2-(Aminomethyl)phenols, a New Class of Saluretic Agents. 5. Fused-Ring Analogues

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A number of bicyclic ring-fused analogues of 2-(aminomethyl)phenol were synthesized and tested orally in rats and intravenously in dogs for saluretic and diuretic effects. Of the 15 alicylic, aromatic, and heterocyclic ring-fused compounds tested, only 2-(aminomethyl)-4-chloro-1-naphthalenol hydrochloride (**2**) and 7-(aminomethyl)-6-hydroxy-5,8-dimethyl-1,2,3,4-tetrahydronaphthalene hydrochloride (**6**) displayed a high order of activity.

In Part 1 of this series,[2] we reported on a number of 2-(aminomethyl)phenols that were shown to possess a high order of diuretic activity in rats and dogs. Subsequent publications have dealt with replacement of the aromatic nucleus with a pyridine ring,[3] functional group reorientation and modification,[4] and nitrogen and/or oxygen substitution of the 2-(aminomethyl)phenol nucleus.[5] This report describes the preparation of a number of alicyclic, aromatic, and heterocyclic ring-fused analogues of 2-(aminomethyl)phenol and the effects of these structural modifications on saluretic activity.

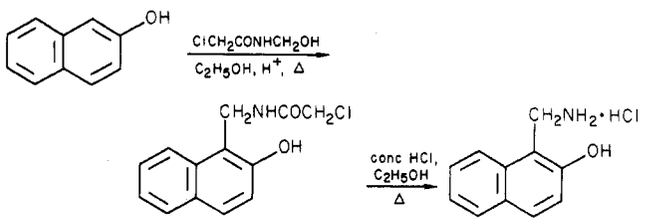
Chemistry. The compounds prepared for this study are listed in Table I, and their routes of syntheses are summarized in Schemes I–III. The alicyclic and aromatic ring-fused 2-(aminomethyl)phenols **1**, **2**, **5**, and **6**, as well as the coumarin analogue **14**, were prepared via acid-catalyzed, nuclear amidoalkylation of the corresponding phenols with 2-chloro-*N*-(hydroxymethyl)acetamide and subsequent hydrolysis of the intermediate amides (Scheme I). 6,7-Dichloro-2-ethyl-2,3-dihydro-1*H*-inden-5-ol (**4**), the precursor to **5**, was prepared by Clemmensen reduction of **3**, which in turn was obtained by dealkylation of the corresponding oxyacetic acid.[6]

The heterocyclic ring-fused 2-(aminomethyl)phenol derivatives **7**–**13** were also prepared from their phenol precursors, but in these cases, *N*-(hydroxymethyl)-phthalimide, a more reactive electrophilic alkylating agent, was used (Scheme II). In general, the imidoalkylation reaction with the heterocyclic phenols was carried out in concentrated sulfuric acid. 5-(Phthalimidomethyl)-6-quinoxolinol (**12a**), the one exception to this procedure, was prepared by using boron trifluoride etherate. Conversion of the intermediate imides into amines required somewhat more rigorous conditions than did hydrolysis of the amides.

Preparation of 4-chloro-7-hydroxy-2,3-dihydro-1*H*-inden-1-one, the precursor to **16**, had been reported in the literature.[7] By a similar procedure, acylation of 2,4-dimethylphenol with 3-chloropropionyl chloride gave the ester **18a**, which was subjected to a Fries rearrangement and subsequent cyclization in the presence of aluminum chloride to yield the indanone **18**. These ketones were converted to their respective oximes **15** and **19**, which were reduced catalytically to amines **16** and **20** (Scheme III). Reaction of **16** with iodine monochloride under aqueous conditions provided **17**.

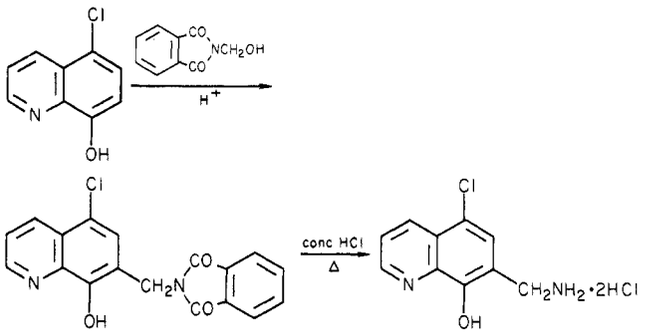
Pharmacology. The target compounds were tested orally in rats for their saluretic properties; the data are limited to Na^+ excretion values, which are presented in a scored foremat in Table I. The data for furosemide and hydrochlorothiazide, as well as that for 2-(aminomethyl)phenol, are included for comparative purposes.

