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THE STRUCTURAL INFORMATION OF THE QUATERNARY AMMONIUM SALTS DERIVED FROM NICOTINE AND SPARTEINE IN THE SOLID STATE

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Abstract – Preparation and X-Ray crystallographic analysis of the benzyl quaternary salts of nicotine and sparteine were described.

Dedicated to the memory of the late Professor Kenji Koga.

INTRODUCTION

Quaternary ammonium salts now occupy a central position in phase-transfer catalysis.[1] Furthermore, they are interesting from the biological point of view.

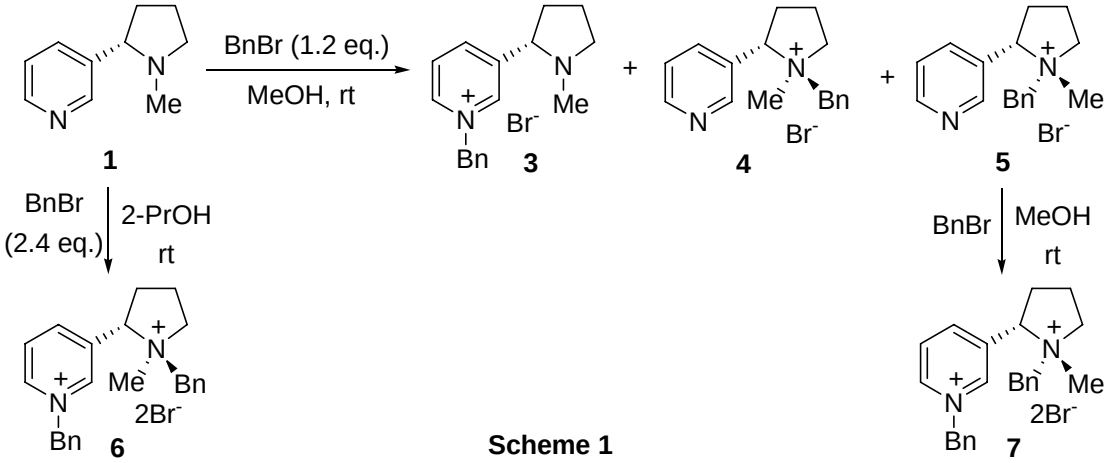
In continuation of our interests[2] on the use of chiral quaternary ammonium salts derived from easily available natural products, we prepared the hitherto unknown benzylammonium salts from nicotine (**1**) and sparteine (**2**) and clarified their structures in the solid state by X-Ray crystallographic analysis.

RESULTS AND DISCUSSION

Nicotine

First, treatment of nicotine (**1**) with 1.2 equivalents of benzyl bromide in MeOH at room temperature afforded a mixture of 1-benzyl-, (1'*S*-*trans*)-1'-benzyl-, and (1'*R*-*cis*)-1'-benzylnicotinium bromides (**3**-**5**). It is already known that the alkylation of **1** first occurs at the pyridine-*N* but not at the pyrrolidine-*N* because of steric reason.[3] Thus the 1-benzyl salt (**3**) was the major product in this benzylation reaction. Alkylation of **1** with 2.4 equivalents of benzyl bromide in 2-PrOH at room temperature afforded the (1'*S*-*trans*)-1,1'-dibenzyl salt (**6**), while (1'*R*-*cis*)-1,1'-dibenzyl salt (**7**) was obtained by benzylation of

(1'*R*-*cis*)-1'-benzyl salt (**5**) in MeOH. The benzyl group was introduced from the less hindered side in both cases. Attempted debenzylation of **6** with triphenylphosphine[4] failed.



