Lactams. XVIII. Oxidation of 1-Substituted 3-tert-Butyl-piperidine with Mercuric Acetate-EDTA

Chem. Pharm. Bull. 29(9)2691—2695(1981)

Lactams. XVIII.[1] Oxidation of 1-Substituted 3-*tert*-Butylpiperidine with Mercuric Acetate–EDTA

Tozo Fujii,* Takashi Hiraga, and Masashi Ohba

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

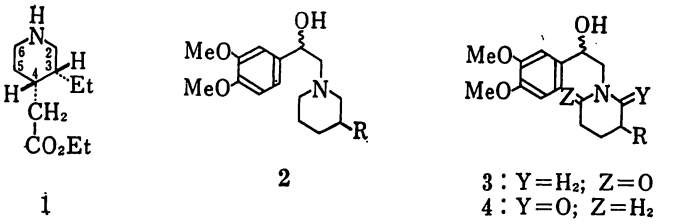
(Received February 16, 1981)

1-(3,4-Dimethoxyphenyl)-2-(3-*tert*-butylpiperidino)ethanol (**7**) was prepared from 3-*tert*-butylpyridine (**5**) through the quaternary salt **6**. The mercuric acetate–EDTA oxidation of **7** produced the 6-piperidone **10** and the 2-piperidone **13** in a ratio of 98: 2. The former piperidone was chemically correlated with the known 6-pyridone **8** through the lactam **9**, and **9** was converted into the benzoquinolizidine **11** by cyclization and reduction of the resulting iminium salt **12**.

Keywords——1,3-disubstituted piperidine; piperidone; benzoquinolizidine; quaternization; catalytic reduction; mercuric acetate–EDTA oxidation; *tert*-butyl group; steric effect; regioselectivity; stereoselectivity

One of the most important aspects of our recent chiral syntheses[2] of the Ipecac and *Alangium* alkaloids was the generation of the lactam carbonyl function at the 6-position of cincholoipon ethyl ester [(+)—**1**], a degradation product of the major *Cinchona* alkaloids,

by the mercuric acetate–ethylenediaminetetraacetic acid (EDTA) oxidation method.[3] In preliminary studies on this operation, we investigated the oxidation of 1,3-disubstituted piperidines (type **2**) with mercuric acetate–EDTA, and the effects of various 3-substituents on the position of oxidation in the heterocyclic ring have been catalogued[4] in terms of the ratios of the isomeric 6- (type **3**) and 2-piperidones (type **4**) formed. We have now extended our studies of the 3-substituent effect to cover the *tert*-butyl group, a highly branched, bulky hydrocarbon substituent. This work was facilitated by our recent discovery[5] of a new synthetic route to the required starting material 3-*tert*-butylpyridine (**5**) from α-*tert*-butylacrolein, which was found to produce base of prime quality.



1 **2** **3**: Y=H_2; Z=O; **4**: Y=O; Z=H_2

Chart 1

Quaternization of **5** with 3,4-dimethoxyphenacyl bromide[6] in benzene gave the salt **6** in 86% yield. Reduction of **6** with hydrogen and Adams catalyst followed by $NaBH_4$ afforded the piperidinoethanol **7** (99% yield), which was presumed to be a mixture of the two possible diastereomers. Since purification of **7** was difficult, it was directly oxidized with mercuric acetate–EDTA (boiling 1% aqueous AcOH, 1.5 h) according to the previously reported[4a] standard procedure, and two isomeric lactam alcohols **10** and **13** were obtained as diastereo-