Scheme I



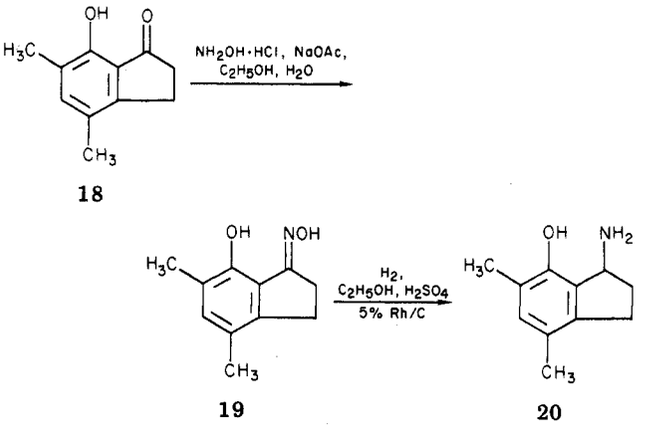
1

Scheme II



8a 8

Scheme III



18

19 20

The testing protocols and scoring system are given in Part 1 of this series.[2] Intravenous dog data are included to

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(1) Deceased, May 31, 1977.
(2) 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.
(3) Stokker, G. E.; Smith, R. L.; Cragoe, E. J., Jr.; Ludden, C. T.; Russo, H. F.; Sweet, C. S.; Watson, L. S. *J. Med. Chem.* **1981**, *24*, 115.
(4) 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.

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demonstrate the presence or absence of a diuretic response in a second species.

According to the testing data in Table I, carbocyclic annulation at the 4,5-position, as well as at the 5,6-position, of the 2-(aminomethyl)phenol enhanced the saluretic activity significantly in the two examples studied. The potency of tetralin **6** is substantially greater than that of the structurally similar monocyclic counterpart, 2-(aminomethyl)-3,4,5,6-tetramethylphenol (compound **121** in Part 1). A series of closely related structures with diuretic, hypotensive, and antiinflammatory activity was recently disclosed by Japanese researchers.[8] Naphthalene **2**, an example of a 5,6-annulated system, gave a better response than did 2-(aminomethyl)-4-chloro-5,6-dimethylphenol (compound **109** in Part 1). Compound **5**, having a 3,4-ring fusion, was inactive when compared to 2-(aminomethyl)-5,6-chloro-3,4-dimethylphenol (compound **115** in Part 1). The remaining 3,4-annulated compound, **1**, possessed only a low order of activity.

Concomitant ring annulation of 2-(aminomethyl)phenol, along with incorporation of a second nitrogen atom in the fused ring, afforded quinolines, which were almost ineffective in producing saluresis in the rat. On the other hand, quinolines **7** and **8**, as well as isoquinoline **11** and quinoxaline **12**, display weak but demonstrable activity in the dog. Based on past structure–activity relationships, it was thought that introduction of a halogen atom adjacent to the hydroxy group in compound **7** might markedly enhance the activity. In fact, quinoline **10** was found to be only very slightly more active than **7** in the rat. The remaining heterocyclic ring-fused 2-(aminomethyl)phenols **9**, **13**, and **14** were inactive in both assays.

Annulation at the α,3-positions of the 2-(aminomethyl)phenol to a five-membered ring afforded 1-aminoindans **16**, **17**, and **20**, which were considerably less active than their ring-opened counterparts (**37**, **98**, and **102** in Part 1).

