

THF from (1) is not possible<sup>[1]</sup>. We have succeeded in preparing this complex, however, by reaction of (3a) with boron trichloride.

Compound (4) precipitates as bright red, needle-like crystals, (decomp. pt. 105°C), has solubility properties comparable to those of (3a) and (3b), but, unlike the latter two compounds, is extremely sensitive toward air and moisture. Its structure was also confirmed by spectroscopic and analytical data. Molecular weight determinations and the mass spectrum are consistent with the monomeric structure of the complex. IR spectrum:  $\nu_{\text{CO}}$  (in  $\text{CH}_2\text{Cl}_2$ ): 2075 (s,  $A_1$ ), 1985 (m,  $A_1$ ), 1960 (s, E)  $\text{cm}^{-1}$ ;  $\nu_{\text{Ge-Cl}}$  (in Nujol): 360 (w), 320 (w)  $\text{cm}^{-1}$ . The germylene complexes (3a), (3b), and (4) can be readily converted into the corresponding ylide complexes by addition of bases (ether, tertiary amines, or tertiary phosphanes).

### Experimental

Preparation of (3a) and (3b): 20 mmol of (2) or (3) [4.48 g (2); 2.40 g (3)] is added dropwise to a solution of (1) (10 mmol, 2.04 g) in benzene (30 ml) and the mixture is stirred for 30 min at 50°C. After removal of volatile components the remaining oil is extracted with petroleum ether (boiling range 50–70°C). On concentration of the extract (3a) and (3b), respectively, crystallize out. Recrystallization from petroleum ether affords the analytically pure complexes. Yields: 4.50 g (79%) (3a); 0.7 g (19%) (3b).

Preparation of (4): A solution of (3a) (10 mmol, 5.67 g) in 100 ml petroleum ether (boiling range 50 to 70°C) is added to a solution of  $\text{BCl}_3$  (6.8 mmol, 0.80 g) in 50 ml petroleum ether at –30°C. An orange-yellow precipitate of (4) immediately separates out and is filtered after 30 minutes' stirring at 0°C. Recrystallization from petroleum ether affords analytically pure (4). Yield 1.25 g (37%).

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(1), 60260-16-4; (2a), 60253-72-7; (2b), 3908-55-2; (3a), 60260-11-9; (3b), 60260-12-0; (4), 60260-13-1;  $\text{BCl}_3$ , 10294-35-5

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[2] G. Huttner, unpublished work.

## Papaverine Crown Ethers<sup>[\*\*]</sup>

By Fritz Vögtle and Klaus Frensch<sup>[\*]</sup>

The endohydrophilic/exolipophilic structure of the crown ethers permits lipophilization of alkali metal ions. As synthetic analogs of the well-known ionophores, neutral ligands of the crown ether type have contributed greatly to our understanding of selective ion transport processes in biological membranes.

The present communication concerns the novel concept of altering the hydrophilic/lipophilic properties of physiologically active molecules by intramolecular incorporation of crown ether rings and especially of enabling or facilitating selective complex formation with alkali or alkaline-earth metal ions. Thereby it ought to be possible to modify the physiological action, e.g. as regards rate and site of attack. The isoquinoline alkaloid papaverine (1a), that constitutes about 0.5 to 1.0% of opium and is used as an antispasmodic, e.g. for relieving spasms of the gastro-intestinal and the bile duct,

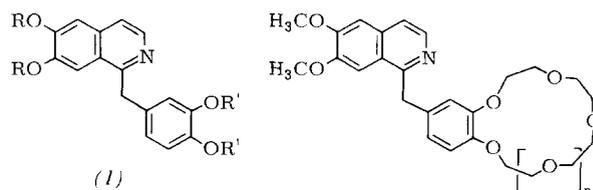
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was considered the best candidate for initial model experiments on account of the two catechol partial structures already present.

We were able to prepare the crown-ether type bridged analog of benzo[15]crown-5<sup>[1]</sup>, papaverine derivative (2) (m.p. 104°C), in 25% yield by reaction of the doubly demethylated papaverine (1b)<sup>[2]</sup> with 1,11-dichloro-3,6,9-trioxaundecane without employing the dilution principle<sup>[3]</sup>.