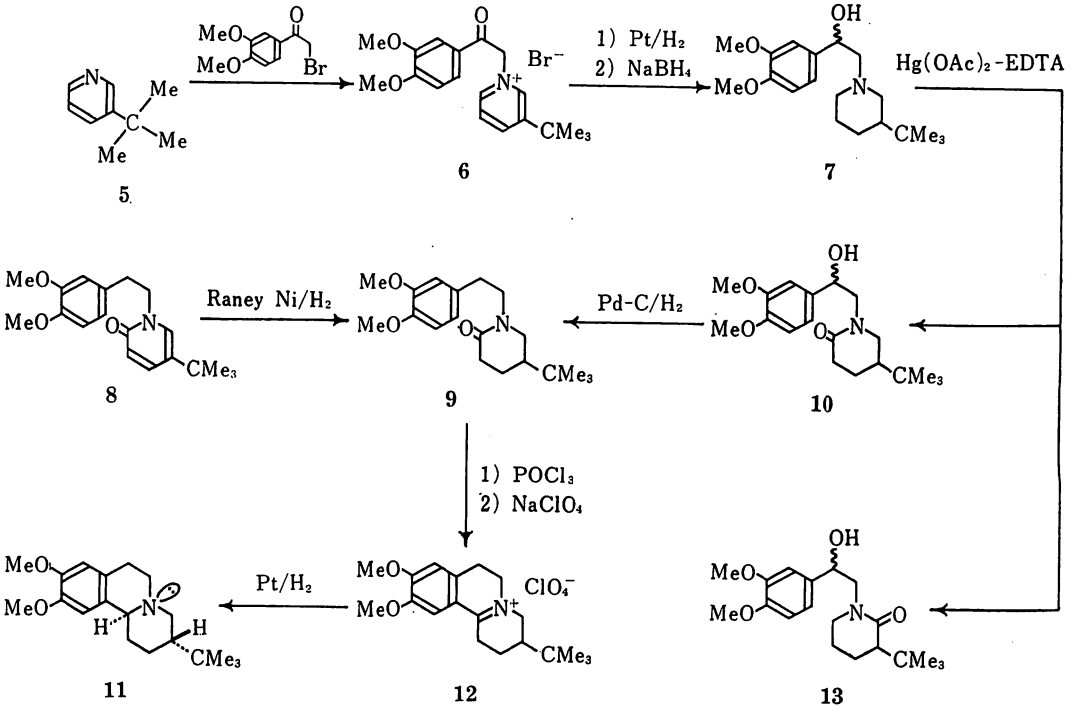


Chart 2

meric mixtures in a combined yield of 79%. The oxidation reaction was run in triplicate and chromatographic analysis of the products was carried out as reported previously;[4a] the isomer ratio of the piperidones was found to be **10**: **13**=98: 2.

The location of the lactam carbonyl group in **10** and **13** was assigned on the basis of the following evidence. On thin-layer chromatography (TLC) (Al_2O_3, AcOEt–hexane), **13** ran faster than **10**, and a similar difference in chromatographic mobility has been observed[4b] for the 2-piperidone **4** and the 6-piperidone **3** (R=Me, Et, *n*-Bu, iso-Pr, $PhCH_2$, or Ph). In the infrared (IR) spectrum in $CHCl_3$, **13** displayed the CO stretching vibration at 1607 cm^{-1}, and **10** at 1612 cm^{-1}. This is in agreement with our previous finding[4b] that 2-piperidones (type **4**: R=alkyl) show slightly lowered lactam ν_{CO} in comparison with the corresponding 6-piperidones (type **3**). In the nuclear magnetic resonance (NMR) spectrum in $CDCl_3$, the *tert*-butyl protons of **13** were less shielded than those of **10** by 0.2—0.3 ppm. The downfield shift observed reflects the deshielding effect of the lactam carbonyl group on the neighboring *tert*-butyl group in **13**. In the case of **10**, final identification as a 6-piperidone rested on its catalytic hydrogenolysis to the lactam **9**, which was identical with a sample prepared from the known 6-pyridone **8**[7] by catalytic reduction. On the other hand, the unavailability[7] of the isomeric 2-pyridone and the paucity of **13** did not permit the achievement of a parallel chemical correlation.