Conclusion

The test data presented in Table I, although not constituting an extensive structure–activity relationship study, do allow for several plausible conclusions. Carbocyclic annulation at the 4,5- or 5,6-positions of 2-(aminomethyl)phenol increases salidiuretic activity as seen with compounds **2** and **6**, which are more active than their monocyclic counterparts. In contrast, in the eight examples we report (**7–14**), fusion of a heterocyclic ring onto the 2-(aminomethyl)phenol nucleus does not provide any significant increase in potency. Alkyl substitution at the α carbon, along with concomitant cyclization, as with compounds **16**, **17**, and **20**, appears to be detrimental to activity.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer, and the 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 noted otherwise.

1-(Aminomethyl)-2-naphthalenol Hydrochloride (1). This compound was prepared in a manner analogous to method A_1 in Part 1 of this series,[2] starting with 2-naphthalenol (10 g, 0.0694 mol). Recrystallization gave **1** (3.6 g).

2-(Aminomethyl)-4-chloro-1-naphthalenol Hydrochloride (2). This compound was prepared in a manner analogous to method A_5 in Part 1 of this series,[2] starting with 4-chloro-1-naphthalenol (8.9 g, 0.05 mol). Recrystallization gave **2** (2.8 g).

6,7-Dichloro-2-ethyl-2,3-dihydro-5-hydroxy-1*H*-inden-1-one (3). This compound was prepared in a manner analogous to step E of ref 6, starting with [(6,7-dichloro-2-ethyl-2,3-dihydro-1-oxo-1*H*-inden-5-yl)oxy]acetic acid[6] (60 g, 0.198 mol). Recrystallization from EtOH gave **3** (39.0 g, 80%), mp 236–238 °C. Anal. ($C_{11}H_{10}Cl_2O_2$) C, H, Cl.

6,7-Dichloro-2-ethyl-2,3-dihydro-1*H*-inden-5-ol (4). A mixture of **3** (14 g, 0.057 mol), concentrated HCl (60 mL), H_2O (25 mL), toluene (75 mL), and zinc amalgam (prepared from 35 g of mossy zinc) was stirred at reflux for 20 h. An additional 50 mL of concentrated HCl was added dropwise during the first 8 h. The reaction mixture was cooled and separated. The toluene solution was dried over $MgSO_4$ and filtered, and the filtrate was evaporated in vacuo. Recrystallization of the residue from hexane gave **4** (9.8 g, 74%), mp 59–60 °C. Anal. ($C_{11}H_{12}Cl_2O$) H; C: calcd, 57.16; found, 57.60.

4-(Aminomethyl)-6,7-dichloro-2-ethyl-2,3-dihydro-1*H*-inden-5-ol Hydrochloride (5). This compound was prepared in a manner analogous to method A_4 in Part 1 of this series,[2] starting with **4** (4 g, 0.0173 mol). Recrystallization gave **5** (2.6 g): ^{1}H NMR (Me_2SO-d_6) δ 0.94 (3 H, t, CH_3), 1.2–1.7 (2 H, m, CH_2), 2.2–3.5 (5 H, m), 4.0 (2 H, br s, CH_2).

7-(Aminomethyl)-5,8-dimethyl-1,2,3,4-tetrahydro-6-naphthalenol Hydrochloride (6). This compound was prepared in a manner analogous to method A_1 in Part 1 of this series,[2] starting with 5,8-dimethyl-1,2,3,4-tetrahydro-6-naphthalenol[9] (3.1 g, 0.0176 mol). Recrystallization gave **6** (1.6 g): ^{1}H NMR (Me_2SO-d_6) δ 1.5–1.9 (4 H, m), 2.1 (3 H, s, CH_3), 2.2 (3 H, s, CH_3), 2.2–2.7 (4 H, m), 3.9–4.3 (2 H, m, CH_3).

Preparation of Compound 7. (a) 5-(Phthalimidomethyl)-6-quinolinol (7a). A mixture of 6-quinolinol (1.45 g, 0.01 mol) and *N*-(hydroxymethyl)phthalimide (1.8 g, 0.01 mol) in concentrated H_2SO_4 (10 mL) was stirred at room temperature for 18 h and then poured into ice and water. The crude imide that separated was collected and air-dried. Recrystallization of a sample of the product from EtOH–H_2O gave **7a** as a white solid: mp 288–292 °C; ^{1}H NMR (CF_3COOD) δ 5.6 (2 H, s, CH_2), 7.9-8.3 (7 H, m), 8.8 (1 H, d, H-2, J = 4 Hz), 9.8 (1 H, d, H-4, J = 8 Hz).

