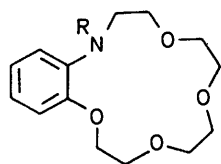


Ligands for the Alkali Metals. Part 3.† Further Examples of Nitrogen-containing 'Crown' Compounds

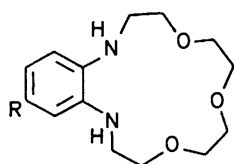
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An unambiguous route from *o*-aminophenol to dibenzo-crowns with two secondary amine links is reported. Some new mono- and di-nitrogen-containing monobenzo-crowns have also been prepared. The simple mononitrogen-containing crowns can be modified by *N*-substitution, with, for example, a pendant donor group, sufficiently flexible to co-ordinate to metals held in a polyether ring.

FURTHER work on the synthesis and modification of mono- and di-nitrogen-containing crowns is reported. A dinitrogen penta-oxygen dibenzo-crown (VI) has been prepared by an unambiguous route. Its spectral characteristics enable confirmation of the structures assigned



- (I) a; R = H
 b; R = CO·CH₂CH₂CO₂H
 c; R = CO·CH₂CH₂Br
 d; R = Prⁿ
 e; R = CH₂CH₂CH₂OEt
 f; R = CH₂CH₂CH₂Br



- (II) a; R = H
 b; R = Me

previously to related monobenzo-crowns,¹ e.g. (Ia) and (IIa). The possibility of adding ancillary groups to cyclic polyethers was explored by studying the *N*-substitution of the monobenzo-crown (Ia). It was hoped thereby to marry some of the characteristics of EDTA-type ligands with those of the cyclic polyethers. The effect of the pendant substituent on the alkali-cation-complexing power of the polyethers is being investigated.

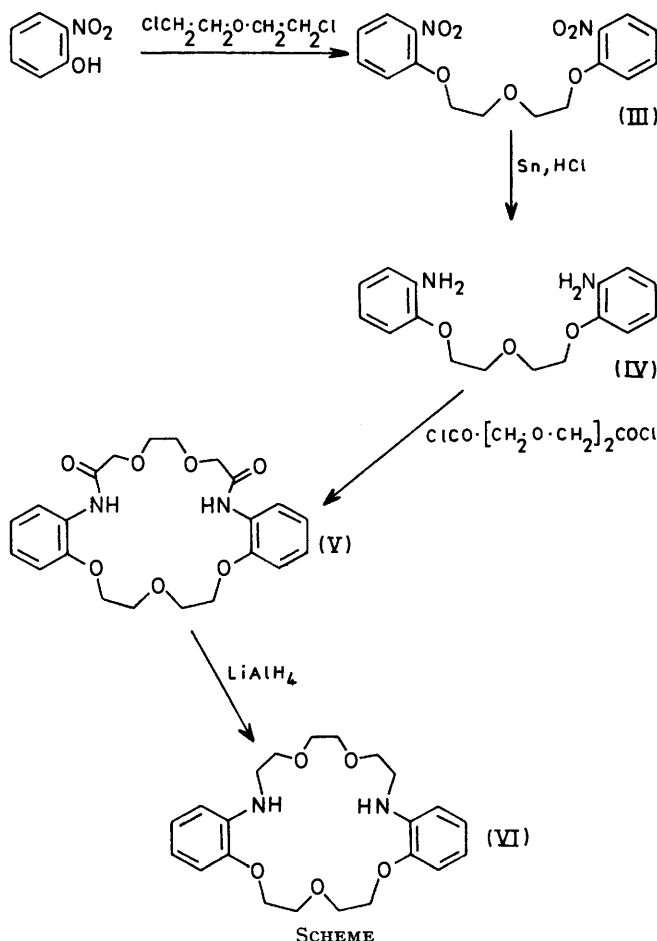
EXPERIMENTAL

Preparation of the Dinitrogen Crown (VI).—This compound was synthesised by the route shown in the Scheme. The intermediate diamine (IV) was made by adapting the method of Cannon *et al.*²

Bis-(2-*o*-nitrophenoxyethyl) ether. Bis-(2-chloroethyl) ether (75 g) was treated with *o*-nitrophenol (95.6 g) in dimethylformamide (250 ml) containing potassium carbonate (28 g). The yellow product contained some *o*-nitrophenol and was recrystallised from methanol to give the dinitro-compound (III) (72 g, ca. 64.4%), m.p. 68°, *M*⁺ 348 (Found: C, 53.1; H, 4.4; N, 8.0. C₁₆H₁₆N₂O₇ requires C, 52.7; H, 4.4; N, 7.7%).

