Novel synthesis of 2-naphthol Mannich bases and their NMR behaviour

Amitabh Jha, Nawal K. Paul, Smriti Trikha, and T. Stanley Cameron

Abstract: A novel two-step procedure involving the formation of 1-arylidene-2-tetralones from 2-tetralone and subsequent Michael addition of a cyclic secondary amine on the alkenone followed by in situ aerial oxidation was developed to produce 2-naphthol Mannich bases. A simple microwave-assisted one-pot synthesis of 2-naphthol Mannich bases was also carried out under solvent-free conditions from 2-naphthol and corresponding aldehydes and amines in the presence of *p*-toluenesulfonic acid. The compounds of this series displayed interesting NMR behaviour. Extensive variable-temperature NMR investigations, including HSQC experiments, are herein reported. NMR results on the conformation in solution phase were found to be consistent with the X-ray crystal structure in the solid state.

Key words: Mannich bases, microwave-assisted Mannich reaction, temperature-variable NMR spectroscopy, NMR dynamics, X-ray crystallography.

Résumé : On a mis au point une nouvelle méthode en deux étapes qui permet de produire des bases de Mannich du 2-naphtol et qui implique la formation de 1-arylidène-2-tétralones à partir de la 2-tétralone, puis une addition subséquente de Michael d'une amine secondaire cyclique sur l'alcénone, suivie d'une oxydation in situ par de l'air. On a aussi réalisé une synthèse des bases de Mannich du 2-naphtol par une simple réaction monotope du 2-naphtol, des aldéhydes et des amines correspondants en présence d'acide *p*-toluènesulfonique, sous l'effet de micro-ondes, dans des conditions sans solvant. Les composés de cette série présentent des comportements RMN intéressants. On a effectué de nombreuses études RMN à température variable, y compris des expériences de « HSQC ». On a trouvé que les résultats de la RMN sur la conformation en solution sont en accord avec la structure cristalline déterminée par diffraction des rayons X, à l'état solide.

Mots clés : bases de Mannich, réaction de Mannich assistée par les micro-ondes, spectroscopie RMN à température variable, dynamique RMN, cristallographie par diffraction des rayons X.

[Traduit par la Rédaction]

Introduction

Numerous chiral aminomethyl phenols have been reported as excellent chelating agents in metal-catalyzed asymmetric induction in a variety of reactions (1–10). Chiral Mannich bases of 2-naphthol are particularly popular in metal-mediated and ligand-accelerated catalysis of enantioselective carbon–carbon bond formation (11–17). Many of these carbon–carbon bond formation reactions involve the use of organozinc compounds as alkylating agents, which are relatively unreactive if uncoordinated (11). These ligands may be used in catalytic amounts. The first synthesis of racemic Mannich bases of 2-naphthol was achieved by Betti (18–22) at the turn of the 20th century. Thereafter, numerous modifications of this reaction surfaced (23–27) and optically pure Betti base analogs were prepared either by resolution or by the induction of chirality by the use of optically active amines (11–17, 28, 29).

In addition, potent oxytocic activity of compounds of this type is reported in the literature (30). Since these compounds have multiple centres for chelation with metal ions, they are likely to be potent inhibitors of metalloenzymes containing Fe, Cu, Zn, Co, etc., ions as cofactors (31–34). Also, these compounds have the potential to be used as scavengers in cases of heavy metal (Pd, Hg, Cd, As, Sb, etc.) poisoning (35, 36).

We herein report a novel synthetic route to this class of compounds (**1**–**4**, Fig. 1) involving two steps starting from 2-tetralones. Also, additional analogs (**5**–**11**, Fig. 1) were obtained in moderate to excellent yields with improved reaction time by modifying a reported microwave-assisted procedure (26). While characterizing the compounds using the usual spectroscopic means, we observed anomalous and interesting NMR behaviour of heterocyclic rings. NMR experiments to study the solution phase dynamics as well as

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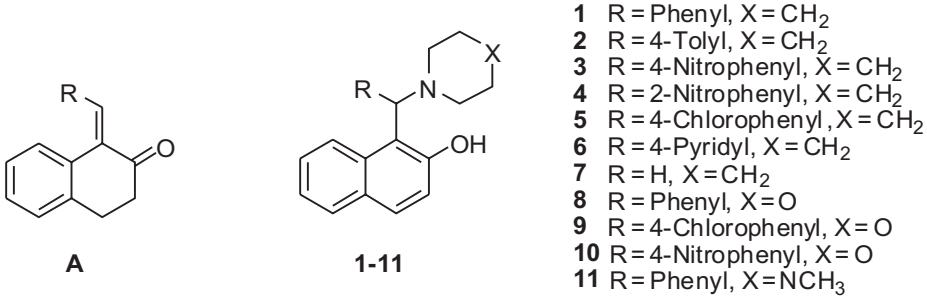
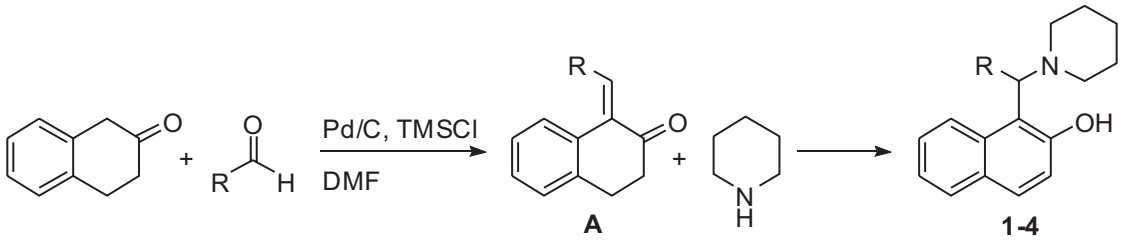
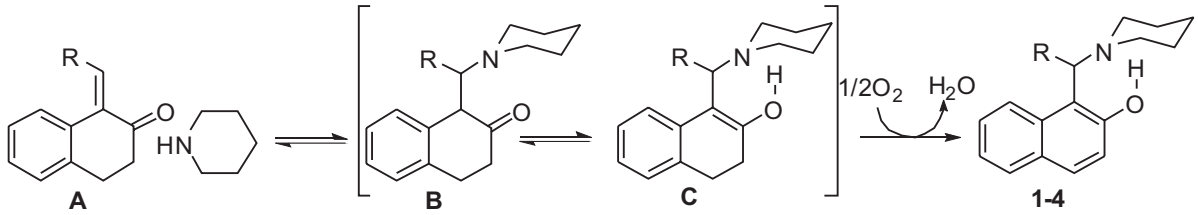
Fig. 1. Molecular structure of the compounds investigated.



Scheme 1. Novel synthethic route to 2-naphthol Mannich bases (**1**–**4**).



Scheme 2. Proposed mechanism for conversion of 1-arylidene-2-tetralone to 2-naphthol Mannich bases following Scheme 1.



solid-state X-ray crystal structure of representative compounds are also reported here.

Experimental

General

All chemicals were obtained from the Sigma-Aldrich Chemical Company, Inc. Column chromatographic purifications were undertaken using silica gel (230–400 mesh) obtained from Silicycle. ^{1}H and ^{13}C NMR were recorded on Bruker AV500 and AV300 NMR spectrometers. HSQC spectra were obtained on a Bruker AV500 spectrometer using 256 increments and a sweep width of 20 kHz in the indirect (carbon) dimension. Coherence selection was achieved using gradients and phase-sensitive HSQC data were obtained using the echo-antiecho method. All 180° pulses in the sequence were replaced with adiabatic shapes for improved broadband inversion and refocussing over the entire carbon frequency range. EI-MS and HR-MS spectra were obtained on a CEC 21-110B Sector instrument. Melting points were recorded on an electrothermal apparatus and are uncorrected. UV–vis and IR spectra were recorded on LKB Biochrom Ultraspec Plus 4054 and Nicolet Avatar 330 FT-IR spectrophotometers, respectively. A domestic microwave oven manufactured by Kenmore was used for the microwave-assisted reactions at highest power (900 W) and 2450 MHz operating frequency.

