8-Carboxy-6-sulfamyldibenz[*b*,*f*][1,4]oxazepines and -thiazepines as Potential High-Ceiling Diuretics

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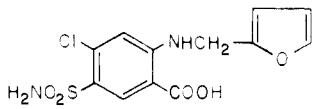
The synthesis of several 8-carboxy-6-sulfamyldibenz[*b*,*f*][1,4]oxazepines and -thiazepines is described. The results of diuretic screening lend support to the thesis that activity is strongly dependent on the conformational mobility of 4-substituents in the 3-amino-5-sulfamylbenzoic acids.

The clinical utility of the high-ceiling diuretic furosemide (1) has in recent years attracted the attention of medicinal



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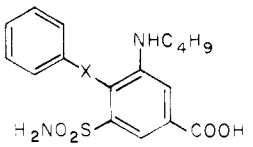
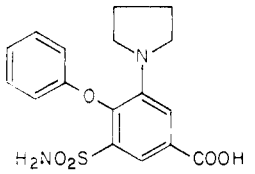


2, X = O
3, X = CH_2



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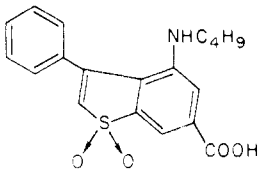
chemists seeking newer agents with therapeutic advantages. The culmination of these efforts has been the synthesis of the more potent bumetanide (**2**)[1] and besunide (**3**)[2] and, more recently, the introduction of piretanide (HOE 118) (**4**) which may be a further therapeutic improvement.[3]

The structure–activity relationships of these newer 3-amino-5-sulfamylbenzoic acid diuretics have been well explored.[1-9] These studies revealed that the dependence of diuretic potency on structural changes tended to be less pronounced in this series as compared with the 5-sulfamylanthranilic acids (furosemide analogues). It was concluded[2] that substituted or unsubstituted phenyl attached by NH, O, S, SO, SO_2, CO, or CH_2 in the 4 position contributed to high-ceiling diuretic activity of high potency. It was further suggested that the major influence of the 4-substituent is steric in nature. Supporting this latter thesis are the lower potency of 4-phenyl derivatives[8] and the inactivity of structurally rigid analogues **5**[9] and **6**.[2] The lack of activity of the latter two compounds could, however, be the result of removal or blockade of the sulfamyl moiety.

It was thus of interest to us to explore conformationally rigid analogues with a free sulfamyl moiety in order to further test this thesis. Introduction of structural rigidity through coupling of the 4- and 3-substituents was deemed appropriate since the lack of steric sensitivity of the 3 position has been amply demonstrated.[3,7,8] In this paper we report the synthesis and diuretic evaluation of several of 8-carboxy-6-sulfamyldibenz[*b*,*f*][1,4]oxazepines and -thiazepines (**13** and **19**) which represent such structurally rigid targets. Additionally, the diuretic evaluation of synthetic precursors **9**, **10**, and **17** is reported.

Chemistry. The synthesis of the requisite 8-carboxy-6-sulfamyldibenzo[*b*,*f*][1,4]thiazepines and -oxazepines is outlined in Scheme I. The readily available[4] 4-chloro-3-nitro-5-sulfamylbenzoic acid was condensed with thiosalicylic acid in the presence of $NaHCO_3$ to afford **7** in high yield. The ease with which this reaction proceeded is somewhat surprising in view of the steric hindrance and



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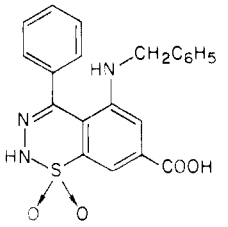

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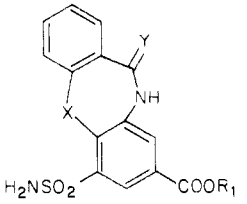
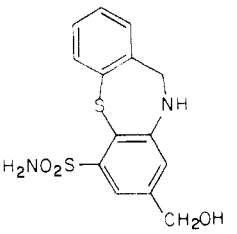


9, X = S; R_1 = H; Y = O
10, X = S; R_1 = CH_3; Y = O
13, X = S; R_1 = H; Y = H_2
17, X = O; R_1 = CH_3; Y = O
19, X = O; R_1 = H; Y = H_2

deactivating nature of the *o*-carboxyl moiety on the attacking nucleophile. Compound **7** was reduced in situ by dithionite to **8** which could be thermally cyclodehydrated to afford **9**. Alternatively, **8** was cyclized and esterified in one step with methanolic HCl to yield **10**. Careful treatment of **10** with borane afforded **12** as the major product, which could be easily separated from unreacted **10** and a small amount of the expected **20**. For larger scale



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preparation of **12**, it was, however, more convenient to catalytically reduce **11** which was prepared from **10** by treatment with $POCl_3$. Hydrolysis of **12** with NaOH afforded the acid **13**.

