MACROHETEROCYCLES.

27.* AMIDOMETHYLATION OF BENZO-CROWN ETHERS

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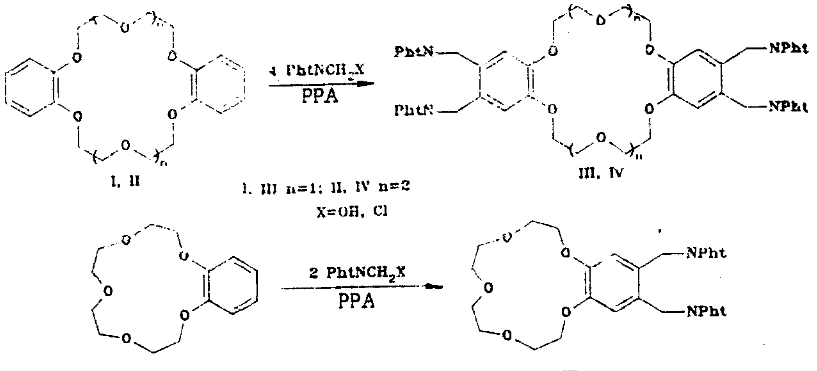
The synthesis of some novel benzo-crown ethers by α-amidomethylation is described.

α-Amidomethylation at carbon (the Chernyak–Einhorn reaction) has been the subject of numerous articles and reviews [2, 3], but there have been no reports of the use of benzo-crown ethers in such reactions, and only a few examples of the use of PPA as catalyst [4, 5]. It is, however, known that PPA is an excellent solvent and catalyst in the alkylation [6, 7] and acylation [8] of benzo-crown ethers.

We have now shown that benzo-crown ethers undergo efficient α-amidomethylation on treatment with N-hydroxymethylphthalimide and N-hydroxymethylamides in PPA.

Examination of molecular models shows that it is only possible to introduce two amidomethyl substituents into the aromatic ring in benzo-crown ethers, in positions 4 and 5. This was confirmed by the observation that amidomethylation of dibenzo-18-crown-6 (I) and dibenzo-24-crown-8 (II) with two equivalents of N-hydroxymethylphthalimide gave a mixture of the unsubstituted crown ether together with mono-, di-, and trisubstituted products. Using a crown ether–electrophile reagent ratio of 1:4 at 100°C, high yields of the tetraphthalimido-compounds (III) and (IV). Under similar conditions, benzo-15-crown-5 gave the diphthalimido-compound (VI). The use of the more reactive N-chloromethylphthalimide as the electrophile enabled the reaction temperature to be reduced to 70°C. Attempts to carry out the reaction in concentrated sulfuric acid were unsuccessful, apparently as a result of hydrolysis of the ether linkages in the macrocycle.



I, II

III, IV

I, III n=1; II, IV n=2

X=OH, Cl

V

VI

$Pht=o\text{-}C_6H_4(CO)_2$

Reaction of N-hydroxymethylphthalimide with the crown ether (I) gave the tetraamidomethyl compound (VII), and N-hydroxymethylbenzamide or bis-N-benzamidomethyl ether with crown ethers (I) and (V) afforded compounds (VIII) and (IX).

It was found that under similar conditions N-hydroxymethyl-p-toluenesulfonamide and N-hydroxymethyl-N-methyl-p-toluenesulfonamide eliminated CH_2O at temperatures as low as 30-40°C, this then undergoing polycondensation with the benzo-crown ether to give polymeric materials.

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*For Communication 26, see [1].