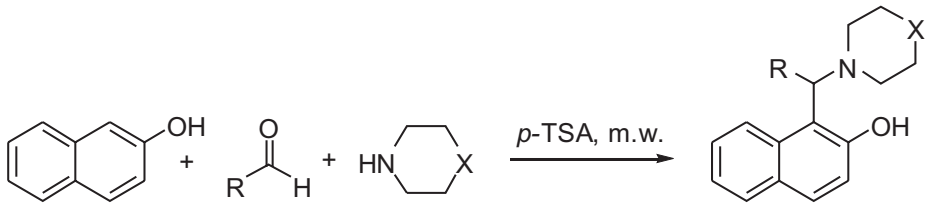
Synthesis of substituted 1-arylidene-2-tetralones (A)

Palladium-catalyzed Knoevenagel-type condensation (37) from 2-tetralone and appropriate aldehydes resulted in 1-arylidene-2-tetralones. To a mixture of 2-tetralone (20 mmol), appropriate aromatic aldehyde (22 mmol), 10% Pd/C (2 mol %), and DMF (30 mL) was added TMSCl (22 mmol) in dropwise fashion at room temperature. After 30 min, the reaction was warmed to 75 °C and stirred for 5 h. DMF was rotary evaporated and the residue was chromatographed with 2% EtOAc in hexanes. The resulting products were characterized as 1-arylidene-2-tetralones (**A**) by comparison of their physical and spectral data with those reported in the literature (38). The melting points (°C) and percentage yields of the compounds in this series were as follows: **A** (R = phenyl): 116 to 117, 76; **A** (R = 4-tolyl): 103 to 104, 73; **A** (R = 4-NO_2-phenyl): 153 to 154, 82; **A** (R = 2-NO_2-phenyl): 122 to 123, 71.

Synthesis of 1-(arylpiperidin-1-yl methyl)naphthalen-2-ols (1–11)

Procedure A (Schemes 1 and 2): Appropriate 1-arylidene-2-tetralones (**A**, 10 mmol) reacted with excess piperidine at room temperature to produce the compounds (**1**–**4**) over a period of 7 days. No reaction progress was observed by TLC after 24 h. The resulting compounds were purified using silica gel column chromatography with 3% ethyl acetate in hexanes as the eluent. Unreacted starting materials (**A**) were also recovered.

Scheme 3. Synthethic route for the microwave-assisted reactions of compounds **1**–**12**.



1-12

Procedure B (Scheme 3): A mixture of 2-naphthol (10 mmol), appropriate aromatic aldehyde (12 mmol), *p*-TSA (50 mg, cat.), and appropriate secondary amine (12 mmol) was irradiated using the microwave for 1 min (30 s × 2, to avoid overheating). The reaction mixture was cooled and methanol was added to it. Several products, viz. compounds **1**, **3**, **5**, **6**, and **8**, were purified by digestion in methanol as follows. The reaction mixture was stirred in hot methanol (20 mL) for 1 h and kept at room temperature overnight for crystallization and precipitation. The solid product was filtered, washed with cold methanol (2 × 5 mL), and dried under vacuum. The rest of the derivatives were purified by column chromatography using silica gel. The desired product eluted with 2% ethyl acetate in hexanes. The products thus obtained were further purified by crystallization.

1-(Phenylpiperidin-1-ylmethyl)naphthalen-2-ol (1)

^{1}H and ^{13}C NMR were identical to those reported in the literature (27). UV–vis (MeOH, nm) λ_{max}: 244, 280, 336. IR (KBr disc, cm^{-1}) ν: 3443, 3050, 2971, 1621, 1599, 1455, 1268, 1238, 702. EI-MS (70 eV) *m*/*z* (% int.): 317 (M$^+$, 11), 231 (100), 200 (2), 84 (41). HR-MS calcd. for $C_{22}H_{23}NO$: 317.1780; found: 317.1785.

1-(4-Methylphenyl)piperidin-1-ylmethyl)naphthalen-2-ol (2)

UV–vis (MeOH, nm) λ_{max}: 244, 291, 336. IR (KBr disc, cm^{-1}) ν: 3439, 3060, 2963, 1621, 1595, 1384, 1359, 1261, 1231, 821. ^{1}H NMR (300 MHz, 273 K, $CDCl_3$) δ: 1.41 (1H, bs, CH), 1.50–1.91 (5H, m, 5 × CH), 2.27–2.46 (4H, m, Ar-CH_3, NCH), 2.92 (1H, bs, NCH), 3.23 (1H, bs, NCH), 3.53 (1H, bs, NCH), 5.23 (1H, s, Ar-CH-Ar′), 7.01–7.08 (1H, m, Ar-H), 7.22–7.28 (2H, m, Ar-H), 7.37–7.42 (3H, m, Ar-H), 7.49–7.52 (2H, m, Ar-H), 7.68–7.73 (1H, m, Ar-H), 7.81–7.84 (1H, m, Ar-H), 13.32 (1H, bs, OH). ^{13}C NMR (75 MHz, 273 K, $CDCl_3$) δ: 21.63, 24.03, 25.72, 26.00, 52.10, 55.20, 64.90, 109.00, 117.82, 120.33, 121.24, 123.06, 126.22, 127.10, 129.11, 129.47, 130.25, 130.87, 134.88, 155.36. EI-MS (70 eV) *m*/*z* (% int.): 331 (M$^+$, 14), 247 (10), 231 (100). HR-MS calcd. for $C_{23}H_{25}NO$: 331.1936; found: 331.1930.

1-(4-Nitrophenyl)piperidin-1-ylmethyl)naphthalen-2-ol (3)

UV–vis (MeOH, nm) λ_{max}: 244, 295, 335. IR (KBr disc, cm^{-1}) ν: 3439, 3080, 3060, 2926, 1621, 1514, 1441, 1414, 1346, 1265, 1231, 830. ^{1}H NMR (300 MHz, 273 K, $CDCl_3$) δ: 1.28 (1H, bs, CH), 1.58–1.73 (5H, m, 5 × CH), 2.02 (1H, bs, -NCH), 2.15 (1H, bs, -NCH), 2.65 (1H, bs, -NCH), 3.37 (1H, bs, -NCH), 5.23 (1H, s, Ar-CH-Ar′), 7.18–7.31 (2H, m, Ar-H), 7.42 (1H, t, *J*= 7.5 Hz, Ar-H), 7.70–7.81 (5H, m, Ar-H), 8.13–8.16 (2H, m, Ar-H), 13.78 (1H, bs, OH). ^{13}C NMR (75 MHz, 273 K, $CDCl_3$) δ: 24.32, 26.10, 26.40, 52.78, 55.03, 71.45, 115.26, 120.48, 120.83, 123.22, 124.61, 127.26, 129.06, 129.61, 130.21, 130.62, 132.33, 147.61, 147.73, 155.74. EI-MS (70 eV) *m*/*z* (% int.): 362 (M$^+$, 14), 279 (9), 260 (61), 231 (39), 230 (100), 85 (54), 58 (14). HR-MS calcd. for $C_{22}H_{22}N_2O_3$: 362.1630; found: 362.1634.

1-(2-Nitrophenyl)piperidin-1-ylmethyl)naphthalen-2-ol (4)

UV–vis (MeOH, nm) λ_{max}: 241, 335. IR (KBr disc, cm^{-1}) ν: 3439, 3052, 2926, 1621, 1595, 1514, 1316, 1265, 1231, 830. ^{1}H NMR (500 MHz, 273 K, $CDCl_3$) δ: 1.25–1.32 (1H, m, CH), 1.67–1.77 (5H, m, 5 × CH), 2.35–2.38 (2H, m, 2 × NCH), 2.58 (1H, d, *J* = 9.5 Hz, NCH), 3.30 (1H, d, *J* = 11.5 Hz, NCH), 6.08 (1H, s, Ar-CH-Ar′), 7.15 (1H, d, *J* = 9.0 Hz, Ar-H), 7.21–7.26 (1H, m, Ar-H), 7.31–7.45 (3H, m, Ar-H), 7.65–7.71 (3H, m, Ar-H), 7.81–7.85 (2H, m, Ar-H), 14.54 (1H, bs, OH). ^{13}C NMR (125 MHz, 273 K, $CDCl_3$) δ: 23.90, 25.93, 26.52, 49.92, 54.62, 64.02, 115.07, 120.20, 120.64, 122.69, 124.29, 126.97, 128.58, 128.86, 128.93, 130.09, 131.55, 132.61, 133.65, 133.70, 150.22, 156.94. EI-MS (70 eV) *m*/*z* (% int.): 362 (M$^+$, 2), 231 (100), 232 (47), 85 (3). HR-MS calcd. for $C_{23}H_{23}NO_3$: 362.1630; found: 362.1633.