Scheme 1

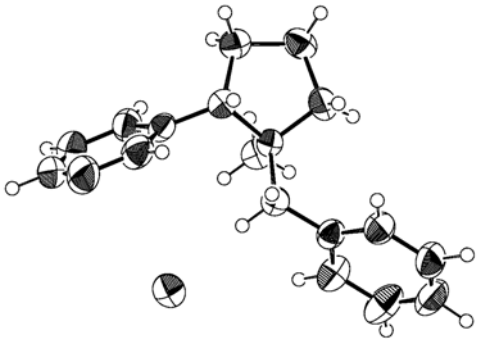


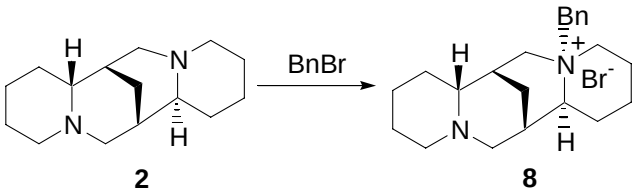
Figure 1. Crystal Structue (ORTEP) of 4

To the best of our knowledge, there has been no report about the X-Ray structural investigations concerning the asymmetric nitrogen on the quaternary ammonium salt alkylated pyrrolidine-*N*. Since we expected that the informations around the pyrrolidine-*N* of the quaternary ammonium salt would be utilized for asymmetric reactions, we chose (1'*S*-*trans*)-1'-benzylnicotinium bromide (**4**) for the X-ray structural investigations. The results of the X-Ray structural investigations are given in Figure 1. The pyridine and pyrrolidine rings are situated in perpendicular, and the phenyl ring is away from the pyridine ring, shown in Figure 1. This will be the first results on the X-Ray crystallographic studies of the quaternary nicotinium salts, which will be useful for the design of related chiral PTC by evaluating the activity for some asymmetric reactions.

Sparteine

Sparteine (**2**) is quite a useful chiral ligand in combination with lithium,[5] but the use of its quaternary ammonium salts as a phase transfer catalyst is not frequent.[6] Thus, 16-*N*-benzylsparteinium bromide (**8**) was prepared by benzylation of sparteine (**2**). The X-Ray result of **8** is shown in Figure 2. This will be the

first example of X-Ray investigations of *N*-alkylsparteinium bromide. The crystal of **8** contains two different conformers. The overall conformations are mainly constructed by the n–π and C-H–π interactions between the benzyl group and the quinolizidine ring and therefore very similar to each other. The major difference is observed for the dihedral angle between both rings, 23.8° and 14.2°, and is due to the effect of crystal packing.



2 **8**

Scheme 2

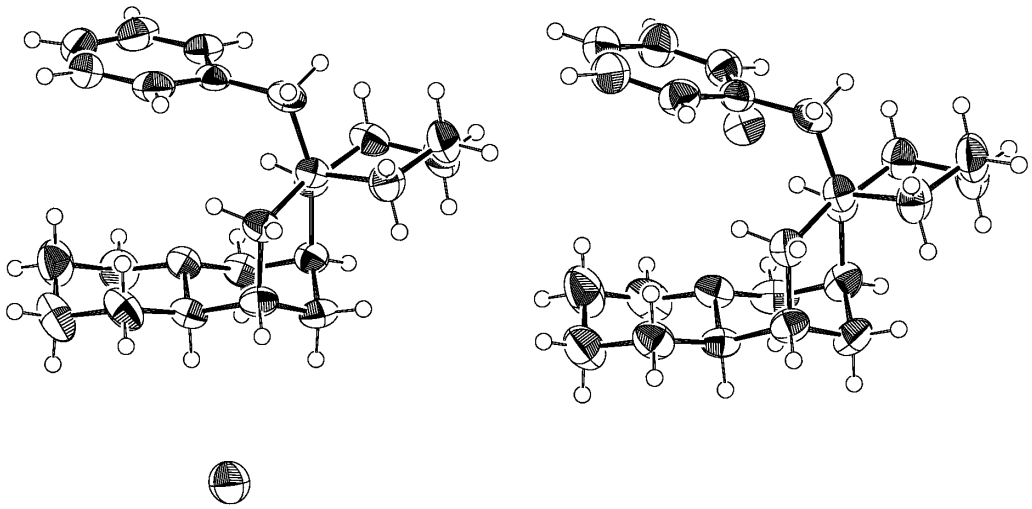


Figure 2. Crystal Structure (ORTEP) of 8

Thus, the benzyl derivatives of nicotine and sparteine were prepared and their structural information in the solid state was obtained by X-Ray crystallography. Utilization of these quaternary ammonium salts as a chiral PTC will be reported in due course.