Contrary to our experience with thiosalicylic acid, salicylic acid or its methyl ester could not be made to react with 4-chloro-3-nitro-5-sulfamylbenzoic acid or its methyl ester under a variety of conditions. Methyl salicylate was, however, easily reacted with methyl 4-chloro-3,5-dinitrobenzoate in pyridine[11] to afford **14** which could be reduced with iron in acetic acid to **15**.[11] Treatment of **15** according to the conditions of the Meerwein reaction afforded **16**. Catalytic reduction of the nitro group followed by refluxing in acidic methanol gave the oxazepinone **17**. Careful reaction of **17** with borane afforded **18** which was subsequently hydrolyzed with NaOH to **19**.

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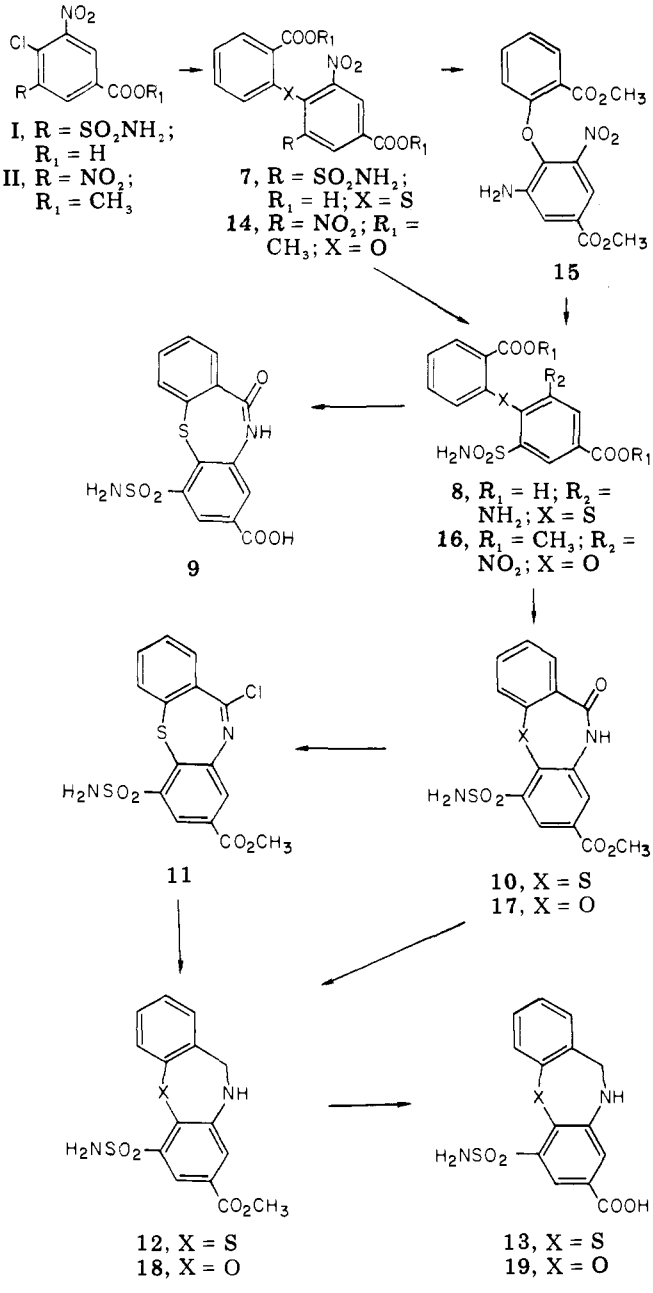
Scheme I



Pharmacology. The results of diuretic testing in the rat of target compounds **9**, **10**, **13**, **17**, and **19**, as well as for standard compound bumetanide (**2**), are given in Table I. All compounds were evaluated at 50 mg/kg po. It can be seen from the data presented that only **17** and **19** showed naturetic activity, albeit of a much lower order than **2**. No compound showed an indication of an increase in urinary volume expected of high-ceiling diuretics such as **2**. Additional evaluation of **9** and **13** at 20 mg/kg po in beagles (n = 4) confirmed the findings of the rat assay. The diminished activity of these structurally rigid analogues of **2** (especially **13** and **19**) supports the suggestion of Feit et al.[2] that the role of the 4-substituent is predominantly steric in nature, at least to the degree that conformational mobility appears to be required. Whether this steric effect is related to distribution or receptor mediated events is not clear at this time.

