 3.16%.

Hofmann degradation of 9.

Typical procedure. After a mixture of **9a** (1.00g) and silver oxide (0.65g) in water (50mL) was refluxed for 4 h, insoluble materials were filtered off while the reaction mixture was still hot. The filtrate was evaporated in vacuo to leave a residue which was dissolved in hot benzene (100mL). The benzene solution was condensed and chromatographed with a 1:1-mixture of benzene and hexane as an eluant, giving **10a** (0.30g, 43%) and **3a** (0.14g, 21%). 9,11-Di-t-butyl-7-methyl-4,5,6,7-tetrahydrobenzo[b] [1,4]oxazonine **(10a)**: colorless plates, mp 99−100°C (methanol); IR 1670 cm^{-1}; ^{1}H-NMR δ=1.28 and 1.38 (each 9H, s), 1.42−1.64 (2H, m), 2.20−2.48 (2H, m), 2.68 (3H, s), 3.03−3.23 (2H, m), 5.10 (1H, double t, J=5.3 and 8 Hz), 5.78 (1H, d, J=5.3 Hz), and 6.72 and 6.86 (each 1H, d, J=2.3 Hz); ^{13}C-NMR δ=24.2 (t). 24.6 (t), 30.5 (q), 31.6 (q), 34.7 (s), 35.1 (s), 37.6 (s), 59.0 (t), 112.1 (d), 112.6 (d), 115.1 (d), 141.6 (s), 142.4 (d), 144.2 (s), 145.6 (s), and 147.0 (s); mass m/e 301 (M^+). Found: C, 79.68; H, 10.44; N, 4.83%. Calcd for $C_{20}H_{31}NO$: C, 79.68; H, 10.37; N, 4.65%.

A mixture of **9b** (1.00g) and silver oxide (0.65g) in water (50mL) was treated as described above, giving **10b** (0.07g, 10%) and **3a** (0.19g, 29%). 9,11-Di-t-butyl-7-ethyl-4,5,6,7-tetrahydrobenzo[b] [1,4]oxazonine **(10b)**: colorless prisms, mp 87−88°C (a mixture of methanol and water); IR 1657cm^{-1}; ^{1}H-NMR δ=1.04 (3H, t, J=8 Hz), 1.28 and 1.38 (each 9H, s), 1.40−1.60 (2H, m), 2.20−2.48 (2H, m), 3.02−3.20 (2H, m), 5.08 (1H, double t, J=5.3 and 8 Hz), 5.75 (1H, d, J=8 Hz), and 6.76 and 6.86 (each 1H, d, J=2.3Hz); ^{13}C-NMR δ=13.0 (q), 24.1 (t), 24.6 (t), 30.6 (q), 31.1 (q), 34.7 (s), 35.1 (s), 42.5 (t), 57.7 (t), 112.1 (d), 114.2 (d), 115.1 (d), 141.7 (s), 142.4 (d), 144.5 (d), 145.0 (s), and 145.5 (s); mass m/e 315 (M^+). Found: C, 80.07; H, 10.71; N, 4.66%, Calcd for $C_{21}H_{33}NO$: C, 79.95; H, 10.54; N, 4.66%.

Reaction of 10a with hydroiodic acid.

A mixture of **10a** (0.10g) and 52% hydroiodic acid (0.5mL) in methanol (10mL) was refluxed for 15 min. It was evaporated in vacuo to leave a residue which was recrystallized from water, giving **9a** (0.06g).

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