EXPERIMENTAL

Melting points were determined on a Yamamoto MP-21 apparatus. Optical rotations were measured with a JASCO DIP-1000 digital polarimeter. IR spectra were measured with a Perkin-Elmer 1600 FTIR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on JEOL JNM-ALPHA 400 or JNM-AL 400 spectrometer with tetramethylsilane or chloroform or dimethyl sulfoxide as an internal standard. High-resolution MS spectra were measured on a JEOL HX-100 spectrometer.

Benzylation of nicotine (1): 1-Benzylnicotinium bromide (3), (1'*S*-*trans*)-1'-Benzylnicotinium bromide (4), and (1'*R*-*cis*)-1'-Benzylnicotinium bromide (5).

To a solution of nicotine (**1**, 16.06 mL, 0.10 mol) in MeOH (200 mL) was added benzyl bromide (13.68 mL, 0.12 mol) dropwise at 0 ℃ and the mixture was stirred at rt. After 12 h, water (300 mL) was added and the mixture was washed with *tert*-butyl methyl ether (300 mL×2). Removal of the solvent followed by crystallization of the crude product from 2-PrOH and acetone (1:5) gave a white solid. After removal of the solvent from the filtrate, crystallization from acetone gave a yellowish solid followed by removal of the solvent and recrystallization from MeCN to give 1-benzylnicotinium bromide (**3**) as a yellowish solid (7.00 g, 21%).

The crude product was suspended in 2-PrOH and EtOH (10:1), stirred at 40 ℃ for 10 h and filtered to give a white solid. After removal of the solvent from the filtrate, the crude product was mixed and the mixture was suspended in EtOH and 2-PrOH (1:1), stirred at 80 ℃ for 1 h and then at rt for 11 h. Removal of the precipitates followed by evaporation to dryness and crystallization from 2-PrOH and acetone (1:5) gave a white solid. After removal of the solvent, the residue was suspended in 2-PrOH and stirred at 80 ℃ for 2 h and then at rt for 23 h to give a white solid. Mixture of the crude products was suspended in EtOH and 2-PrOH (1:10) and stirred at 80 ℃ for 30 min and then at rt for 7 h. After separation of the precipitates, the filtrate was evaporated to dryness followed by crystallization from MeCN to give (1'*S*-*trans*)-1'-benzylnicotinium (**4**) bromide as a white solid (0.78 g, 2%).

The precipitates were recrystallized from EtOH and 2-PrOH (2:3) to give (1'*R*-*cis*)-1'-benzylnicotinium bromide (**5**) as a white solid (0.95 g, 3%).

1-Benzylnicotinium bromide (3); mp: 139℃; $[\alpha]_D^{20}$= –83.8° (c 1.06, MeOH); IR (nujol) ν : 1629, 1498, 1289, 1210, 1154, 1141, 1043, 980, 899, 793, 776, 749, 685, 641, 558; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ : 1.64 (m, 1H), 1.84 (m, 1H), 2.06 (s, 3H), 2.24 (m, 1H), 2.49 (dd, *J* = 8.8, 17.6 Hz, 1H), 3.17 (t, *J* = 7.3 Hz, 1H), 3.44 (t, *J* = 8.3 Hz, 1H), 5.89 (s, 2H), 7.43 (m, 5H), 7.54 (dd, *J* = 1.5, 7.8 Hz, 2H), 8.13 (dd, *J* = 6.3, 7.8 Hz, 1H), 8.56 (d, *J* = 8.3 Hz, 1H), 9.10 (d, *J* = 6.3 Hz, 1H), 9.23 (s, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ : 22.6, 34.8, 56.3, 63.1, 66.4, 128.3, 128.6, 129.2, 129.3, 134.4, 143.4, 144.6, 145.3; Anal. Calcd for $C_{17}H_{21}N_2Br$: C, 61.27; H, 6.35; N, 8.41. Found: C, 61.14; H, 6.34; N, 8.46.