Bis-(2-*o*-aminophenoxyethyl) ether. The dinitro-compound (III) (58 g) was reduced in a stirred refluxing solution of tin(II) chloride dihydrate (250 g) in concentrated hydrochloric acid (750 ml). Tin was removed as tin(II) sulphide and the filtrate was extracted with ether (3 × 250 ml). The

extracts gave an oily residue (38 g). A portion of the oil (10 g) was adsorbed onto Celite,³ which was then placed on a neutral alumina (200 g; grade IV) column. The column was eluted with 9:1 light petroleum-ether (2 l). The solvent was removed to give the diamine (IV) (8.5 g) a pale yellow oil (Found: C, 66.3; H, 6.8; N, 9.6. C₁₆H₂₀N₂O₃ requires C, 66.7; H, 7.0; N, 9.7%), *M*⁺ 288, *v*_{max} 3350 and 3480 cm⁻¹ (NH₂); hydrochloride (solid)⁴ (Found: C, 51.9;



H, 5.6; Cl, 18.2; N, 7.3. C₁₆H₂₁N₂O₃Cl requires C, 53.3; H, 6.1; Cl, 19.6; N, 7.7%).

² R. D. Cannon, B. Chiswell, and L. M. Venanzi, *J. Chem. Soc. (A)*, 1967, 1277.

³ J. R. Blackborow, J. C. Lockhart, D. E. Minnikin, A. C. Robson, and M. E. Thompson, *J. Chromatog.*, 1975, **107**, 380.

⁴ A. C. Linsdell, Ph.D. Thesis, Newcastle upon Tyne, 1971.

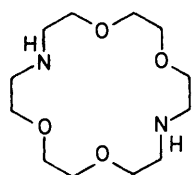
† Refs. 1 and 3 are considered as Parts 1 and 2, respectively.

¹ J. C. Lockhart, A. C. Robson, M. E. Thompson, D. Furtado, C. K. Kaura, and A. R. Allan, *J.C.S. Perkin I*, 1973, 577.

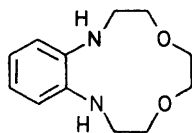
The diamide (V). Solutions of the diamine (IV) (7.08 g, 0.025 mol) and ethylenedioxybis(acetyl chloride) (2.7 g, 0.0125 mol), each in anhydrous benzene (500 ml), were added simultaneously to anhydrous benzene (1 l) (modification of the cryptand synthesis⁵) stirred under nitrogen during 5 h. The mixture was stirred under nitrogen for a further 5 days, then filtered, and the solvent was removed to give a yellow *solid* (4 g, ca. 88%) (Found: C, 60.8; H, 5.9; N, 6.3. $C_{22}H_{26}N_2O_7$ requires C, 61.4; H, 6.05; N, 6.51%), M^+ 430.

The crown (VI). The diamide (V) (3.8 g) was dissolved in anhydrous tetrahydrofuran (100 ml) and slowly added to a suspension of lithium aluminium hydride (2 g) in anhydrous tetrahydrofuran (250 ml). The mixture was refluxed under nitrogen for a further 8 h. The solution was cooled, the excess of hydride destroyed by addition of 2 : 1 tetrahydrofuran-water, and the mixture filtered. Solvent was removed under reduced pressure to give a brown solid, which was purified by chromatography on a neutral alumina (100 g; grade IV) column, eluted with benzene. Removal of the solvent left the product (2.2 g), which was recrystallised from methanol to yield 5,6,7,9,10,12,13,14,20,21,23,24-dodecahydrodibenzo[h,t][1,4,7,13,16,10,19]pentaaxadiazacycloheneicosine, a white crystalline solid, m.p. 117 °C (Found: C, 65.6; H, 7.4; N, 7.0. $C_{22}H_{30}N_2O_5$ requires C, 65.7; H, 7.5; N, 7.0%), τ (CDCl₃) 6.75 (N-CH₂), 6.40 (O-CH₂), 5.90 (ArO-CH₂), 5.13 (NH), and 3.30 (ArH), ν_{NH} 3 400 cm⁻¹, M^+ 402.

