Preparation of Some Nitrogen-containing Polyether ' Crown ' Compounds

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New polyether crown ligands containing four and five donor sites per molecule and with one or two of the ether linkages replaced by secondary or tertiary amino-groups have been synthesised. The synthesis did not work for potential crowns containing three donor atoms (nine-membered rings) but gave morpholines exclusively. Characterisation of the structures obtained by a variety of spectroscopic methods is discussed.

CONSIDERABLE interest has been displayed in cyclic polyether ligands, e.g. crowns [1] and cryptates,[2] which are capable of highly specific interactions with alkali and alkaline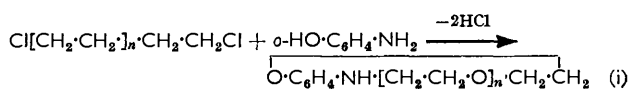 earth metals. Synthesis of some chiral nitrogen-containing crowns has recently been reported.[3] The new crowns reported here have a different location for nitrogen atoms within the ring system. In general

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[1] C. J. Pedersen, J. Amer. Chem. Soc., 1967, **89**, 2495, 7017.

[2] J. M. Lehn and J. Cheney, Chem. Comm. 1972, 487; B. Dietrich, J. M. Lehn, and J. P. Sauvage, Tetrahedron Letters, 1969, 2885, 2889.

[3] F. Wudl and F. Gaeta, Chem. Comm., 1972, 107.

the syntheses involved condensation of a dichloro-polyether [equation (i)] with an o-aminophenol or an

$$Cl[CH_2 \cdot CH_2 \cdot]_n \cdot CH_2 \cdot CH_2Cl + o\text{-}HO \cdot C_6H_4 \cdot NH_2 \xrightarrow{-2HCl}$$

$$\overline{O \cdot C_6H_4 \cdot NH \cdot [CH_2 \cdot CH_2 \cdot O]_n \cdot CH_2 \cdot CH_2} \quad \text{(i)}$$

o-phenylenediamine. The simplest ether ($n = 1$) gave the alternative morpholine condensation product (1),

EXPERIMENTAL

General Method.—A solution of the amine (*ca.* 10·7 g, 0·1 mol) was refluxed for 48 h under nitrogen with 1 mol. equiv. of the dichloro-ether [equation (i) or (ii)]. For experiments in water the products were extracted with chloroform; the extracts gave highly crystalline morpholines, or dark viscous oils in the case of higher polyethers. Products from reactions in dimethylformamide were

TABLE 1

Compound *	M.p. (°C)	Accurate mass or m/e value Calc.	Accurate mass or m/e value Obs.	Calc. (%) C	Calc. (%) H	Calc. (%) N	Found (%) C	Found (%) H	Found (%) N
(1a)	130 [a,b]	m/e 179		67·0	7·8		66·2	7·3	
(1b)	118	m/e 213		56·2	5·7	6·6	56·9	5·7	6·6
(1c)	135	m/e 224		53·6	5·4	12·5	53·6	5·3	12·6
(1d)	98—99 [c]	m/e 178		67·4	7·9		67·7	8·4	
(1e)	138 [d]	m/e 223							
(1f)	134	m/e 228		73·7	7·1	12·2	72·6	6·9	13·2
(2)	80	223·1208	223·1207	64·5	7·7	6·3	64·0	7·5	6·2
(3)	101·5	m/e 267		63·0	7·9	5·2	63·45	8·0	5·3
(4)	90	267·1470	267·1465	63·0	7·9	5·2	62·7	7·9	5·1
(5)	92—94	222·1368	222·1364	64·9	8·1	12·6	65·2	8·0	12·8
(6)	110	266·1630	266·1629	63·1	8·3	10·5	63·9	8·2	10·7
(7)	108 [e]	446·2417	446·2417	64·5	7·7	6·3	64·9	7·7	6·5

