A new and convenient synthetic method for 1,2,3,5,6,11b-hexahydroimidazo[1,2-*d*][1,4]benzoxazepine and its derivatives[$]

Shehadeh A. Mizyed,[a] Muhammad Ashram[b]* and Firas F. Awwadi[c]

[a]*Chemistry Department,Yarmouk University, Irbid, Jordan*
[b]*Chemistry Department, Mutah University, Al-Karak, Jordan*
[c]*Department of Chemistry, Tafila Technical University, Tafila 66110, Jordan*
E-mail: ashram_1961@yahoo.com

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Abstract

A convenient approach is described for the general synthesis of novel tricyclic scaffolds incorporating an imidazolidine ring and medium sized rings, such as a benzoxazepine ring, through condensation of either aliphatic or aromatic 1,2-diamines with a 2-(2-bromoethoxy)benzaldehyde. The operational simplicity and the availability of the substrate make the process cost effective and practical.

Keywords: 2,3,4,5-Tetrahydro-1,4-benzoxazepines, 1,2,3,5,6,11b-Hexahydroimidazo[1,2-*d*] [1,4]benzoxazepines

Introduction

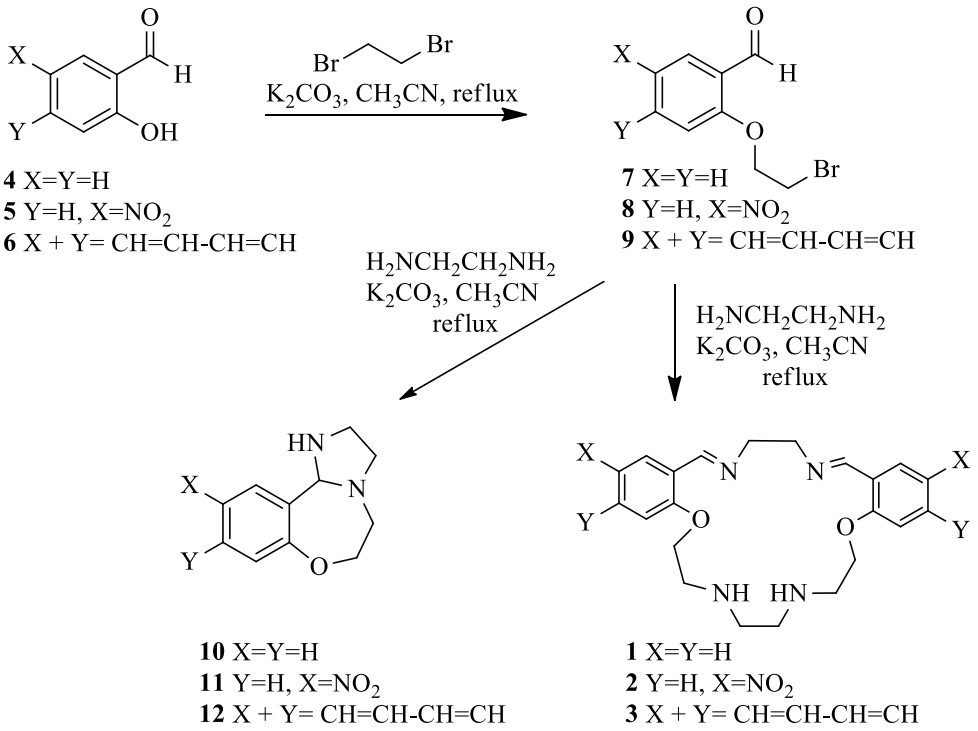
Compounds containing a fused seven-membered benzoxazepine ring have attracted considerable attention in the past few years owing to its wide range of biological activities and pharmacological properties.[1-5] Most syntheses of 2,3,4,5-tetrahydro-1,4-benzoxazepines involve the reduction of the carbonyl group(s) as for 5-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine, 3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine, and 3,5-dioxo-2,3,4,5-tetrahydro-1,4-benzoxazepine, or the reduction of a double bond as for 2,3-dihydro-1,4-benzoxazepine.[1,6-8]

Alternatively, 2,3,4,5-tetrahydro-1,4-benzoxazepines are accessible by one of the following known benzoxazepine syntheses: (i) condensation of 2-aryloxyethylamines with 2-formylbenzoic acid to form aminonaphthalides followed by cyclization: (ii) rearrangement of methyl 2-(8-methoxy-2,3-dihydro-1,4-benzoxazepin-5-yl)benzoate using Bischler-Napieralski conditions; (iii) scandium or copper triflate-catalyzed acylaminoalkylation of α-methoxy-isoindolones with the formation of 1,4-benzoxazepines.[9-11]