Experimental Section

Pharmacology. The assay for diuretic activity was adapted from the method of Kagawa and Kalm.[10]

Table I. Diuretic Screening Results

compd no.	drug/urea ratios[a]		
	diuresis	Na^+	K^+
9	0.56 ± 0.16	0.71 ± 0.16	0.62 ± 0.16
10	0.25 ± 0.10	0.42 ± 0.07	0.41 ± 0.11
13	0.07 ± 0.03	0.13 ± 0.01	0.05 ± 0.01
17	0.79 ± 0.21	1.24 ± 0.51	0.63 ± 0.14
19	0.47 ± 0.12	1.00 ± 0.18	0.90 ± 0.10
2	2.60 ± 0.33	4.66 ± 0.53	0.97 ± 0.15
vehicle control	0.44 ± 0.05	0.47 ± 0.07	0.57 ± 0.08

[a] All drugs screened at 50 mg/kg po. See the Experimental Section. Values given are ratios ± SEM.

Groups of six female Wistar rats (150–200 g) were deprived of food for 16 h prior to testing. Drugs were prepared in 1% saline and administered in a dosage volume of 15 mL/kg orally. After dosing each animal was placed in an individual metabolic cage. Water was permitted ad libitum. Urine was collected from 0 to 5 h after dosing. Each test consisted of a vehicle control, a positive control group of urea treated (1000 mg/kg), and the potential diuretic agent (50 mg/kg). The individual urine samples were analyzed for sodium and potassium using a flame photometer (IL Model 343). Sodium and potassium values were normalized as the mean milliequivalents (mequiv)/kg/5 h and diuresis as the mean milliliters (mL)/kg/5 h.

Results are given in Table I. The mean values obtained for sodium, potassium, and diuresis are expressed in a ratio to the sodium, potassium, and diuresis values obtained for the urea treated group. This ratio is called the "drug to urea ratio". A drug to urea ratio greater than or equal to one for diuresis and/or sodium is indicative of diuretic activity.

Chemistry. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses were performed by Micro-Tech Labs., Skokie, Ill. Where analyses are reported by the symbols of the elements, results were within ±0.4% of calculated values. The structures of all compounds are supported by their IR (Perkin-Elmer 457) and NMR (JEOL C6OHL) spectra.

Intermediates **14** and **15** were prepared according to the methods of Allen.[11]

4-(2-Carboxyphenylthio)-3-nitro-5-sulfamylbenzoic Acid (7). A mixture of 4-chloro-3-nitro-5-sulfamylbenzoic acid[4] (2.8 g, 10 mmol), thiosalicylic acid (1.54 g, 10 mmol), $NaHCO_3$ (2.52 g, 30 mmol), and H_2O (30 mL) was refluxed under N_2 for 3.5 h. The mixture was cooled, diluted to 50 mL with water, layered over 50 mL of $CHCl_3$, acidified (HCl) with rapid stirring, and filtered to yield 3.78 g (95%) of crude product, mp 263–267 °C dec. Crystallization from water afforded 2.4 g (60%) of light yellow crystals, mp 273–274 °C dec. Anal. ($C_{14}H_{10}N_2O_8S_2$) C, H, N, S.

3-Amino-4-(2-carboxyphenylthio)-5-sulfamylbenzoic Acid (8). A mixture of 4-chloro-3-nitro-5-sulfamylbenzoic acid[4] (2.8 g, 10 mmol), thiosalicylic acid (1.54 g, 10 mmol), $NaHCO_3$ (2.52 g, 30 mmol), and H_2O (30 mL) was refluxed under N_2 for 3.5 h. The mixture was cooled to 65 °C and additional $NaHCO_3$ (5.8 g, 70 mmol) was added, followed by $Na_2S_2O_4$ (6.1 g, 35 mmol) in small portions as rapidly as the vigorous gas evolution would allow. The reaction mixture was heated to 80–85 °C for 30 min, acidified to pH 3, and evaporated in vacuo. The resulting residue was extracted several times with boiling 2-propanol, evaporation of which yielded 1.7 g (46%) of crude product. Crystallization several times from CH_3OH·H_2O (1:4) afforded 0.6 g (16%) of product, mp 173–175 °C (resolidifies, mp >300 °C). Anal. ($C_{14}H_{12}N_2O_6S_2$) H, N; C: calcd, 45.64; found, 45.17. S: calcd, 17.41; found, 16.96.