In our previous reports[4] dealing with the mercuric acetate–EDTA oxidation of 1,3-disubstituted piperidines (type **2**), we have already suggested that the 3-substituents (R in **2**) exert both steric and electronic effects to determine the regioselectivity in the lactam formation. The isomer ratio (**10**: **13**=98: 2) observed for the 3-*tert*-butyl group in the present study thus provides an additional and valuable example of the steric effect operating in such a reaction.

Finally, the lactam **9** was converted into the iminium salt **12** in 96% yield by cyclization with $POCl_3$ followed by treatment with $NaClO_4$. Catalytic hydrogenation of **12** afforded the benzoquinolizidine **11** (85% yield), which was shown to be isomer-free on TLC and NMR spectral analyses. The assignment of the *trans*-quinolizidine structure **11** with the equatorial *tert*-butyl group at the 3-position was based on Bohlmann's IR criterion[8] and a consideration of preferred conformation. Interestingly enough, this stereochemical result presents a contrast to our previous finding[9] that the stereoselectivity in a similar reduction of the methyl analog (**12**: Me for CMe_3) is not high.

Experimental

General Comments——All melting points were determined by using a Yamato MP-1 capillary melting point apparatus, and are corrected. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. IR spectra were recorded on a JASCO IRA-2 spectrophotometer in Nujol mulls or in $CHCl_3$ solutions at 0.2 M concentration. NMR spectra were measured on a JEOL JNM-PMX-60 or JNM-FX-100 spectrometer at 24°C with Me_4Si as an internal standard (δ=0 ppm). See ref. 2*b* for other instrumentation and measurements. The following abbreviations are used: b=broad, d=doublet, d-d=doublet-of-doublets, m=multiplet, s=singlet. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University.

1-(3,4-Dimethoxyphenacyl)-3-(1,1-dimethylethyl)pyridinium Bromide (**6**)——A mixture of 3-*tert*-butylpyridine (**5**)[5] (4.08 g, 30 mmol) and 3,4-dimethoxyphenacyl bromide[6] (8.57 g, 33 mmol) in dry benzene (75 ml) was stirred at room temp. for 48 h. The crystals that resulted were filtered off and washed with benzene (50 ml) to give a first crop. The filtrate and washings were combined, concentrated to a volume of 20 ml, and stirred at room temp. for 5 h to produce a second crop of crystals. Recrystallization of first and second crops of crystals from EtOH–ether (1: 1, v/v) yielded **6**·H_2O (10.64 g, 86%) as colorless needles, mp 100—108°C (dried over P_2O_5 at room temp. and 2 mmHg for 24 h); UV λ_{max}^{EtOH} 232.5 nm (ε 19900), 275 (16200), 311.5 (11100); IR ν_{max}^{Nujol} cm^{-1}: 3460, 3400 (H_2O), 1683 (CO); NMR ($CDCl_3$) δ: 1.43 (9H, s, Me_3C), 2.15 (s, H_2O), 3.82 and 3.83 (6H, s each, two MeO's), 6.82 (1H, d, J=8.8 Hz, $H_{(5')}$), 7.17 (2H, s, NCH_2CO), 7.47 (1H, d, J=1.6 Hz, $H_{(2')}$), 7.82 (1H, d-d, J=8.8 and 1.6 Hz, $H_{(6')}$), 7.85 (1H, d-d, J=7.6 and 5.6 Hz, $H_{(5)}$), 8.32 (1H, d, J=7.6 Hz, $H_{(4)}$), 9.12 (1H, d, J=5.6 Hz, $H_{(6)}$), 9.28 (1H, s, $H_{(2)}$). *Anal.* Calcd for $C_{19}H_{24}BrNO_3 \cdot H_2O$: C, 55.35; H, 6.36; N, 3.40. Found: C, 55.18; H, 6.23; N, 3.47.

