After completion of our studies, preliminary reports appeared indicating possible effectiveness in ulcerative colitis patients of two other azo-linked derivatives of 5-ASA, sodium azodisalicylate[49] and salicylazobenzoic acid,[50] administered as retention enemas. More recently a sustained-release preparation of 5-ASA has been described[51] which delivers 5-ASA to both the small and large intestines during its transit through the gastrointestinal tract.

In summary, comparable total release of 5-ASA and metabolites has been demonstrated in rats for polymer 7 and SASP, and polymer 7 has been shown to be more effective than SASP in reducing the inflammation of the guinea pig ulcerative colitis model. Since SASP metabolism proceeds by the same reductive pathway in both rats and man,[7] polymer 7 may provide a new oral dosage form for the site-specific delivery of therapeutic levels of 5-ASA to the lower human bowel, which will eliminate the adverse side effects currently limiting the SASP therapy of inflammatory bowel disease.[52]

Acknowledgment. The authors gratefully acknowledge M. Kronstadt and R. Phillips for polymer analyses and for providing previously unpublished results; P. Brock, L. Bunes, D. Dawson, S. Ng, and S. Swanson for helpful chemical discussions and for providing model analytical compounds; R. Cisneros, F. Enderlin, and C. Smith for technical assistance with the biological studies; and K. Isselbacher for discussions concerning the therapeutic mechanism of SASP.

Registry No. 13, 86260-27-7.

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Notes

Heterocyclic Oxyacetic Acid Diuretics: Indazole, Benzisothiazole, and Benzisothiazole 1,1-Dioxide Analogues of [[7-Chloro-3-(2-fluorophenyl)-1,2-benzisoxazol-6-yl]oxy]acetic Acid

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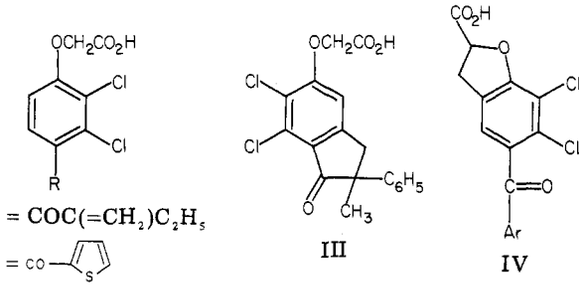
Hoechst-Roussel Pharmaceuticals, Inc., Somerville, New Jersey 08876. *Received December 1, 1982*

The indazole, benzisothiazole, and benzisothiazole 1,1-dioxide analogues of [[7-chloro-3-(2-fluorophenyl)-1,2-benzisoxazol-6-yl]oxy]acetic acid were synthesized and tested for diuretic activity in saline-loaded mice. Each analogue was found to be less active than the parent benzisoxazole: the diuretic activity followed the order O > S > N = SO_2 in regard to the heteroatom in the 1-position of the ring.

We recently reported[1] a series of [(3-aryl-1,2-benzisoxazol-6-yl)oxy]acetic acids with potent diuretic activity in mice and dogs. These compounds are new members of the family of phenoxyacetic acid diuretics (Chart I), a family that has grown from ethacrynic acid (I) and tienilic acid (II) to include indacrinone (III), as well as the 5-acylbenzofuran-2-carboxylic acids (IV) and the [4-(arylsulfonyl)phenoxy]acetic acids (V). These compounds are characterized by their uricosuric, as well as diuretic, properties: the spectrum of activity ranges from loop diuretics that cause uric acid retention (I), to uricosuric loop diuretics (III), to uricosuric diuretics with a low-ceiling profile (II). The [(3-aryl-1,2-benzisoxazol-6-yl)oxy]acetic acids occupy their own niche among the phenoxyacetic acid diuretics with a unique profile of diuretic and uricosuric activity.

Among the heterocyclic oxyacetic acids in our previous publication, diuretic activity was maximal in compounds **1a–c** in which the 3-aryl substituent was 2-chloro- or (better) 2-fluorophenyl and the benzisoxazole ring was substituted in the 7-position with either chlorine (**1a,b**) or bromine (**1c**). These compounds also showed good intravenous activity in the dog. Because **1c** (HP 522) demonstrated good diuretic activity, as well as mild uricosuria, with no rebound after chronic oral dosing in chimpanzees,

Chart I. Structures of Some Phenoxyacetic Acid Diuretics



[†] Chemical Research Department.
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[§] Department of Biological Sciences.