(a):  $R = R' = \text{CH}_3$

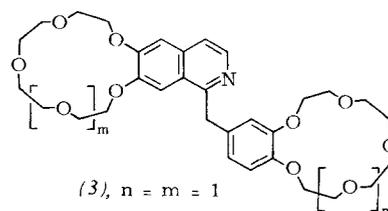
(b):  $R = \text{CH}_3, R' = \text{H}$

(c):  $R = R' = \text{H}$

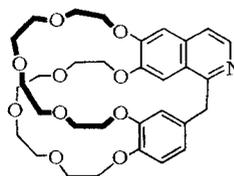
(2),  $n = 1$

Reaction of the hydrobromide of (1c)<sup>[2,4]</sup> with 1,11-dichloro-3,6,9-trioxaundecane afforded a doubly crowned product of the composition (3) or (4) (m.p. 109–110°C; sinters at 100°C) in 20% yield<sup>[3]</sup>. From a comparison of the NMR spectra of (2) and (3) it was assumed that (3) was present, yet nanogram thin-layer chromatography of the analytically pure substance (silica gel  $F_{254}$ , methanol/water = 1:1) revealed the presence of further components, presumably (4a), (4b) or corresponding oligomers.

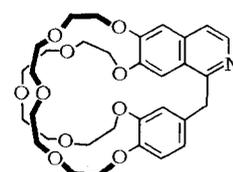
The composition of (2) and (3) was confirmed by elemental analysis and by high resolution mass spectrometry.



(3),  $n = m = 1$



(4a)



(4b)

The <sup>1</sup>H-NMR spectra of (2) and (3) show besides the characteristic signals for the papaverine moiety<sup>[5]</sup>—including the benzylic —CH<sub>2</sub>— singlet at  $\delta = 4.52$  ppm—the characteristic —OCH<sub>2</sub>— absorption pattern for the crown ether bridges centered around  $\delta = 3.75$  and 3.95 ppm (in  $\text{CDCl}_3$  and  $\text{CD}_3\text{OD}$ , resp.).

While solid potassium permanganate cannot be dissolved in chloroform with papaverine, this is readily possible with the bridged papaverines (2) and (3). As expected the violet color of the solution is much more intense with the doubly crowned ether (3) than with (2). (2), of which we obtained gram amounts, reacts with  $\text{Ca}(\text{SCN})_2 \cdot 4\text{H}_2\text{O}$  even in the cold in ethyl acetate with formation of mm-long crystalline needles of the 1:1 complex, which contains one molecule of water of crystallization and melts at 173°C<sup>[6]</sup>. Its IR spectrum shows a strong and sharp characteristic band at 2055  $\text{cm}^{-1}$ , its <sup>1</sup>H-NMR spectrum slight shifts of the  $\text{OCH}_2\text{—CH}_2\text{O—}$  protons [in  $(\text{CD}_3)_2\text{SO}$ ].

CAS Registry numbers:

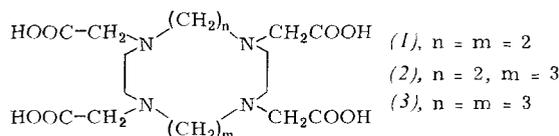
(1a), 58-74-2; (1b), 16637-56-2; (1c) HBr, 23740-74-1; (2), 60239-23-8; (3), 60239-24-9; (4a), 60239-25-0; (4b), 60239-26-1; 1,11-dichloro-3,6,9-trioxadecane, 638-56-2

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 [3] The yields quoted are not optimized.  
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 [6] A similar Ca(SCN)<sub>2</sub> complex of, benzo[15]crown-5 has just recently been reported: D. G. Parsons and J. N. Wingfield, *Inorg. Chim. Acta* 18, 263 (1976).

### Complex Formation with Tetraazacycloalkane-*N,N',N'',N'''*-tetraacetic Acids as a Function of Ring Size<sup>[\*\*]</sup>

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Reaction of 1,4,7,10-tetraazacyclododecane<sup>[1,2]</sup>, 1,4,7,10-tetraazacyclotridecane<sup>[1]</sup>, and 1,4,8,11-tetraazacyclotetradecane<sup>[1]</sup> with chloroacetic acid in aqueous alkali medium affords 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid (1) [m.p. of trishydrochloride 222°C (decomp.)], 1,4,7,10-tetraazacyclotridecane-*N,N',N'',N'''*-tetraacetic acid (2) [m.p. of trishydrochloride 185°C (decomp.)], and 1,4,8,11-tetraazacyclotetradecane-*N,N',N'',N'''*-tetraacetic acid (3) [m.p. 310°C (decomp.)].



The inorganic salts were separated and purified with the strongly basic ion-exchanger DOWEX 2X8. The capacity of (1), (2), and (3) to form complexes was determined by potentiometric titration after a method developed by G. Schwarzenbach<sup>[3,4]</sup>. The results are listed in Table 1. (1) is the strongest complexing agent known so far for calcium with a pK

Table 1. Basicity and stability constants [H<sub>2</sub>O, 20°C, 0.1 N KCl] of some complexes of compounds (1) to (3). Values for ethylenediaminetetraacetic acid (EDTA) [4, 5] and 1,2-diaminocyclohexane-*N,N*-tetraacetic acid (CyDTA) [6] are given for comparison.