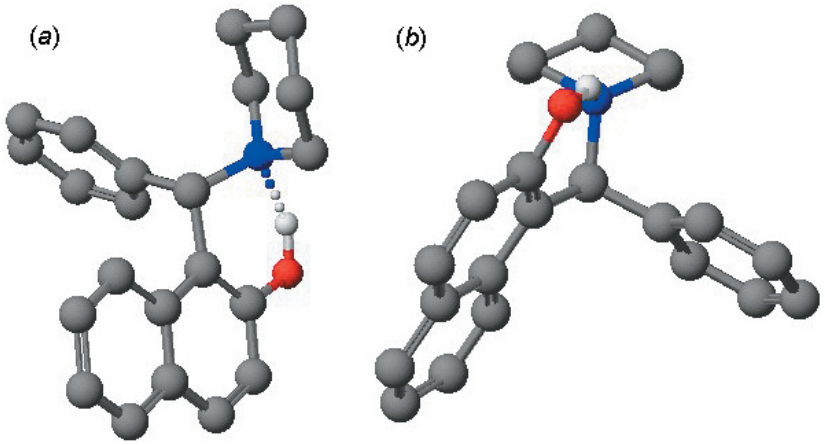
1-(4-Chlorophenyl)piperidin-1-ylmethyl)naphthalen-2-ol (5)

UV–vis (MeOH, nm) λ_{max}: 242, 291, 336. IR (KBr disc, cm^{-1}) ν: 3440, 3080, 2951, 1620, 1519, 1474, 1384, 1104, 742, 515. ^{1}H NMR (300 MHz, 273 K, $CDCl_3$) δ: 1.27 (1H, bs, CH), 1.62–1.70 (5H, bs, 5 × CH), 1.97 (1H, bs, NCH), 2.03 (1H, bs, NCH), 2.73 (1H, bs, NCH), 3.36 (1H, bs, NCH), 5.07 (1H, s, Ar-CH-Ar′), 7.19–7.41 (4H, m, Ar-H), 7.43–7.46 (1H, m, Ar-H), 7.54–7.68 (2H, m, Ar-H), 7.71–7.81 (3H, m, Ar-H), 3.12 (1H, bs, OH). ^{13}C NMR (75 MHz, 273 K, $CDCl_3$) δ: 24.35, 26.10, 26.30, 52.41, 55.14, 71.49, 117.13, 120.45, 121.20, 123.06, 127.08, 129.51, 129.77, 130.22 130.94, 131.16, 132.50, 134.21, 138.33, 156.12. EI-MS (70 eV) *m*/*z* (% int.): 353 (M + 2, 0.7), 350 (M$^+$, 2), 266 (2), 264 (2), 231 (6), 84 (100). HR-MS calcd. for $C_{22}H_{22}ClNO$: 351.1390; found: 351.1387.

1-(Piperidin-1-yl-pyridin-4-ylmethyl)naphthalen-2-ol (6)

UV–vis (MeOH, nm) λ_{max}: 241, 298. IR (KBr disc, cm^{-1}) ν: 3442, 3044, 2944, 1621, 1598, 1451, 1384, 1267, 1236, 816. ^{1}H NMR (300 MHz, 273 K, $CDCl_3$) δ: 1.61 (1H, bs, CH), 1.72–1.88 (5H, bs, 5 × CH), 2.10 (1H, bs, -NCH), 2.71 (1H, bs, -NCH), 3.16 (1H, bs, -NCH), 3.35 (1H, bs, -NCH),

Fig. 2. Energy minimized molecular model of compound **1** in two orientations. Hydrogen atoms are omitted for clarity.



5.07 (1H, s, Ar-CH-Ar′), 7.15–7.82 (8H, m, Ar-H), 8.50–8.52 (2H, d, J = 8 Hz, Ar-H), 13.75 (1H, bs, OH). ^{13}C NMR (75 MHz, 273 K, $CDCl_3$) δ: 24.40, 26.42, 26.44, 52.71, 54.94, 71.26, 115.17, 120.41, 120.94, 123.15, 124.12, 127.17, 129.01, 129.55, 130.48, 132.39, 149.11, 150.67, 155.87. EI-MS (70 eV) *m/z* (% int.): 318 (M^+, 5), 235 (4), 233 (100), 232 (51). HR-MS calcd. for $C_{21}H_{22}N_2O$: 318.1732; found: 318.1727.

1-Piperidin-1-ylmethylnaphthalen-2-ol (7)

UV–vis (MeOH, nm) λ_{max}: 245, 288, 334. IR (KBr disc, cm^{-1}) ν: 3448, 3051, 2935, 1621, 1599, 1474, 1384, 1271, 786. ^{1}H NMR (300 MHz, 273K, $CDCl_3$) δ: 1.23 (1H, bs, CH), 1.77 (5H, m, CH_2, -NCH_2), 2.37 (2H, bs, 2 × NCH), 3.36 (2H, bs, 2 × NCH), 4.37 (2H, s, -NCH_2Ar), 7.28–7.35 (2H, m, Ar-H), 7.46–7.51 (1H, m, Ar-H), 7.73–7.84 (3H, m, Ar-H), 13.2 (1H, bs, OH). ^{13}C NMR (75 MHz, 273K, $CDCl_3$) δ: 24.38, 26.25, 54.60, 57.68, 111.39, 119.67, 121.34, 122.68, 126.59, 128.79, 129.26, 129.36, 133.09, 157.17. EI-MS (70 eV) *m/z* (% int.): 241 (M^+, 5), 157 (5), 84 (100). HR-MS calcd. for $C_{16}H_{19}NO$: 241.1467; found: 241.1474.

1-(Morpholin-4-ylphenylmethyl)naphthalen-2-ol (8)

^{1}H and ^{13}C NMR were identical to those reported in literature (27). UV–vis (MeOH, nm) λ_{max}: 242, 291, 325. IR (KBr disc, cm^{-1}) ν: 3443, 3058, 2971, 2842, 1619, 1598, 1454, 1384, 1236, 1116. EI-MS (70 eV) *m/z* (% int.): 319 (M^+, 7), 233 (4), 231 (100), 86 (1). HR-MS calcd. for $C_{21}H_{21}NO_2$: 319.1572; found: 319.1566.

1-[(4-Chlorophenyl)morpholin-4-ylmethyl]naphthalen-2-ol (9)

UV–vis (MeOH, nm) λ_{max}: 242, 293, 319. IR (KBr disc, cm^{-1}) ν: 3438, 3062, 2958, 1619, 1597, 1450, 1411, 1384, 1238, 1117. ^{1}H NMR (300 MHz, 273 K, $CDCl_3$) δ: 2.32–2.54 (3H, m, 3 × NCH), 3.14–3.18 (1H, m, NCH), 3.51–3.71 (4H, m, 4 × OCH), 5.14 (1H, s, Ar-CH-Ar′), 7.17–7.31 (4H, m, Ar-H), 7.40–7.45 (1H, m, Ar-H), 7.53–7.56 (2H, m, Ar-H), 7.71–7.76 (3H, m, Ar-H), 13.15 (1H, bs, OH). ^{13}C NMR (75 MHz, 273 K, $CDCl_3$) δ: 51.95, 54.28, 67.10, 67.30, 71.59, 115.03, 120.27, 121.19, 123.33, 127.23, 129.22, 129.50, 129.91, 130.55, 131.10, 132.44, 134.55, 137.37, 154.95. EI-MS (70 eV) *m/z* (% int.): 355 (M+2, 4) 353 (M^+, 12), 268 (12), 265 (38), 231 (100), 202 (23), 86 (15). HR-MS calcd. for $C_{21}H_{20}ClNO_2$: 353.1183; found: 353.1193.