(1) Shutske, G. M.; Setescak, L. L.; Allen, R. C.; Davis L.; Effland, R. C.; Ranbom, K.; Kitzen, J. M.; Wilker, J. C.; Novick, Jr., W. J. *J. Med. Chem.* **1982**, *25*, 36.

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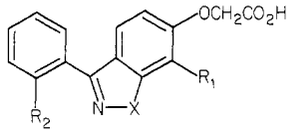


1a, X = O; R_1 = Cl; R_2 = Cl
b, X = O; R_1 = Cl; R_2 = F
c, X = O; R_1 = Br; R_2 = F
2a, X = NH; R_1 = Cl; R_2 = F
3a, X = S; R_1 = Cl; R_2 = F
4, X = SO_2; R_1 = Cl; R_2 = F

it was chosen for clinical investigation. Clearance studies in dogs[2] have suggested that **1c** has at least one site of action in the ascending limb of Henle's loop.

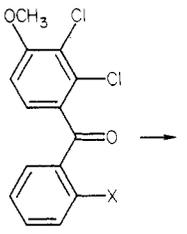
In view of the bioisosteric relationship that is often observed among certain bivalent atoms and groups,[3] we wanted to investigate the effect that replacing the benzisoxazole oxygen with nitrogen or sulfur would have on diuretic activity. We would now describe the synthesis and diuretic activity of the indazole (**2a**), benzisothiazole (**3a**), and benzisothiazole 1,1-dioxide (**4**) analogues of compound **1b**.

Chemistry. Our initial attempts to synthesize indazole **2a** paralleled some of the benzisoxazole chemistry previously employed,[1] in which 2,3-dichloro-2′-fluoro-4-methoxybenzophenone (**5a**) was treated with hydroxylamine and then subjected to cyclization under basic conditions. Treatment of **5a** with either hydrazine or methylhydrazine (Scheme I), however, gave almost exclusively the 3-(2,3-dichloro-4-methoxyphenyl)indazoles (**6**) resulting from displacement of the more labile fluorine. The reaction of 2,2′,3-trichloro-4-methoxybenzophenone (**5b**) with methylhydrazine gave a mixture of **6a** and a 3-(2-chlorophenyl)indazole (**10**) that could be separated, but a more indirect route had to be employed in order to obtain the desired 3-(2-fluorophenyl)indazole. Each methoxyindazole (**6a,b** and **10**) was elaborated to the corresponding oxyacetic acid by reactions previously reported.[1]

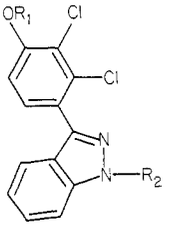
The synthesis of the 3-(2-fluorophenyl)indazoles is described in Scheme II. The *N*-pivaloylaniline (**13**) was metallated with *n*-butyllithium as described by Gschwend[4] and treated with hexachloroethane to give, after acid hydrolysis of the amide, 2-chloro-3-methoxyaniline (**14**) in good yield. The ortho-directed acylation of **14** with 2-fluorobenzonitrile with BCl_3 and $AlCl_3$ as described by Sugasawa[5] gave the 2-aminobenzophenone **15**, which underwent diazotization under strongly acidic conditions (HBF_4) to give a 3-hydroxy-3*H*-indazole (**16**) after reduction with sodium dithionite. Compounds of this type have been previously formulated as 2-hydroxy-2*H*-indazoles,[6,7] but Boulton has recently suggested[8] that they are 3-hydroxy-3*H*-indazoles. Further reduction of **16** with stannous chloride gave the 1*H*-indazole (**11a**), which was subjected to the standard transformations[1] leading to the desired **2a**.

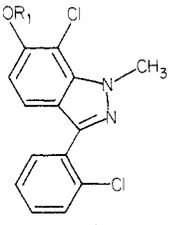
Although benzophenone **5a** was not suitable for the synthesis of indazole **2a**, it was employed for the synthesis of 1,2-benzisothiazole **3a** (Scheme III). Treatment of **5a** with ammonia and sulfur in a sealed reaction vessel according to the direction of Hagen[9] gave a mixture of 7-chloro-3-(2-fluorophenyl)-1,2-benzisothiazole (**17a**), 3-(2,3-dichloro-4-methoxyphenyl)-1,2-benzisothiazole (**18**), and 4-chloro-3-methoxy-9*H*-thioxanthen-9-one (**19**), which was separated by preparative high performance liquid chromatography. 2,3-Dichloro-4-methoxybenzophenone **5c** yielded 7-chloro-3-phenyl-1,2-benzisothiazole (**17b**) after simple recrystallization. Compounds **17a,b** and **18** were elaborated to the corresponding oxyacetic acids **3a,b** and **22**, of which **3a** and **22** were oxidized to the corresponding

