discussions on ^1H NMR data. We also thank Mrs. T. H. Brunner for manuscript preparation.

Registry No. **1a**, 58456-93-2; **2a**, 58456-91-0; **3**, 61645-97-4; **4**, 61615-84-7; **5**, 61626-83-3; **6**, 61615-86-9; **7**, 61615-85-8; **8**, 61615-88-1; **9**, 61615-81-4; **10**, 61615-80-3; **11**, 84193-98-6; **12**, 61615-79-0; **13**, 61615-83-6; **14**, 61615-87-0; **15**, 61615-90-5; **16**, 61695-30-5; **18**, 84193-99-7; **19**, 84194-00-3; **20**, 66061-05-0; **21**, 66061-12-9; **22**, 66061-04-9; **22a**, 66061-11-8; **23**, 84194-01-4; **24**, 66061-07-2; **25**, 84194-02-5; **26**, 66061-08-3; **27**, 66061-09-4; **28**, 84194-03-6; **29**, 84194-04-7; cyclopentanone, 120-92-3; bis(dimethylamino)methane, 51-80-9; cyclohexanone, 108-94-1; 1-methyl-4-piperidinone, 1445-73-4; cyclododecanone, 830-13-7; tricyclo[2.2.1.0^{2,6}]heptan-3-one, 695-05-6; 2-adamantanone, 700-58-3; 4-*tert*-butylcyclohexanone, 98-53-3; 3,3,5,5-tetramethylcyclohexanone, 14376-79-5; 4-oxocyclohexanecarboxylic acid, 874-61-3; tetrahydro-4*H*-thiopyran-4-one, 1072-72-6; 1-(2-phenylethyl)-4-piperidinone, 39742-60-4; 1-acetyl-4-piperidinone, 32161-06-1; 1,4-cyclohexanedione, 637-88-7; 4-methylcyclohexanone, 589-92-4; acetone, 67-64-1.

Anticoccidial Activity of Crown Polyethers

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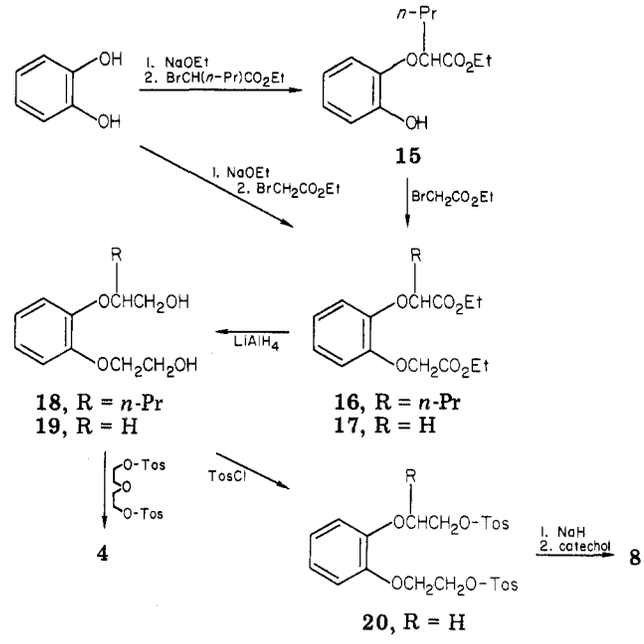
ICI Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England. *Received July 13, 1982*

Anticoccidial activity in vitro against *Eimeria tenella* is reported for crown polyethers with ring sizes from 14 to 30 atoms. The most potent compounds, **4** and **9**, were found active at 0.33 ppm, but none were active in vivo. Test results are discussed in terms of lipophilic shielding of complexed cations.

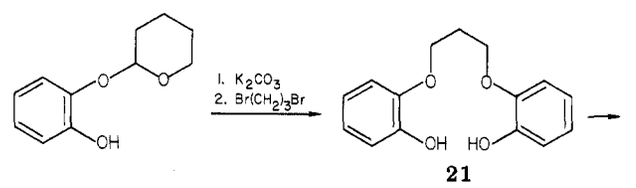
There is a need to discover new agents for the control of coccidial infections in poultry farms because these parasites restrict the growth of birds and can be eventually lethal. In addition, the prophylactic use of chemotherapy has led to the development of drug resistance by coccidia to many agents. Thus, the discovery[1] that a derivative of benzo-15-crown-5 (**1**) was moderately active against the coccidia *Eimeria tenella* in chicken kidney tissue culture prompted the examination of the anticoccidial activity of a number of crown polyethers (Table I) with different ring sizes. Whereas the mechanism by which antibiotic ionophores, such as lasalocid (**22**), exhibit anticoccidial activity is unknown, their distinctive ability to transport metal cations across artificial or biological membranes is likely to be involved. Since it is known[2] that the crown polyethers can also transport metal cations accross membranes, the varying anticoccidial activity found with crown polyethers of different ring size has been considered in relation to their ion-binding properties. Although it is likely that the anticoccidial action of lasalocid and the crown ethers relate to their ionophoretic properties, these two types of ionophore have different transport modes.[2] Crown ether complexes acquire the charge of the complexed cation, and transport is related to membrane potential. In contrast, lasoloid forms neutral cation complexes, and transport is independant of membrane potential.