1-[(4-Nitrophenyl)morpholin-4-ylmethyl]naphthalen-2-ol (10)

^{1}H and ^{13}C NMR were identical to those reported in literature (27). UV–vis (MeOH, nm) λ_{max}: 242, 298. IR (KBr disc, cm^{-1}) ν: 3448, 3051, 2935, 1621, 1599, 1519, 1466, 1384, 1364, 786, 739. EI-MS (70 eV) *m/z* (% int.): 364 (M^+, 1), 231 (2), 221 (100). HR-MS calcd. for $C_{21}H_{20}N_2O_4$: 364.1423; found: 364.1429.

1-[(4-Methylpiperazin-1-yl)phenylmethyl)]naphthalen-2-ol (11)

UV–vis (MeOH, nm) λ_{max}: 241, 293, 320. IR (KBr disc, cm^{-1}) ν: 3448, 3056, 1621, 1581, 1450, 1310, 1240, 1137. ^{1}H NMR (300 MHz, 273 K, $CDCl_3$) δ: 2.40–2.57 (8H, m, 5 × NCH, NCH_3), 2.95 (2H, bs, 2 × NCH), 3.25 (1H, bs, NCH), 5.17 (1H, s, Ar-CH-Ar′), 7.14–7.29 (4H, m, Ar-H), 7.39–7.44 (1H, m, Ar-H), 7.53–757 (2H, m, Ar-H), 7.68–7.71 (3H, m, Ar-H), 7.83–7.87 (1H, m, Ar-H), 13.37 (1H, bs, OH). ^{13}C NMR (75 MHz, 273 K, $CDCl_3$) δ: 46.16, 51.20, 53.74, 55.31, 55.62, 71.94, 115.98, 120.27, 121.54, 123.03, 127.01, 128.12, 128.60, 128.81, 129.08, 129.34, 130.11, 132.61, 139.51, 155.31. EI-MS (70 eV) *m/z* (% int.): 332 (M^+, 13), 233 (3), 232 (16), 231 (100). HR-MS calcd. for $C_{23}H_{24}NO_3$: 332.1889; found: 332.1882.

Molecular modeling

The molecular modeling on compound **1** was performed using CaChe WorkSystem Pro Version 5. After having set a weak bond between the hydroxyl hydrogen and the N of the piperidine ring, an energy minimization experiment was performed in two steps. First, the "fastest procedure" (augmented MM3 parameters) was used, followed by the "standard procedure" (PM3 parameters). The energy-minimized conformation indicated strong H-bonding in the molecule (Fig. 2).

X-ray crystallography

Crystals of compound **9** were grown from a saturated dichloromethane–methanol (1:1) solution, while crystals of compound **11** were grown from saturated diethyl ether solu-

Table 1. Crystallographic data collection parameters for **9** and **11**.

Parameter	Compound **9**	Compound **11**
Empirical formula	$C_{21}H_{20}ClNO_2$	$C_{22}H_{24}N_2O$
Formula weight	353.85	332.44
Crystal color, habit	Colorless, needle	Colorless, block
Crystal dimensions (mm^3)	0.17 × 0.22 × 0.30	0.24 × 0.27 × 0.38
$F(000)$	744	712
Crystal system	Monoclinic	Orthorhombic
Space group	Cc (No. 9)[a]	$Pna2_1$ (No. 33)
Z	4	4
a (Å)	9.782(5)	10.723(6)
b (Å)	18.645(5)	13.483(8)
c (Å)	10.240(4)	12.849(8)
β (°)	91.42(3)	
V ($Å^3$)	1867(1)	1857(2)
d_{calcd} (g cm^{-3})	1.259	1.189
Temperature (K)	213	213
Radiation	Mo Kα (λ = 0.710 69 Å)	Mo Kα (λ = 0.710 69 Å)
μ (mm^{-1})	0.217	0.073
Total reflections	2975	3090
Observed reflections ($F_o > 4\sigma(F_o)$)	2893	2836
No. of variables	231	227
R_{int}	0.067	0.000
θ range (°)	0–30	0–30
S (GoF) on F^2	0.950	0.942
R_1 ($I > 4\sigma(I)$)[b]	0.039	0.039
wR_2 (all data)[c]	0.138	0.202
Largest diff. peak and hole (e $Å^{-3}$)	0.19 and –0.17	0.20 and –0.17

[a]Flack parameter 0.0 (1).
[b]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$.
[c]$wR_2 = [\Sigma(w(F_o^2 - F_c^2)^2)/\Sigma w(F_o^2)^2]^{1/2}$, where $w = 1/[\sigma^2(F_o^2) + (0.0664P)^2 + (0.0000P)]$ (**9**) and $w = 1/[\sigma^2(F_o^2) + (0.1000P)^2 + (0.0000P)]$ (**11**), where $P = (\max(F_o^2, 0) + 2F_c^2)/3$.

tion. Crystals were mounted using a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Mo Kα radiation.

The data were collected at a temperature of –60 ± 1 °C to a maximum 2θ value of 60.2°. The structure was solved by direct methods (39) and expanded using Fourier techniques (40). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The neutral atom scattering factors were taken from Cromer and Weber (41). Anomalous dispersion effects were included in F_{calcd} (42); the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley (43). The values for the mass attenuation coefficients are those of Creagh and Hubbell (44). All calculations were performed using the CrystalStructure crystallographic software package (45, 46) except for refinement, which was performed using SHELXL-97 (47).

The crystallographic data collection parameters, bond lengths, and bond angles for **9** and **11** are presented in Tables 1–3. The full details of the structure have been deposited.[3]

Results and discussion

One of the interests of this laboratory lies in the use of 2-tetralone–2-naphthol skeletons as versatile building blocks (48–50). Substituted 1-arylidene-2-tetralones (**A**) were prepared from 2-tetralone and appropriate aldehydes by palladium-catalyzed Knoevenagel-type condensation (37). Subsequently, 1-arylidene-2-tetralones reacted with piperidine to produce the compounds **1**–**4** instead of the expected aza-Michael adducts (**B** or **C**). Based on this observation, it appears highly probable that aza-Michael adducts (**B** or **C**) are unstable and that they collapse back to the starting materials if they are not trapped by aerial oxidation of the dihydronaphthalene ring to form stable and aromatic 1-(aryl-piperidin-1-ylmethyl)naphthalen-2-ols (**1**–**4**), as shown in Scheme 2. This rather unusual conversion, driven by the aromatization, was found to be slow and the best yield after a reaction time of 7 days was ~30%. Although the reactions suffer from rather long reaction times and low yields, this is a novel conversion.

[3] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5046. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 606518 and 606519 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://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 336033; or deposit@ccdc.cam.ac.uk).

Table 2. Bond lengths and angles for **9**.