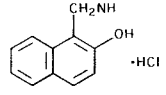
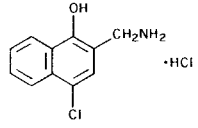
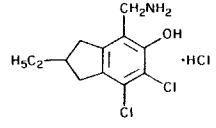
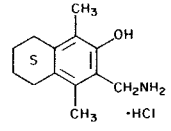
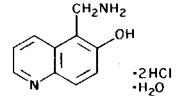
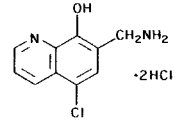
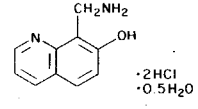
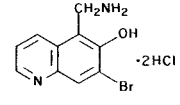
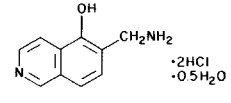
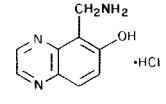
(b) 5-(Aminomethyl)-6-quinolinol Dihydrochloride Hydrate (7). A mixture of **7a** in EtOH (150 mL), H_2O (5 mL), and concentrated HCl (5 mL) was heated at reflux for 2 h and then concentrated to dryness. After addition of cold water and filtration to remove the phthalic acid, the solution was concentrated to dryness. Recrystallization gave **7** as a pale yellow solid (1.1 g): ^{1}H NMR (D_2O) δ 4.8 (2 H, s, CH_2), 7.9 (1 H, d, H-7, J = 8 Hz), 8.2 (1 H, dd, H-3, J = 5 and 8 Hz), 8.4 (1 H, d, H-8, J = 8 Hz), 9.1 (1 H, dd, H-2, J = 1 and 5 Hz), 9.4 (1 H, dd, H-4, J = 1 and 8 Hz).

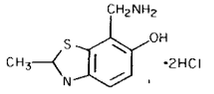
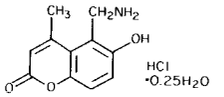
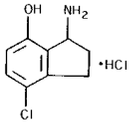
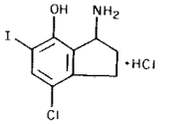
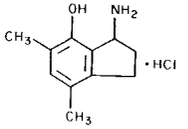
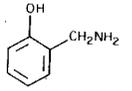
Preparation of Compound 8. (a) 5-Chloro-7-(phthalimidomethyl)-8-quinolinol (8a). *N*-(Hydroxymethyl)phthalimide (19 g, 0.107 mol) was added portionwise (1 h) to a well stirred solution of 5-chloro-8-quinolinol (18 g, 0.1 mol) in concentrated H_2SO_4 (200 mL) with cooling in an ice bath. After removal of the ice bath, the reaction mixture was heated on the steam bath for 25 h and poured into ice and water. The crude yellow imide that separated was collected and air-dried. Recrystallization of a sample of the product from C_6H_6 gave **8a** as a white crystalline solid: mp 245–247 °C dec; ^{1}H NMR (pyridine-d_5) δ 5.5 (2 H, s, CH_2), 7.4-8.1 (6 H, m), 8.6 (1 H, dd, H-4, J = 2 and 8 Hz), 9.0 (1 H, dd, H-2, J = 2 and 4 Hz). Anal. ($C_{18}H_{11}ClN_2O_3$).

(b) 7-(Aminomethyl)-5-chloro-8-quinolinol Dihydrochloride (8). A mixture of **8a** in concentrated HCl (2 L) was

(5) 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.* **1982**, *25*, 735.
(6) Woltersdorf, O. W., Jr.; deSolms, S. J.; Schultz, E. M.; Cragoe, E. J., Jr. *J. Med. Chem.* **1977**, *20*, 1400.
(7) Buck, J. S.; Cutler, R. A.; Nachod, F. C.; Powles, R. G.; Rakoczy, R.; Slauson, T. J.; Tullar, B. F. *J. Am. Chem. Soc.* **1957**, *79*, 3559.
(8) Konno, M.; Itoh, H.; Tokuhiro, T. German Patent 2 855 064, 1978.
(9) Fieser, L. F.; Lothrop, W. C. *J. Am. Chem. Soc.* **1936**, *58*, 2050.