(1'*S*-*trans*)-1'-Benzylnicotinium bromide (4); mp: 200℃ (decomp); $[\alpha]_D^{20}$= +35.0° (c 1.04, MeOH); IR (nujol) ν : 3010, 1595, 1578, 1414, 1282, 1186, 1029, 990, 946, 926, 908, 892, 812, 777, 618; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ : 2.15 (m, 2H), 2.49 (m, 1H), 2.67 (s, 3H), 2.76 (m, 1H), 3.26 (m, 1H), 3.96 (dd, *J* = 10.3, 20.6 Hz, 1H), 4.15 (d, *J* = 12.2 Hz, 1H), 4.78 (d, *J* = 12.2 Hz, 1H), 5.16 (dd, *J* = 8.3, 11.7 Hz, 1H), 7.47 (m, 3H), 7.60 (m, 3H), 8.20 (d, *J* = 7.8 Hz, 1H), 8.76 (dd, *J* = 1.5, 4.4 Hz, 1H), 8.88 (d, *J* = 2.0 Hz, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ : 18.6, 25.5, 41.2, 62.2, 64.8, 76.0, 124.0, 125.8, 128.8, 128.9, 130.0, 132.5, 138.8, 151.6, 152.3; Anal. Calcd for $C_{17}H_{21}N_2Br$: C, 61.27; H, 6.35; N, 8.41.

Found: C, 60.98; H, 6.30; N, 8.32.
The crystal data of **4** are shown in Table 1.

(1'*R*-*cis*)-1'-Benzylnicotinium bromide (5); mp: 212℃ (decomp); $[\alpha]_D^{20}$= +28.7° (c 1.05, MeOH); IR (nujol) ν : 2729, 1594, 1577, 1346, 1315, 1184, 1047, 1028, 979, 923, 878, 842, 815, 765, 615; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ : 2.25 (m, 1H), 2.44 (m, 1H), 2.54 (m, 1H), 2.93 (m, 1H), 2.99 (s, 3H), 3.33 (dd, *J* = 9.8, 21.5 Hz, 1H), 3.55 (m, 1H), 3.74 (d, *J* = 12.2 Hz, 1H), 4.54 (d, *J* = 12.7 Hz, 1H), 5.25 (dd, *J* = 8.3, 10.8 Hz, 1H), 7.49 (m, 5H), 7.61 (dd, *J* = 4.9, 7.8 Hz), 8.25 (ddd, *J* = 2.0, 3.9, 8.3 Hz, 1H), 8.76 (dd, *J* = 1.5, 4.9 Hz, 1H), 8.88 (d, *J* = 2.0 Hz, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ : 18.9, 25.6, 46.8, 57.6, 59.8, 77.2, 124.0, 125.6, 128.0, 128.8, 130.1, 132.9, 138.8, 151.7, 152.3; Anal. Calcd for $C_{17}H_{21}N_2Br$: C, 61.27; H, 6.35; N, 8.41. Found: C, 61.09; H, 6.34; N, 8.30.