1-(3,4-Dimethoxyphenyl)-2-[3-(1,1-dimethylethyl)piperidino]ethanol (**7**)——A mixture of **6** (10.64 g, 25.8 mmol) and EtOH (120 ml) was hydrogenated over Adams catalyst (300 mg) at 25°C and atmospheric

pressure. When *ca.* 3.2 mol eq of H_2 had been taken up during 15 h, the reaction was discontinued and the reaction mixture was filtered to remove the catalyst. The filtrate was neutralized with 2 N aq. NaOH (12.8 ml), and $NaBH_4$ (1.03 g, 27.2 mmol) was added in small portions. The resulting mixture was stirred at room temp. overnight and then concentrated *in vacuo*. The residue was partitioned between benzene and H_2O. The benzene extracts were dried (K_2CO_3) and concentrated to leave **7** (8.22 g, 99%) as a colorless, viscous oil, MS *m/e*: 321 (M^+); UV λ_{max}^{EtOH} 230 nm (ε 8900), 279 (3000); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH); NMR ($CDCl_3$) δ: 0.85 and 0.88 (9H, s each, diastereomeric Me_3C's), 1.0—3.6 (11H, unresolved m, two ring-CH_2's and -CH, three NCH_2's), 3.3—3.7 (1H, b, OH), 3.83 and 3.86 (6H, s each, two MeO's), 4.48—4.76 [1H, m, ArC<u>H</u>(OH)], 6.76—6.98 (3H, m, aromatic protons).

Mercuric Acetate-EDTA Oxidation of 7——The oxidation of **7** (10 mmol), presumed to be a diastereomeric mixture, was effected in triplicate and the product was worked up according to the previously reported[4a] standard procedure, giving the 6-piperidone **10** and the 2-piperidone **13** as diastereomeric mixtures in a combined yield of 79%. Separation of the two piperidones was accomplished by means of column chromatography using Al_2O_3 (300 g) and AcOEt–hexane (1: 2, v/v), and **13** was eluted faster than **10**. The average of the isomer ratios taken from three runs was **10**: **13** = 98: 2. The piperidones thus isolated were presumed to be diastereomeric mixtures but were characterized as follows.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-(1,1-dimethylethyl)-2-piperidone (13)——A slightly reddish, viscous oil, MS *m/e*: 335 (M^+); UV λ_{max}^{EtOH} 229.5 nm (ε 9900), 279 (3100); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360 (OH), 1607 (lactam CO); NMR ($CDCl_3$) δ: 1.06 (9H, s, Me_3C), 1.3—2.0 (4H, m, $H_{(4)}$'s, $H_{(5)}$'s), 2.0—2.5 (1H, b, $H_{(3)}$), 2.6—3.3 (2H, b, $H_{(6)}$'s), 3.3—3.8 [2H, m, ArCH(OH)C<u>H</u>$_2$], 3.81 and 3.84 (6H, s each, two MeO's), 4.0—4.6 (1H, b, OH), 4.69—5.06 [1H, m, ArC<u>H</u>(OH)], 6.69—7.02 (3H, m, aromatic protons).

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-(1,1-dimethylethyl)-2-piperidone (10)——Recrystallized from AcOEt as colorless needles, mp 134.5—138°C; MS *m/e*: 335 (M^+); UV λ_{max}^{EtOH} 230 nm (ε 9400), 279 (2900); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (OH), 1612 (lactam CO); NMR ($CDCl_3$) δ: 0.77 and 0.83 (9H, s each, diastereomeric Me_3C's), 3.80 and 3.83 (6H, s each, two MeO's), 4.03 (1H, b, OH), 4.80—5.03 [1H, m, ArC<u>H</u>(OH)], 6.73—7.00 (3H, m, aromatic protons). *Anal.* Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.77; H, 8.84; N, 4.28.