Chemistry. We have proviously described[1] the preparation of **1** and the crown polyethers **2**, **3**, **6**, **7**, and **9**–**13** are commercially available.[3] The *n*-propylcrown **4** was synthesized from catechol (Scheme I). Alkylation of catechol with ethyl 2-bromovalerate did not proceed in the presence of potassium carbonate in ahydrous acetone but gave a 30% yield of **15** in an ethanolic solution of sodium ethoxide. Further etherification of **15** and reduction gave **16** and **18**; the latter compound was ring closed to the polyether **4** with diethylene glycol ditosylate in the presence of sodium hydride. The diol **19** was also prepared by Scheme I and was ditosylated to **20** before reaction with catechol to give polyether **8**. This ring-closure procedure gave a yield of 67% for **8** but very little of the smaller crown ethers found by Pedersen.[4]

Scheme I



Scheme II

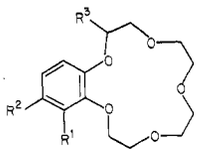


Dibenzo-14-crown-4 (**5**) was prepared from 2-(tetrahydropyran-2-yloxy)phenol[5] and 1,3-dibromopropane to give the bisphenol **21** (Scheme II). Potassium carbonate in acetone gave a better yield for this reaction than when sodium hydride in DMF was used as base. Ring closure to give **5** was carried out by Pedersen's method.[4]

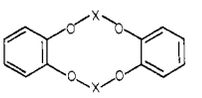
(1) G. R. Brown and A. J. Foubister, *J. Med. Chem.*, **22**, 997 (1979).
(2) B. C. Pressman, *Annu. Rev. Biochem.*, **45**, 502 (1976).
(3) Parish Chemical Co., Provo, UT.
(4) C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 7017 (1967).
(5) G. R. Brown, J. Grundy, and J. H. P. Tyman, *J. Chem. Soc., Perkin Trans 1*, 336 (1981).

0022-2623/83/1826-0590$01.50/0

Table I. Anticoccidial Activity of Crown Polyethers



1-4



5-13, 22

compd		ring cavity size	mol formula	lethal dose, ppm, of *E. tenella* in vitro
1	R^1 = Me; R^2 = R^3 = H	15	$C_{15}H_{22}O_5$	9
2	R^1 = R^2 = R^3 = H	15	$C_{14}H_{20}O_5$	9
3	R^1 = R^3 = H; R^2 = *t*-Bu	15	$C_{18}H_{28}O_5$	81
4	R^1 = R^2 = H; R^3 = *n*-Pr	15	$C_{17}H_{26}O_5$	0.33
5	X = $(CH_2)_3$	14	$C_{18}H_{20}O_4$	81
6	X = $(CH_2)_2O(CH_2)_2$	18	$C_{20}H_{24}O_6$	9
7	X = $(CH_2)_2O(CH_2)_2O(CH_2)_2$	24	$C_{24}H_{32}O_8$	1
8	X = *p*-$(CH_2)_2O$-C_6H_4-$O(CH_2)_2$	24	$C_{32}H_{32}O_8$	81
9	X = $(CH_2)_2O(CH_2)_2O(CH_2)_2O(CH_2)_2$	30	$C_{28}H_{40}O_{10}$	0.33
10	(15-crown-5)	15	$C_{10}H_{20}O_5$	81
11	(cyclohexyl-15-crown-5)	15	$C_{14}H_{26}O_5$	81
12	(18-crown-6)	18	$C_{12}H_{24}O_6$	81
13	(dicyclohexyl-18-crown-6)	18	$C_{20}H_{36}O_6$	81
22	(lasalocid)		$C_{34}H_{34}O_8$	0.01

Biological Results

Compounds were tested against *E. tenella* infections in chickens by dosing in feed at 1000 ppm as previously described[6], but no in vivo anticoccidial activity was found. Test results (Table I) against this parasitic infection in chicken kidney cell cultures[6] showed that anticoccidial activity was widespread in the benzocrown polyethers. In particular, a benzo-15-crown-5 derivative (**4**) and dibenzo-30-crown-10-were found to be active at concentrations below 1 ppm. In comparison with the ionophore lasalocid, however, these most active benzocrowns were an order of magnitude less active against *E. tenella* in tissue culture.