Scheme I



5a, X = F
b, X = Cl

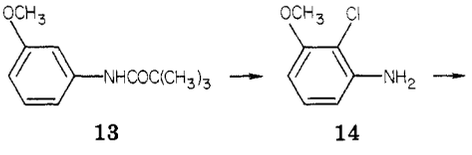




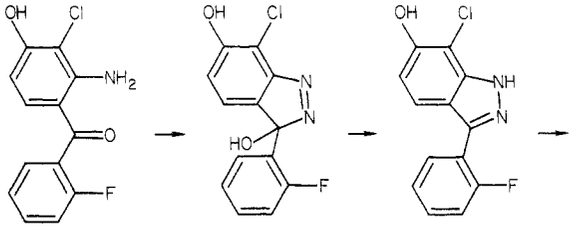
6a, R_1 = R_2 = CH_3
b, R_1 = CH_3; R_2 = H
7a, R_1 = H; R_2 = CH_3
b, R_1 = R_2 = H
8a, R_1 = $CH_2CO_2C_2H_5$; R_2 = CH_3
8b, R_1 = $CH_2CO_2C_2H_5$; R_2 = H
9a, R_1 = CH_2CO_2H; R_2 = CH_3
b, R_1 = CH_2CO_2H; R_2 = H

10, R_1 = CH_3
11b, R_1 = H
12b, R_1 = $CH_2CO_2C_2H_5$
2b, R_1 = CH_2CO_2H

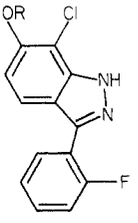
Scheme II



13 14



15 16 11a



12a, R = $CH_2CO_2C_2H_5$
2a, R = CH_2CO_2H

(2) Kitzen, J. M.; Schwenkler, M. A.; Bixby, P. R.; Wilson, S. J.; Shutske, G. M.; Setescak, L. L.; Allen, R. C.; Rosenblum, I. *Life Sci.* **1980**, *27*, 2547.
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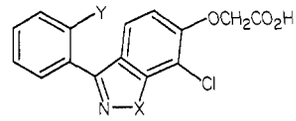
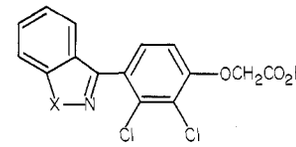
Table I. Indazole- and Benzisothiazole-Substituted Oxyacetic Acids[a]



1-4

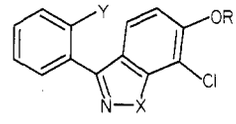


9, 22, 23

compd	X	Y	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula[e]	oral diuretic act.[f] in the mouse, (mequiv of Na^+/kg)/5 h: 64 mg/kg	vc
2a	NH	F	228-229	87	C	$C_{15}H_{10}ClFN_2O_3$	0.45	0.27
2b	NCH_3	Cl	196-198	88	C-K	$C_{16}H_{12}Cl_2N_2O_3$	2.29	0.68
3a	S	F	228-230	61[g]	I	$C_{15}H_9ClFNO_3S$	4.59	0.25
3b	S	H	225-227	49[h]	F	$C_{15}H_{10}ClNO_3S$	2.28	1.22
4	SO_2	F	212-214	97	E-H	$C_{15}H_9ClFNO_5S$	0.18	0.80
9a	NCH_3		265-267	80	B-K	$C_{16}H_{12}Cl_2N_2O_3$	0.61	0.42
9b	NH		225-227	88	A-K	$C_{15}H_{10}Cl_2N_2O_3$	0.65	0.56
22	S		224-226	84[g]	B-K	$C_{15}H_9Cl_2NO_3S$	1.18	0.72
23	SO_2		230-232	60	G-H	$C_{15}H_9Cl_2NO_5S$	2.03	0.80
1a	O	Cl	*i*	*i*	*i*	*i*	9.10	0.60
1b	O	F	*i*	*i*	*i*	*i*	10.00	0.05
ethacrynic acid							4.14	0.30
indacrinone							7.60	0.20
tienilic acid							3.31	0.10

[a] All compounds exhibited IR, MS, ^1H NMR and ^{13}C NMR spectra consistent with the assigned structures. [b] Melting points are uncorrected. [c] Yields were not optimized. [d] A = acetic acid; B = acetonitrile; D = cyclohexane; E = dichloromethane; F = ethanol; G = ethyl acetate; H = hexane; I = 2-propanol; J = toluene; K = water. [e] All compounds gave satisfactory C, H, and N analyses, except where indicated. [f] See Experimental Section for testing methadology. The mean vehicle control value for each group of mice (vc) is given as an indication of the reliability of the results. [g] This yield is from the corresponding phenol. [h] This yield is from the corresponding methoxy compound. [i] Reference 1.