In 1981, Levan *et al*,[12,13] reported the isolation and characterization of unsubstituted 1,2,3,5,6,11b-hexahydroimidazo[1,2-*d*][1,4]benzoxazepine in a tedious way without specifying the product yield. The compound was isolated as by-product after demetalation of an isolated intermediate complex from the transformation of bis-[*N*-[2-(1-aziridinyl)ethyl]salicyl aldimino]nickel(II) to disalicylidene ethylenediamino nickel (II). This is the first example of this tricyclic system. In this manuscript we report the synthesis of 1,2,3,5,6,11b-hexahydro imidazo[1,2-*d*][1,4]benzoxazepine and its derivatives in high yield and in a straightforward way.

Results and Discussion

As part of our ongoing research into developing new and more selective macrocyclic crown ethers, we undertook a program to synthesize crown ether Schiff-bases **1**-**3** (Scheme 1) in order to evaluate their potential as new hosts and to study their binding properties with metal cations and fullerenes.[14-16] For ligands **2**, additional benefits can be obtained from the presence of the nitro group as a substituent on the benzene rings.



Scheme 1. Synthesis of compounds **10-12.**

Reduction of the nitro group would provide a potential attachment site for a chromogenic group or modification for coupling with a monoclonal antibody.[17,18] The synthetic approach planned toward preparation of macrocycles **1-3** is shown in Scheme 1. Alkylation of

salicylaldehyde, 5-nitrosalicylaldehyde or 3-hydroxy-2-naphthaldehyde with an excess of 1,2-dibromoethane (10 equiv.) in the presence of one equivalent of anhydrous K_2CO_3 in refluxing CH_3CN afforded, after column chromatographic purification, products **7-9** as yellow solids in 70, 72 and 81% yield, respectively. However, condensation of aldehydes **7-9** with ethylenediamine in presence of anhydrous K_2CO_3 and anhydrous CH_3CN at reflux temperature for 24 h did not afford the expected products **1-3**. The ^{1}H NMR spectra of the crude products obtained from the reactions show no indication for the presence of the two singlet signals at $\delta \approx 4.00$ and 8.85 ppm expected for the products. The structure of the products could not be readily derived from the NMR spectra alone. However, when single crystals of the product obtained from the reaction of **7** with ethylenediamine became available, an X-ray diffraction analysis revealed the structure of heterotricyclic product **10** (Figure 1).

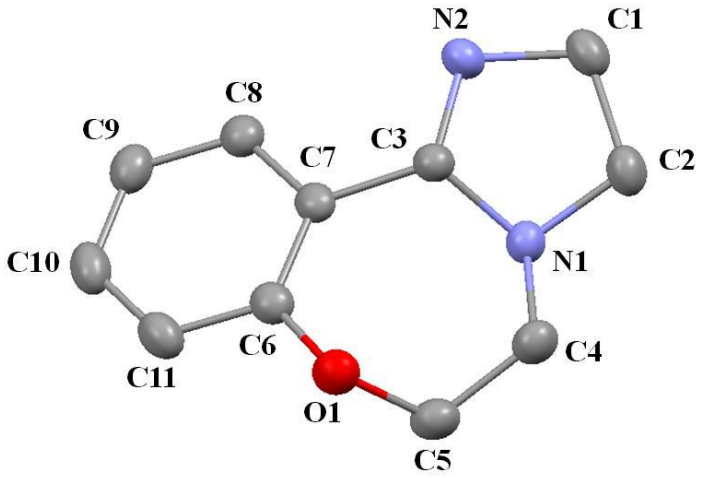


Figure 1. X-Ray crystal structure of oxazepine **10**. Thermal ellipsoids are shown at 50% probability level. Hydrogen atoms are omitted for clarity.