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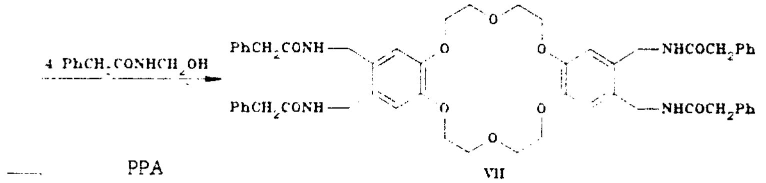
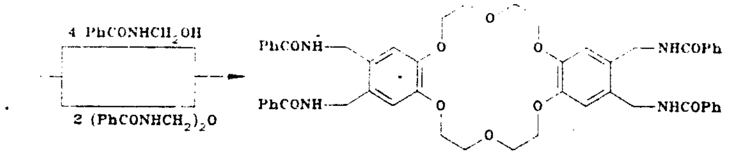
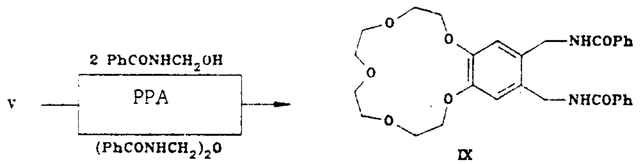


VII

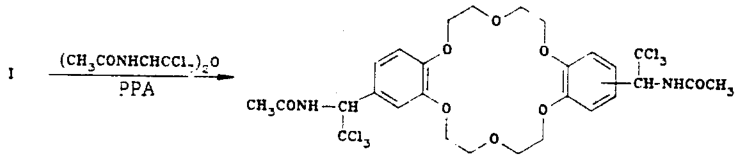


VIII



IX

The reaction of the crown ether (I) with α,α'-di(trichloromethyl)-N-bisacetamidomethyl ether in a ratio of 1:2 gave, unlike the previous examples, only the disubstituted compound (X). This appears to be due to the electronic and steric effects of the trichloromethyl group.



X

These compounds are clearly of considerable interest for further modification.

EXPERIMENTAL

The PMR spectra of 5-10% (by volume) solutions of the compounds were recorded on a Tesla BS-467 spectrometer (60 MHz), internal standard hexamethyldisiloxane. Mass spectra were obtained on a Varian MAT-112 spectrometer with direct sample introduction, ionizing electron energy 70 eV.

TABLE 1. Properties of Crown Ethers (III), (IV), and (VI)-(X)

Compound	mp, °C	PMR spectrum (CF$_3$COOH), δ, ppm	Mass spec. M$^+$	Found, %			Empirical formula	Calculated %			Yield, %
				C	H	N		C	H	N	
III	207—210	3.60 (m, 16H); 4,83 (s, 8H); 6,55 (s, 4H); 7,45 (s, 16H)	997	67,5	4,8	5,5	$C_{56}H_{44}N_4O_{14}$ (996,9)	67,5	4,5	5,6	87
IV	110	3,53 (m, 24H); 4,80 (s, 8H); 6,66 (s, 4H); 7,42 (s, 16H)	—	66,1	4,8	5,2	$C_{60}H_{52}N_4O_{16}$ (1058,1)	66,4	4,8	5,2	91
VI	225—228	3.53 (s, 8H); 3,83 (m, 8H); 5,08 (s, 4H); 6,92 (s, 2H); 7,65 (s, 8H)*	586	65,3	5,0	5,0	$C_{32}H_{30}N_2O_9$ (586.6)	65,5	5,2	4,8	94
VII	147—150	3.75 (m, 32H); 6.48 (s, 4H); 6.93 (s, 20H); 7,57 (m, 4H)	949	70,5	6,0	5.6	$C_{56}H_{60}N_4O_{10}$ (949.1)	70.9	6.4	5.9	86
VIII	185—190	3.76 (m, 16H); 4,36 (m, 12H); 6.93 (m, 24H)	893	70.4	5,7	6.3	$C_{52}H_{52}N_4O_{10}$ (892.9)	70,4	5,9	6.3	72
IX	197	3.70 (m, 16H); 4.48 d, 4H); 5,00 (t, 2H); 6.77 (s, 2H); 7,46 (m, 10H)*	534	67.7	7.3	5.1	$C_{30}H_{34}N_2O_7$ (534.6)	67,4	7.3	5.2	76
X	137—140	2.03 (s, 6H); 4.08 (m, 16H); 5.83 (d, 2H); 6.83 (m, 8H)*	737	45.9	4.2	4,0	$C_{28}H_{32}Cl_6N_2O_8$ (737,30)	45.6	4.4	3.8	79

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*Solution in CDCl$_3$.