Table II. Indazole and Benzisothiazole Intermediates



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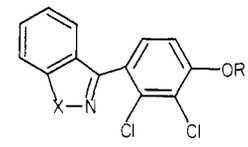


7, 8, 21

compd	X	Y	R	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula[e]
11b	NCH_3	Cl	H	220-222	97	C	$C_{14}H_{10}Cl_2N_2O$
12a	NH	F	$CH_2CO_2C_2H_5$	135-136	56	J	$C_{17}H_{14}ClFN_2O_3$
12b	NCH_3	Cl	$CH_2CO_2C_2H_5$	70-72	91	D	$C_{18}H_{16}Cl_2N_2O_3$
20	S	F	H	220-221	86	J	$C_{13}H_7ClFNOS$
7a	NCH_3		H	179-181	94	C	$C_{14}H_{10}Cl_2N_2O$[f]
7b	NH		H	216-218	98	J	$C_{13}H_8ClN_2O$[g]
8a	NCH_3		$CH_2CO_2C_2H_5$	135-137	83	C-K	$C_{18}H_{16}Cl_2N_2O_3$
8b	NH		$CH_2CO_2C_2H_5$	153-154	78	D-E	$C_{17}H_{14}Cl_2N_2O_3$
21	S		H	185-186	86	J	$C_{13}H_7Cl_2NOS$[f]

[a-e] See corresponding footnotes to Table I. [f] Hemihydrate. [g] C: calcd, 55.94; found, 56.44.

1,1-dioxides **4** and **23** with peracetic acid as suggested by Böshagen.[10]

Diuretic Activity. Based upon our earlier observation that the benzisoxazole oxyacetic acids that did not show good diuretic activity in mice were similarly weakly active diuretics in water-loaded dogs,[1] compounds **2–4**, **9**, **22**, and **23** were evaluated for diuretic activity per os in saline-loaded mice at 64 mg/kg. Only Na^+ excretion is presented for brevity (Table I). It can be seen within the heterocyclic oxyacetic acids (**1–4**) that diuretic activity follows the relationship O > S > N = SO_2: compound **3a**—the benzisothiazole analogue of **1b**—showed moderate diuretic activity at 64 mg/kg compared to **1b**, while **2a,b** and **4**—the indazole and benzisothiazole 1,1-dioxide analogues—were only weakly active at best. The lack of activity of **4** was not expected, since **4** can be viewed as a hybrid of our heterocyclic oxyacetic acids and the benzisothiazole 1,1-dioxides reported by Feit.[11,12] It is interesting that even within this limited series of compounds the critical importance of the 3-(2-fluorophenyl) group was demonstrated by the difference in diuretic activity between compounds **3a** and **3b**.

As in our initial publication,[1] the heterocyclic-substituted phenoxyacetic acids, i.e., compounds **9**, **22**, and **23**, showed weak activity, which reached a maximum in compound **23**.