In a similar manner, treatment of aldehydes **8** and **9** with ethylenediamine afforded the expected tricyclic products **11** and **12**, respectively. ^{1}H NMR spectra of compounds **10-12** (Figure 2 as an example) have identical patterns in the chemical shift range $\delta \approx 2.6$-4.6 ppm. The secondary amine proton shows up as a slightly broadened signal at $\delta = 2.35$ (H/D exchange with D_2O) the four magnetically non-equivalent aliphatic protons of the benzoxazepine ring display complex multiplets at $\delta \approx 2.6$, 3.0, 3.9 and 4.3 ppm the four methylene protons in the imidazolidine ring are observed as a complex multiplet at $\delta \approx 3.3$ the C*H*NN proton shows up as sharp singlet at $\delta = 4.6$ ppm. The structures of **10-12** are also supported by the ^{13}C NMR spectra. All of them show five signals in the ranges $\delta = 44.1$-44.2, 55.99-56.1, 56.15-56.50, 72.3-73.1 and 78.85-78.9 ppm.

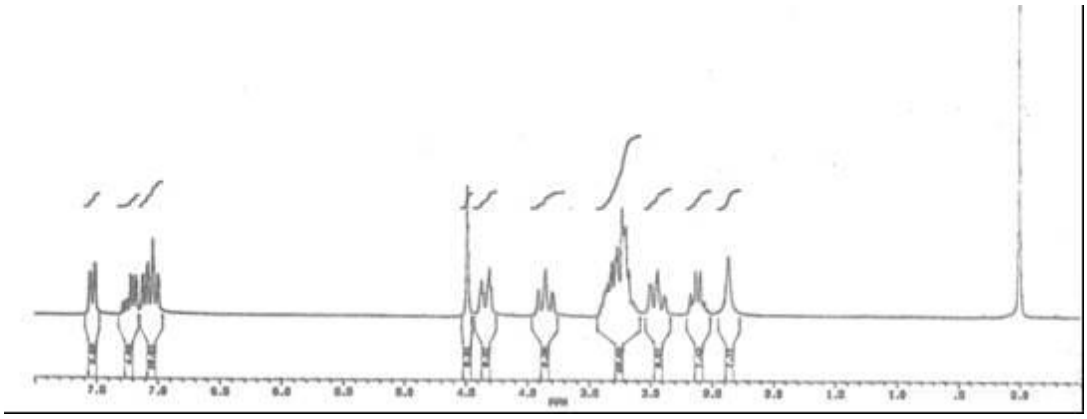
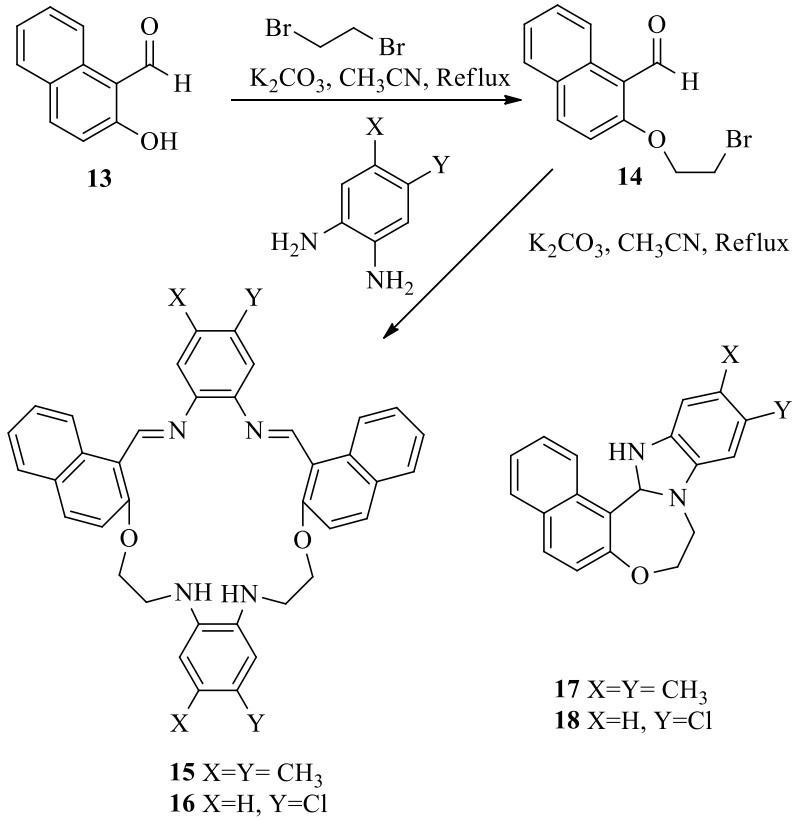


Figure 2. ^{1}H NMR spectrum of compound **10** in $CDCl_3$.