(1'*S*-*trans*)-1,1'-Dibenzylnicotinium dibromide (6).
To a solution of benzyl bromide (1.43 mL, 12 mmol) in 2-PrOH (2 mL) was added nicotine (0.80 mL, 5 mmol) dropwise and the mixture was stirred at rt. After 18 h, water (5 mL) was added and the mixture was washed with *tert*-butyl methyl ether (5 mL×4). Removal of the solvent followed by recrystallization of the crude product from EtOH and 2-PrOH (1:5) gave (1'*S*-*trans*)-1,1'-dibenzylnicotinium dibromide (**6**) as a white solid (1.52 g, 60%); mp: 208℃ (decomp); $[\alpha]_D^{20}$= +71.8° (c 1.02, MeOH); IR (nujol) ν : 3372, 1640, 1509, 1213, 1168, 1023, 922, 844, 817, 769, 741, 694, 687, 622, 560; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ : 2.12 (m, 1H), 2.23 (m, 1H), 2.49 (m, 1H), 2.77 (s, 3H), 2.86 (m, 1H), 3.33 (m, 1H), 4.06 (dd, *J* = 10.2, 20.0 Hz, 1H), 4.43 (d, *J* = 12.2 Hz, 1H), 4.80 (d, *J* = 12.7 Hz, 1H), 5.38 (dd, *J* = 8.9, 11.2 Hz, 1H), 6.00 (dd, *J* = 14.2, 16.6, 1H), 7.49 (m, 6H), 7.58 (m, 2H), 7.67 (m, 2H), 8.40 (dd, *J* = 6.3, 7.8 Hz, 1H), 9.03 (d, *J* = 7.8 Hz), 9.43 (d, *J* = 6.3 Hz, 1H), 9.86 (s, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ : 18.7, 25.6, 41.3, 62.8, 63.3, 64.9, 74.4, 128.5, 128.9, 129.0, 129.2, 129.4, 130.2, 131.2, 132.5, 133.9, 146.1, 147.5, 148.2; ; HRMS (FAB) calcd for $C_{24}H_{28}N_2$ $[M-2Br]^+$: 344.2252. Found: 344.2263.

(1'*R*-cis)-1,1'-Dibenzylnicotinium dibromide (7).
To a solution of (1'*R*-*cis*)-1'-benzylnicotinium bromide (**5**, 447 mg, 1.34 mmol) in MeOH (3 mL) was added benzyl bromide (0.32 mL, 2.68 mmol) and the mixture was stirred at rt. After 12 h, water (5 mL) was added and the mixture was washed with *tert*-butyl methyl ether (3 mL×2). Removal of the solvent followed by recrystallization of the crude product from EtOH and 2-PrOH (1:1) gave (1'*R*-*cis*)-1,1'-dibenzylnicotinium dibromide (**7**) as a white solid (394 mg, 58%); mp: 202℃ (decomp); $[\alpha]_D^{20}$= +28.6° (c 1.13, MeOH); IR (nujol) ν : 3401, 1636, 1509, 1289, 1215, 1151, 1031, 958, 923, 858, 824, 774, 748, 689, 652, 568; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ : 2.31 (m, 1H), 2.49 (m, 1H), 2.64 (m,

1H), 2.98 (m, 1H), 3.09 (s, 3H), 3.40 (dd, *J* = 9.5, 21.5 Hz, 1H), 3.61 (m, 1H), 4.03 (d, *J* = 12.2 Hz, 1H), 4.59 (d, *J* = 12.4 Hz, 1H), 5.45 (dd, *J* = 8.9, 10.3 Hz, 1H), 6.01 (s, 1H), 7.49 (m, 8H), 7.67 (m, 2H), 8.40 (dd, *J* = 6.3, 8.1 Hz, 1H), 9.05 (d, *J* = 8.3 Hz), 9.41 (d, *J* = 6.1 Hz, 1H), 9.91 (s, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ : 19.1, 25.8, 47.2, 57.9, 60.4, 63.4, 75.6, 127.7, 128.9, 129.0, 129.1, 129.2, 129.4, 130.3, 131.1, 132.9, 133.9, 146.0, 147.5, 148.2; Anal. Calcd for $C_{24}H_{28}N_2Br_2$: C, 57.16; H, 5.60; N, 5.55. Found: C, 56.84; H, 5.58; N, 5.57.

16-*N*-Benzylsparteinium bromide (8).