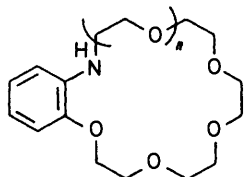
The following new monobenzo-crowns were made by routes described previously;^{1,3} they had appropriate n.m.r. and i.r. spectra: 1,2,3,5,6,8,9,11,12,13-decahydro-15-methyl-4,7,10,1,13-benzotrioxadiazacyclopentadecine (IIb), a pale yellow oil (Found: C, 64.6; H, 8.5; N, 9.9%; M^+ , 280.



(VII)



(VIII)

(IX) $n = 1$ (X) $n = 2$ (XI) $n = 3$

$C_{15}H_{24}N_2O_3$ requires C, 64.8; H, 8.6; N, 10.0%; M , 280); 2,3,5,6,8,9,11,12,14,15-decahydro-16H-1,4,7,10,13,16-benzo-pentaoxa-azacyclo-octadecine (IX), a pale yellow oil (Found: C, 60.0; H, 8.8; N, 4.1%; M^+ , 311. $C_{16}H_{25}NO_5$ requires C, 61.7; H, 8.1; N, 4.5%; M , 311); 2,3,5,6,8,9,11,12,14,15,17,18-dodecahydro-19H-1,4,7,10,13,16,19-benzohexaoxa-azacycloheneicosine (X), a pale yellow oil (Found: C, 61.6;

H, 8.2; N, 3.95%; M^+ , 355. $C_{18}H_{25}NO_6$ requires C, 60.8; H, 8.2; N, 3.9%; M , 355); 2,3,5,6,8,9,11,12,14,15,17,18,20,21-tetradeca-hydro-22H-1,4,7,10,13,16,19,22-benzohepta-oxa-azacyclotetracosine (XI), a pale yellow oil (Found: C, 59.9; H, 8.1; N, 2.9%; M^+ , 399. $C_{20}H_{33}NO_7$ requires C, 60.1; H, 8.3; N, 3.5%; M , 399).

N-Substituted Derivatives of the Monobenzo-crown (Ia).—3-Carboxypropionyl derivative (Ib). 3-Carboxypropionyl chloride (0.46 g 2.92 mmol) was added to the crown (Ia) (0.78 g, 2.92 mmol) in anhydrous benzene (50 ml.). A viscous liquid (0.95 g) obtained from this benzene layer after hydrolysis showed m/e 366 as the highest mass fragment in its mass spectrum [(Ib) would give m/e 367]. The liquid was purified by column chromatography (adsorbed on Celite³ and then placed on neutral alumina grade IV, and eluted with benzene and 9 : 1 light petroleum-ether). The product was detected as a brown spot on t.l.c. (R_F 0.56) and recovered as a *solid* (0.63 g) (Found: C, 58.8; H, 7.1; N, 4.0. $C_{18}H_{25}NO_7$ requires C, 58.9; H, 6.9; N, 3.8%), ν_{CO} 1 655 and 1 735 cm⁻¹.

N-3-Bromopropionyl derivative (Ic). 3-Bromopropionyl chloride (0.95 g, 5.5 mmol) was added to a stirred solution of the crown (Ia) (1.47 g, 5.5 mmol) and potassium carbonate (3.04 g, 11 mmol) in benzene (250 ml). The mixture was stirred overnight, filtered, and evaporated to leave a brown *liquid* (2.1 g) (Found: C, 51.5; H, 5.8; N, 3.6%; M^+ , 403/401. $C_{17}H_{24}BrNO_5$ requires C, 50.8; H, 6.0; N, 3.5%; M , 401/403), ν_{CO} 1 650 cm⁻¹.

Reduction of the amide (Ic). (i) *With lithium aluminium hydride.* The amide (Ic) (0.44 g, 2.2 mmol) was added to lithium aluminium hydride (168 mg, 4.4 mmol) at reflux in anhydrous tetrahydrofuran under nitrogen. After 3 h the mixture was cooled and the excess hydride removed. A viscous brown *liquid* (0.2 g) was recovered, m/e 309, i.r. and n.m.r. data consistent with *N*-propyl structure (Id) (Found: C, 64.2; H, 8.3; N, 4.3. $C_{17}H_{27}NO_4$ requires C, 66.0; H, 8.7; N, 4.5%; M , 309).