The,[1] H or ^{13}C NMR spectra in the given ranges are very similar to the spectral patterns of the benzoxazepine derivative reported by Levan *et al.*[13]

On the other hand, when 1,2-diaminobenzene derivatives were condensed with 2-(2-bromoethoxy)-1-naphthaldehyde **14** (Scheme 2) in a similar fashion as above, oxazepines **17** and **18** in addition to the Schiff base crown ethers **15** or **16** were formed.



Scheme 2. Synthesis of compounds **17** and **18**.

It seems that condensation of aromatic diamines with 2-bromoethoxyaldehyde produces a mixture of oxazepines and Schiff base crown ether, while condensation of aliphatic diamines with the 2-bromoethoxybenzaldehyde produces only oxazepines. Compounds **17** and **18** were fully characterized by ^{1}H NMR, ^{13}C NMR, mass spectra, elemental analysis and X-ray crystal structure analysis for compound **17** as shown in Figure 3.

In the ^{1}H NMR spectra, both **17** and **18** show better resolved signals in the range δ = 3.5-5.3 ppm compared to compounds **10**, **11** and **12**. This is due to the absence of the four methylene protons of the imidazolidine ring. The ^{13}C NMR spectra of compounds **17** and **18** show only three signals at $\delta \approx$ 40, 74 and 76 ppm corresponding to the two carbon atoms of the benzoxazepine ring and the aminal carbon atom.

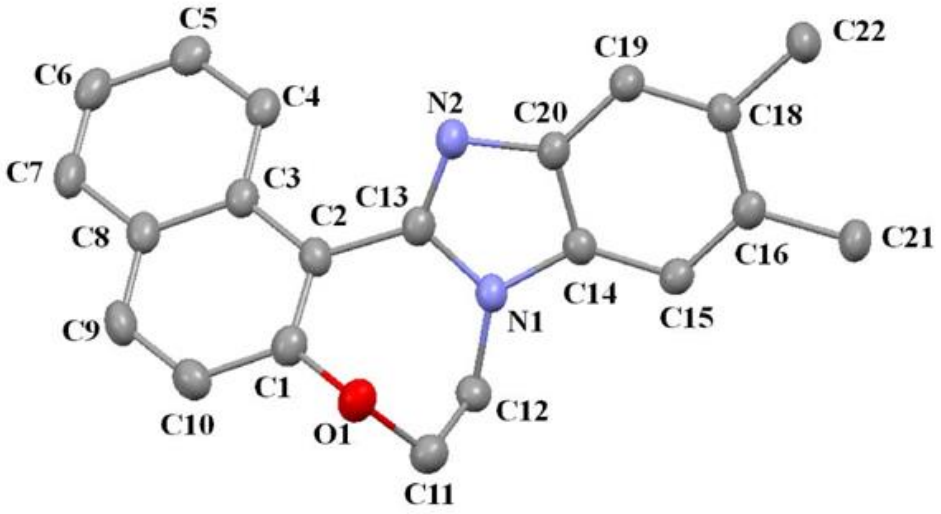


Figure 3. X-Ray crystal structure of oxazepine **17**. Thermal ellipsoids are shown at 50% probability level. Hydrogen atoms are omitted for clarity

In conclusion, we report a general, direct, high yielding and convenient approach to 1,2,3,5,6,11b-hexahydroimidazo[1,2-*d*][1,4]benzoxazepine and its derivatives. We are unaware of any other reports of similar one-pot cyclization from **7-9** to give 1,2,3,5,6,11b-hexahydroimidazo[1,2-*d*][1,4]benzoxazepine or its derivatives in high yield and in a straightforward way. To generalize this reaction to be a new and useful method for the preparation of oxazepines, a follow-up study on other aldehydes and diamines will be reported in due course.

Experimental Section

General. NMR spectra were recorded on a Bruker instrument at 200 (or 400) MHz for ^{1}H NMR and 50.33 (or 100) MHz for ^{13}C NMR. Unless otherwise noted, samples were dissolved in $CDCl_3$

using TMS as internal standard. Mass spectra were determined with a VG7070E spectrometer with uncertainty in *m/e* of ±1. Elemental analyses (C, H, N) were performed on Euro elemental analysis 3000 from Euro Vector S.P.A. SN 8910.