Bond lengths (Å)		Bond angles (°)	
Cl(1)—C(5)	1.745(4)	Cl(1)-C(5)-C(4)	119.5(4)
O(1)—C(19)	1.413(6)	Cl(1)-C(5)-C(6)	120.4(3)
O(1)—C(20)	1.414(6)	**O(1)-C(19)-C(18)**	112.2(4)
O(2)—C(9)	1.351(5)	C(20)-O(1)-C(19)	110.5(4)
N(1)—C(1)	1.492(5)	**O(1)-C(20)-C(21)**	111.0(4)
N(1)—C(18)	1.470(6)	O(2)-C(9)-C(8)	123.6(4)
N(1)—C(21)	1.483(6)	O(2)-C(9)-C(10)	116.1(4)
C(1)—C(2)	1.516(6)	C(18)-N(1)-C(1)	113.5(3)
C(1)—C(8)	1.530(5)	C(21)-N(1)-C(1)	108.9(3)
C(2)—C(3)	1.385(6)	N(1)-C(1)-C(8)	111.1(3)
C(2)—C(7)	1.391(6)	N(1)-C(1)-C(2)	113.2(3)
C(3)—C(4)	1.365(7)	**N(1)-C(18)-C(19)**	109.3(4)
C(4)—C(5)	1.372(7)	C(21)-N(1)-C(18)	108.5(3)
C(5)—C(6)	1.366(6)	**N(1)-C(21)-C(20)**	109.3(4)
C(6)—C(7)	1.362(6)	C(1)-C(2)-C(3)	122.4(4)
C(8)—C(9)	1.378(6)	C(8)-C(1)-C(2)	109.6(3)
C(8)—C(17)	1.432(6)	C(1)-C(2)-C(7)	121.3(3)
C(9)—C(10)	1.425(6)	C(1)-C(8)-C(9)	121.0(4)
C(10)—C(11)	1.347(7)	C(1)-C(8)-C(17)	119.5(4)
C(11)—C(12)	1.402(7)	C(2)-C(3)-C(4)	122.3(5)
C(12)—C(13)	1.409(7)	C(7)-C(2)-C(3)	116.2(4)
C(12)—C(17)	1.436(6)	C(2)-C(7)-C(6)	122.2(4)
C(13)—C(14)	1.344(8)	C(3)-C(4)-C(5)	119.4(5)
C(14)—C(15)	1.408(8)	C(4)-C(5)-C(6)	120.1(4)
C(15)—C(16)	1.361(7)	C(5)-C(6)-C(7)	119.6(4)
C(16)—C(17)	1.398(6)	C(8)-C(9)-C(10)	120.2(4)
C(18)—C(19)	1.508(7)	C(17)-C(8)-C(9)	119.5(4)
C(20)—C(21)	1.511(7)	C(8)-C(17)-C(16)	123.9(4)
		C(8)-C(17)-C(12)	119.2(4)
		C(9)-C(10)-C(11)	120.8(4)
		C(10)-C(11)-C(12)	121.6(4)
		C(11)-C(12)-C(17)	118.7(4)
		C(11)-C(12)-C(13)	122.0(4)
		C(17)-C(12)-C(13)	119.3(4)
		C(12)-C(13)-C(14)	121.1(5)
		C(12)-C(17)-C(16)	116.9(4)
		C(13)-C(14)-C(15)	120.6(5)
		C(14)-C(15)-C(16)	119.2(5)
		C(15)-C(16)-C(17)	122.8(5)

Table 3. Bond lengths and angles for **11**.

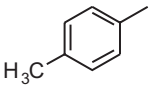
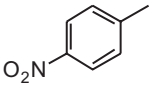
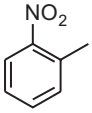
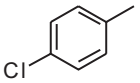
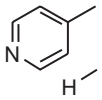
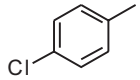
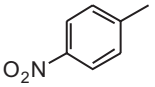
Bond lengths (Å)		Bond angles (°)	
O(1)—C(9)	1.361(7)	O(1)-C(9)-C(8)	123.1(4)
N(1)—C(1)	1.499(6)	O(1)-C(9)-C(10)	116.2(5)
N(1)—C(18)	1.470(7)	N(1)-C(1)-C(2)	113.4(4)
N(1)—C(21)	1.452(8)	N(1)-C(1)-C(8)	109.0(4)
N(2)—C(19)	1.413(9)	C(21)-N(1)-C(1)	110.3(4)
N(2)—C(20)	1.454(7)	C(18)-N(1)-C(1)	114.5(4)
N(2)—C(22)	1.481(8)	C(21)-N(1)-C(18)	108.4(4)
C(1)—C(2)	1.507(7)	**N(1)-C(18)-C(19)**	108.5(4)
C(1)—C(8)	1.529(7)	**N(1)-C(21)-C(20)**	111.4(5)
C(2)—C(3)	1.389(8)	**N(2)-C(19)-C(18)**	112.3(6)
C(2)—C(7)	1.386(8)	C(20)-N(2)-C(19)	109.8(4)
C(3)—C(4)	1.39(1)	C(22)-N(2)-C(19)	111.7(5)
C(4)—C(5)	1.36(1)	**N(2)-C(20)-C(21)**	110.1(5)
C(5)—C(6)	1.36(1)	C(22)-N(2)-C(20)	109.6(5)
C(6)—C(7)	1.38(1)	C(1)-C(2)-C(7)	122.6(5)
C(8)—C(9)	1.371(7)	C(8)-C(1)-C(2)	111.3(4)
C(8)—C(17)	1.428(7)	C(1)-C(2)-C(3)	120.5(5)
C(9)—C(10)	1.423(7)	C(1)-C(8)-C(9)	121.0(4)
C(10)—C(11)	1.341(9)	C(1)-C(8)-C(17)	119.3(4)
C(11)—C(12)	1.406(9)	C(7)-C(2)-C(3)	116.9(5)
C(12)—C(13)	1.426(9)	C(2)-C(3)-C(4)	121.1(6)
C(12)—C(17)	1.442(7)	C(2)-C(7)-C(6)	121.1(6)
C(13)—C(14)	1.34(1)	C(3)-C(4)-C(5)	120.8(6)
C(14)—C(15)	1.41(1)	C(4)-C(5)-C(6)	118.9(7)
C(15)—C(16)	1.365(9)	C(5)-C(6)-C(7)	121.2(7)
C(16)—C(17)	1.395(8)	C(8)-C(9)-C(10)	120.7(5)
C(18)—C(19)	1.514(8)	C(17)-C(8)-C(9)	119.5(4)
C(20)—C(21)	1.513(9)	C(8)-C(17)-C(16)	123.5(4)
		C(8)-C(17)-C(12)	118.6(5)
		C(9)-C(10)-C(11)	121.0(5)
		C(10)-C(11)-C(12)	120.9(5)
		C(11)-C(12)-C(17)	119.3(5)
		C(11)-C(12)-C(13)	122.3(5)
		C(17)-C(12)-C(13)	118.3(5)
		C(12)-C(13)-C(14)	120.8(6)
		C(12)-C(17)-C(16)	117.9(5)
		C(13)-C(14)-C(15)	121.3(7)
		C(14)-C(15)-C(16)	119.0(7)
		C(15)-C(16)-C(17)	122.6(5)

Several attempts were made to expedite the reaction course by addition of oxidizing agents (viz., H_2O_2, MnO_2, DDQ, and O_2). No decline in the reaction time could be achieved; rather, undesired products and complex mixtures were obtained. No attempts were made to identify the undesired products. The results suggest that the first elementary step (formation of **B** or **C**, Scheme 2) is rate-limiting and the presence of oxidizing agents lead to undesired reactions with the starting materials. We are in the process of optimizing the conditions.

We prepared additional analogs (**1**–**11**, Table 4) by modifying a reported microwave-assisted procedure (26) for which we achieved an appreciable improvement in yields and reaction time (Scheme 3). Sharifi et al. (26) have reported the synthesis of related compounds on acidic alumina support under solvent-free conditions and microwave irradiation with an average yield of 64% in the reaction time range of 4–8 min, compared to an average yield of 75.1% and a reaction time of 1 min under our conditions. The irradiation time was split into two 30 s pulses with a nearly 30 s intervening gap to avoid superheating and charring the reaction contents. Our procedure involved solvent-free conditions and the use of only catalytic amounts of *p*-TSA, thus avoiding the use of excessive acidic alumina. Numerous trials of microwave-assisted reaction under solvent-free conditions using 2-nitrobenzaldehyde (for compound **4**) were not successful and violent splashing of the contents was noticed within the irradiation period of ~10 s; TLC did not indicate the formation of any product even after continued irradiation for up to 2 min. The use of solvent (DMF) and solid support (silica gel) under microwave irradiation did not change the outcome.

Although the Mannich bases of 2-naphthols with heterocyclic amines were reported in the past (24, 26, 27, 51), their

Table 4. Comparative reaction data for compounds synthesized by two different procedures.