Table I. Fused-Ring Analogues of 2-(Aminomethyl)phenol

compd	structure	precursor[b]	yield, %	recrystn solvent	mp, °C	formula[c]	score[a] rat[d] po	score[a] dog[e] iv
1		CA	25	H_2O	218–218.5 dec	$C_{11}H_{11}NO\cdot HCl$	±	1
2		CA	23	95% EtOH–conc HCl	221–222 dec	$C_{11}H_{10}ClNO\cdot HCl$	2	6
3		4	51	95% EtOH–conc HCl	244–244.5 dec	$C_{12}H_{15}Cl_2NO\cdot HCl$	0	0
6		LP (9)	38	95% EtOH–H_2O–HCl	235–235.5 dec	$C_{13}H_{19}NO\cdot HCl$	5	4[f]
7		CA	42	H_2O–conc HCl–EtOH	>300 dec	$C_{10}H_{10}N_2O\cdot 2HCl\cdot H_2O$	0	1[f,g]
8		CA	55	H_2O–conc HCl–EtOH	237–241 dec	$C_{10}H_9ClN_2O\cdot 2HCl$	±	1[f]
9		CA	44	H_2O–conc HCl–EtOH	>240 dec	$C_{10}H_{10}N_2O\cdot 2HCl\cdot 0.5H_2O$	0	0
10		LP (10)	61	H_2O–EtOH	260–265 dec	$C_{10}H_9BrN_2O\cdot 2HCl$	±	
11		CA	25	H_2O–conc HCl–EtOH	>380 dec	$C_{10}H_{10}N_2O\cdot 2HCl\cdot 0.5H_2O$	0	1[g]
12		LP (11)	29	95% EtOH	>300 dec	$C_9H_9N_3O\cdot HCl$	0	1[h]

13		LP (12)	50	H_2O–conc HCl–EtOH	>300 dec	$C_9H_{10}N_2OS \cdot 2HCl$	0	0[g]
14		LP (13)	44	EtOH–conc HCl	240–241 dec	$C_{11}H_{11}NO_3 \cdot HCl \cdot 0.25H_2O$	0	0
16		15	36	EtOH–H_2O	218–219 dec	$C_9H_{10}ClNO \cdot HCl$		1
17		16	40	EtOH–H_2O	208–210 dec	$C_9H_9ClNO \cdot HCl$	±	
20		19	69	EtOH–Et_2O	204–206 dec	$C_{11}H_{15}NO \cdot HCl$	0	0
							0	0
furosemide							3	6[i]
hydrochlorothiazide							2	1[h]

[a] For testing protocols and scoring system, see ref 2. [b] The starting materials were commercially available (CA), prepared as described under Experimental Section (compound number), or prepared by known literature procedures (LP), which is followed by ref number in parentheses. [c] Analytical results are within ±0.4% of theoretical values. [d] Score is for geometric mean of three animals per cage, three cages per dose, and is based on the use of a maximum dose of 50 mg/kg for compounds **1**, **2**, **5**, **6**, and **14** and a dose of 81 mg/kg for the remaining compounds. [e] Score is for average of two anesthetized dogs at 5 mg/kg stat (weight range 15.2–21 kg) unless otherwise designated. [f] Used conscious dogs. [g] Score is for a single dog. [h] Score is the average of three dogs. [i] 1 mg/kg.

heated at reflux with stirring for 52 h and then concentrated to 150 mL. The aqueous mixture was cooled and filtered to remove the phthalic acid, and the solution was concentrated to dryness. Recrystallization gave **8** as a yellow crystalline solid (15.5 g): ^{1}H NMR (Me_2SO-d_6) δ 4.3 (2 H, br q, CH_2), 7.8 (1 H, dd, H-3, J = 4 and 8 Hz), 8.0 (1 H, s, H-6), 8.7 (1 H, dd, H-4, J = 2 and 8 Hz), 9.0 (1 H, dd, H-2, J = 2 and 4 Hz).