[a] Lit., 134°; 131° (L. Birkofer and G. Daum, *Chem. Ber.*, 1962, **95**, 183; A. W. Campbell and M. C. Reed, *Ind. Eng. Chem.*, 1936, **28**, 656). [b] Base hydrobromide, m.p. 205° (Found: Br, 30·6%). Calc. Br, 30·7%). [c] Lit., 98—98·5°; 96·5° [K. H. Saunders, *J. Chem. Soc.*, 1955, 3275; V. Bieska and J. Deguits, *Zhur. org. Khim.*, 1965, **1**, 1842 (*Chem. Abs.*, 1966, **64**, 3533g); C. B. Kremer, M. Meltsner, and L. Greenstein, *J. Amer. Chem. Soc.*, 1939, **61**, 2552]. A second compound, m/e 248 ($C_{14}H_{20}N_2O_2$), m.p. 132°, was isolated from the reaction, possibly the o-dimorpholinobenzene. [d] This is probably the 4-nitro-isomer, since the known 5-nitro-compound has m.p. 155°. [e] This compound, a dimer of (2), was obtained in crystalline form from one synthesis only and its structure was not discovered.

* The products are named as follows: (1a) 2-morpholinophenol, (1b) 4-chloro-2-morpholinophenol, (1c) 2-morpholino-4-nitrophenol, (1d) 2-morpholinoaniline, (1e) 2-morpholino-4-nitroaniline, (1f) 3-morpholino-2-naphthylamine, (2) 2,3,5,6,8,9-hexahydro-10H-1,4,7,10-benzotrioxa-azacyclododecin, (3) 2,3,5,6,8,9,11,12-octahydro-13H-1,4,7,10,13-benzotetraoxa-azacyclopentadecin, (4) 2-(1,4,7-trioxa-10-azacyclododecan-10-yl)phenol, (5) 1,2,3,5,6,8,9,10-octahydro-4,7,1,10-benzodioxadiazacyclodedecin, and (6) 1,2,3,5,6,8,9,11,12,13-decahydro-4,7,10,1,13-benzotrioxadiazacyclopentadecin.
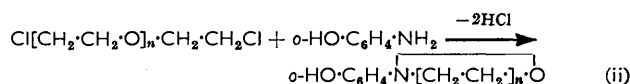
TABLE 2

N.m.r. spectra of crowns and morpholines (τ values relative to Me$_4$Si; solvent CDCl$_3$ except where stated otherwise)

Compound	ArH	Ar-O·CH$_2$	CH$_2$·O·CH$_2$	CH$_2$·CH$_2$·N	NH or OH
Pedersen (I)	3·05 [a]	5·67	6·17		
Pedersen (II)	3·05 [a]	5·82	6·22		
(1a)	ca. 3·0 [b]		6·19	7·17	
(1b)	ca. 2·9 [b]		6·1	7·1	OH 6·55
(1d)	ca. 3·18 [b]		6·19	7·16	
(1f)	2·4, 3·0		6·1	7·1	
(2)	3·21 [a]	5·77	6·37	6·67	NH 4·44
(3) [f]	3·3 [b]	5·8—6·0	6·37, 6·2	6·8	NH 5·02 [d]
(4) [e]	3·18 [b]		6·33, 6·51	6·88	OH 1·92 [f]
(5) [f]	3·32 [e]		6·43	6·5, 6·7	NH 5·92
(6)	3·32 [a,c]		6·37	6·77	NH 5·96

[a] Symmetrical pattern. [b] No symmetry. Approximate centre of multiplet quoted. [c] (5), singlet in CCl$_4$; (6), singlet in CD$_3$OD, doublet in CDCl$_3$. [d] Broad triplet. [e] In C$_6$D$_6$. [f] In CCl$_4$.

with an *ortho* phenolic or amino substituent, as shown in equation (ii). o-Aminophenol on reaction with the chloro-ether with $n = 3$ gave both the fifteen-membered ring product (3) with five donor atoms as in equation (i) and the twelve-membered ring (4) containing four donor atoms as in equation (ii). The products described

$$Cl[CH_2 \cdot CH_2 \cdot O]_n \cdot CH_2 \cdot CH_2Cl + o\text{-}HO \cdot C_6H_4 \cdot NH_2 \xrightarrow{-2HCl}$$

$$o\text{-}HO \cdot C_6H_4 \cdot \overline{N \cdot [CH_2 \cdot CH_2 \cdot]_n \cdot O} \quad \text{(ii)}$$

here show specific interaction with metal ions, but interaction with Group 1 (alkali) metals is less than with oxygen crowns, as found also by Pederson.[1]

[4] Unpublished data with D. R. Minnikin.

similarly obtained as crystals or oils after evaporation of solvent. The oils were chromatographed on alumina (eluant light petroleum–ether) and gave highly crystalline white solid crown compounds. Details of the chromatography will be published elsewhere.[4] The products were characterised by elemental analysis, and n.m.r., i.r., and mass spectrometry (Tables 1—5).