8-Carboxy-6-sulfamyldibenzo[*b*,*f*][1,4]thiazepin-11-(10*H*)-one (9). Compound **8** (2.8 g, 7.6 mmol) was heated to 170–180 °C (0.2–0.3 mm) for 1 h. Crystallization of the resulting solid from DMF–H_2O afforded 0.65 g (25%) of pure product, mp >300 °C. Anal. ($C_{14}H_{10}N_2O_5S_2$) C, H, N.

8-Methoxycarbonyl-6-sulfamyldibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-one (10). A solution of **8** (1.6 g, 4.35 mmol) in methanol (50 mL) was saturated at reflux with gaseous HCl. Refluxing was continued for 4 h, at which time a precipitate had formed. The mixture was cooled and filtered. The resulting solid

was washed successively with ether (2 × 25 mL), $NaHCO_3$ solution (20 mL, half saturated), and water and dried. Crystallization from methanol afforded 0.6 g (40%) of product, mp >300 °C. Anal. ($C_{15}H_{12}N_2O_5S_2$) C, H, N, S.

11-Chloro-8-methoxycarbonyl-6-sulfamyldibenzo[*b*,*f*][1,4]thiazepine (11). A mixture of **10** (0.90 g, 2.5 mmol) and $POCl_3$ (15 mL) was refluxed for 16 h. The resulting solution was cooled, diluted with ether, and filtered to yield 0.7 g (74%) of solid, mp 224–246 °C. Crystallization from ethyl acetate afforded 0.5 g (53%) of product, mp 257–258 °C. Anal. ($C_{15}H_{11}ClN_2O_4S_2$) C, H, N.

10,11-Dihydro-8-methoxycarbonyl-6-sulfamyldibenzo[*b*,*f*][1,4]thiazepine (12). To a stirred suspension of **10** (2.2 g, 6.04 mmol) in dry dioxane (60 mL) was added dropwise at ambient temperature 16.5 mL (16.5 mmol) of a 1 M BH_3–THF solution. After ca. 8 h, the reaction was quenched with a mixture of dilute HCl and acetone and allowed to stir overnight. Adjustment of the pH to 7 with sodium bicarbonate, followed by removal of the solvent and addition of water, afforded 2.2 g of crude product. Trituration of this solid with 150 mL of ethyl acetate, followed by filtration (to remove ca. 0.4 g of **10**) and concentration of the filtrate to 50 mL, yielded 0.66 g (31%) of product, mp 243–245 °C. Anal. ($C_{15}H_{14}N_2O_4S_2$) C, H, N. Evaporation of the filtrate and crystallization of the residue from 2-propanol and ethanol afforded **20**, mp 212–213 °C dec. Anal. ($C_{14}H_{14}N_2S_2O_3$) C, H, N, S.

A mixture of **11** (10 g, 26.1 mmol), 10% Pd/C (2 g), 250 mL of dry THF, and 5 mL of glacial HOAc was hydrogenated at 50 psi, 55–60 °C, for 4–5 h. Cooling, filtration of the catalyst, and removal of the solvent followed by $NaHCO_3$ wash afforded **12** in essentially quantitative yield.

8-Carboxy-10,11-dihydro-6-sulfamyldibenzo[*b*,*f*][1,4]thiazepine (13). A mixture of **12** (0.66 g, 1.88 mmol), water (10 mL), methanol (10 mL), and 50% sodium hydroxide solution (2 mL) was refluxed for 0.5 h. The solvent was removed in vacuo and the residue dissolved in water and filtered. Acidification with concentrated HCl afforded 0.5 g (80%) of pure yellow product, mp >300 °C. Anal. ($C_{14}H_{12}N_2O_4S_2$) C, H, N, S.

Methyl 4-(2-Methoxycarbonylphenoxy)-3-nitro-5-sulfamylbenzoate (16). **15** (2.0 g, 5.8 mmol) was suspended in 10.4 mL of concentrated HCl. A solution of 0.5 g of $NaNO_2$ (7.2 mmol) in 1.1 mL of H_2O was added, maintaining the temperature below 0 °C. The cold diazonium salt solution was poured at room temperature with stirring into a mixture of 14 mL of SO_2 saturated glacial acetic acid, 0.21 g of $CuCl_2$, and 0.42 mL of water. After stirring 80 min water was added and the mixture was extracted three times with $CHCl_3$; the combined $CHCl_3$ solutions were washed three times with water, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in 10 mL of $CHCl_3$; after addition of 2.9 g of $(NH_4)_2CO_3$ the mixture was refluxed for about 1 h. The reaction was cooled, the mixture evaporated under reduced pressure, and the residue washed with water and then treated with methanol. The resulting precipitate was filtered and recrystallized from methanol to yield 1.0 g (45%), mp 202–204 °C. Anal. ($C_{16}H_{13}N_2O_9S$) C, H, N.