The purities of (III), (IV), and (VI)-(X) were established by TLC on plates with a bound layer of Silufol UV-254 silica gel, the eluents being selected in accordance with the properties of the compounds, and visualization was by iodine vapor.

4',5',4",5"-Tetra-(N-phthalimidomethyl)dibenzo-18-crown-6 (III), 4',5',4",5"-Tetra-(N-phthalimidomethyl)dibenzo-24-crown-8 (IV), and 4',5'-Di-(N-phthalimidomethyl)benzo-15-crown-5 (VI) (general method). A mixture of 2.8 mmole of the dibenzo-crown ether, 1.965 g (11.2 mmole) of N-hydroxymethylphthalimide, and 10 g of PPA was stirred at 100°C for 20 min, then 70 ml of water was added. The solid which separated was filtered off and washed on the filter with water (150 ml) and acetone (40 ml). Compound (VI) was obtained similarly from 1 g (3.7 mmole) of the crown ether (V) and 1.321 g (7.4 mmole) of N-hydroxymethylphthalimide. Alkylation of crown ethers (I), (II), and (V) by the appropriate amounts of N-chloromethylphthalimide was carried out at 70°C.

4',5',4",5"-Tetra-(N-phenylacetamidomethyl)dibenzo-18-crown-6 (VII). A mixture of 0.432 g (1.2 mmole) of the crown ether (I), 0.788 g (4.8 mmole) of N-hydroxymethylphenylacetamide, and 5 g of PPA was stirred at 60°C for 30 min. Water (50 ml) was then added, and the solid which separated was filtered off and washed with water (100 ml) and methanol (30 ml). Yield 0.97 g (86%).

4',5',4",5"-Tetra-(N-benzamidomethyl)dibenzo-18-crown-6 (VIII). A mixture of 0.5 g (1.4 mmole) of the crown ether (I), 0.839 g (5.6 mmole) of N-hydroxymethylbenzamide [or 0.789 g (2.8 mmole) of bis-N-benzamidomethyl ether] and 5 g of PPA was stirred at 60°C for 20 min, and 50 ml of water added. The solid which separated was filtered off, washed with water (100 ml), and dissolved in 10 ml of DMF. To this solution was added 20 ml of acetone, and the mixture filtered. The filtrate was added to 50 ml of cold water, and the solid which separated was filtered off and air-dried for 10 h. Yield 0.89 g (72%).

4',5'-Di-(N-benzamidomethyl)benzo-15-crown-5 (IX). A mixture of 0.5 g (1.9 mmole) of the crown ether (V), 0.562 g (3.8 mmole) of N-hydroxymethylbenzamide [or 0.53 g (1.9 mmole) of bis-N-benzamidomethyl ether] and 5 g of PPA was heated at 60°C for 20 min, and 50 ml of water added. The product was extracted with chloroform (50 ml), and the organic layer dried over anhydrous sodium sulfate, concentrated to half its volume, and 50 ml of hexane added. The solid which separated was filtered off. Yield 0.75 g (76%).

4',4"(5")-Di-(α-trichloromethyl-N-acetamidomethyl)dibenzo-18-crown-6 (X). A mixture of 0.5 g (1.4 mmole) of the crown ether (I), 1.097 g (2.8 mmole) of α,α'-di-(trichloromethyl)-bis-N-acetamidomethyl ether and 5 g of PPA was stirred at 100°C for 20 min, and 50 ml of water added. The solid which separated was filtered off, washed with water (100 ml), and dissolved in 70 ml of chloroform. Following drying over anhydrous sodium sulfate, the solvent was removed. Yield 0.8 g (79%).

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