RESULTS AND DISCUSSION

The synthesis was ambiguous in that the products could have either a secondary amine structure [*e.g.* (3)] or the isomeric tertiary amine structure [*e.g.* (4)]. Many physical properties were measured in attempts to identify the structure of the isomers obtained, but the results of these measurements were frequently also

TABLE 3

Assignment of NH and OH stretching frequencies in the
i.r. spectra of crowns and morpholines (Nujol mulls)

Compound	ν_{max}/cm^{-1}	Assignment
(1a)	2600—2700br	OH (H-bonded)
(1b)	3300	OH
(1c)	3100	OH
(1d)	3300, 3220	NH_2 ⎫
(1e)	3325, 3250	NH_2 ⎬ Primary
(1f)	3335, 3430	NH_2 ⎭
(2)	3275	NH ⎫ Secondary
(3)	3370br	NH ⎭
(4)	3280—3290br	OH
(5)	3310, 3322	NH
(6)	3210, 3310	NH

TABLE 4

Abundance (%) of peaks in mass spectra of morpholines

Compd.	M	$M - 15$	$M - 31$	$M - 45$	$M - 58$	$M - 59$
(1a)	99	2	16·7	15	99 $\xrightarrow{*}$	100
(1b)	100	2	7·5	6	48 $_*$	52
(1c)	100	2	6	7	56 $\longrightarrow$	58
(1d)	100	27	32	18		80
(1e)	62·5	18	23	6	14·6	100
(1f)	100	60	10	15	20	95

TABLE 5

Important fragment ions common to nitrogen crowns and
morpholines and their abundances (%)

Compd.	m/e: 119	120/121/122	133/134/135/136		Base peak
(1a)		80	18		M
(2)		70	73	23 23	M
(3)		48	48	12	M
(4)		95 85 35		35	M
(1d)	80		15		M
(5)	50	38	100		m/e 133
(6)	86		69		M
Pedersen (II)		50		100	m/e 136
Pedersen (III)		40		100	m/e 136

X   Y
a; OH   H
b; OH   4-Cl
c; OH   4-NO_2
d; NH_2 H
e; NH_2 4-NO_2
f; NH_2 4,5-C_6H_4

^{1}H N.m.r. Spectra.—The distinction between the tertiary and secondary amine structures was made on the basis of (i) chemical shift differences, (ii) signal patterns, (iii) clarification of spectra afforded by lanthanide shift reagent, and (iv) behaviour of the basic nitrogen systems on protonation and exchange of hydrogen. These four points are now elaborated. (i) Details of the n.m.r. spectra of the series of nitrogen

ambiguous. No single line of evidence was sufficient to distinguish the secondary from the tertiary amine structure for every compound; ^{1}H n.m.r. and i.r. spectra were sometimes definitive, mass spectra equivocal. The evidence for structure rests on accumulated data from all these sources, and their comparison with those for authentic oxygen crowns [1] and morpholines.[5]
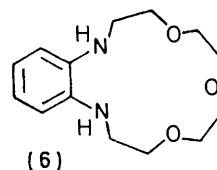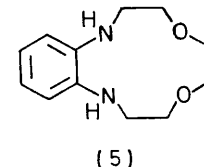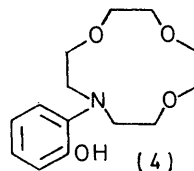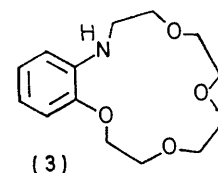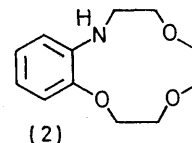
The condensation products where $n > 1$ usually have the secondary amine structure [(2), (5), (6)]. One compound was obtained as isomer (4) (twelve-membered ring) from reaction in water, but as isomer (3) (fifteen-membered ring) from dimethylformamide. Reactions in both water and dimethylformamide gave only the secondary amine (2) for $n = 2$, since the corresponding tertiary amine isomer would have a nine-membered ring. The compounds derived from the system where $n = 1$ were all obtained in the six-membered ring (morpholine) form (1), rather than the alternative nine-membered ring. Morpholines (1a) and (1d) were previously known from unambiguous syntheses and spectral comparison characterises the other compounds of the set (1a—f) as morpholines also.