Preparation of Compound 9. (a) 8-(Phthalimidomethyl)-7-quinolinol (9a). This compound was prepared in a manner analogous to **7a**, starting with 7-quinolinol (2.7 g, 0.015 mol). Recrystallization of a sample of the crude product from EtOH-H_2O yielded **9a**: mp 181–184 °C; ^{1}H NMR (Me_2SO-d_6) δ 5.5 (2 H, s, CH_2), 7.2 (1 H, d, H-6, J = 9 Hz), 7.3 (1 H, dd, H-3, J = 4 and 8 Hz), 7.8–8.0 (5 H, m), 8.3 (1 H, dd, H-4, J = 2 and 8 Hz), 8.8 (1 H, dd, H-2, J = 2 and 4 Hz).

(b) 8-(Aminomethyl)-7-quinolinol Dihydrochloride Hemihydrate (9). A mixture of **9a** in concentrated HCl (150 mL) was heated at reflux with stirring for 24 h and then worked up as for **7**. Recrystallization gave **9** as a white crystalline solid (1.7 g): ^{1}H NMR (D_2O) δ 4.8 (2 H, s, CH_2), 7.7 (1 H, d, H-6, J = 9 Hz), 8.0 (1 H, dd, H-3, J = 6 and 7 Hz), 8.3 (1 H, d, H-5, J = 9 Hz), 9.0–9.2 (2 H, m, H-2,4).

A small yield of 6,8-bis(aminomethyl)-7-quinolinol trihydrochloride was also isolated: mp >300 °C dec; ^{1}H NMR (D_2O) δ 4.5 (2 H, s, 6-CH_2), 4.8 (2 H, s, 8-CH_2), 8.1 (1 H, dd, H-3, J = 5 and 9 Hz), 8.2 (1 H, s, H-5), 9.2 (1 H, dd, H-2, J = 2 and 5 Hz), 9.4 (1 H, dd, H-4, J = 2 and 9 Hz). Anal. ($C_{11}H_{13}N_3O$·3HCl) C, H; N: calcd, 13.44; found, 12.91.

Preparation of Compound 10. (a) 7-Bromo-5-(phthalimidomethyl)-6-quinolinol (10a). This compound was prepared in a manner analogous to **7a**, starting with 7-bromo-6-quinolinol[10] (0.45 g, 0.002 mol). Recrystallization of a sample of the crude product from EtOH–H_2O yielded **10a**: mp 217–220 °C; ^{1}H NMR (Me_2SO-d_6) δ 5.3 (2 H, s, CH_2), 7.6 (1 H, dd, H-3, J = 5 and 9 Hz), 7.8 (4 H, s, C_6H_4), 8.3 (1 H, s, H-8), 8.5-8.8 (2 H, m, H-2,4).

(b) 5-(Aminomethyl)-7-bromo-6-quinolinol Dihydrochloride (10). A mixture of **10a** in concentrated HCl (40 mL) was heated at reflux with stirring for 6 h and then worked up as for **7**. Recrystallization gave **10** as a yellow crystalline solid (0.4 g): ^{1}H NMR (CF_3COOD) δ 5.2 (2 H, s, CH_2), 8.3 (1 H, dd, H-3, J = 5 and 8 Hz), 8.9 (1 H, s, H-8), 9.1 (1 H, d, H-2, J = 5 Hz), 9.5 (1 H, d, H-4, J = 8 Hz).

Preparation of Compound 11. (a) 6-(Phthalimidomethyl)-5-isoquinolinol (11a). This compound was prepared in a manner analogous to **7a**, starting with 5-isoquinolinol (1.45 g, 0.01 mol). Recrystallization of a sample of the crude product from EtOH–H_2O gave **11a** as a pale tan solid: mp >300 °C dec; ^{1}H NMR (CF_3COOD) δ 5.5 (2 H, s, CH_2), 7.8 (1 H, d, H-8, J = 8 Hz), 8.0 (4 H, s, C_6H_4), 8.3 (1 H, d, H-7, J = 8 Hz), 8.6 (1 H, d, H-4, J = 6 Hz), 8.9 (1 H, d, H-3, J = 6 Hz), 10.4 (1 H, s, H-1).