1-(3,4-Dimethoxyphenethyl)-5-(1,1-dimethylethyl)-2-piperidone (9)——i) Hydrogenolysis of **10**: A mixture of the above diastereomeric mixture (336 mg, 1 mmol) of **10**, EtOH (20 ml), and 70% aq. $HClO_4$ (0.2 ml) was hydrogenated over 10% Pd-C (300 mg) at 3.3—3.4 atm and 29—30°C for 10 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was partitioned between benzene and H_2O. The benzene extracts were washed successively with sat. aq. $NaHCO_3$ and H_2O, dried, and concentrated to leave **9** (319 mg, 100%) as a slightly yellow solid. Recrystallization of the solid from hexane gave a pure sample as colorless needles, mp 76—79°C, which were identical (by mixture melting point test and comparison of IR spectra and TLC behavior) with a specimen obtained by method (ii).

ii) Hydrogenation of **8**: A solution of the pyridone **8**[7] (1.58 g, 5 mmol) in EtOH (30 ml) was hydrogenated over Raney Ni W-2 catalyst (5 ml) at ordinary pressure and 21°C for 9 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in benzene (30 ml), and the benzene solution was washed successively with 5% aq. HCl, H_2O, 5% aq. NaOH, and H_2O, dried, and concentrated to leave a solid (1.42 g, 89%) of mp 75—79°C. On recrystallization from hexane, it furnished **9** as colorless needles, mp 76—79°C; MS *m/e*: 319 (M^+); UV λ_{max}^{EtOH} 230 nm (ε 9100), 281 (2900); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1624 (lactam CO); NMR ($CDCl_3$) δ: 0.82 (9H, s, Me_3C), 3.77 and 3.80 (6H, s each, two MeO's), 6.65 (3H, s, aromatic protons). *Anal.* Calcd for $C_{19}H_{28}NO_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.37; H, 9.28; N, 4.67.

3-(1,1-Dimethylethyl)-1,2,3,4,6,7-hexahydro-9,10-dimethoxybenzo[*a*]quinolizinium Perchlorate (12)——A stirred mixture of **9** (958 mg, 3 mmol), $POCl_3$ (6 ml), and dry benzene (12 ml) was refluxed for 3 h. Concentration of the mixture under vacuum left a yellowish-orange oil, which was washed with hexane and dissolved in H_2O (30 ml). The aqueous solution was washed with benzene and a solution of $NaClO_4$ (735 mg, 6 mmol) in H_2O (5 ml) was added. The crystals (1.16 g, 96%) that resulted were filtered off and recrystallized from 95% aq. EtOH to afford **12** as colorless prisms, mp 225—227°C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 1662 (C=N$^+$); NMR ($CDCl_3$) δ: 0.97 (9H, s, Me_3C), 3.90 and 3.96 (6H, s each, two MeO's), 6.81 (1H, s, $H_{(8)}$), 7.19 (1H, s, $H_{(11)}$). *Anal.* Calcd for $C_{19}H_{28}ClNO_6$: C, 56.78; H, 7.02; N, 3.49. Found: C, 56.60; H, 7.05; N, 3.52.

(±)-3*α*-(1,1-Dimethylethyl)-1,3,4,6,7,11b*α*-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine (11)——A solution of **12** (402 mg, 1 mmol) in 50% aq. EtOH (20 ml) was hydrogenated over Adams catalyst (50 mg) at atmospheric pressure and 18°C for 2 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to leave an oil, which was dissolved in H_2O (10 ml). The aqueous solution was made basic with 10% aq. NaOH and extracted with benzene. Drying (K_2CO_3) and concentration of the benzene extracts left a yellow oil, which was purified by column chromatography [Al_2O_3 (30 g), hexane–AcOEt (5: 1 v/v)] to provide **11** (258 mg, 85%) as a slightly yellowish solid. Recrystallization from hexane gave an analytical sample as colorless needles, mp 101.5—103°C; MS *m/e*: 303 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2770 (*trans* quinolizidine[8]); NMR ($CDCl_3$) δ: 0.91 (9H, s, Me_3C), 3.84 (6H, s, two MeO's), 6.57 (1H, s, $H_{(8)}$), 6.70 (1H, s $H_{(11)}$). *Anal.* Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62. Found: C, 74.97; H, 9.91; N, 4.81.