crowns are given in Table 2 (see also Figures 1 and 2), where they are compared with data for authentic oxygen crowns [Pederson (I) and (II)] and morpholines. Different chemical shifts are observed for methylene hydrogen nuclei on aryl-O-CH_2, aryl-N-CH_2, and CH_2-O-CH_2 residues in the authentic oxygen crowns and morpholines. This enables us to identify these three types of methylene environment when they occur in the new nitrogen crowns (2)—(6). A clear distinction between isomers (3) and (4) can be made on this basis. (ii) The aryl proton signals for (5) and (6) form a symmetric pattern as expected. Although the pattern for (3) is asymmetric (Figure 1), (2) shows an accidentally symmetric pattern which would not be anticipated for either secondary or tertiary amine structures. (iii) Addition of $Eu(fod)_3$ reagent [6] to carbon tetrachloride solutions of crowns gave useful information for compounds (1a), (3) (Figure 1), and (6) (Figure 2). For (1a) the aryl-N-CH_2 proton signals are greatly shifted (see Figure 3) indicating the nitrogen to be the preferred donor site in this molecule for $Eu(fod)_3$. This turned out to be a poor model compound for (3) and (6), since

[5] A. J. Birch and E. G. Hutchinson, J. Chem. Soc. (C), 1971, 3671.

[6] R. E. Rondeau and R. E. Sievers, J. Amer. Chem. Soc., 1971, 93, 1522.

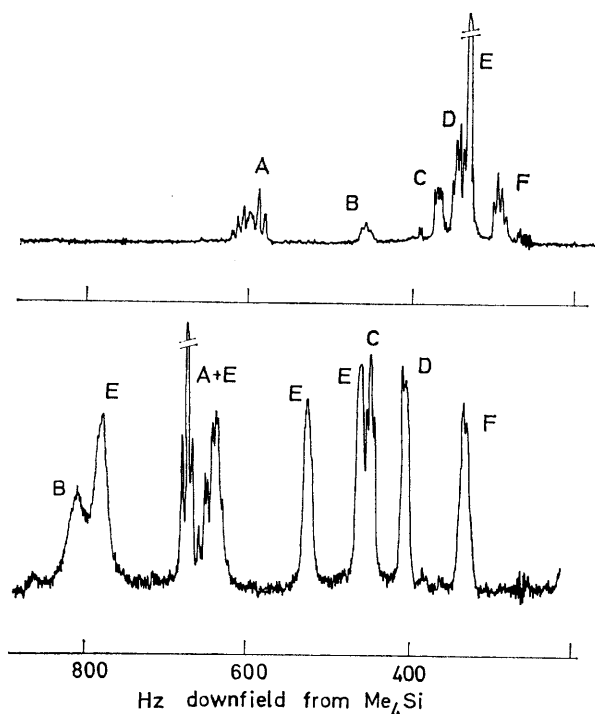the ethylene oxide signals in their spectra moved furthest downfield on addition of the shift reagent,