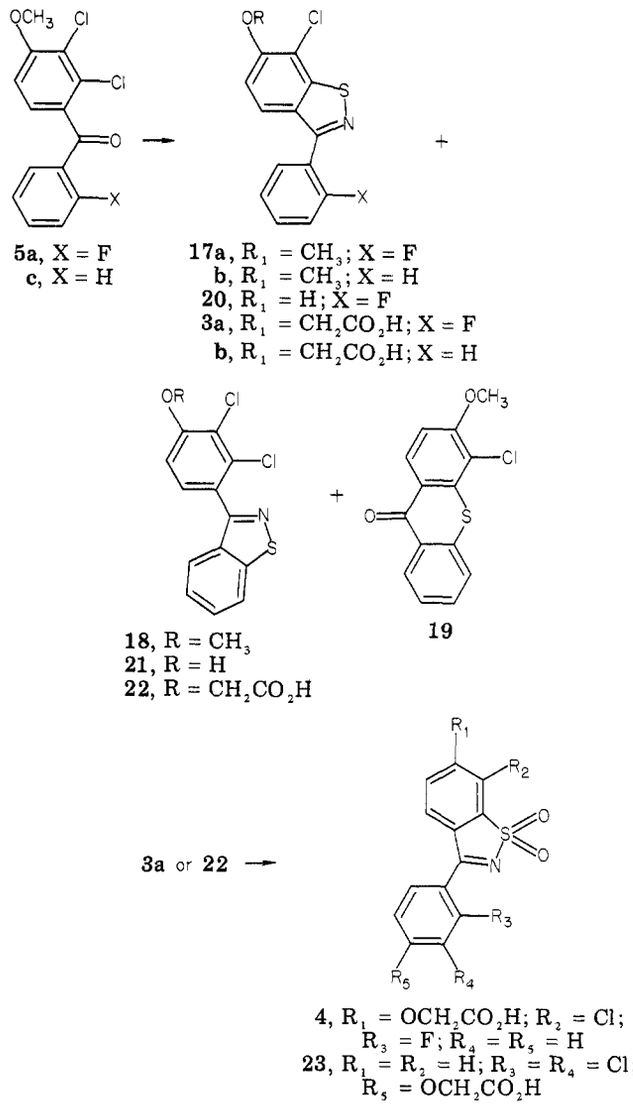
These data indicate that the requirements for maximal diuretic activity within our heterocyclic oxyacetic acids are

(10) Böshagen, H.; Geiger, W.; Medenwald, H. *Chem. Ber.* **1970**, *103*, 3166.

(11) Nielsen, O. B. T.; Nielsen, C. K.; Feit, P. W. *J. Med. Chem.* **1973**, 16, 1170.

(12) Nielsen, O. B. T.; Bruun, H.; Bretting, C.; Feit, P. W. *J. Med. Chem.* **1975**, *18*, 41.

Scheme III



not only very specific in regard to the 3-(2-fluorophenyl) substituent and the chloro or bromo substituent in the 7-position of the heterocyclic ring[1] but also quite inflexible in regard to the heteroatom in the 1-position of the ring.

Experimental Section

The structures of all compounds are supported by the IR (Perkin-Elmer 457), ^{1}H NMR (JEOL C60HL; tetramethylsilane), and ^{13}C NMR (JEOL FX60) spectra. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro Tech Laboratories, Skokie, IL. Results are within 0.4% of theoretical values unless otherwise noted in the tables. Reactions with moisture-sensitive reagents were maintained under a dry nitrogen atmosphere. Solvents dried over molecular sieves were employed for reactions requiring anhydrous solvents. The term evaporated refers to the removal of a solvent under reduced pressure.

Preparative high-performance liquid chromatography was performed on a Waters Associates Prep LC/System 500 equipped with a UV detector from Gow-Mac Instrument Co., Bridgewater, NJ, and with prepacked silica gel columns. The appropriate pure fractions were combined, and the solvent was removed under reduced pressure.

3-(2,3-Dichloro-4-methoxyphenyl)-1-methyl-1*H*-indazole (6a). 2,3-Dichloro-2′-fluoro-4-methoxybenzophenone (**5a**; 10.0 g, 33 mmol) was refluxed in 30 mL of EtOH containing 5.0 g (110 mmol) of methylhydrazine. After 1.5 h, the precipitated product was filtered from the cooled reaction mixture and washed with Et_2O to give 8.51 g (84%) of **6a**, mp 165–167 °C. Anal. ($C_{15}H_{12}Cl_2N_2O$) C, H, N.

3-(2,3-Dichloro-4-methoxyphenyl)-1*H*-indazole (6b). Ten grams of **5a** (33 mmol) were warmed at 80 °C for 3 h in 30 mL of Me_2SO containing 4.0 g of 95% hydrazine (119 mmol). At the end of this time, the reaction mixture was distributed between Et_2O and H_2O. The organic phase was washed well with H_2O and then dried and evaporated to give **6b** as a solid. After recrystallization from toluene, 7.15 g (74%) was obtained, mp 155–157 °C. Anal. ($C_{14}H_{10}Cl_2N_2O$) C, H, N.

3-(2,3-Dichloro-4-hydroxyphenyl)-1-methyl-1*H*-indazole (7a) and 3-(2,3-dichloro-4-hydroxyphenyl)-1*H*-indazole (7b) were obtained from **6a** and **6b**, respectively, by refluxing with $AlCl_3$ in 1,2-dichloroethane, a method previously reported.[1] Likewise, the alkylation of **7a** and **7b** with ethyl bromoacetate–K_2CO_3–DMF to give esters **8a** and **8b** and the hydrolysis of **8a** and **8b** to acids **9a** and **9b** have been reported. The physical properties of these compounds are reported in Tables I and II.