(b) 6-(Aminomethyl)-5-isoquinolinol Dihydrochloride Hemihydrate (11). A mixture of **11a** in concentrated HCl (100 mL) was heated at reflux with stirring for 4 h and then worked up as for **7**. Recrystallization gave **11** as a yellow solid (0.65 g): ^{1}H NMR (D_2O) δ 4.8 (2 H, s, CH_2), 7.6 (1 H, d, H-8, J = 8 Hz), 8.0 (1 H, d, H-7, J = 8 Hz), 8.6 (2 H, s, H-3, 4), 9.9 (1 H, s, H-1).

A small yield (3%) of 6,8-bis(aminomethyl)-5-isoquinolinol trihydrochloride was also isolated as a hemihydrate: mp >300 °C dec; ^{1}H NMR (D_2O) δ 4.8 (4 H, s, 2 CH_2), 8.2 (1 H, s, H-7), 8.8 (1 H, s, H-4, J = 7 Hz), 8.9 (1 H, s, H-3, J = 7 Hz), 10.0 (1 H, s, H-1). Anal. ($C_{11}H_{13}N_3O$·3HCl·0.5H_2O) C, H, N.

Preparation of Compound 12. (a) 5-(Phthalimidomethyl)-6-quinoxalinol (12a). *N*-(Hydroxymethyl)phthalimide (11.5 g, 0.065 mol) was added portionwise (30 min) with stirring to a mixture of 6-quinoxalinol[11] (8.7 g, 0.06 mol) in BF_3·Et_2O (17 mL) at 60 °C. The reaction mixture was heated at 80–85 °C for 4 h and concentrated to dryness. The residue was taken up in H_2O, and the mixture filtered to give the imide. Recrystallization of a sample of the crude product from EtOH–H_2O yielded **12a**: mp 217–220 °C; ^{1}H NMR (Me_2SO-d_6) δ 5.4 (2 H, s, CH_2), 7.4 (1 H, d, H-7, J = 8 Hz), 7.8 (4 H, s, C_6H_4), 7.9 (1 H, d, H-9, J = 8 Hz), 8.7 (1 H, d, H-2 or H-3, J = 2 Hz), 8.8 (1 H, d, H-2 or H-3, J = 2 Hz).

(b) 5-(Aminomethyl)-6-quinoxalinol Hydrochloride (12). A mixture of **12a** in concentrated HCl (350 mL) was heated at reflux with stirring under N_2 for 3 h and then worked up as for **7**. Recrystallization gave **12** as a yellow crystalline solid (3.7 g): ^{1}H NMR (Me_2SO-d_6) δ 4.5 (2 H, br q, CH_2), 7.8 (1 H, d, H-7, J = 8 Hz), 8.0 (1 H, d, H-8, J = 8 Hz), 8.8 (1 H, d, H-2 or H-3, J = 2 Hz), 8.9 (1 H, d, H-2 or H-3, J = 2 Hz).

Preparation of Compound 13. (a) 2-Methyl-7-(phthalimidomethyl)-6-benzothiazolol (13a). This compound was prepared in a manner analogous to **7a**, starting with 2-methyl-6-benzothiazolol[12] (0.8 g, 0.0005 mol). Recrystallization of a sample of the crude product from DMF–H_2O yielded **13a**: mp 258–262 °C dec; ^{1}H NMR (CF_3COOD) δ 3.2 (3 H, s, CH_3), 5.3 (2 H, s, CH_2), 7.6 (1 H, d, H-5, J = 8 Hz), 8.0 (4 H, s, C_6H_4), 8.1 (1 H, d, H-4, J = 8 Hz).

In a prior run, a small yield of 2-methyl-5,7-bis(phthalimidomethyl)-6-benzothiazolol was isolated as a hemihydrate: mp 279–283 °C dec; ^{1}H NMR (CF_3COOD) δ 3.2 (3 H, s, CH_3), 5.2 (4 H, s, both CH_2), 8.0 (8 H, s, both C_6H_4), 8.2 (1 H, s, H-4).