	(1)	(2)	(3)	EDTA	CyDTA
pK <sub>Ca</sub>	19.06	17.29	18.60	18.30	21.30
pK <sub>Ni</sub>	17.25	15.75	15.26	18.40	19.40
pK <sub>Co</sub>	18.42	14.98	15.00	16.10	18.92
pK <sub>Zn</sub>	18.90	14.42	15.81	16.10	18.60
pK <sub>Pb</sub>	19.89	15.63	14.73	18.20	19.68
pK <sub>Cd</sub>	19.08	16.54	15.53	16.40	19.23
pK <sub>Mg</sub>	11.03	6.36	3.02	9.12	10.32
pK <sub>Ca</sub>	15.85	8.06	9.48	11.00	12.50
pK <sub>Sr</sub>	12.80	11.70	6.15	8.80	10.00
pK <sub>Ba</sub>	—	7.24	4.32	7.78	7.99
pK <sub>H<sub>2</sub>Y</sub>	4.41	3.28	3.46	2.00	2.40
pK <sub>H<sub>3</sub>Y</sub>	4.54	4.59	4.31	2.67	3.50
pK <sub>H<sub>2</sub>Y</sub>	9.73	9.18	9.75	6.13	6.12
pK <sub>H<sub>4</sub>Y</sub>	11.36	11.22	11.07	10.26	11.70

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value of 15.85. In the case of (2) stability of the strontium complex (pK=11.70) is outstanding compared with that of the other alkaline earth metal complexes, while (3) is characterized by strongly differing complex formation with magnesium and calcium.

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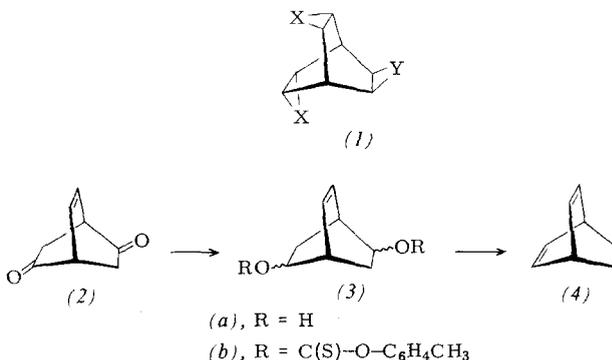
(1), 60239-18-1; (1) 3HCl, 60239-19-2; (2), 60239-20-5; (2) 3HCl, 60239-21-6; (3), 60239-22-7; 1,4,7,10-tetraazacyclododecane, 294-90-6; 1,4,7,10-tetraazacyclotridecane, 295-14-7; 1,4,8,11-tetraazacyclotetradecane, 295-37-4; chloroacetic acid, 79-11-8

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### 3,7,10-Trioxapentacyclo[3.3.3.0<sup>2,4</sup>.0<sup>6,8</sup>.0<sup>9,11</sup>]-undecane (3,7,10-Trioxatrishomobarrelene)<sup>[\*\*]</sup>

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Pentacyclo[3.3.3.0<sup>2,4</sup>.0<sup>6,8</sup>.0<sup>9,11</sup>]undecane (trishomobarrelene) (1), X=Y=CH<sub>2</sub><sup>[1]</sup> is characterized by its extraordinary bridgehead reactivity<sup>[2]</sup> and its propeller-like molecular shape<sup>[3]</sup>. For the same reasons heteratrishomobarrelenes, *i.e.* compounds of the type (1) with X=CH<sub>2</sub>, Y=O, S, NH or Y=CH<sub>2</sub>, X=O, S, NH and particularly the C<sub>3h</sub> symmetrical substances with X=Y=O, S, NH, are also of interest.



Preparation of the first representative of this series was accomplished using the barrelene (4) as starting material, which according to Zimmerman *et al.*<sup>[4]</sup> is accessible via a nine-step synthesis, but for which we have found a simpler route, namely reduction of the bicyclo[2.2.2]oct-7-ene-2,5-dione (2)<sup>[5]</sup> with LiAlH<sub>4</sub> to the bicyclo[2.2.2]oct-7-ene-2,5-diol (3a)<sup>[6]</sup>, reaction with 4-methylphenyl chlorothioformate<sup>[7]</sup> to give the bis(4-methylphenyl)thionocarbonate (3b)<sup>[6]</sup> the thermolysis of which at 170°C affords (4) in an overall yield of 20%<sup>[8]</sup>.

In the oxidation of (4) with a 50% excess of 3-chloroperoxybenzoic acid in dichloromethane in the presence of potassium hydrogen carbonate, *exo,exo*-3,7-dioxatetracyclo[3.3.2.0<sup>2,4</sup>.0<sup>6,8</sup>]dec-9-ene (5) and *endo,exo,syn*-3,7,10-trioxatrishomobarrelene (6) were formed. Sublimation of the crude

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