(ii) *By the Borch method.*⁶ The amide (Ic) (0.8 g, 2 mmol) was treated in dry dichloromethane (50 ml) under nitrogen with 1*M*-triethylxonium tetrafluoroborate (2.5 ml). Evaporation left a solid residue which was stirred in ethanol (100 ml) (cooled in an ice-bath) while sodium borohydride (0.1 g, 2.6 mmol) was added. The solution was warmed slowly to room temperature and stirred for a further 18 h. Ethanol was removed under vacuum and water (40 ml) added to the residue, then solid potassium hydroxide to adjust the pH to 14. Ethereal extracts of the alkaline solution (3 × 50 ml) gave a brown *liquid* (0.53 g), the *N*-3-ethoxypropyl derivative (Ie) (Found: C, 61.8; H, 8.4; N, 3.8%; M^+ , 353. $C_{19}H_{31}NO_5$ requires C, 64.6; H, 8.8; N, 4.0%; M , 353).

(iii) *With diborane.* Diborane⁷ was passed in a stream of nitrogen into tetrahydrofuran (100 ml) containing the amide (Ic) (0.8 g, 2 mmol) for 1 h. The solution was stirred overnight, hydrochloric acid added to destroy the excess of diborane, and the solvent evaporated off. The residue was treated with water (25 ml) and alkali and extracted with ether. The extracts (3 × 50 ml) afforded a viscous liquid (0.67 g) which was purified by adsorption on Celite³ and column chromatography on alumina (25 g) to give the *N*-3-bromopropyl derivative (If) as a *solid* (Found: C, 51.8; H, 6.5; N, 3.5%; M^+ , 387/389. $C_{17}H_{26}BrNO_4$ requires C,

⁵ B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Tetrahedron Letters*, 1969, 2885.

⁶ R. F. Borch, *Tetrahedron Letters*, 1968, 61, 65.

⁷ H. C. Brown, *J. Amer. Chem. Soc.*, 1960, 82, 4233.

52.6; H, 6.7; N, 3.6%; *M*, 387/389). Attempts to condense (Ia) directly with chloroacetic acid as in a typical EDTA synthesis⁸ were unsuccessful.

Diethyl 1,4,10,13-Tetraoxa-7,16-diazacyclo-octadecane-7,16-diacetate.—*n*-Butyl-lithium (28 g of 15% solution in hexane; 6.6 mmol) was treated with a solution of 1,4,10,13-tetraoxa-7,16-diazacyclo-octadecane (VII)⁵ (0.576 g, 2.2 mmol) in bis-(2-methoxyethyl) ether (50 ml) under nitrogen. After 1 h ethyl bromoacetate (0.715 g, 4.4 mmol) was added, and stirring was continued for 48 h. The solution was filtered and evaporated to leave a brown liquid *ester* (0.58 g) (Found: C, 52.1; H, 8.2; N, 6.0%; *M*⁺, 434. C₂₀H₃₆N₂O₈ requires C, 55.4; H, 8.75; N, 6.45%; *M*, 434) ν_{\max} (Nujol) 1 652 and 1 730 cm⁻¹ (CO), τ (CDCl₃) 8.77 (6 H, t, CH₂), 7.1 (8 H, t, ring N-CH₂), 6.4 (16 H, m, ring O-CH₂), 5.97 (4 H, q, CH₂Me), and 5.47 (4 H, s, N-CH₂-CO₂). Several attempts at the corresponding alkylation of the crown (Ia) were unsuccessful.

N-Substitution of 1,2,3,5,6,8,9,10-Octahydro-4,7,1,10-benzodioxadiacyclododecine (VIII).—The reaction of 3-carboxypropionyl chloride (0.789 g, 5.0 mmol) with the crown (VIII)¹ was carried out as for (Ia) to give, on hydrolysis, a red viscous liquid (0.62 g), the di-*N*-(3-carboxypropionyl) derivative (*cf.* ref. 9) (Found: C, 61.5; H, 6.8; N, 10.1%; *M*⁺, 526. Calc. for C₂₀H₂₆N₂O₈: C, 63.8; H, 7.2; N, 10.6%; *M*, 526); ν_{CO} (Nujol) 1 660 cm⁻¹.