7-Chloro-3-(2-chlorophenyl)-6-methoxy-1-methyl-1*H*-indazole (10). Ten grams of 2,2′,3-trichloro-4-methoxybenzophenone (**5b**; 3.17 mmol) was refluxed for 3 days in 30 mL of EtOH containing 4.8 g of methylhydrazine (100 mmol). While the reaction mixture was cooled, a precipitate formed, which was shown by TLC to be a mixture of two components, one of which was **6a**. The new product (**10**) was separated by preparative HPLC (10% EtOAc–hexane, 250 mL/min), amounting to 3.75 g (38.5%), mp 133–134 °C. Anal. ($C_{15}H_{12}Cl_2N_2O$) C, H, N.

7-Chloro-3-(2-chlorophenyl)-6-hydroxy-1-methyl-1*H*-indazole (11b) and the corresponding ester (**12b**) and acid (**2b**) were synthesized in the same manner as compounds **7–9** above. Their physical properties are also reported in Tables I and II.

2-Chloro-3-methoxyaniline (14). 3-Methoxy-*N*-pivaloylaniline (**13**) was prepared as described by Gschwend[4] in 89% yield, mp 124–125 °C (lit.[4] mp 130–131 °C).

The **13** thus prepared (20.7 g, 100 mmol) was dissolved in 300 mL of dry THF at 0 °C, and *n*-butyllithium was added (119 mL of 2.1 M, 250 mmol). After the mixture was stirred for 2 h at 0 °C, a solution of hexachloroethane (23.6 g, 100 mmol) in 50 mL of THF was added, and stirring was continued overnight as the reaction came to room temperature. The reaction mixture was distributed between Et_2O and H_2O, and then the organic phase was separated and passed quickly over a pad of silica gel to remove some dark, polar impurities. The crude 2-chloro-3-methoxy-*N*-pivaloylaniline obtained upon evaporation of the organic phase was hydrolyzed for 6 h in a refluxing solution of 300 mL of EtOH and 100 mL of concentrated hydrochloric acid. The hydrochloride crystallized upon cooling and was filtered off. The filtrate was neutralized with NH_4OH and extracted with Et_2O. Additional hydrochloride was obtained from this Et_2O phase by precipitation with ethereal HCl. In this way a total of 14.5 g (74.8%) of **14**·HCl were obtained, mp 200 °C (sublimes). An analytical sample was obtained by sublimation. Anal. (C_7H_8ClNO·HCl) C, H, N. The free base **14** was obtained by distributing **14**·HCl between Et_2O and aqueous NH_3. The Et_2O phase was then evaporated, and the residue was distilled, bp 80–81 °C (0.2 mm).

2-Amino-3-chloro-2′-fluoro-4-hydroxybenzophenone (15). To 50 mL of 1,1,2,2-tetrachloroethane containing 110 mL of 1 M BCl_3 in CH_2Cl_2 (110 mmol) at 0 °C was added **14** (15.8 g, 100 mmol) in 100 mL of tetrachloroethane. To this mixture was then added 2-fluorobenzonitrile (24.20 g, 200 mmol), followed by $AlCl_3$ (14.67 g, 110 mmol). The solvents were then distilled at atmospheric pressure until the internal temperature was 135 °C, and then the reaction was refluxed for 7 h. At the end of this time, ice and 400 mL of 2 N hydrochloric acid were added, and refluxing was continued for 1 h. The organic phase was then separated and, after evaporation, chromatographed over silica gel (CH_2Cl_2) to give 12.92 g of **15**, mp 170–172 °C. An additional 4.40 g of faster eluting material was obtained, which was shown by ^{1}H NMR to be 2-amino-3-chloro-2′-fluoro-4-methoxybenzophenone. This was refluxed for 1 h in 50 mL of 1,2-dichloroethane containing 4.3 g (32.2 mmol) of $AlCl_3$. After this reaction mixture was distributed between CH_2Cl_2 and H_2O, an additional 3.95 g of **15** was obtained upon evaporation of the organic phase, for a total yield of 16.87 g of **15** (63%). Analytically pure **15** was obtained by recrystallization from $CHCl_3$–Et_2O, mp 169–171 °C. Anal. ($C_{13}H_9ClFNO_2$) C, H, N.