To sparteine (**2**, 0.60 mL, 2.61 mmol) was added benzyl bromide (2.00 mL, 16.81 mmol) and the mixture was stirred under N_2 at 2 ℃. After 95 h, acetone (4 mL) was added to the mixture and precipitates were filtrated. The crude product was suspended in acetone and *tert*-butyl methyl ether (1:1, 4 mL), stirred at 0 ℃ for 3 h and filtered again to give 16-*N*-benzylsparteinium bromide (**8**) as a white solid (240 mg, 23%); mp: 137℃; $[\alpha]_D^{20}$= –11.3° (c 1.04, MeOH); IR (nujol) ν : 3390, 1650, 1305, 1266, 1187, 1143, 1131, 1073, 1053, 983, 893, 860, 750, 701, 547 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ : 0.86 (m, 2H), 1.05 (m, 1H), 1.32 (dd, *J* = 2.7, 3.7 Hz, 2H), 1.55 (m, 2H), 1.86 (m, 6H), 2.03 (m, 3H), 2.33 (m, 3H), 2.53 (m, 2H), 3.71 (br, 1H), 3.78 (dd, *J* = 2.7, 13.4 Hz, 1H), 3.88 (dt, *J* = 4.4, 13.9 Hz, 1H), 3.98 (dd, *J* = 9.8, 13.4 Hz, 1H), 4.26 (dd, *J* = 4.4, 13.9 Hz, 1H), 4.93 (d, *J* = 13.2 Hz, 1H), 5.41 (d, *J* = 13.2 Hz, 1H), 7.38 (m, 3H), 7.63 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ : 16.3, 20.9, 23.7, 25.0, 28.3, 29.1, 30.6, 33.8, 54.9, 57.1, 60.1, 62.3, 62.5, 65.2, 66.3, 128.3, 129.0, 130.4, 133.7; HRMS (FAB) calcd for $C_{22}H_{33}N_2$ [M-Br]$^+$: 325.2644. Found: 325.2630.

The crystal of **8** for X-Ray analysis was obtained by recrystallization from MeOH-AcOEt, and its data are shown in Table 1.

X-Ray Structure Determination

The X-ray data were collected with a Bruker AXS SMART APEX CCD camera using graphite-monochromated MoKα radiation (1= 0.71073 Å) at 283 K. The crystal structures were solved by a direct method using the SHELXS97 program.[7] Atomic scattering factors were taken from International Tables for X-Ray Crystallography.[8] Positional parameters of non-H atoms were refined by a full matrix least squares method with anisotropic thermal parameters using the SHELXL97 program.[9] The structural data were deposited with the following designations: **4**: CCDC 285344, **8**: CCDC 285345. These can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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Table 1. Crystal Data and Data Collection of the Quaternary Ammonium Bromides (4) and (8)

	Data for **4**	Data for **8**
Formula	$C_{17}H_{21}N_2Br$	$C_{22}H_{33}N_2Br \cdot 1.5H_2O$
Molecular weight	333.27	432.44
Crystal system	orthorhombic	orthorhombic
Space group	*P2₁2₁2₁*	*P2₁2₁2₁*
Cell constant		
a (Å)	8.427 (1)	8.745 (2)
b (Å)	10.651 (1)	17.375 (4)
c (Å)	17.861 (1)	29.382 (7)
α (°)	90.00	90.00
β (°)	90.00	90.00
γ (°)	90.00	90.00
Volume ($Å^3$)	1603.1 (2)	4464.6 (17)
Z	4	8
D (calc), g· cm^{-3}	1.381	1.287
μ (Mo-Kα) (mm^{-1})	2.56	1.86
F (000)	688	1832
Crystal size (mm^3)	0.35×0.30×0.05	1.00×0.30×0.02
Temperature (K)	283	283
Data collection method	phi and omegascaṇs	phi and omegascaṇs
Data range measured	-10<*h*<10, -14<*k*<13, -22<*l*<21	-11<*h*<10, -17<*k*<23, -38<*l*<38
θ max, °	28.27	28.31
No. of independent reflections	3713	10275
No. of observed reflections	2997	7005
Criterion for observed reflections	I>2σ(I)	I>2σ(I)
Flack χ parameter	-0.009(9)	0.015 (7)
No. of parameters	181	478
Goodness of fit	0.941	0.927
R ; R_W	0.034 ; 0.077	0.041; 0.100

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