Chromatographic separations were performed on silica gel columns (60-120 mesh, CDH). Unless otherwise noted, all reactions were carried out under dry nitrogen. 2-(2-Bromoethoxy)benzaldehyde **7** was prepared according to the literature.[19] 5-nitro-2-(2-bromoethoxy)benzaldehyde **8** and 3-(2-bromoethoxy)-2-naphthaldehyde **9** were prepared as **7** to give after column chromatographic purification using ethyl acetate/hexane (1:4) the pure samples.

5-Nitro-2-(2-bromoethoxy)benzaldehyde (8). Pale-yellow solid, yield 40%, mp 75-76 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 3.80 (t, *J* = 6 Hz, 2H), 4.59 (t, *J* = 6 Hz, 2H), 7.11 (d, t, *J* = 6 Hz, 1H), 8.46 (d, *J* = 7 Hz, 1H), 8.75 (s, 1H), 10.52 (s, 1H). ^{13}C NMR (50.33 MHz, $CDCl_3$): δ_C 28.0, 69.1, 112.4, 124.5, 130.1, 164.0, 187.4. MS (EI, 70 eV): *m/z* (%) = 275.4 (100) [M, ^{81}Br]$^+$, 273.4 (100) [M,^{79} Br]$^+$.

3-(2-Bromoethoxy)-2-naphthaldehyde (9). Yellow solid, yield 78%, mp 81-82 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 3.73 (t, *J* = 6 Hz, 2H), 4.45 (t, *J* = 6 Hz, 2H), 7.11 (s, 1H), 7.37 (t, *J* = 7 Hz, 1H), 7.52 (t, *J* = 6 Hz, 1H), 7.69 (d, *J* = 9 Hz, 1H), 7.85 (d, *J* = 9 Hz, 1H), 8.34 (s, 1H), 10.6 (s, 1H). ^{13}C NMR (50.33 MHz, $CDCl_3$): δ_C 28.9, 68.1, 107.4, 125.1, 125.6, 126.7, 128.1, 129.4, 130.0, 130.7, 137.3, 156.1, 190.0. MS (EI, 70 eV): *m/z* (%) = 280.4 (100) [M, ^{81}Br]$^+$, 278.4 (100) [M,^{79} Br]$^+$.

2-(2-Bromoethoxy)-1-naphthaldehyde (14). Brown solid, yield 48%, mp 80-82 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 3.74 (t, *J* = 6.0 Hz, 2H), 4.52 (t, *J* = 6.0 Hz, 2H), 7.21 (t, *J* = 6.0 Hz, 1H), 7.39 (t, *J* = 7.0 Hz, 1H), 7.61 (t, *J* = 7.1 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 9.32 (d, *J* = 8.9 Hz, 1H), 10.9 (s, 1H). ^{13}C NMR (50.33 MHz, $CDCl_3$,): δ_C 28.9, 69.3, 113.6, 117.6, 125.2, 125.3, 128.4, 129.0, 130.1, 131.6, 137.7, 162.5, 192.1. MS (EI, 70 eV): *m/z* (%) = 280.4 (100) [M, ^{81}Br]$^+$, 278.4 (100) [M, ^{79}Br]$^+$.

General procedure for synthesis of benzoxazepines (10-12) and (17-18)

In a 250 mL three-necked flask equipped with a magnetic stirrer bar, a reflux condenser and a gas line to maintain a nitrogen atmosphere, K_2CO_3 (0.11 g, 3.6 mmol) was suspended in anhydrous CH_3CN (100 mL). To this well-stirred solution at reflux temperature was added simultaneously dropwise over a period of 12 h, a solution of aldehyde (1.8 mmol) in dry CH_3CN (50 mL) and a solution of diamine (0.11 g, 1.8 mmol) in dry CH_3CN (50 mL). The reaction mixture was further refluxed with stirring overnight. The reaction mixture was filtered, and the solvent was evaporated. The crude product was purified either by washing with ethyl acetate or by chromatographic separation.

1,2,3,5,6,11b-Hexahydroimidazo[1,2-*d*][1,4]benzoxazepine (10). The crude product was purified by washing with ethylacetate to give a pale-yellow solid, yield 72%, mp 78.5-80.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.36 (s, 1H), 2.63 (br, 1H), 2.99 (br, 1H), 3.28 (br, 4H), 3.89

(br, 1H), 4.32 (br, 1H), 4.51 (s, 1H), 6.98-7.22 (m, 3H), 7.51 (d, *J* = 5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 44.1, 56.0, 56.1, 72.1, 78.7, 121.0, 123.9, 126.0, 128.8, 133.7, 158.3. MS (EI, 70 eV): *m/z* (%) = 189 (100) $[M-H]^+$; Anal. Calcd for $C_{11}H_{14}N_2O$ (190.24): C, 69.45; H, 7.42; N, 14.72%. Found: C, 68.52; H, 7.39; N, 14.29%.