FIGURE 1 ^{1}H N.m.r. spectra of compound (3) in CCl_4 before (upper trace) and after addition of $Eu(fod)_3$ (lower trace); relative intensities of signals in parentheses: A, aryl H (4); B, NH (1); C, aryl-O-CH_2 (2); D, N·CH_2·CH_2·O; E, O·CH_2·CH_2·O; F, N·CH_2·CH_2·O (2)

showing that nitrogen is not always the preferred donor in competition with ether oxygen [7] (Figures 1, 2, and 4). The spectrum of (3) is greatly simplified (Figure 1) giving rise to eight sets of signals each corresponding to two protons. This simplification is probably due to the different chemical environment of axial and equatorial
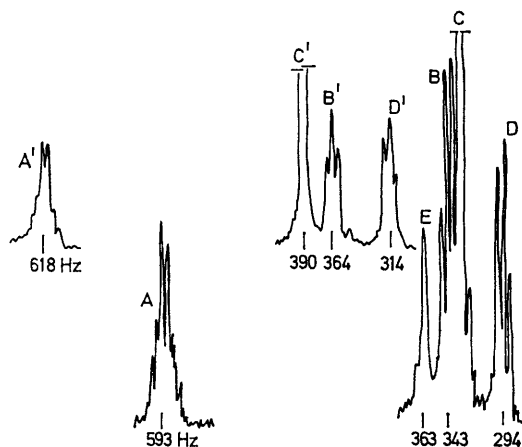

FIGURE 2 ^{1}H N.m.r. spectra in CCl_4 at 90 MHz and room temp.; relative intensities of signals in parentheses. Lower trace: compound (6) (15·1 mg in 931 mg CCl_4): A, aryl H (4); B, O·CH_2·CH_2·N; C, OCH_2·CH_2·O (B + C = 12); D, N·CH_2 (4); E, NH (2). Upper trace (offset) fro same solution of (6) in CCl_4 containing 10·1 mg $Eu(fod)_3$: A', aryl H (4); B', O·CH_2·CH_2·N (4); C', O·CH_2·CH_2·O; D', N·CH_2 (4)

protons in the polyether ring which produces a variation in chemical shift. Four sets of methylene proton signals are observed for (6), each of relative intensity four, and one NH signal of intensity two, consistent with either a secondary or tertiary amine structure (Figure 2). (iv) In strong acid solution the morpholine (1d) showed two separate NH signals in the ratio 3 : 1 corresponding to NH_3^+ and NH^+ for the morpholine
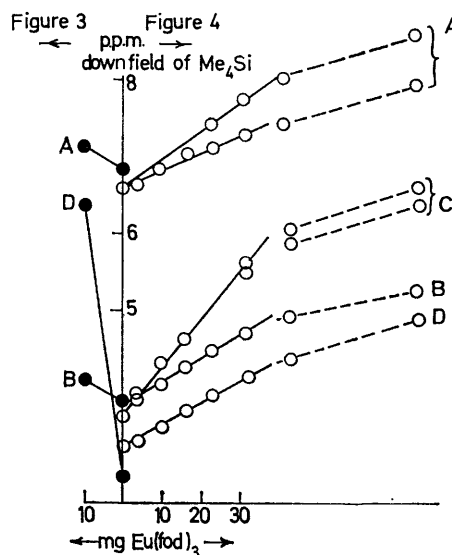

(I)   (II)

(III)
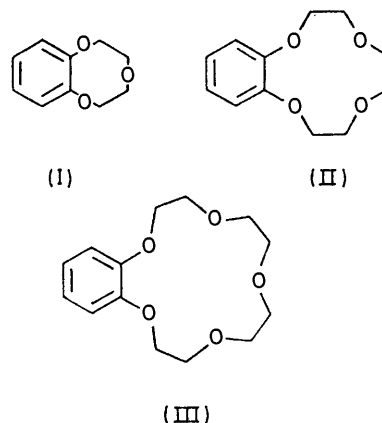
Pedersen's crown compounds; see ref. 1.

FIGURE 3 Lanthanide-induced shifts (LIS) for compound (1a) (18·1 mg) in CCl_4 (ca. 1 ml): A, aryl H; B, O·CH_2·CH_2·N; D, O·CHCH_2·N. Nitrogen is the strongest donor

FIGURE 4 LIS for compound (6) (15·1 mg) in CCl_4 (ca. 1 ml): A, aryl H; B, O·CH_2·CH_2·N; C, O·CH_2·CH_2·O; D, O·CH_2·CH_2·N. The oxygens nearest to C hydrogens are stronger donors than nitrogen and there is apparently multiple-site donation.

structure. Under similar conditions (6) showed only one NH signal of area corresponding to two NH_2^+ groups, but the possibility exists that rapid hydrogen exchange could create such a signal even for the tertiary-primary amine isomer. A clear distinction between (3) and (4) was however possible, since the spectrum of (3) contained a broad triplet typical of NH coupled to CH_2

[7] J. K. M. Sanders and D. H. Williams, J. Amer. Chem. Soc., 1971, 93, 641.