7-Chloro-3-(2-fluorophenyl)-3,6-dihydroxy-3*H*-indazole (16). Sixteen grams of **15** (60.2 mmol) was dissolved in 600 mL

of 50% aqueous HBF_4 at 70 °C and added to an ice-cold solution of 4.16 g of $NaNO_2$ (60.3 mmol) in 40 mL of H_2O at a rate such that the internal temperature did not rise above 25 °C. This solution was stirred in the cold for 0.5 h, and then the yellow diazonium tetrafluoroborate was filtered off and kept wet. It was added portionwise to a well-stirred solution of 200 g of $Na_2S_2O_4$ in 800 mL of H_2O. After the solution was stirred for 10 min, the product was extracted into Et_2O. Evaporation of the Et_2O phase gave 11.8 g (71%) of **16**, which had mp 170 °C dec after recrystallization from Et_2O–hexane. Anal. ($C_{13}H_8ClFN_2O_2$) C, H, N.

7-Chloro-3-(2-fluorophenyl)-6-hydroxy-1*H*-indazole (11a). Compound **16** (10.80 g, 39 mmol) was dissolved in 200 mL of MeOH containing 5 mL of concentrated hydrochloric acid and treated with 12 g of $SnCl_2 \cdot 2H_2O$. After 0.5 h, the reaction mixture was poured into H_2O, and the precipitated **11a** was filtered off and dried to give 8.40 g (82%), mp 212–214 °C. An analytical sample was recrystallized from Et_2O–hexane and had mp 214–215 °C. Anal. ($C_{13}H_8ClFN_2O$) H, N; C: calcd, 59.44; found, 58.86.

Ethyl [[7-chloro-3-(2-fluorophenyl)-1*H*-indazol-6-yl]oxy]acetate (12a) and the corresponding acid **2a** were synthesized by standard conditions, reported above. Their physical properties are reported in Tables I and II.

7-Chloro-3-(2-fluorophenyl)-6-methoxy-1,2-benzisothiazole (17a) and 3-(2,3-Dichloro-4-methoxyphenyl)-1,2-benzisothiazole (18). Benzophenone **1a** (16.8 g, 56 mmol) was heated in a sealed reaction vessel with 85 mL of ethylene glycol methyl ether containing 8.5 g of NH_3 and 1.9 g of sulfur. It was heated for 13 h at 130 °C and then allowed to cool to room temperature. A quantity of 4-chloro-3-methoxy-9*H*-thioxanthen-9-one (**19**) separated at this time, which was filtered off and recrystallized from toluene to give 5.2 g (34%), mp 225 °C. Anal. ($C_{14}H_9ClO_2S$) C, H. The filtrate, containing both **17a** and **18**, was evaporated, and the mixture was separated by preparative HPLC (40% CH_2Cl_2–hexane, 250 mL/min). Combination of the appropriate fractions gave 2.96 g (18%) of **17a** after recrystallization from hexane, mp 127–128 °C. Anal. ($C_{14}H_9ClFNOS$) C, H, N. In like manner, 2.61 g (15%) of **18** was obtained after recrystallization from CH_3CN, mp 176–177 °C. Anal. ($C_{14}H_9Cl_2NOS$) C, H, N.

7-Chloro-6-methoxy-3-phenylbenzisothiazole (17b). 2,3-Dichloro-4-methoxybenzophenone (**5c**; 18.0 g, 64 mmol) was treated with NH_3 and sulfur as for **5a** above. Evaporation of the reaction mixture and two recrystallizations from ethyl acetate gave 5.9 g (34%) of **17b**, mp 174–175 °C. Anal. ($C_{14}H_{10}ClNOS$) C, H, N.

7-Chloro-3-(2-fluorophenyl)-6-hydroxy-1,2-benzisothiazole (20) and 3-(2,3-dichloro-4-hydroxyphenyl)-1,2-benzisothiazole (21) were obtained from **17a** and **18**, respectively, by treatment with BBr_3 in refluxing 1,2-dichloroethane, a method previously reported.[1] Their properties are reported in Table II. The hydroxy compound derived in like manner from **17b** was taken on to the corresponding oxyacetic acid (**3b**) without purification. The other acids in the benzisothiazole series (**3a** and **22**) were likewise obtained from **20** and **21**, respectively, without isolation of the intermediate esters. The properties of **3a,b** and **22** are given in Table I.

