2,3-Dihydro-7-hydroxy-4,6-dimethyl-1*H*-inden-1-one (18). Aluminum chloride (113 g, 0.85 mol) was added portionwise (ca. 15 min) to **18a** (76.2 g, 0.36 mol), and the well-stirred mixture was heated at 100 °C for 5 h and at ~170 °C for 2 h. After addition of ice, water, and concentrated HCl (200 mL), the product was obtained by steam distillation. Recrystallization from EtOH–H_2O gave 18 (11.3 g, 18%): mp 117–119 °C; ^{1}H NMR ($CDCl_3$) δ 2.1 (6 H, s, both CH_3), 2.7 (4 H, m, CH_2CH_2), 7.0 (1 H, s, H-5). Anal. ($C_{11}H_{12}O_2$) C, H.

2,3-Dihydro-4,6-dimethyl-7-hydroxy-1*H*-inden-1-one Oxime (19). This compound was prepared in a manner analogous to compound **15**, starting with **18** (12.0 g, 0.07 mol). Recrystallization from EtOH–H_2O gave **19** (12.8 g, 95%), mp 150–152 °C. Anal. ($C_{11}H_{13}NO_2$) H, N; C: calcd, 69.09; found, 69.51.

1-Amino-2,3-dihydro-4,6-dimethyl-1*H*-inden-7-ol Hydrochloride (20). This compound was prepared in a manner analogous to compound **16**, starting with **19** (6.35 g, 0.033 mol). Recrystallization gave **20** (4.9 g): ^{1}H NMR (Me_2SO-d_6) δ 2.1 (6 H, s, both CH_3), 2.4–3.0 (4 H, m, CH_2CH_2), 4.7 (1 H, br s, CH), 6.8 (H, s, H-5).

A prior run gave 1,1′-aminobis[2,3-dihydro-4,6-dimethyl-7-hydroxy-1*H*-indene] hydrochloride as the only product. Recrystallization from EtOH–Et_2O gave a 38% yield of this product: mp 183–186 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.1 (6 H, s, CH_3), 2.15 (6 H, s, CH_3), 2.5 (8 H, m, CH_2CH_2), 5.1 (2 H, br s, CH), 6.8 (2 H, s, H-5). Anal. ($C_{22}H_{27}NO_2$·HCl) C, H, N.

Acknowledgment. We extend our appreciation to O. W. Woltersdorf for the preparation of intermediates **3** and **4**, K. B. Streeter (retired) and his staff for elemental analyses, W. R. McGaughran (retired) and Dr. D. W. Cochran for NMR spectra, and to Mrs. T. H. Brunner for manuscript preparation.

Registry No. 1, 7523-34-4; **2**, 52780-66-2; **3**, 27366-42-3; **4**, 84174-48-1; **5**, 84174-49-2; **6**, 52780-64-0; **7**, 84174-50-5; **7a**, 84174-51-6; **8**, 66233-86-1; **8a**, 61627-00-7; **9**, 84174-52-7; **9a**, 84174-53-8; **10**, 84192-55-2; **10a**, 84174-54-9; **11**, 84174-55-0; **11a**, 84174-56-1; **12**, 84174-57-2; **12a**, 84174-58-3; **13**, 84174-59-4; **13a**, 84174-60-7; **14**, 84174-61-8; **15**, 84174-62-9; **16**, 84174-63-0; **17**, 84174-64-1; **18**, 84174-65-2; **18a**, 84174-66-3; **19**, 84174-67-4; **20**, 84174-68-5; $ClCH_2CONHCH_2OH$, 2832-19-1; 2-naphthalenol, 135-19-3; 2-chloro-*N*-[(2-hydroxynaphthalen-1-yl)methyl]acetamide, 84174-69-6; 4-chloro-1-naphthalenol, 604-44-4; [(6,7-dichloro-2-ethyl-2,3-dihydro-1-oxo-1*H*-inden-5-yl)oxy]acetic acid, 27366-21-8; 5,8-dimethyl-1,2,3,4-tetrahydro-6-naphthalenol, 28567-18-2; 6-quinolinol, 580-16-5; *N*-(hydroxymethyl)phthalimide, 118-29-6; 5-chloro-8-quinolinol, 130-16-5; 7-quinolinol, 580-20-1; 6,8-bis(aminomethyl)-7-quinolinol trihydrochloride, 84174-70-9; 7-bromo-6-quinolinol, 84174-71-0; 5-isoquinolinol, 2439-04-5; 6,8-bis(aminomethyl)-5-isoquinolinol trihydrochloride, 84174-72-1; 6-quinoxalinol, 7467-91-6; 2-methyl-6-benzothiazolol, 68867-18-5; 2-methyl-5,7-bis(phthalimidomethyl)-6-benzothiazolol, 84192-56-3; 6-hydroxy-4-methylcoumarin, 2373-31-1; 4-chloro-2,3-dihydro-7-hydroxy-1*H*-inden-1-one, 81945-10-0; 2,4-dimethylphenol, 105-67-9; 3-chloropropionyl chloride, 625-36-5; 1,1′-aminobis[2,3-dihydro-4,6-dimethyl-7-hydroxy-1*H*-indene] hydrochloride, 84174-73-2.