G.l.c.—Mononitrogen crowns, like oxygen crowns,^{10,11} could be characterized by *g.l.c.* The crowns

$\text{O-C}_6\text{H}_4\text{-NH-}[\text{CH}_2\text{-CH}_2\text{-O}]_n\text{-CH}_2\text{-CH}_2$, injected in ethanolic solution into a 5 ft × 3/8 in SE30 (3%) on Chromosorb W column, had characteristic retention times (*e.g.* *n* = 3, *t*_R 0.93 min; *n* = 4, 2.24 min; *n* = 5, 4.86 min; *n* = 6, 10.86 min, with helium as carrier gas, flow rate 50 ml min⁻¹ at 237 °C). A plot of log *t*_R versus *n* was a straight line for *n* = 3–6 (column at 237 °C) and for *n* = 4–8 (column at 267 °C). Exceptions were the morpholinophenol and the phenolic crown [(Ia) and (4), respectively in ref. 1], already shown to have different types of structure.

RESULTS AND DISCUSSION

We have shown that the NH group of a simple mononitrogen crown (Ia) provides a convenient location for substituents which can modify the properties of the molecule. We did not succeed in alkylating nitrogen benzo-crowns such as (Ia) with *n*-butyl-lithium, nor in cross-linking the NH₂ groups of the diamine (IV) with bis-(2-chloroethyl) ether. The product of the latter reaction had the required *m/e* value (388) for the dibenzo-crown but gave a positive result in an azo dye test, and was probably a morpholine.⁴ Condensation of (IV) with bis-acid chlorides followed by reduction of the amide links was satisfactory.

⁸ R. Smith, J. L. Bullock, F. C. Bersworth, and A. E. Martell, *J. Org. Chem.*, 1949, **14**, 355.

⁹ R. J. Hayward and O. Meth-Cohn, *J.C.S. Perkin I*, 1975, 212.

In studies of crown ethers designed to discover and exploit the reasons for complexing of alkali and alkaline earth metal cations, considerable emphasis has been placed on thermodynamic descriptions of complex formation. Interest in the simple 1 : 1 type of complex formation [equation (i)] centres on attaining two effects: (a) the greatest overall equilibrium constants *K* for equation (i) and (b) the greatest differential between stability constants of the complexes as *M*⁺ is varied. In the explanation of complexing, (a) is intrinsically important, but



in its exploitation the differential effect (b) is more important, and highest complexing power may be sacrificed to obtain (b). The sodium–potassium differentials are of the greatest interest in biological, medical, and industrial applications. The relative affinity of particular crowns for particular cations is, of course, strongly dependent on the conditions of measurement.

For example, Frensdorff¹² measured a series of log *K* values in methanol which indicated 18-crown-6 to have the highest log *K* value for potassium, whereas selectivity between potassium and sodium was greatest for dibenzo-30-crown-10. Considering the simple effect of replacing one oxygen donor of a crown by a nitrogen, we note that the nitrogen crown does not compete as a complexing agent. Frensdorff's log *K* value for the mononitrogen analogue of 18-crown-6 shows that the complexing power for potassium is reduced (one hundred-fold difference in *K*).¹² Moreover, spectrophotometric comparison of *K* in methanol for ligands (Ia) and benzo-15-crown-5 complexing with sodium shows a hundred-fold reduction in *K* for the nitrogen compound. Yet the selectivity [effect (b)] of the nitrogen ligands is in some applications greater. In solvent extraction studies¹³ the absolute amount of alkali metal ion extracted by nitrogen crowns was less, but the selectivity for potassium over sodium was improved in comparison with analogous crowns with only oxygen donors. When we added a pendant donor group (carboxylic acid) to the nitrogen function, it improved overall extraction [effect (a)] but not selectivity. A more extensive physical evaluation of nitrogen crowns is proceeding.

We thank Drs. J. R. Blackborow and H. C. Kelly for discussions, and the S.R.C. and Albright and Wilson for financial support (CASE Studentship to M. E. T.).

[6/1104 Received, 10th June, 1976]

¹⁰ K. Madan and D. J. Cram, *J.C.S. Chem. Comm.*, 1975, 427.

¹¹ D. A. Jaeger and R. R. Whitney, *J. Org. Chem.*, 1975, **40**, 92.

¹² H. K. Frensdorff, *J. Amer. Chem. Soc.*, 1971, **93**, 600.

¹³ C. J. Pedersen, *Fed. Proc.*, 1968, **27**, 1305.