(b) 7-(Aminomethyl)-2-methyl-6-benzothiazolol Dihydrochloride (13). A mixture of **13a** in concentrated HCl (50 mL) was heated at reflux with stirring for 18 h and then worked up as for **7**. Recrystallization gave **13** as a white crystalline solid (0.65 g): ^{1}H NMR (D_2O) δ 3.1 (3 H, s, CH_3), 4.4 (2 H, s, CH_2), 7.3 (1 H, d, H-5, J = 8 Hz), 7.9 (1 H, d, H-4, J = 8 Hz).

5-(Aminomethyl)-6-hydroxy-4-methyl-2*H*-1-benzopyran-2-one Hydrochloride Quartahydrate (14). This compound was prepared in a manner analogous to method A_2 in Part 1 of this series,[2] starting with 6-hydroxy-4-methylcoumarin[13] (8.8 g, 0.05 mol). Recrystallization gave **14** (5.4 g): ^{1}H NMR (Me_2SO-d_6) δ 2.7 (3 H, s, CH_3), 4.4 (2 H, br s, CH_2), 6.5 (1 H, s, H-3), 7.3 (1 H, d, J = 9 Hz), 7.5 (1 H, d, J = 9 Hz).

4-Chloro-2,3-dihydro-7-hydroxy-1*H*-inden-1-one Oxime (15). To a well-stirred solution of 4-chloro-2,3-dihydro-7-hydroxy-1*H*-inden-1-one (18.2 g, 0.10 mol)[7] in EtOH (300 mL) was added a solution of NH_2OH–HCl (16.4 g, 0.24 mol) in EtOH (30 mL)–H_2O (30 mL), followed by a solution of NaOAc (19.4 g, 0.24 mol) in EtOH (30 mL)–H_2O (30 mL). After heating at reflux for 3.5 h, the reaction mixture was poured into H_2O to give **15** (18.3 g, 93%). A sample was recrystallized from EtOH–H_2O, mp 142–143 °C. Anal. ($C_9H_8ClNO_2$) C, H, N.

1-Amino-4-chloro-2,3-dihydro-1*H*-inden-7-ol Hydrochloride (16). A mixture of **15** (3.94 g, 0.02 mol) in EtOH (200 mL) and concentrated H_2SO_4 (10 mL) was hydrogenated in a Parr Apparatus with 5% Rh/C as the catalyst for 48 h. After filtration, the solution was concentrated in vacuo to remove the solvent, and the residue was taken up in H_2O; the aqueous solution was made basic with NH_4OH to give the amine, mp 118–112 °C. The amine was dissolved in EtOH (50 mL), and the solution was treated with HCl (2 mL) to give **16** (1.6 g): ^{1}H NMR (Me_2SO-d_6) δ 2.0–2.6 (2 H, m), 2.7–3.1 (2 H, m), 4.5–5.0 (1 H, m, CH), 6.8 (1 H, d, J = 9 Hz), 7.2 (1 H, d, J = 9 Hz).

1-Amino-4-chloro-2,3-dihydro-6-iodo-1*H*-inden-7-ol Hydrochloride (17). This compound was prepared in a manner analogous to method C in Part 1 of this series,[2] starting with **16** (2.2 g, 0.01 mol). Recrystallization gave **17** (1.4 g): ^{1}H NMR (Me_2SO-d_6) δ 2.0–2.6 (2 H, m), 2.7–3.2 (2 H, m), 4.8–5.2 (1 H, m, CH), 7.6 (1 H, s, H-5).

Preparation of Compound 18. 2,4-Dimethylphenyl 3-Chloropropionate (18a). 2,4-Dimethylphenol (97.6 g, 0.8 mol) and 3-chloropropionyl chloride (105 g, 0.82 mol) were added to toluene (200 mL), and the mixture was heated at reflux with stirring for 3 h. The solution was washed with dilute aqueous NaOH and dried over Na_2SO_4. After filtration, the solution was concentrated, and the product, **18a**, was obtained by distillation at 0.7 mm (152.4 g, 90%): bp 103–108 °C; ^{1}H NMR ($CDCl_3$) δ 2.1 (3 H, s, CH_3), 2.2 (3 H, s, CH_3), 3.0 (2 H, t, CH_2, J = 6 Hz), 3.8 (2 H, t, CH_2, J = 6 Hz), 6.9 (3 H, m, C_6H_3).

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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; ^1H 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): ^1H 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; ^1H 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.

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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.
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