Supplementary Material Available: Intravenous dog data providing the milliequivalent per minute values for Na^+, K^+, and Cl^-, along with urine volume and creatinine clearance vs. controls and time of maximum effect (1 page). Ordering information is given on any current masthead page.

Notes

2-(Aminomethyl)phenols, a New Class of Saluretic Agents. 6.[1] Effects of N,O-Spiroannulation and Subsequent Quaternization

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The syntheses of a number of 3,4-dihydrospiro-2*H*-1,3-benzoxazines and their corresponding benzoxazinium salts are reported. The saluretic effects displayed by these N,O-spiroannulated 2-(aminomethyl)phenols appear to be, in part, inversely related to their respective in vivo rates of hydrolysis. Good antihypertensive effects are found only in spirobenzoxazinium **22**. Thus, a combination of spiroannulation and quaternization on **2** to produce **22** leads to a loss of saluretic effects with maintenance of antihypertensive effects and, thereby, serves to separate these pharmacological properties.

In Part 4[3] of this series, we demonstrated that, in general, monosubstitution on N with groups other than lower alkyl or substitution on N and/or O with groups resistant to hydrolysis substantially reduced saluretic effects.

In the present study, we have investigated the influence of N,O-spiroannulation and subsequent quaternization on the saluretic and antihypertensive effects of two of the more potent saluretic members of the 2-(aminomethyl)-phenol series (**1** and **2**).[4]

Chemistry. The preparation of spirobenzoxazines **3–16** (Table I) is outlined in Scheme I. Thus, condensation of equimolar amounts of the 2-(aminomethyl)phenol and a ketone in benzene with azeotropic removal of the water, either with or without the addition of a catalytic amount of HOAc (methods B or A,[5] respectively), afforded the desired compounds. Two other sets of reaction conditions

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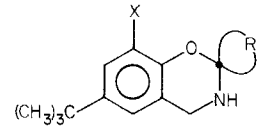
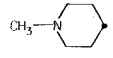
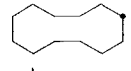
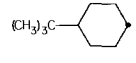
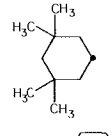
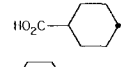
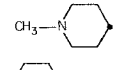
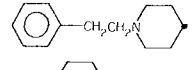
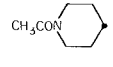
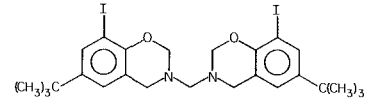
(1) For Part 5 see: Deana, A. A.; Stokker, G. E.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Russo, H. F.; Watson, L. S. *J. Med. Chem.*, under Articles in this issue.
(2) Deceased, May 31, 1977.
(3) Stokker, G. E.; Deana, A. A.; deSolms, S. J.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Baer, J. E.; Russo, H. F.; Watson, L. S. *J. Med. Chem.* **1981**, *24*, 1063.
(4) Stokker, G. E.; Deana, A. A.; deSolms, S. J.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Baer, J. E.; Ludden, C. T.; Russo, H. F.; Scriabine, A.; Sweet, C. S.; Watson, L. S. *J. Med. Chem.* **1980**, *23*, 1414.
(5) For an extensive study on the synthesis and chemical properties of 3,4-dihydrospirobenzoxazines, see McDonagh, A. F.; Smith, H. E. *J. Org. Chem.* **1968**, *33*, 1.