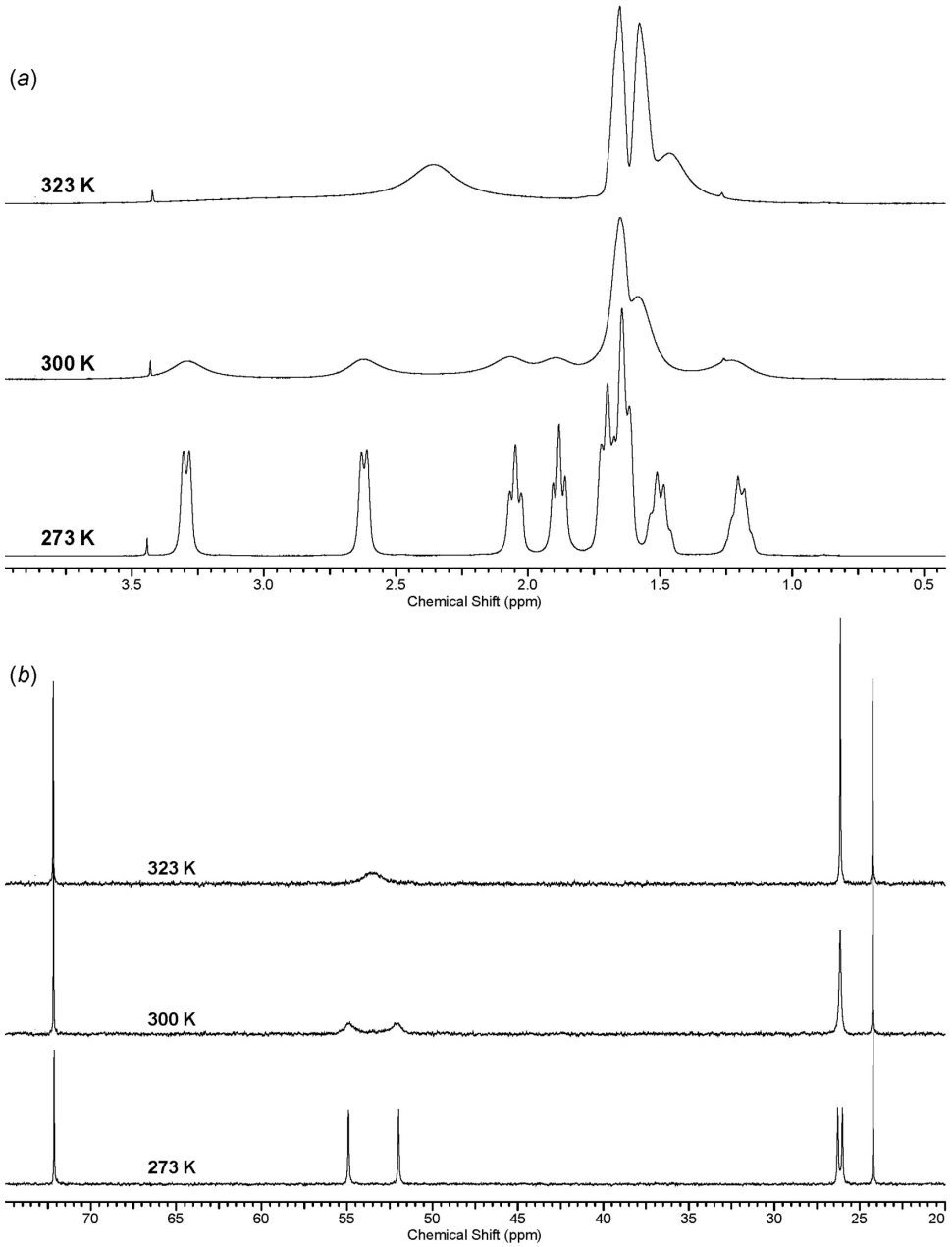
No.	R	X	Scheme 1 Time: 7 days		Scheme 2 Time 1 min		
			Yield (%)	mp (°C)	Yield (%)	mp (°C)	Lit. mp (°C)
1		CH_2	22.0	194 to 195	79.7	192–194	198 to 199 (27)
2		CH_2	17.5	145–147	82.7	144–146	—
3		CH_2	29.5	187–190	83.3	186–188	—
4		CH_2	18.5	194 to 195	Ns[a]	—	—
5		CH_2	Nd[b]	—	72.0	165 to 166	—
6		CH_2	Nd	—	82.4	185–187	—
7		CH_2	Nd	—	43.1	88–90	95 to 96 (51)
8		O	Nd	—	85.8	177–179	181–183 (27)
9		O	Nd	—	71.7	132–134	—
10		O	Nd	—	72.0	178 to 179	177–179 (27)
11		NCH_3	Nd	—	78.1	138–140	—

[a]Ns (Not successful).
[b]Nd (Not done).

detailed NMR behavior has not been examined, to the best of our knowledge; some NMR peaks are reported in broad range (27). We consistently noted interesting NMR activities of the compounds under investigation, as they often gave poorly resolved heterocyclic proton and carbon peaks in their respective spectra at ambient temperature. We decided to systematically investigate this behaviour. Besides the indispensable use of NMR spectroscopy in structure elucidation, it remains a powerful technique for stereochemical analysis of organic molecules. From the point of view of conformational analysis, six-membered saturated carbocycles and heterocycles have been studied (52–55). A recent study on 1-(2-hydroxy-2,2-diarylethyl)piperidin-4-ones describes a new mechanism of N-inversion — a concerted H-bond dissociation – N inversion process (56). The piperidine ring is a common structural fragment of many alkaloids and, therefore, conformational analysis of these biologically active amines is necessary for the comprehension of the molecular mechanisms of their action.

The ^{1}H and ^{13}C NMR spectra obtained at ambient temperature (300 K) suffered from the broadening of several peaks suggesting dynamism in the piperidine conformation, making the interpretation ambiguous. Thus, we resorted to recording the NMR experiments at lower temperatures. As expected, the ^{1}H NMR spectrum of compound **1** at 273 K gave better resolved peaks. The peak at δ 14.1, integrating for one proton of -OH group at position 2 of the naphthalene ring, clearly indicated strong H-bonding with the N of the piperidine ring. In addition, most of the protons on the piperidine ring gave discrete peaks, making it obvious that the symmetry of the piperidine ring was lost. This observation was also supported by the ^{13}C NMR spectrum of compound **1** at 273 K, which not only resulted in better resolved peaks but also showed distinct peaks for each CH_2 of the piperidene ring. This was another indication that the magnetic equivalence of the two pairs of methylene carbons is destroyed by restricted rotation of the piperidine ring with two flanking aromatic rings and the H bond. The NMR experiments that were recorded in a temperature span of 50 °C (three each for ^{1}H and ^{13}C) clearly demonstrated an increase in molecular dynamics with the rise in temperature. The portion of NMR plots of compound **1** that were most affected by the temperature change is shown in Fig. 3. The five C peaks of nonsymmetric piperidine at 273 K converge into

Fig. 3. Stack plot of (*a*) a portion of ^{1}H NMR and (*b*) ^{13}C NMR of compound **1** at various temperatures.

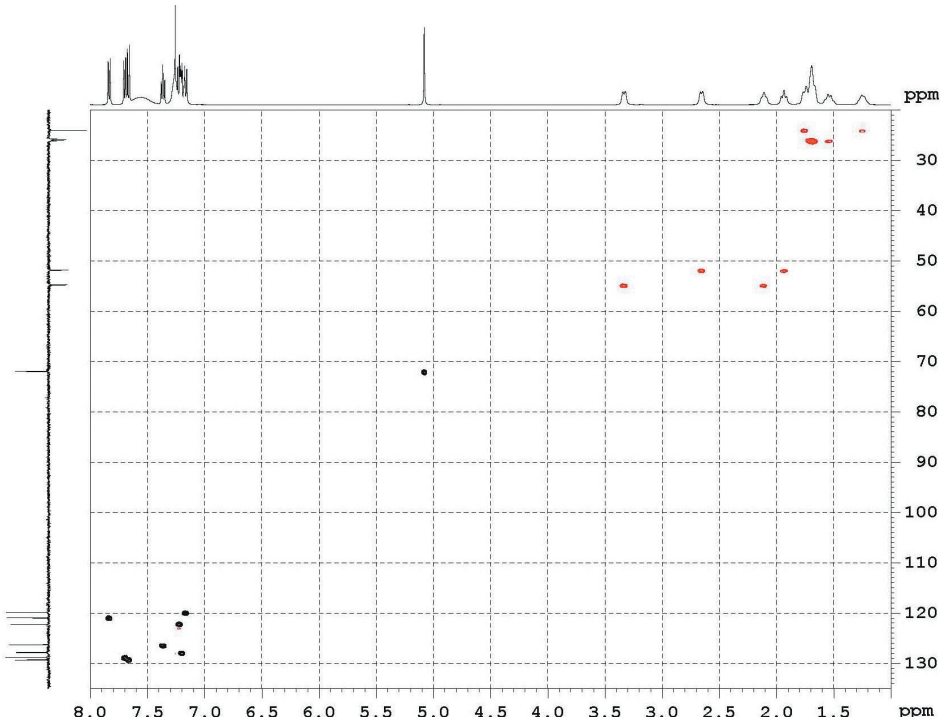


three C peaks of symmetric piperidine at 323 K. A similar observation was made in the H spectrum at corresponding temperatures, albeit at the cost of resolution.

