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RING INTERCONVERSION BETWEEN A 7-MEMBERED RING (2,3-DIHYDRO-1,4-BENZODIAZEPINE) AND A 14-MEMBERED RING (2,3,9,10-DIBENZO-1,5,8,12-TETRA-AZACYCLOTETRADECA-4,11-DIENE)

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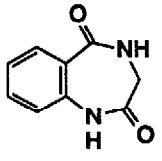
Abstract: Structure elucidation of the macrocyclic ligand **6** and interconversion to the benzodiazepine **4** is reported. Also, a versatile synthesis of the macrocyclic ligands **6** and **13** is described.

In connection with structure determinations of some benzo-1,4-diazepine derivatives obtained[1] by reaction of the anion (**3**)[2] with α-haloacyl halides, we became interested in the benzo-1,4-diazepinedione **1**[3], as well as certain derivatives of **1**. The benzo-1,4-diazepine **4** seemed then to be an interesting candidate for structure correlations as Uskokovic[4] had already described the reductive ($LiAlH_4$ in THF) conversion (**1** → **4**). More forcing reduction[5] with $LiAlH_4$ yielded **5**. The reduction of **4** has now been repeated and the reaction mixture has carefully been separated and the products studied in detail.



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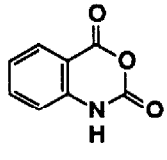

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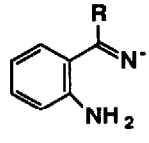

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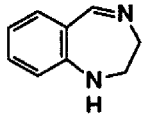

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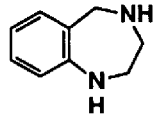

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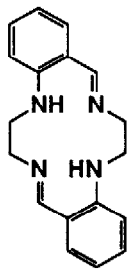
Evidence, such as the low solubility and high mp, was obtained indicating that the imine ($C_9H_{10}N$) with the previously assigned structure **4** has in fact the macrocyclic structure **6.** These assumptions were corroborated by conversion ($NaBH_3CN$ in HOAc) of **6** into **7**.[6] Furthermore

compound **6** gave a nickel complex (dark red) similar in properties to the much studied complex[7] obtained from the isomeric ligand **8.** Heating of the 14-membered ring **6** with aqueous acetic acid gave, *via* a hydrolytic ring-opening and recyclization, the true 7-membered ring **4**, which is a kinetic product as indicated by the fact that it is slowly converted into the 14-membered ring when dissolved in DMSO. A similar phenomenon has previously been described[8] for the system **9** and **10**. Interestingly alkylation of **10** gave[9] a quaternized derivative of **9**.



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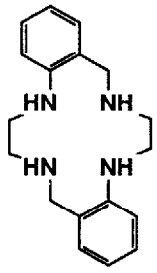

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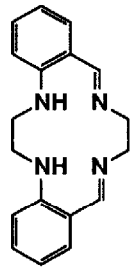

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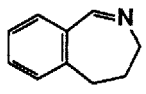

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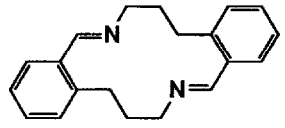
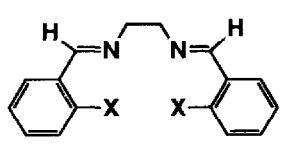


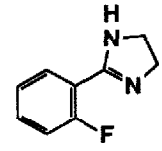
10

In 1974 Coffen *et al.* briefly mentioned[10] the preparation of **4** from *o*-fluorobenzaldehyde and ethylenediamine. The mp was given as 134-136°C but no reason for the discrepancy with that given (244-246 °C) by Uskokovic was discussed. The reaction between *o*-fluorobenzaldehyde and ethylenediamine under various conditions has now been studied and the products **11a** and **12** have been isolated. Heating of **11a** with ethylenediamine at reflux temperature yielded **6**, whereas the isomer **8** was not formed. This fact shows that at least one of the imine bonds is broken (most likely *via* addition of another molecule of ethylenediamine) during this operation (*cf* ref. 11).

A similar experiment with the known[12] compound **11b** further demonstrated the inertness of this compound towards refluxing ethylenediamine. However addition of the established catalyst (Cu-powder) for this type of nucleophilic aromatic substitution resulted in a quick and fast access[13,14] to the interesting macrocyclic ligand **6**. 1,3–Diaminopropane similarly gave the 16-membered macrocycle **13** indicating that a convenient new route to macrocycles is under way.