[[7-Chloro-3-(2-fluorophenyl)-1,2-benzisothiazol-6-yl]oxy]acetic Acid 1,1-Dioxide (4). Acid **3a** (4.60 g, 13.6 mmol) was warmed for 1 h at 90 °C in 300 mL of glacial HOAc containing 75 mL of 30% H_2O_2. At the end of this time the reaction mixture was poured into ice–H_2O, and the product was filtered off. The physical properties of **4** are reported in Table I.

4-(1,2-Benzisothiazol-3-yl)-2,3-dichlorophenoxyacetic acid 1′,1′-dioxide (23) was synthesized in like manner. Its physical properties are reported in Table I.

Acute Diuretic Evaluation in Sodium-Loaded Mice. The acute sodium-loaded mouse experiments were performed with groups of male CD-1 mice weighing 18–24 g. Drugs were prepared in 1% saline and orally administered in a dosage volume of 10 mL/kg. The animals were housed in metabolic cages, each treatment group consisting of 10 animals, 5 per cage. Tests consisted of a vehicle control and potential diuretic agent given at 64 mg/kg. The pooled urine samples were analyzed for sodium by a flame photometer (IL Model 343). Sodium values were expressed as the mean milliequivalents (mequiv) per kilogram per 5 h.

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Registry No. **1a**, 72482-82-7; **1b**, 72498-57-8; **2a**, 85893-69-2; **2b**, 85893-70-5; **3a**, 85893-71-6; **3b**, 85893-72-7; **4**, 85893-73-8; **5a**, 72498-53-4; **5c**, 85893-74-9; **6a**, 85893-75-0; **6b**, 85893-76-1; **7a**, 85893-77-2; **7b**, 85893-78-3; **8a**, 85893-79-4; **8b**, 85893-80-7; **9a**, 85893-81-8; **9b**, 85893-82-9; **10**, 85893-83-0; **11a**, 85893-84-1; **12a**, 85893-85-2; **12b**, 85893-86-3; **13**, 56619-93-3; **14**·HCl, 85893-87-4; **15**, 85893-88-5; **16**, 85893-89-6; **17a**, 85893-98-9; **17b**, 85893-91-0; **18**, 85893-92-1; **19**, 85893-93-2; **20**, 85908-79-8; **21**, 85893-94-3; **22**, 85893-95-4; **23**, 85893-96-5; 2-chloro-3-methoxy-*N*-pivaloylaniline, 85893-97-6; methylhydrazine, 60-34-4; hydrazine, 302-01-2; ethyl bromoacetate, 105-36-2; 2-fluorobenzonitrile, 394-47-8.

N^2-1*H*-Benzimidazol-2-yl-N^4-phenyl-2,4-pyrimidinediamines and N^2-1*H*-Benzimidazol-2-yl-5,6,7,8-tetrahydro-N^4-phenyl-2,4-quinazolinediamines as Potential Antifilarial Agents[1,2]

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A series of N^2-1*H*-benzimidazol-2-yl-N^4-phenyl-2,4-pyrimidinediamines and N^2-1*H*-benzimidazol-2-yl-5,6,7,8-tetrahydro-N^4-phenyl-2,4-quinazolinediamines (XI) was synthesized for antifilarial evaluation. Condensation of the requisite β-keto ester (VI) with *N*-cyanoguanidine afforded 2-pyrimidinylcyanamides (VIIa,b) and (5,6,7,8-tetrahydro-4-hydroxy-2-quinazolinyl)cyanamide (VIIc). Reaction of VII with a substituted *o*-phenylenediamine gave 2-(1*H*-benzimidazol-2-ylamino)-4-pyrimidinols and 2-[(5,6-dichloro-1*H*-benzimidazol-2-yl)amino]-5,6,7,8-tetrahydro-4-quinazolinol (IX). Chlorination with phosphoryl chloride, followed by condensation with the appropriate substituted benzenamine, gave the desired N^2-1*H*-benzimidazol-2-yl-N^4-phenyl-2,4-pyrimidinediamines and N^2-1*H*-benzimidazol-2-yl-5,6,7,8-tetrahydro-N^4-phenyl-2,4-quinazolinediamines (XI). None of these compounds possessed antifilarial activity against *Litomosoides carinii* or *Brugia pahangi* infections in jirds.

Filariasis is a nematode infection that invades the lymphatic system or connective tissue and affects millions worldwide. Its main human forms results from the parasites *Wuchereria bancrofti*, *Brugia malayi*, and *Oncho-*

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