0022-2623/83/1826-0585$01.50/0

Table I. Effects of N,O-Spiroannulation

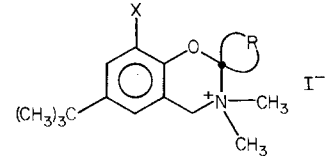


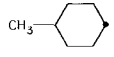
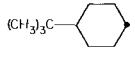
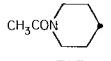
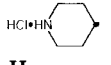
no.	X	R	method	yield, %	recrystn solvent[a]	mp, °C	formula	saluretic score[c] rat,[d,e] po	saluretic score[c] dog,[f,g] 5 mg/kg po	antihypertensive score[c] dose, mg/kg po	antihypertensive score[c] SH rat score[k,i]
1	Cl		*j*	44	EtOH/HCl	251–251.5 dec	$C_{11}H_{16}ClNO\cdot HCl$	6	4+	20 40	0 2
3	Cl		A	93	1	107–108	$C_{17}H_{24}ClNO$	3	5	20[k]	0
4	Cl		B	37	cyclohexane	135–137	$C_{17}H_{25}ClN_2O$	3	5	20	0[l]
2	I		*j*	81	EtOH/HCl	200–201 dec	$C_{11}H_{16}INO\cdot HCl$	6	6	5 1.25 0.31 0.08	3[m] 2[m] 1[m] 0[m]
5	I		A	64	1	100–101	$C_{17}H_{24}INO$	5	5	20 40	0[l] 1[l]
6	I		B	70	1	135–136.5	$C_{23}H_{36}INO$	4	2[i]	20 5	1+[l] 0[l]
7	I		B	63	1	141–142	$C_{18}H_{22}INO$	5	5	20 5	2+[m] 1[l]
8	I		B	89	1	165–166	$C_{21}H_{28}INO$	3	0	20 5	2 0[l]
9	I		A	54	1	108–109	$C_{21}H_{32}INO$	4	5	20[k]	0
10	I		A	63	1	171–172	$C_{21}H_{32}INO$	4		20 5	1[l] 0
11	I		A	67	EtOH/hexane	171–172	$C_{18}H_{24}INO_3\cdot {}^1/_6C_6H_{14}$	4	5	20 5	2 2+[l]
12	I		A	73	1	123–124	$C_{16}H_{22}INOS$	4	2[i]	20 5	2+ 0
13	I		B	57	1	155–156.5	$C_{17}H_{25}IN_2O$	4	5	20 20[k]	1[l] 2+
14	I		B	67	1	138–139	$C_{24}H_{31}IN_2O$	4	5+	20 5	1[m] 0[l]
15	I		B	29	C_6H_6	155–160	$C_{18}H_{25}IN_2O_2\cdot {}^1/_6C_6H_6$		4	20[k]	0

16	I		A	40	C_6H_6	177–178	$C_{28}H_{36}I_2N_2O_2$	2	±	20 5	2+ 0
19			*n*	31	C_6H_6/ hexane	181–182	$C_{25}H_{32}I_2N_2O_2$	±		20[k]	0

[a] Solvents of recrystallization: 1, EtOH; 2, EtOH–H_2O; 3, EtOH–Et_2O. [b] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [c] For testing protocols, see ref 4. [d] For scoring system, see ref 4. [e] Score is for geometric mean of three animals per cage, three cages per dose. [f] Millequivalents of Na excreted in first 5 h: 0, <2 mequiv; ±, >2 mequiv; 1, <8 mequiv; 2, <15 mequiv; 3, <25 mequiv; 4, <35 mequiv; 5, <45 mequiv; 6, <55 mequiv. [g] Score is for single dog unless otherwise designated. [h] Maximum fall in mmHg: 0, <20 mm; 1, <30 mm; 2, <40 mm; 3, >40 mm. [i] Score is for average of two animals. [j] Ref 4. [k] Intraperitoneal administration. [l] Score is for average value of four animals. [m] Score is for average value of six animals. [n] See Experimental Section.