10-Nitro-1,2,3,5,6,11b-hexahydroimidazo[1,2-*d*][1,4]benzoxazepine (11). The crude product was purified by washing with ethyl acetate to give a pale-red solid, yield 70%, mp 138-140 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.38 (br, 2H), 2.64-2.75 (m, 2H), 2.95-3.08 (m, 2H), 3.20-3.38 (m, 8H), 3.90-4.02 (m, 2H), 4.40-4.50 (m, 2H), 4.60 (s, 2H), 7.10 (d, *J* = 8 Hz, 2H), 8.08 (dd, *J* = 2 Hz, 8 Hz, 2H), 8.62 (d, *J* = 2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 44.6, 55.1, 56.5, 72.9, 122.0, 123.4, 124.7, 136.0, 143.9, 164.0. MS (EI, 70 eV): *m/z* (%) = 234 (100) $[M-H]^+$; Anal. Calcd for $C_{11}H_{13}N_3O_3$ (235.24): C, 56.16; H, 5.57; N, 17.86%. Found: C, 56.10; H, 5.33; N, 17.63%.

1,2,3,5,6,13b-Hexahydroimidazo[1,2-*d*]naphtho[2,3-*f*][1,4]oxazepine (12). The crude product was purified by washing with ethyl acetate to give pale-yellow solid, yield 81%, mp 71-72 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.43 (br, 2H), 2.64-2.69 (m, 2H), 2.96-3.04 (m, 2H), 3.20-3.37 (m, 8H), 3.84-3.92 (m, 2H), 4.39-4.44 (m, 2H), 4.64 (s, 2H), 7.34-7.41 (m, 4H), 7.43 (s, 2H), 7.70 (d, *J* = 9 Hz, 2H), 7.80 (d, *J* = 9 Hz, 2H), 8.02 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 44.3, 56.0, 56.5, 73.1, 78.9, 117.5, 124.9, 125.6, 126.3, 126.8, 128.1, 130.5, 133.8, 134.5, 156.7. MS (EI, 70 eV): *m/z* (100%) = 239.5 (100) $[M]^+$; Anal. Calcd for $C_{15}H_{16}N_2O$ (240.30): C, 74.97; H, 6.71; N, 11.66%. Found: C, 74.04; H, 6.63; N, 11.74%.

12,13-Dimethyl-8,9,15,15a-tetrahydronaphtho[1′,2′:6,7][1,4]oxazepino[4,5-*a*]benzimidazole (17). The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (8:2) to give **15** (which is still under investigation) and **17** as a pale-yellow solid, yield 40%, mp 168-170 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.38 (6 H, s, CH_3), 3.55 (b, 1H), 3.74 (b, 1H), 4.24 (b, 1H), 4.28 (b, 1H), 4.99 (s, 1H), 5.26 (s, 1H), 7.25 (d, *J* = 9.5 Hz, 1H), 7.52 (t, *J* = 8.7 Hz, 1H), 7.59 (s, 1H), 7.63 (t, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 9.5 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 1H,). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 20.4, 20.7, 41.2, 74.4, 76.7, 108.8, 118.9, 120.3, 121.9, 125.5, 126.3, 127.7, 127.9, 131.3, 132.1, 132.3, 132.6, 142.2, 149.4, 152.9. MS (EI, 70 eV): *m/z* (%) = 315 (100) $[M-H]^+$; Anal. Calcd for $C_{21}H_{20}N_2O$ (316.40): C, 79.72; H, 6.37; N 8.85%. Found: C, 79.49; H, 6.23; N 8.76%.