A similar hydrogenation of the crude iminium chloride (**12**: Cl^- for ClO_4^-), described above as **12**, ii

H_2O produced **11** in 81% overall yield (from **9**).

The Hydrochloride of **11**: A small portion of **11** was dissolved in an excess of 10% (w/w) ethanolic HCl, and dry ether was added. The resulting precipitate was filtered off and recrystallized from acetone–EtOH (1: 1, v/v) to yield the hydrochloride as colorless scales, mp 249—251°C (dec.) (dried over P_2O_5 at 2 mmHg and room temp. for 20 h); IR ν_{max}^{Nujol} cm^{-1}: 2510 (NH^+), 1715 (Me_2CO contained); NMR (Me_2SO-d_6) δ: 0.92 (9H, s, Me_3C), 2.08 (2H, 1/3 Me_2CO), 3.75 (6H, s, two MeO's), 4.22 (1H, dull d-d, $H_{(11b)}$), 6.78 and 6.85 (1H each, s, aromatic protons), 10.8 (1H, b, NH^+). *Anal.* Calcd for $C_{19}H_{30}ClNO_2 \cdot 1/3CH_3COCH_3$: C, 66.86; H, 8.98; N, 3.90. Found: C, 66.85; H, 9.11; N, 3.97.

Acknowledgment We are grateful to Emeritus Professor Dr. S. Sugasawa, University of Tokyo, for his interest and encouragement and to the Foundation for the Promotion of Research on Medicinal Resources for financial assistance.

References and Notes

1) Paper XVII in this series, T. Fujii, S. Yoshifuji, and K. Ikeda, *Chem. Pharm. Bull.*, **27**, 2841 (1979).
2) *a*) T. Fujii and S. Yoshifuji, *Tetrahedron*, **36**, 1539 (1980); *b*) *Idem*, *J. Org. Chem.*, **45**, 1889 (1980); *c*) T. Fujii, S. Yoshifuji, S. Minami, S. C. Pakrashi, and E. Ali, *Heterocycles*, **8**, 175 (1977); *d*) T. Fujii, H. Kogen, and M. Ohba, *Tetrahedron Lett.*, **1978**, 3111; *e*) T. Fujii, M. Ohba, S. C. Pakrashi, and E. Ali, *ibid.*, **1979**, 4955.
3) *a*) J. Knabe, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **292**, 416 (1959); *b*) H. Möhrle, *ibid.*, **297**, 474 (1964); *c*) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.*, **20**, 1451 (1972).
4) *a*) T. Fujii, S. Yoshifuji, K. Michishita, M. Mitsukuchi, and K. Yoshida, *Chem. Pharm. Bull.*, **21**, 2695 (1973); *b*) T. Fujii, K. Yoshida, M. Ohba, and S. Yoshifuji, *ibid.*, **25**, 2336 (1977); *c*) T. Fujii, M. Ohba, and S. Yoshifuji, *ibid.*, **25**, 3042 (1977).
5) T. Fujii, T. Hiraga, S. Yoshifuji, M. Ohba, and K. Yoshida, *Chem. Pharm. Bull.*, **26**, 3233 (1978).
6) T. Fujii, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.*, **26**, 3218 (1978).
7) T. Fujii, T. Hiraga, S. Yoshifuji, M. Ohba, and K. Yoshida, *Heterocycles*, **10**, 23 (1978).
8) *a*) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956); *b*) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).
9) T. Fujii, M. Nohara, M. Mitsukuchi, M. Ohba, K. Shikata, S. Yoshifuji, and S. Ikegami, *Chem. Pharm. Bull.*, **23**, 144 (1975).