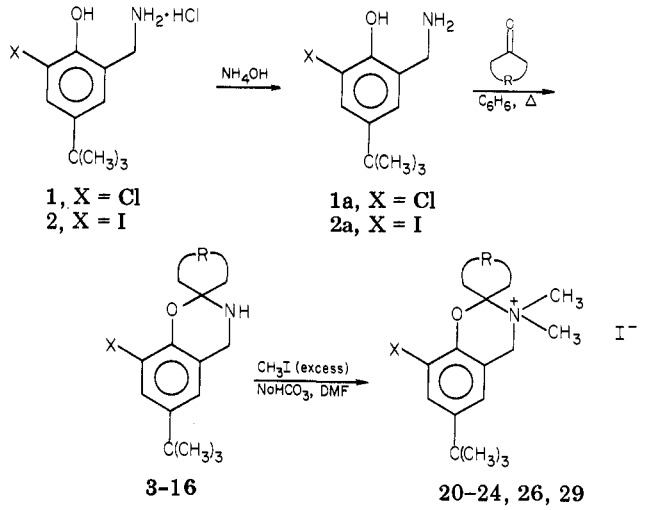
Table II. Effects of Quaternization



no.	X	R	method	yield, %	recrystn solvent[a]	mp, °C	formula[b]	saluretic score[c] rat,[d,e] po	saluretic score[c] dog,[f,g] 5 mg/kg po	antihypertensive score[c] dose, mg/kg po	antihypertensive score[c] SH rat score[h,i]
20	Cl		C	58	2	175–176 dec	$C_{19}H_{29}ClINO$[j]	0	±	20 20[k]	0 0.5
21	I		D	23	3	192.5–193	$C_{18}H_{27}I_2NO$			20 20[k]q	0 3
22	I		C	80	2	199–200 dec	$C_{19}H_{29}I_2NO$	0	0	5 0.31 0.08	2[l] 2[l] 0[l]
22a[m]	I		*n*	66	3	159–160 dec	$C_{21}H_{32}INO_3 \cdot 0.5H_2O$	0	0	5 0.31	2[l] 1[l]
23	I		D	32	3	184–184.5 dec	$C_{20}H_{31}I_2NO$[q]			20	0
24	I		C	63	2	151–153 dec	$C_{23}H_{37}I_2NO \cdot 0.5H_2O$	0	0	20 20[k]	0 2
25	I		*n*	55	1	150–151	$C_{22}H_{30}INO$	2	0	20[k]	0
26	I		C	70	2	148–150 dec	$C_{20}H_{30}I_2N_2O_2 \cdot 1.5H_2O$	0	0	20 5	2 0
27	I		*n*	62	3	163–164 dec	$C_{18}H_{28}ClIN_2O \cdot HCl \cdot 0.5H_2O$	0	0	20 20[k]	0 0
28	I	H_2	*n*	38	1	226–227 dec	$C_{14}H_{21}I_2NO$	0		5 20[k]	0 2
29[o]	I	$(CH_3)_2$	D	4[p]	3	210–211 dec	$C_{16}H_{25}I_2NO$[q]			20[k]	0

[a–i] See footnotes *a–i*, Table I. [j] Anal. Calcd: C, 50.74. Found: C, 50.28. [k] Intraperitoneal administration. [l] Score is for average value of four animals. [m] Acetate instead of iodide. [n] See Experimental Section. [o] NMR and IR spectra of intermediate condensation product indicates ca. 15% of the imine is present. For 29: ^1H NMR (Me_2SO-d_6) δ 1.25 (9 H, s), 1.8 (6 H, s), 4.8 (2 H, s), 7.3 (1 H, d, J = 2 Hz), 7.8 (1 H, d, J = 2 Hz). [p] Plus an equal amount of the corresponding hydroxytrimethylammonium iodide.[3] [q] Anal. Calcd: C, 43.26. Found: 43.68.

Scheme I



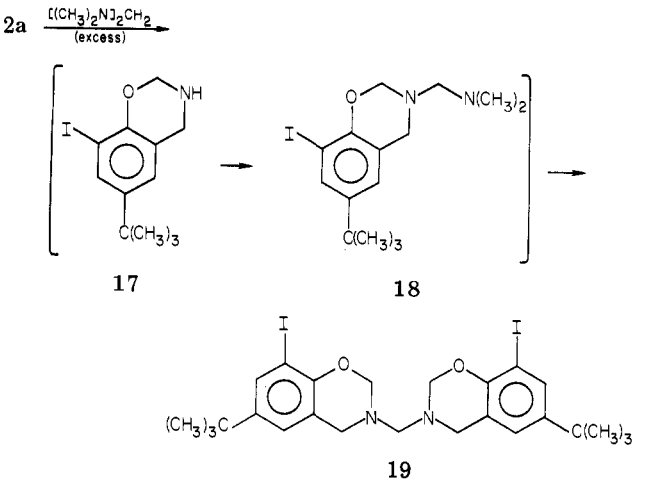
1, X = Cl
2, X = I

1a, X = Cl
2a, X = I

3-16

20-24, 26, 29

Scheme II



17

18

19

for condensation with nonbasic ketones (i.e., the preparation of **5** and **8**) were explored very briefly and were found to reproduce the yields and purity of methods A or B. These consisted of allowing a solution of **2a** and the ketone in THF or benzene (or just excess ketone as solvent, as in the first step of **29**) to stand over anhydrous $MgSO_4$ or 4 Å Linde molecular sieves for several hours at 20 °C, followed by filtration and evaporation.[5]