The molecular model shown in Fig. 2 also demonstrates the existence of a very strong H bond (calculated distance = 1.83 Å) and a consequent loss of symmetry. This is more evident in Fig. 3*b,* where methylene Cs on the right side of N are magnetically nonequivalent to those on the left side because of restricted rotation. At lower temperature, this system may be regarded as a hindered spirocyclic system. As the temperature is increased, the H bond is disrupted allowing rotation of the piperidine ring along the benzylic C—N axis with concurrent ring flipping and (or) N-inversion. Being rather fast for the NMR timescale, the convergence of a pair of piperidine methylene takes place with loss of resolution in the ^{13}C NMR. As seen in Fig. 3, as the two discrete piperidine -NCH_2, appearing at 51.83 and 54.77 ppm, observed at 273 K coalesce to a broad peak at ~53.30 ppm when recorded at 323 K, it can be qualitatively said that a temperature increase of 50 °C leads to approximately 800 conformational interchanges per second (based on the expression for the rotational rate constant at the coalescence point (57) ($k_{coal} = \pi\ (\Delta\nu)/\sqrt{2}$). Thus, at the coalescence temperature, the interchanging conformations have a lifetime of about 1.25 ms ($1/k_{coal}$). Contrary to this, for the C-3 and C-5 carbons of piperidine that are away from the crowded centre, a similar effect is achieved with a temperature increase of ~27 °C (k_{coal} ~ 75 s^{-1}). The ^{1}H NMR also shows this behaviour where peak broadening is more severe.

The HSQC experiment with shaped pulse recorded at 273 K resulted in the expected correlations (Fig. 4). In addition to the presence of piperidine methylenes (inverted

Fig. 4. HSQC with shaped pulse for inversion of compound **1** recorded at 273 K.



peaks), the HSQC experiment also showed the presence of at least eight magnetically nonequivalent protons on the piperidine ring. A pronounced disparity in the appearance of seemingly similar diastereotopic methylene (C2, C6 pair) protons was observed. The more deshielded protons on the two carbons are 0.65 ppm apart, while the more shielded ones are 0.20 ppm apart. Also, the amount of shielding and deshielding on the protons on these carbons is considerably disparate (1.23 vs. 0.78 ppm).

Similar NMR behaviour was consistently noticed for all the compounds (except compound **7**) irrespective of the heterocycle substituents. At 273 K, piperidinyl, morpholinyl, and *N*-methylpiperzinyl groups showed magnetic nonequivalence of all constituent carbons and hydrogens. Compound **7**, being devoid of an aryl group compared to others in the series, has significantly reduced crowding near the heterocyclic nitrogen atom and, therefore, the heterocyclic ring retains the symmetry even at 273 K.

Finally, X-ray crystal structures of compounds **9** and **11** were solved to compare the NMR solution- and solid-phase crystal conformations. The prominent feature of both compounds **9** and **11** is an internal hydrogen bond from the hydrogen atom of the OH group to N(1), the nitrogen of the piperidine or morpholine ring, which are bonded to C(1). It can be seen in Fig. 5 that the O—H bond approaches the piperidine or morpholine ring obliquely so that the C(18) and C(21) carbon atoms of this ring are not equivalent. This is a strong hydrogen bond; the observed H(20)—N(1) and H(24)—N(1) distances in **9** and **11** are 1.78 and 1.75 Å, respectively. This H-bonding also persists in solution as evidenced by the appearance of the hydrogen-bonded -OH peak at values >13 ppm in ^{1}H NMR. This H bond forms a six-membered cycle and restricts the free rotation of the heterocyclic ring along the benzylic C—N bond. A close inspection of the bond lengths and angles of the heterocyclic ring (shown in bold face in Tables 2 and 3) reveal that the ring is slightly distorted, compounding the magnetic nonequivalence of Hs and Cs on seemingly symmetric heterocyclic rings.

Conclusion

2-Naphthol Mannich bases with heterocyclic amines were synthesized using two different approaches. Variable-temperature NMR investigations proved helpful in resolving complicated NMR spectra of these rather simple molecules. Molecular modeling and X-ray crystallography supported the NMR results. These results can be explained by the loss of magnetic equivalence of certain heterocyclic Cs and Hs caused by restricted rotation of the heterocyclic ring when N is involved in strong H-bonding with phenolic -OH.

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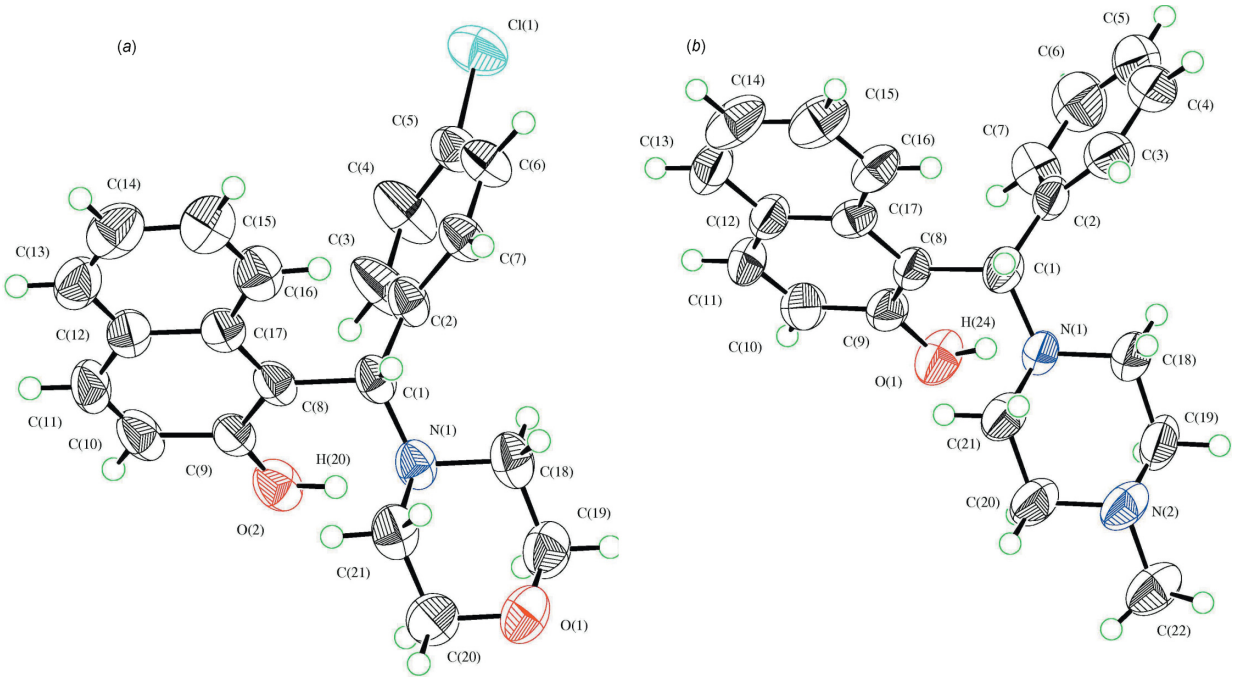
References

1. P. Kocovsky, S. Vyskocil, and M. Smrcina. Chem. Rev. **103**, 3213 (2003).

Fig. 5. ORTEP diagrams of compounds (*a*) **9** and (*b*) **11**.