12-Chloro-8,9,15,15a-tetrahydronaphtho[1′,2′:6,7][1,4]oxazepino[4,5-*a*]benzimidazole (18). The crude product was purified by preparative layer chromatography on silica gel using hexane:ethyl acetate (9:1) to give **16** (which is still under investigation) and **18** as a pale-yellow solid, yield 38%, mp 167-169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.50 (b, 1H), 3.77 (b, 1H), 4.16 (b, 1H), 4.29 (b, 1H), 4.93 (s, 1H), 5.29 (s, 1H), 7.30 (s, 1H), 7.43 (m, 3H), 7.52 (t, *J* = 8.3 Hz, 1H), 7.61 (t, *J* =8.3 Hz, 1H), 8.02 (m, 2H), 8.9 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 41.4, 74.0, 76.6, 108.7, 118.3, 121.1, 121.8, 123.0, 125.6, 126.0, 127.8, 128.7, 131.3, 132.0, 132.7, 134.7, 142.2, 153.2. MS (EI, 70 eV): *m/z* (%) = 321(24) $[M-H]^+$; Anal. Calcd. for $C_{19}H_{15}ClN_2O$ (322.79): C, 70.70; H, 4.68; Cl, 10.98; N, 8.68%. Found: C, 70.58; H, 4.63; Cl, 10.88; N, 8.72%.

Single-crystal X-ray data collection and structure determination

The crystal structure of **10** was determined at 138 K. The data collection was carried out on a Rigaku Saturn diffractometer. Frame data were acquired and processed using Crystal Clear software to give an *hkl* file corrected for Lp/decay.[20] For **17**, the diffraction data were collected at 173 K on a Bruker diffractometer equipped with SMART CCD detector. Frame data were acquired with the SMART software,[21] and the frames were processed using SAINT software to give an *hkl* file corrected for Lp/decay.[22] Absorption corrections were performed using SADABS.[23] For both structures, the SHELXTL package was used for the structure solution and refinement.[24] The structures were refined by least-squares method on F^2. All non-hydrogen atoms were refined anistropically. Crystallographic data (cif) have been deposited with the Cambridge Structural Data Centre (CCDC) with reference numbers 799025-799026. See http://www.ccdc.cam.ac.uk/conts/retrieving.html for crystallographic data in cif or other electronic format. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 44-(0)1223–336033 or E-mail[25]]. Data collection parameters and refinement results are given in Table 1.

Table 1. Summary of data collection and refinement parameters for **10** and **17**

Crystal	**10**	**17**
Formula	$C_{11}H_{14}N_2O$	$C_{42}H_{38}N_4O_3$
M_r	190.24	646.76
Cryst. size, mm	0.51 × 0.46 × 0.35	0.50 x 0.25 x 0.25
Crystal system	monoclinic	triclinic
Space group	$P2_1/c$	$P\bar{1}$
a, Å	7.4757 (17)	8.7556 (7)
b, Å	6.3370 (15)	10.3610 (8)
c, Å	20.147 (5)	10.3890 (8)
α, deg	90.00	109.323 (1)
β, deg	94.704	94.179 (1)
γ, deg	90.00	110.396 (1)
V, Å^3	951.2 (4)	814.52 (11)
Z	4	1
D_{calcd}, mg/ m^{-3}	1.33	1.32
μ(MoK_α), mm^{-1}	0.1	0.1
F(000), e	408	342
hkl range	$-9 \le h \le +9 -7 \le k \le +7 -25 \le l \le +25$	$-11 \le h \le +10 -13 \le k \le +13 -13 \le l \le +11$
$((\sin\theta)/\lambda)_{max}$, Å^{-1}	0.627	0.6414
Refl. measured	7980	5844
Refl. unique	1960	3506
R_{int}	0.0206	0.0179

Table 1. Continued

Crystal	10	17
Param. refined	129	228
$R(F)$, $wR(F^2)^a$ (all reflexions)	0.0449/0.1136	0.0676/0.1244
GoF $(F^2)^a$	1.069	1.030
$\Delta\rho_{fin}$ (max/min), e Å^{-3}	0.195/ – 0.205	0.291/ – 0.184

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References

[$]Preliminary results of this work were published previously in Toxicological & Environmental Chemistry, Volume 91, Issue 6, 2009, 1095 – 1104. In this earlier publication, structures for compounds **1**, **2** and **3** were assigned depending on ^{1}H and ^{13}C NMR data. Re-characterization of the product which was formed from the reaction of ethylenediamine and salicyaldehyde using x-ray analysis, showed that the product which was actually formed is not crown ether Schiff base **1** but benzoxazepine **10**. Consequently, we concluded that compounds **2** and **3** may not be crown ether Schiff bases but really benzoxazepines **11** and **12** form their ^{1}H and ^{13}C NMR spectra similarity with ^{1}H and ^{13}C NMR spectra of compound **10**.

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