8-Methoxycarbonyl-6-sulfamyldibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-one (17). A mixture of **16** (7.8 g, 22.5 mmol), 10% Pd/C (1.2 g), and 2.5 mL of concentrated HCl in 200 mL of THF was hydrogenated 7 h at 45 °C at 45 psi. The mixture was cooled and filtered and the mother liquor evaporated under reduced pressure. The resulting residue was suspended in 150 mL of methanol with 12 drops of concentrated H_2SO_4 and refluxed overnight. The crystalline precipitate was filtered and washed with a small amount of methanol to give 6.0 g (90%). Recrystallization of 1.5 g from acetone–methanol gave 1.2 g, mp >300 °C. Anal. ($C_{15}H_{12}N_2O_6S$) C, H, N, S.

10,11-Dihydro-8-methoxycarbonyl-6-sulfamyldibenz[*b*,*f*][1,4]oxazepine (18). To a stirred slurry of 2.0 g (5.75 mmol) of **17** in 100 mL of absolute THF was added 40 mL (40 mmol) of 1 M BH_3–THF at 0 °C over 20 min. The mixture was allowed to come to room temperature and was kept there for 5 h. After cooling to 15 °C, 40 mL of 3 N HCl was added slowly. The THF was removed by distillation at aspirator pressure and the aqueous phase was neutralized with saturated $NaHCO_3$ solution. The precipitated product was filtered, washed with water, and dried to yield 1.5 g of crude material which was chromatographed on silica gel with $CHCl_3$–MeOH (95:5) as eluent to yield 0.5 g (26%) of product, mp 242–244 °C. Anal. ($C_{15}H_{14}N_2O_5S$) C, H, N, S.

8-Carboxy-10,11-dihydro-6-sulfamyldibenz[*b*,*f*][1,4]oxazepine (19). A solution of 450 mg (1.4 mmol) of **18** in 17 mL of CH_3OH–H_2O (1:1) and 1.2 mL of 33% NaOH was refluxed for 0.5 h. After cooling, the solution was acidified with concentrated HCl. The resulting colorless precipitate was filtered, washed with water, and dried to yield 380 mg (88%) of product, mp 280–282 °C. Anal. ($C_{14}H_{12}N_2O_5S$) C, H, N, S.

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References and Notes

(1) P. W. Feit, *J. Med. Chem.*, 14, 432 (1971).
(2) O. B. T. Nielsen, C. K. Nielsen, and P. W. Feit, *J. Med. Chem.*, 16, 1170 (1973).
(3) W. Merkel, D. Bormann, D. Mania, R. Muschaweck, and M. Hropot, *Eur. J. Med. Chem.*, 11, 399 (1976).
(4) P. W. Feit, H. Bruun, and C. K. Nielsen, *J. Med. Chem.*, 13, 1071 (1970).
(5) P. W. Feit and O. B. T. Nielsen, *J. Med. Chem.*, 15, 79 (1972).
(6) P. W. Feit, O. B. T. Nielsen, and N. Rastrup-Andersen, *J. Med. Chem.*, 16, 127 (1973).
(7) P. W. Feit, O. B. T. Nielsen, and H. Bruun, *J. Med. Chem.*, 17, 572 (1974).
(8) O. B. T. Nielsen, H. Bruun, C. Bretting, and P. W. Feit, *J. Med. Chem.*, 18, 41 (1975).
(9) P. W. Feit and O. B. T. Nielsen, *J. Med. Chem.*, 19, 402 (1976).
(10) C. M. Kagawa and M. J. Kalm, *Arch. Int. Pharmacodyn. Ther.*, 137, 241 (1962).
(11) M. Allen and R. Y. Moir, *Can. J. Chem.*, 37, 1799 (1959).

1-[4-(4-Chlorophenyl)-2-(2,6-dichlorophenylthio)-*n*-butyl]-1*H*-imidazole Nitrate, a New Potent Antifungal Agent[1]

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The preparation and antifungal properties of 1-[4-(4-chlorophenyl)-2-(2,6-dichlorophenylthio)-*n*-butyl]-1*H*-imidazole nitrate **1** are described. It is particularly effective against in vivo *Candida albicans* infections (mice), maintaining good activity down to 0.25% formulation strength and showing unusually low reinfection rates after treatment is ended.

Many antifungal compounds containing an imidazole group are known and largely fall into two general classes: the (poly)arylmethylimidazoles[2] (e.g., clotrimazole) and the arylethylimidazoles[3] (e.g., miconazole). As the result of

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