2. S. Vyskocil, S. Jaracz, M. Smrcina, M. Sticha, V. Hanus, M. Polasek, and P. Kocovsky. J. Org. Chem. **63**, 7727 (1998).
3. M. Smrcina, S. Vyskocil, B. Maca, M. Polasek, T.A. Claxton, A.P. Abbott, and P. Kocovsky. J. Org. Chem. **59**, 2156 (1994).
4. M. Smrcina, M. Lorenc, V. Hanus, P. Sedmera, and P. Kocovsky. J. Org. Chem. **57**, 1917 (1992).
5. Y. Kim, R.A. Singer, and E.M. Carreira. Angew. Chem. Int. Ed. **37**, 1261 (1998).
6. E.M. Carreira, W. Lee, and R.A. Singer. J. Am. Chem. Soc. **117**, 3649 (1995).
7. R.A. Singer and E.M. Carreira. J. Am. Chem. Soc. **117**, 12360 (1995).
8. Y.N. Belokon, K.A. Kochetkov, T.D. Churkina, N.S. Ikonnikov, O.V. Larionov, S.R. Harutyunyan, S. Vyskocil, M. North, and H.B. Kagan. Angew. Chem. Int. Ed. **40**, 1948 (2001).
9. Y. Yuan, X. Li, I. Sun, and K.L. Ding. J. Am. Chem. Soc. **124**, 14866 (2002).
10. G. Bernardinelli, D. Fernandez, R. Gosmini, P. Meier, A. Ripa, P. Schupfer, B. Treptow, and E.P. Kundig. Chirality, **12**, 529 (2000).
11. C. Cardellicchio, G. Ciccarella, F. Naso, F. Perna, and P. Tortorella. Tetrahedron, **55**, 14685 (1999).
12. C. Cardellicchio, G. Ciccarella, F. Naso, E. Schingaro, and F. Scordari. Tetrahedron: Asymmetry, **9**, 3667 (1998).
13. G. Palmieri. Tetrahedron: Asymmetry, **11**, 3361 (2000).
14. D.-X. Liu, L.-C. Zhang, Q. Wang, C.-S. Da, Z.-Q. Xin, R. Wang, M.C.K. Choi, and A.S.C. Chan. Org. Lett. **3**, 2733 (2001).
15. C. Cimarelli, G. Palmieri, and E. Volpini. Tetrahedron: Asymmetry. **13**, 2417 (2002).
16. C. Cimarelli, A. Mazzanti, G. Palmieri, and E. Volpini. J. Org. Chem. **66**, 4759 (2001).
17. J.X. Ji, L.Q. Qiu, C.W. Yip, and A.S.C. Chan. J. Org. Chem. **68**, 1589 (2002).
18. M. Betti. Gazz. Chim. Ital. **30 II**, 310 (1900).
19. M. Betti. Gazz. Chim. Ital. **31 I**, 377 (1901).
20. M. Betti. Gazz. Chim. Ital. **31 II**, 170 (1901).
21. M. Betti. Gazz. Chim. Ital. **33 I**, 1 (1903).
22. M. Betti. Org. Syn. Coll. Vol. **1**, 381 (1941).
23. K.-W. Chi, Y.S. Ahn, K.T. Shim, T.H. Park, and J.S. Ahn. Bull. Korean Chem. Soc. **20**, 973 (1999).
24. M.R. Saidi, N. Azizi, and M.R. Naimi-Jamal. Tetrahedron Lett. **42**, 8111 (2001).
25. M. Saidi and H.R. Khalaji. J. Chem. Res. Synop. 340 (1997).
26. A. Sharifi, M. Mirzaei, and M.R. Naimi-Jamal. Monatsh. Chem. **132**, 875 (2001).
27. A.R. Katritzky, A.A.A. Abdel-Fattah, D.O. Tymoshenko, S.A. Belyakov, I. Ghiviriga, and P.J. Steel. J. Org. Chem. **64**, 6071 (1999).
28. Y. Dong, J. Sun, X. Wang, L. Cao, and Y. Hu. Tetrahedron: Asymmetry, **15**, 1667 (2004).
29. M.R. Saidi and N. Azizi. Tetrahedron: Asymmetry, **14**, 389 (2003).
30. A. Cohen, R.A. Hall, B. Heath-Brown, M.W. Parkes, and A.H. Rees. Br. J. Pharmacol. Chemother. **12**, 194 (1957).
31. P.D. Brown. Med. Oncol. **14**, 1 (1997).
32. K.W. Johnson, D. Lofland, and H.E. Moser. Curr. Drug Targets: Infect. Disord. **5**, 39 (2005).
33. W.T. Lowther and B.W. Matthews. Biochim. Biophys. Acta, **1477**, 157 (2000).
34. A.S. Waller and J.M. Clements. Curr. Opin. Drug Discovery Dev. **5**, 685 (2002).
35. L.T. Chappell. Altern. Med. Rev. **3**, 426 (1998).
36. M.D. Ford. Heavy metals. 4th ed. McGraw Hill, New York. 1996.
37. Y. Zhu and Y. Pan. Chem. Lett. **33**, 668 (2004).
38. J.R. Dimmock, M.P. Padmanilyam, G.A. Zello, J. Wilson Quail, E.O. Oloo, J.S. Prisciak, H.-B. Kraatz, A. Cherkasov, J.S. Lee, and T.M. Allen. Eur. J. Med. Chem. **37**, 813 (2002).
39. A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polidori, and M. Camalli. J. Appl. Crystallogr. **27**, 435 (1994).
40. P.T. Beurskens, G. Admiraal, G. Beurskens, W.P. Bosman, R. de Gelder, R. Israel, and J.M. M. Smits. The DIRDIFF-99 program system: technical report of the crystallography labora-

tory. University of Nijmegem, Nijmegem, The Netherlands, 1999.
41. D.T. Cromer and D.J. Weber. *In* International tables of X-ray crystallography. Vol. IV. The Kynoch Press, Birmingham, UK. 1974. Table 2.2. A.
42. J.A. Ibers and W.C. Hamilton. Acta Crystallogr. **17**, 781 (1964).
43. D.C. Creagh and W.J. McAuley. *In* International tables of crystallography. Vol. C. Kluwer Academic Publishers, Boston, 1992. Table 4.2.6.8. pp. 219–222.
44. D.C. Creagh and J.H. Hubbell. *In* International tables of crystallography. Vol. C. Kluwer Academic Publishers, Boston, 1992. Table 4.2.4.3. pp. 200–206.
45. Rigaku and Rigaku/MSC. CrystalStructure 3.6.0 [computer program]. Rigaku and Rigaku/MSC, The Woodlands, Tex. 2000–2004.
46. D.J. Watkin, C.K. Prout, J.R. Carruthers, and P.W. Betteridge. Crystals issue 10 [computer program]. Chemical Crystallography Laboratory, Oxford, UK. 1996.
47. G.M. Sheldrick. SHELXL97 [computer program]. University of Göttingen, Göttingen, Germany. 1997.
48. A. Jha and J. Beal. Tetrahedron Lett. **45**, 8999 (2004).
49. A. Jha and J.R. Dimmock. Can. J. Chem. **81**, 293 (2003).
50. A. Jha, M.P. Padmanilayam, and J.R. Dimmock. Synthesis, 463 (2002).
51. J.R. Feldman and E.C. Wagner. J. Org. Chem. **7**, 31 (1942).
52. R.J. Abraham, N. Aboitiz, J. Merrett, B. Sherborne, and I. Whitecombe. J. Chem. Soc. Perkin Trans. 2, 2382 (2000).
53. R.J. Abraham and D.S. Ribeiro. J. Chem. Soc. Perkin Trans. 2, 302 (2001).
54. A.M. Belostoskii, H.E. Gottlieb, P. Aped, and A. Hassner. Chem. Eur. J. **5**, 449 (1999).
55. Y. Fu, Z. Zhou, P. Hazendonk, A.D. Bain, F.R. Fronczek, J. Escobedo, M.L. McLaughlin, and R.P. Hammer. J. Mol. Struct. **687**, 65 (2004).
56. A.M. Belostoskii, H.E. Gottlieb, and P. Aped. Chem. Eur. J. **8**, 3016 (2002).
57. M. Oki. Applications of dynamic NMR spectroscopy to organic chemistry. VCH Publishers, Deerfields Beach, Fla, 1985.