11 a X=F
b X=Cl



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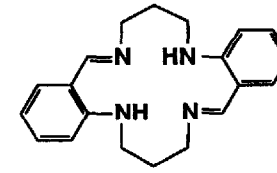

13

SPECTRAL DATA

4 : mp 133-35°C[15] IR(KBr) : 3230, 2944, 1626, 1608, 1531, 1161, and 748 cm^{-1}. ^{13}CNMR(DMSO-d6):161.5(d), 149.1(s), 135.3(d), 130.9(d), 117.6(s), 116.3(d), 115.4(d), 60.1(t), and 45.7(t) ppm. ^{1}HNMR(DMSO-d6): 8.1(1H, s), 7.3(1H, m), 7.1(1H, m), 6.9(1H, br s),6.7(1H, m), 6.6(1H, m), 3.9(2H, m), and 3.1(2H, m) ppm.

6 : mp 241-43°C.IR(KBr) : 3200, 2834, 1630, 1579, 1524, and 752 cm^{-1}. ^{13}CNMR(DMSO-d6) 164.4(d), 149.3(s), 133.9(d), 131.5(d), 117.2(s), 114.5(d), 110.5(d), 57.8(t), and 43.6(t) ppm.^{1}HNMR($CDCl_3$): 10.2(1H, s), 8.4(1H, s), 7.2(2H, m), 6.7(1H, d), 6.6(1H, m), 3.9(2H, m), and 3.4(2H, m) ppm. MS (m/z) : 292(M^+), 159, 146, 131, and 118(100).

7 : mp 141-142°C ^{13}C-NMR($CDCl_3$): 148.9(s), 129.4(d), 128.6(d), 123.6(s), 116.1(d), 110.0(d), 53.8(t), 47.9(t), and 43.0(t) ppm. ^{1}HNMR($CDCl_3$): 7.2(1H, m), 7.0(1H, m), 6.9(1H, br s), 6.7(1H, m), 6.5(1H, m), 3.8(2H,s), 3.0(2H, m), and 2.9(2H, m) ppm.

13 : mp 236-238°C. IR(KBr) : 3250, 2940, 1630, 1581,1523, and 744 cm^{-1}. ^{13}CNMR(DMSO-d6) : 164.4(d), 148.8(s), 133.7(d), 131.2(d), 116.6(s), 113.9(d), 109.7(d), 57.9(t), 39.7(t), and 30.1(t) ppm. ^{1}HNMR(DMSO-d6): 9.1(1H, t), 8.3(1H, s), 7.2(2H,m), 6.65(1H, d), 6.5(1H, m), 3.5(2H, t), 3.2(2H, dt), and 1.8(2H, p) ppm. MS(m/z) : 320(M^+), 188, 173, 161, 160, 146, 132, and 118(100).

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1. Bergman, J.; Brynolf, A.; Elman, B. *Heterocycles* **1983**, *20*, 2141.
2. This anion is readily obtained from anthranilonitrile and RMgX or RLi.
3. a) Readily available[3b] from isatoic anhydride (**2**) and esters of glycine.

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6. a) The isomeric reduction product obtained from **8** is well known[6b].
   b) Henrick, K. ; Lindoy, L. F.; McPartlin, M.; Tasker, P. A.; Wood, M. P. *J.Am.Chem.Soc.* **1984**, *106*, 1641.
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11. Butler, R. N.; Fitzgerald, K. J. *J. Chem. Soc. Perkin Trans.I* **1989**, 155.
12. Black, D. St. C.; Lane, M. J. *Aust. J. Chem.* **1970**, *23*, 2039.
13. a) Ried has recently described[13b] the reaction between *o*-chlorobenzaldehyde and ethylenediamine. However the structure of the product was incorrectly given as the 7-membered ring **4**. Hence it also appears likely that many of the secondary products (obtained by acylation, alkylation etc) should be reinvestigated.(*cf* ref. 9)
    b) Betakis, E.; Piesch, S.; Ried, W. *Synthesis* **1988**, 820.
14. a) The macrocyclic ligand **6** is already commercially available [14b], albeit incorrectly advertised as **4**.
    b) Maybridge Chemical Co, Extra Supplement to Intermediates Catalogue 2 (1988).
15. The melt solidified, when kept at ~140°C, and melted again at 241-243°C.

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