Discussion

The ability of ionophores to transport cations across biological membranes is dependant on several factors in addition to the charge of the complex. The stability of the ion complex must be such that the cation is selectively complexed and appropriately released after membrane transport. Also, the ion must be shielded in the complex, so that the complex is sufficiently lipophilic to pass through biological membranes. The nature of the inorganic counterion of a cation complex is also known to affect the extent of cation transport through membranes.[7] When the biological activities of these crown polyethers are compared, it has thus been assumed that they will all exist in the same environment of inorganic anions and have the same counterions.

The more basic saturated crown polyethers, **10–13**, which contain only alkyl ether groups, were inactive (i.e., not active at 81 ppm). The ring-open synthetic intermediates **15–21** also failed to show anticoccidial activity, which may be due to poor shielding of the complexed cation. Benzocrowns showed an increase in activity as cavity size increased (i.e., **9** > **7** > **6** = **2** > **5**) with the exception of **4** and **8**. As ring size increased, there was a corresponding increase in the shielding of the complexed cation. In dibenzo-14-crown-4 (**5**) the cation would lie above the planar ring system, whereas in dibenzo-30-crown-10 (**9**) the backbone is known to be able to convolute into a cage where the cation is completely surrounded by ether bonds.[8] In the anomalous benzo-15-crown-5 derivative **4**, the *n*-propyl group offers additional lipophilic shielding of the complexed cation. To rule out the possibility that the additional lipophilic character conferred on **4** by the *n*-propyl group [π (*n*-Pr) = 1.55] was responsible for the increase in anticoccidial activity, the *tert*-butyl analogue [π (*t*-Bu) = 1.98] was tested, but it was not active. The inactive tetrabenzocrown **8** has a more rigid structure than the flexible dibenzocrown **7** which has the same ring size and increased ability to shield the complexed cation.

In conclusion, the anticoccidial activity of crown polyethers in vitro is found only in benzocrowns. Increased shielding of the complexed cation leads to improved activity.

Experimental Section

Melting points are uncorrected. IR and NMR were determined on a Perkin-Elmer 157 and a Varian HA 100 spectrometer, respectively. Spectral data were consistent with the assigned structures and were supported by MS fragmentations from a Hitachi RMU-6E instrument. Where analyses are indicated only by symbols, elementary analyses are within ±0.4% of the theoretical values.

Ethyl 2-(2-Hydroxyphenoxy)valerate (15). A solution of Na (2.3 g, 100 mmol) in EtOH (100 mL) was added under N_2 to a stirred solution of catechol (11.0 g, 100 mmol) in EtOH (50 mL) and the mixture was heated to boiling. Ethyl 2-bromovalerate (20.9 g, 100 mmol) was added and the mixture was heated under reflux for 18 h. The EtOH was evaporated, and the residue was shaken with H_2O and EtOAc. The EtOAc was dried ($MgSO_4$) and evaporated to an oil (11.0 g), which was distilled to give **15** as an oil (6.2 g, 31.0%): bp 96–98 °C (0.1 mm); MS, *m/e* 238 (M^+). Anal. ($C_{13}H_{18}O_4$) C, H.

Ethyl 2-[2-[(Ethoxycarbonyl)methoxy]phenoxy]valerate (16). The phenol **15** (4.2 g, 17.6 mmol) was dissolved in EtOH (25 mL) under N_2, and a solution of Na (0.41 g, 17.6 mmol) in EtOH (50 mL) was added with stirring. The mixture was heated to reflux, and ethyl bromoacetate (3.0 g, 17.9 mmol) was added. Heating was continued for 16 h, and the EtOH was evaporated. The residue was shaken with H_2O, and the EtOAc was dried ($MgSO_4$) and evaporated to an oil. The oil was purified by column chromatography on silica gel (EtOAc) to give **16** as ann oil (3.2

(6) J. F. Ryley and R. G. Wilson, *Parisitology*, **73**, 137 (1976).
(7) J. J. Christensen, M. S. Astin, R. M. Izatt, S. R. Izatt, J. D. Lamb, S. E. Starr, B. D. Stitt, and G. C. Weed, *J. Am. Chem. Soc.*, **100**, 3219 (1978).
(8) M. A. Bush and M. R. Truter, *J. Chem. Soc., Chem. Commun.*, 1439 (1970).

g 58%): MS, m/e 324 (M^+). Anal. ($C_{17}H_{24}O_6 \cdot 0.5H_2O$) C, H.