In order to examine the saluretic and antihypertensive properties of the simplest, properly substituted benzoxazine, the synthesis of **17** was attempted. Condensation of **2a** with an equimolar amount of formaldehyde yielded only the corresponding 1,3,5-tris(*o*-hydroxybenzyl)hexahydro-*s*-triazine in accordance with McDonaghs' observations using 2-(aminomethyl)phenol per se.[5] Condensation of **2a** with excess bis(dimethylamino)methane (formaldehyde equivalent)[6] as shown in Scheme II provided methylenebis(benzoxazine) **19** which arose via intermediates **17** [isolated and characterized as the quaternary salt (**28**)] and **18** (isolated and characterized; see Experimental Section). This result is consistent with the earlier observation of Holly and Cope[7] that the condensation of 2-(aminomethyl)phenol with a large excess of formaldehyde yields 3,3′-methylenebis(3,4-dihydro-2*H*-1,3-benzoxazine).

The NMR of spirobenzoxazines **3–16** in chloroform-*d* are in strict agreement with their assigned structures, with the exceptions of **6** and **7**, which show unequivocal evidence for the presence of small amounts of the tautomeric Shiff base (CH_2N = R, δ 4.8). However, the infrared spectra (KBr disk) of **6** and **7** displayed a lack of C=N absorption (1675 cm^{-1}) and showed only NH absorption at 3310–3330 cm^{-1}; therefore, within detectable limits, these two compounds exist only as the ring-closed tautomer in the solid state.

The resistance of spirobenzoxazines **3–16** to hydrolysis (retrospiroannulation) is governed by the aromatic halogen and also, to a lesser extent, by the spiroannulated ketone. The effect of halogen can be illustrated by the following examples: (a) **13** may be crystallized from 95% EtOH, whereas **4** is hydrolyzed in this solvent; (b) **5** is stable to aqueous buffered solutions at pH's 7 and 8 (25 °C for 4 h), whereas **3** is hydrolyzed at pH 5–8. Therefore, the iodo compounds appear to be more stable than their chloro counterparts. The effects of the spiroannulated ketones on the apparent rates of hydrolysis of a selected number of iodospirobenzoxazines were examined in aqueous buffered solutions at pH 5–8 at 25 °C for 4 h and were found to be **13** > **5** > **7** ≈ **8**.

The majority of the quaternary salts listed in Table II were prepared by exhaustive methylation of the antecedent spirobenzoxazines (method C) in DMF, as illustrated in Scheme I, or by a "one-pot" sequence without isolation of the intermediate spirobenzoxazines (method D). Acetate **22a** was prepared by anion exchange on **22**, while **27** was prepared by acidic hydrolysis of **26**, followed by an anion exchange. The synthesis of **28** was described earlier.

Exhaustive methylation of **8** (method C) provided none of the expected quaternary salt but only the monomethyl compound (**25**). The failure of **25** to form a quaternary salt can be understood by examination of a model of **25**, wherein severe steric interaction of the 2,6-diaxial hydrogen atoms of the spiroannulated adamantyl ring prevents the approach of a second methyl group. This rigid structure precludes oxazine ring flip via nitrogen inversion, as shown by the nonequivalence of the oxazine methylene protons in the ^1H NMR spectra (δ 3.5 and 4.2, respectively). Interestingly, whereas the exhaustive methylation of **5** may also be accomplished in EtOH, the use of EtOH for the preparation of **25** provided none of the methylated product.

Pharmacology. The saluretic data in Table I indicate that spiroannulation of potent 2-(aminomethyl)phenols **1** or **2** with cyclic ketones generally leads to slight diminution of effects in the rat. In some instances, the effects were diminished in the dog as well. The saluretic effects of these spirobenzoxazines appear to be inversely related (in a limited way) to their respective in vivo hydrolytic stability, at least in dogs. Comparison of the scores of **5**, **7**, **8**, and **13** with their respective hydrolytic stability (vida supra) reveals that **8** (the most stable spirobenzoxazine tested) was also the least active in rats and dogs.