[possible for (3) only]. This coupling was confirmed when the pattern for the *N*-methylene protons was altered by NH exchange with D_2O. The spectrum of isomer (4) contained a broad signal indicative of hydrogen-bonding appropriate to a phenol group, and no coupling was disturbed when this signal was removed by deuteriation.

I.r. Spectra.—The frequencies associated with N–H and O–H stretching modes were of most use in structure assignment (Table 3). The proposed phenols had a single absorption at *ca.* 3300 cm⁻¹ [excepting (1a)]; the proposed primary amines had typical NH_2 absorptions at 3200—3400. Single secondary NH absorptions in the 3370 cm⁻¹ region for (2) and (3) differentiated them from the probable phenol (4) (a broader band at 3280—3290 cm⁻¹). Compound (2) gave a crystalline hydrobromide, in the spectrum of which the N–H absorption was replaced by a broad band centred at 2500 cm⁻¹. Compound (4) also gave a hydrobromide: in its spectrum the signal at 3280—3290 cm⁻¹ was retained but broadened (confirming assignment as O–H stretching) while a new band at *ca.* 2600 cm⁻¹ consistent with the now-protonated tertiary amine absorption was found.

Mass Spectra.—The mass spectra of the series of nitrogen crowns (2)—(6) were compared with those obtained for the Pederson crowns and morpholines (Tables 4 and 5). The nitrogen crowns (which have the heterocyclic ring attached to a benzo residue) and the morpholines (attached to a phenyl residue) had similar breakdown patterns which seem to depend on the functional groups O or NH and it seems unlikely that breakdown patterns could be diagnostic for a crown (benzo) as opposed to a morpholine (phenyl) structure of new nitrogen crowns. The nitrogen crowns have as base peak the parent ion and the major fragment ions are *m/e* 120 and 121 for the compounds with one nitrogen atom (*cf.* the morpholinophenols) and *m/e* 119 for the compounds with two nitrogen atoms (*cf.* the morpholino-

anilines); the latter are derived by loss of CH_2 from the intense *m/e* 133 fragments (*cf. m/e* 136 for the Pederson crowns): *m/e* 120 is obtained by loss of CH_2 from *m/e* 134. The two isomers (3) and (4) gave spectra with ions and also metastable peaks at identical *m/e* values, but with different intensities. The spectra are thus not suitable for distinguishing between the secondary and tertiary amine structures.

The abundances of particular fragment ions are shown in Table 4 for the morpholines. The base peak is usually the parent ion. The main fragmentation is loss of 59 mass units (metastable usually observed) from the morpholinoanilines to give as the next most intense (or in one instance the base) peak an ion [accurate mass (1e), 164·0460; calc. for $C_7H_6N_3O_2$, 164·0470]. The loss of 59 units from the morpholinophenols occurs *via* loss of 58 a.m.u. [to give an ion *m/e* 121·0527 for (1a); calc. for C_7H_6NO, 121·0538] followed by rearrangement with loss of hydrogen (metastable transitions support this contention). The $M - 58$ and $M - 59$ ions are about equally intense but not so pronounced as for the anilines. This $M - 59$ fragment further loses HCN to give $M - 86$, metastables being observed for this process in (1a, b, and d). The simple Pedersen crowns have a very simple breakdown pattern, the base peak being *m/e* 136 in each case, obtained by loss of two (II) or three (III) ethylene oxide units (metastable ions observed for $M - 88$ and $M - 132$). Metastable transitions also indicate *m/e* 136 —➤ 121 —➤ 108. The dibenzo-18-crown-6 (see Pedersen [1]) has *m/e* 137 as base peak, and no ethylene oxide units are lost.