2-[2-(2-Hydroxyethoxy)phenoxy]pentan-1-ol (18). A solution of the ester **16** (3.0 g, 9.6 mmol) in THF (15 mL) was added under N_2 to a stirred suspension of $LiAlH_4$ (0.41 g, 10.8 mmol) in THF (20 mL), which was cooled by ice–H_2O. H_2O (15 mL) and 2 N HCl (15 mL) were added dropwise, and the mixture was extracted with EtOAc. The EtOAc was dried ($MgSO_4$) and evaporated to an oil. The oil was purified by column chromatography on silica gel ($CHCl_3$), and elution with 1:1 $CHCl_3$–EtOAc gave **18** as an oil (1.8 g, 82%): MS, m/e 240 (M^+). Anal. ($C_{13}H_{20}O_4$) C, H.

5-*n*-Propyl-2,3-benzo-15-crown-5 (4). NaH, (50%, 0.44 g, 9.2 mmol) was added under N_2 to a stirred solution of **18** (1.1 g, 4.6 mmol) in THF (50 mL), and the mixture was heated to reflux. Ditosyldiethylene glycol (1.89 g, 5.1 mmol) in THF (50 mL) was added during 3.5 h to the boiling mixture, and heating was continued for a further 18 h. The mixture was cooled by ice–H_2O, and H_2O (10 drops) was added before filtration. The filtrate was evaporated to remove the THF, and the residue was purified by column chromatography on silica gel ($CHCl_3$). Elution with 1:1 $CHCl_3$/EtOAc gave **4** as an oil (0.45 g, 32%) MS, m/e 310 (M^+). Anal. ($C_{17}H_{26}O_5$) C, H.

Ethyl 2-[2-[(Ethoxycarbonyl)methoxy]phenoxy]acetate (17). Catechol (11.0 g, 100 mmol) was added to a stirred solution of Na (4.6 g, 200 mmol) in EtOH (200 mL) under N_2. Ethyl bromoacetate (33.4 g, 200 mmol) was added during 10 min, and the mixture was heated under reflux for 16 h. The EtOH was evaporated, and the residue was shaken with EtOAc and H_2O. The EtOAc was washed with 5% NaOH solution and H_2O, dried ($MgSO_4$), and evaporated to an oil (13.7 g 49%), bp 138–139 °C (0.2 mm). Anal. ($C_{14}H_{18}O_6$) C, H.

2-[(2-Hydroxyethoxy)phenoxy]ethanol (19). The ester **17** (6.9 g, 24 mmol) in THF (25 mL) was added under N_2 during 45 min to stirred $LiAlH_4$ (1.1 g, 29 mmol) in THF (90 mL). The mixture was heated under reflux for 30 min and cooled in ice–H_2O. H_2O (20 mL) and 2 N HCl (20 mL) were added cautiously, and the mixture was extracted with EtOAc. The EtOAc was dried ($MgSO_4$) and evaporated. The residue was crystallized from toluene to give **19** (4.7 g, 100%), mp 81–82 °C. Anal. ($C_{10}H_{14}O_4$) C, H.

2,3,8,9,14,15,20,21-Tetrabenzo-24-crown-8 (8). *p*-Toluenesulfonyl chloride (5.7 g, 30 mmol) was added during 15 min to a solution of the diol **19** (2.95 g, 15 mmol) in pyridine (10 mL) cooled to 5 °C by ice H_2O. The mixture was stirred for 4 h at 10 °C and poured on to ice–H_2O. The solid product was collected and crystallized from toluene to give **20** (6.1 g, 80%), mp 91–93 °C. A solution of catechol (1.1 g, 10 mmol) in dimethylacetamide (DMAc) (25 mL) was added during 10 min to a suspension of 50% NaH (1.0 g, 21 mmol) in DMAc (25 mL) under N_2. The mixture was warmed to 60 °C, and **20** (5.1 g, 10 mmol) in DMAc (10 mL) was added during 10 min. The mixture was heated and stirred at 160 °C for 16 h and cooled before evaporation of the DMAc. The residue was purified by filtration through alumina in $CHCl_3$. The $CHCl_3$ was evaporated to give a solid, which crystallized from EtOAc to give **8** (0.9 g, 67%): mp 150–151 °C (lit.[4] mp 150–152 °C); MS, m/e 544 (M^+). Anal. ($C_{32}H_{32}O_8$) C, H.