The increase in lipophilicity of the spirobenzoxazines over that of the parent 2-(aminomethyl)phenols by elimination of their amphoteric properties may also be a factor. A positive consequence of this property was demonstrated by observing a very slight enhancement of saluretic effects of **5** and **12** over that of **2** when applied topically (**2** elicits only a slightly lower saluretic response when applied topically than when administered, iv, ip, or po, a mode of administration not effective with hydrochlorothiazide or furosemide).[8] A similar potentiation was also observed in antiinflammatory activity upon topical application to

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(8) Russo, H. F.; Watson, L. S., unpublished results.

croton oil induced swelling in mouse ears, particularly in the case of **12**.[9]

When evaluated in spontaneously hypertensive (SH) rats, spirobenzoxazines **5–19** exhibited greatly reduced antihypertensive effects in all cases (Table I).

Without exception, quaternization of the spirobenzoxazines abolished saluretic effects (Table II). These results confirm the detrimental influence of quaternization noted in Part 4.[3] Moreover, the scores for these spirobenzoxazinium salts, in conjunction with their remarkable stability under both acid and basic conditions, lend credence to the inverse correlation between saluretic effects and hydrolytic stability.

An interesting observation to emerge from this study was the discovery that the quaternization of **5** to yield **22** resulted in restoration of antihypertensive activity (SH rat, Table II) to nearly the level of that elicited by **2** [the most potent antihypertensive agent prepared in the course of our study of 2-(aminomethyl)phenols]. The severe structural requirements necessary for this activity may be seen by comparing the relative inactivity caused by ring contraction (**21**), or 4′-methylation (**23**), with that of **22**. Thus, a combination of these two chemical operations (spiroannulation with cyclohexanone and quaternization with methyl iodide) leads to a loss of saluretic effects with retention of antihypertensive effects and, thus, serves to separate these pharmacological properties.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. ^{1}H NMR spectra were recorded on either a Varian T-60 or EM-390 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as the internal standard. Elemental analysis for carbon, hydrogen, and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of theory unless noted otherwise. All starting materials were commercially available unless so indicated.

2-(Aminomethyl)-6-chloro-4-(1,1-dimethylethyl)phenol (1a). This compound was prepared similarly to **2a**[3] by neutralization of **2** with 15 N NH_4OH: yield of **2a** 98%; mp 195–197 °C.

Method A. 6-(1,1-Dimethylethyl)-3,4-dihydro-8-iodospiro[2*H*-1,3-benzoxazine-2,4′-tetrahydrothiopyran] (12). A mixture of **2a**[3] (3.0 g, 10 mmol), tetrahydrothiopyran-4-one (1.18 g, 10 mmol) and benzene (100 mL) was refluxed under a Dean–Stark trap for 4 h. The solvent was evaporated, and the residue was crystallized to yield **12** (2.5 g): ^{1}H NMR ($CDCl_3$) δ 1.2 (9 H, s), 1.8–3.2 (8 H, m), 4.0 (2 H, s), 6.9 (1 H, d, J = 2 Hz), 7.6 (1 H, d, J = 2 Hz).

Method B. 6-(1,1-Dimethylethyl)-3,4-dihydro-8-iodo-1′-methylspiro[2*H*-1,3-benzoxazine-2,4′-piperidine] (13). A mixture of **2a** (6.0 g, 20 mmol), 1-methyl-4-piperidinone (2.24 g, 20 mmol), acetic acid (2 mL), and benzene (100 mL) was refluxed under a Dean–Stark trap for 4 h. The clear yellow solution was cooled and washed successively with 2% NaOH solution, H_2O, and saturated brine and dried ($MgSO_4$). The residue that remained after evaporation of the solvent was crystallized to afford **13** (4.6 g): ^{1}H NMR ($CDCl_3$) δ 1.2 (9 H, s), 1.9 (4 H, t, J = 4 Hz), 2.4 (3 H, s), 2.6 (4 H, t, J = 4 Hz), 4.0 (2 H, br s), 7.0 (1 H, d, J = 2 Hz), 7.7 (1 H, d, J = 2 Hz).

Method C. 6-(1,1-Dimethylethyl)-3,4-dihydro-8-iodo-3,3-dimethylspiro[2*H*-1,3-benzoxazinium-2,1′-cyclohexane] Iodide (22). Sodium bicarbonate (840 mg, 10 mmol) was added to a solution of **5** (3.8 g, 10 mmol) in dry DMF (50 mL) immediately followed by methyl iodide (10 mL). The mixture was stirred at 20 °C for 16 h, diluted with Et_2O (100 mL), and filtered, and the crystals were washed with H_2O. After crystallization, the yield of **22** was 8.6 g: ^{1}H NMR (Me_2SO-d_6) δ 1.3 (9 H, s), 1.5–2.3 (10 H, m), 3.2 (6 H, s), 4.9 (2 H, br s), 7.3 (1 H, d, J = 2 Hz), 7.8 (1 H, d, J = 2 Hz).

Method D. 6-(1,1-Dimethylethyl)-3,4-dihydro-8-iodo-3,3-dimethylspiro[2*H*-1,3-benzoxazinium-2,1′-cyclopentane] Iodide (21). A solution of **2a** (1.5 g, 5 mmol), cyclopentanone (0.5 g, 5.9 mmol), and benzene (50 mL) was refluxed under a Dean–Stark trap for 3 h. The benzene was evaporated, and the residue was dissolved in dry DMF (20 mL). Sodium bicarbonate (420 mg, 5 mmol) and methyl iodide (5 mL, excess) were added. The mixture was stirred at 20 °C for 16 h and then diluted with Et_2O (200 mL) and filtered, and the crystals were washed with H_2O: yield of **21** after crystallization 600 mg; ^{1}H NMR (Me_2SO-d_6), δ 1.3 (9 H, s), 1.7–2.2 (8 H, m), 3.3 (6 H, s), 4.9 (2 H, s), 7.3 (1 H, d, J = 2 Hz), 7.8 (1 H, d, J = 2 Hz).

3,3′-Methylenebis[6-(1,1-dimethylethyl)-3,4-dihydro-8-iodo-2*H*-1,3-benzoxazine] (19). A mixture of **2a** (6 g, 20 mmol) in bis(dimethylamino)methane (50 mL, large excess) was stirred at reflux for 15 min (clear solution formed on heating). Evaporation and subsequent crystallization provided **19** (3 g): ^{1}H NMR ($CDCl_3$) δ 1.2 (18 H, s), 3.7 (2 H, s), 4.0 (4 H, s), 4.9 (4 H, s), 6.8 (1 H, d, J = 2 Hz), 7.5 (1 H, d, J = 2 Hz).

In the first preparation, the crude product was crystallized from petroleum ether to provide **18** (750 mg from 750 mg of **2a**, 80%): mp 82–84 °C; ^{1}H NMR ($CDCl_3$) δ 1.2 (9 H, s), 2.2 (6 H, s), 3.2 (2 H, s), 4.0 (2 H, s), 5.0 (2 H, s), 6.9 (1 H, d, J = 2 Hz), 7.5 (H, d, J = 2 Hz). Anal. Calcd for $C_{15}H_{23}IN_2O$: C, 48.14; N, 7.48. Found: C, 48.73; N, 7.00. However, subsequent attempts at obtaining **18** afforded only the disproportionated product **19** as does recrystallization of **18** at a higher temperature (benzene–hexane).

6-(1,1-Dimethylethyl)-3,4-dihydro-8-iodo-3,3-dimethylspiro[2*H*-1,3-benzoxazinium-2,1′-cyclohexane] Acetate Hemihydrate. (22a). Benzoxazinium iodide **22** (1.36 g, 2.5 mmol) was dissolved in 50% aqueous HOAc (200 mL) and passed down a column of Dowex-1 X2 (CH_3CO_2) resin. The first 350 mL collected was evaporated, and the residue was crystallized to give **22a** (800 mg): ^{1}H NMR ($CDCl_3$) δ 1.3 (9 H, s), 1.6–2.35 (10 H, m), 2.0 (3 H, s), 3.5 (6 H, s), 5.1 (2 H, s), 7.2 (1 H, d, J = 2 Hz), 7.8 (1 H, d, J = 2 Hz).

6-(1,1-Dimethylethyl)-3,4-dihydro-8-iodo-3,3-dimethylspiro[2*H*-1,3-benzoxazinium-2,4′-piperidine] Chloride Hydrochloride Hemihydrate (27). A solution of **26** (7.75 g, 13 mmol) in EtOH (40 mL) and concentrated HCl (20 mL) was refluxed for 1.5 h. The residue from evaporation of the solvent was dissolved in H_2O (50 mL) and passed down a column of Dowex-1 (Cl^-) resin. The first 150 mL of eluate was evaporated and crystallized to yield **27** (4 g): ^{1}H NMR (Me_2SO-d_6) δ 1.2 (9 H, s), 1.9–3.5 (8 H, m), 3.3 (6 H, s), 3.9 (1 H, s, H_2O), 5.1 (2 H, br s), 7.3 (1 H, d, J = 2 Hz), 7.8 (1 H, d, J = 2 Hz).