1,3-Bis(2-hydroxyphenoxy)propane (21). 1,3-Dibromopropane (5.0 g, 25 mmol), anhydrous K_2CO_3 (2.8 g, 20 mmol) and 2-(tetrahydropyran-2-yloxy)phenol (9.8 g, 50 mmol) were heated in acetone (40 mL) under reflux under N_2 for 22 h. The mixture was poured into H_2O (1 L) and extracted with EtOAc. The EtOAc was dried ($MgSO_4$), and concentrated HCl (5 drops) was added. The EtOAc was evaporated to give a solid, which crystallized fro $CHCl_3$ to give **21** (1.0 g, 15%), mp 117–118 °C. Anal. ($C_{15}H_{16}O_4$) C, H.

Registry No. **1**, 70844-47-2; **2**, 14098-44-3; **3**, 15196-73-3; **4**, 84433-54-5; **5**, 14174-06-2; **6**, 14187-32-7; **7**, 14174-09-5; **8**, 14098-25-0; **9**, 17455-25-3; **10**, 33100-27-5; **11**, 17454-48-7; **12**, 17455-13-9; **13**, 16069-36-6; **15**, 84433-55-6; **16**, 84433-56-7; **17**, 52376-09-7; **18**, 84433-57-8; **19**, 10234-40-9; **20**, 54535-06-7; **21**, 42397-72-8; catechol, 120-80-9; ethyl 2-bromovalerate, 615-83-8; ethyl bromoacetate, 105-36-2; 1,3-dibromopropane, 109-64-8; 2-(tetrahydropyran-2-yloxy)phenol, 21645-25-0.

Antifertility Agents. 38. Effect of the Side Chain and Its Position on the Activity of 3,4-Diarylchromans[1]

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In a study of the effect of the substituent on the receptor binding affinity (RBA), estrogenicity, and antiimplantation (AI) activity in *trans*-3,4-diarylchromans, it has been found that demethylation of *trans*-2,2-dimethyl-3-phenyl-4-[*p*-(β-pyrrolidinoethoxy)phenyl]-7-methoxychroman (centchroman, **1**)[2,3] to the corresponding 7-hydroxy compound (**7**) results in a 20-fold increase in RBA (112%) without any appreciable change in AI activity. On the other hand, absence of the pyrrolidinoethyl group from the 4-phenyl residue (**6**) leads to a drop in both RBA and AI activity. A chain length of two to three carbon atoms and a pyrrolidino ring appear to be necessary for activity in these compounds. It has been found that while the trans isomers with the tertiary aminoalkoxy side chain in the para position of the 4-phenyl radical were the most active, in the corresponding *cis*-chromans and chromenes, analogues with this chain in the meta position were most active; the ortho substituted compounds of all these series were inactive. In 3-phenyl-substituted compounds, the trans isomer carrying the *p*-hydroxy substituent (**33**) was found to be the most active; the corresponding pyrrolidinoethyl ether (**13**) showed a lower order of activity. The implication of these observations on the mapping of the different subsites on the receptor has been discussed.

In a study on antifertility activity, it has been found that the activity is confined mainly to the trans diastereomer for the 2,2-dimethyl-3,4-diphenylchromans[2] and to the levo enantiomer for the two optical antipodes. As a result of the detailed biological evaluation of these compounds, *trans*-2,2-dimethyl-3-phenyl-4-[*p*-(β-pyrrolidinoethoxy)-phenyl]-7-methoxychroman (centchroman, **1**, Chart I)[2,3] has emerged as a candidate drug for postcoital contraception and is in phase III clinical studies. In a substructure analysis, the effect of the tertiary aminoalkoxy side chain and of 7-methoxy group toward cytosol receptor binding affinity (RBA), estrogenicity, and antiimplantation (AI) activity has now been studied, and the results are reported in this paper.

Chemistry. *trans*-2,2-Dimethyl-3-phenyl-4-(*p*-hydroxyphenyl)-7-methoxychroman (**6**) was prepared by dimsyl cation isomerization, followed by debenzylation of

(1) CDRI communication no. 3152.
(2) Suprabhat Ray, P. K. Grover, V. P. Kamboj, B. S. Setty, A. B. Kar, and N. Anand, *J. Med. Chem.*, **19**, 276 (1976).
(3) N. Anand and S. Ray, *Indian J. Exp. Biol.*, **15**, 1142–1143 (1977).
(4) Md. Salman, Suprabhat Ray, V. P. Kamboj, and N. Anand, U.K. Patent Application GB 2055836A (1980).

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