6-(1,1-Dimethylethyl)-3,4-dihydro-8-iodo-3-methylspiro-[2*H*-1,3-benzoxazine-2,2′-tricyclo[3.3.1.1^{3,7}]decane] (25). Sodium bicarbonate (1.7 g, 20 mmol) was added to a solution of **8** (8.8 g, 20 mmol) in dry DMF (100 mL), followed immediately by methyl iodide (20 mL, excess). After stirring at 20 °C for 16 h, the mixture was evaporated, and the residue was triturated with H_2O. Crystallization of the crude solid provided **25** (5 g): ^{1}H NMR (Me_2SO-d_6) δ 1.2 (9 H, s), 1.4–2.2 (14 H, m), 2.2 (3 H, s), 3.5 (1 H, d, J = 18 Hz), 4.2 (1 H, d, J = 18 Hz), 7.0 (1 H, d, J = 2 Hz), 7.5 (1 H, d, J = 2 Hz).

6-(1,1-Dimethylethyl)-3,4-dihydro-8-iodo-3,3-dimethyl-2*H*-1,3-benzoxazinium Iodode (28). A solution of **2a** (1.5 g, 5 mmol) and bis(dimethylamino)methane (550 mg, 5.5 mmol) in THF (20 mL) was refluxed for 5 min, cooled to 20 °C, and then treated with $NaHCO_3$ (420 mg, 5 mmol) and methyl iodide (5 mL, excess). After stirring the mixture at 20 °C for 40 h, it was cooled to −20 °C and filtered, and the solid was washed with H_2O and then Et_2O to give crude **28** (1.2 g), mp 226–227 °C dec. Crystallization provided pure **28** (900 mg): ^{1}H NMR (Me_2SO-d_6) δ 1.3 (9 H, s), 3.3 (6 H, s), 4.8 (2 H, s), 5.3 (2 H, s), 7.3 (1 H, d, J = 2 Hz), 7.7 (1 H, d, J = 2 Hz).

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Anticoccidial Activity of Crown Polyethers

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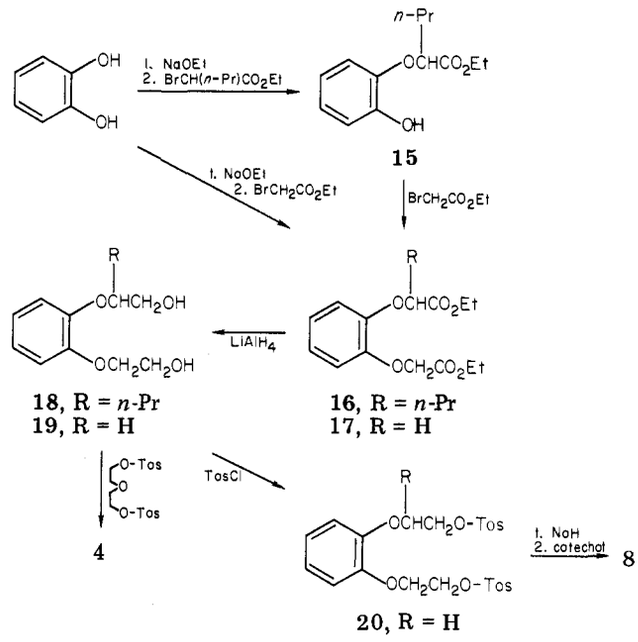
Anticoccidial activity in vitro against *Eimeria tenella* is reported for crown polyethers with ring sizes from 14 to 30 atoms. The most potent compounds, 4 and 9, were found active at 0.33 ppm, but none were active in vivo. Test results are discussed in terms of lipophilic shielding of complexed cations.

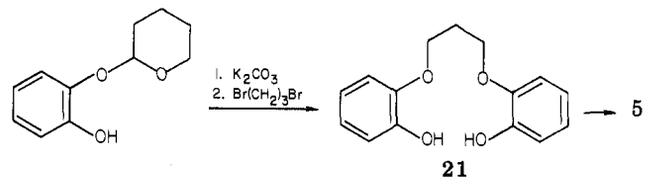
There is a need to discover new agents for the control of coccidial infections in poultry farms because these parasites restrict the growth of birds and can be eventually lethal. In addition, the prophylactic use of chemotherapy has led to the development of drug resistance by coccidia to many agents. 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]

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