(54 g, 0.39 mole), anhyd Me_2CO (400 g, 6.9 moles), and NaOH (100 g, 2.5 moles) at such a rate (*ca.* 1 hr) to maintain gentle reflux. The reaction mixt was then refluxed for an addl 4 hr and concd under reduced pressure. After addn of H_2O (600 ml) the mixt was passed through a filter while hot, the filtrate cooled, acidified (HCl), and extd ($CHCl_3$). The ext was purified by treatment with decolorizing C. After evapn of the solvent the residue was taken up in 2 *N* NaOH, the soln treated with activated C and, subsequently, acidified with dil HCl. On cooling a solid formed that was filtered off, washed (cold H_2O), dried, and recrystd from CCl_4 to give 36 g (40%) of product, mp 123–124°. *Anal.* ($C_{10}H_{11}NO_5$) C, H, N, O.

Ethyl 2-(4-Aminophenoxy)-2-methylpropionate HCl Salt (IV). A mixt of 2-(4-nitrophenoxy)-2-methylpropionic acid (14 g, 0.062 mole), 10% Pd/C (1 g), and 10 ml of concd HCl in 100 ml of EtOH was shaken under H_2 until the uptake of gas ceased (*ca.* 3 hr). After filtration the solvent was evapd under reduced pressure. The wet residue was dissolved in EtOH–PhH. After evapn of the azeotropic mixt, 14.3 g (99%) of cryst 2-(4-aminophenoxy)-2-methylpropionic acid·HCl was obtained. This product (14.3 g, 0.062 mole), without further purification, was dissolved in 200 ml of abs EtOH. Dry HCl was passed through the soln which was then heated under reflux for 1 hr, concd to 25 ml, and cooled. Addn of 200 ml of Et_2O caused pptn of a white cryst material which was collected on a filter, washed (Et_2O), and dried. Crude material (13.4 g, 83%) (mp 159–163°) was obtd. A sample was recrystd from MeCN, mp 163–165°. *Anal.* ($C_{12}H_{18}ClNO_3$) C, H, Cl, N, O.

Ethyl 2-{4-[*N*,*N*-Bis(2-hydroxyethyl)amino]phenoxy}-2-methylpropionate (V). To the crude ester IV (11.4 g, 0.044 mole) in 100 ml of H_2O was added 5 g of $NaHCO_3$, 80 ml of glac AcOH, and 10 ml of EtOH. The soln was cooled to −5°, 30 ml of liq ethylene oxide added, and the mixt allowed to stand at room temp for 4 days. The mixt was then neutralized with $NaHCO_3$ and extd (CH_2Cl_2, 3 × 125 ml). The combined exts were washed (H_2O, 4 × 125 ml) to remove glycol polymers, and dried ($MgSO_4$). The soln was evapd under reduced pressure to yield 11.1 g of an oily material. The oil was dissolved in warm Et_2O and treated with activated C. After evapn of the solvent under reduced pressure 11 g (80%) of a light tan oily product was obtd. The HCl salt had mp 113–115°. *Anal.* ($C_{16}H_{26}ClNO_5$) C, H, Cl.

Ethyl 2-{4-[*N*,*N*-Bis(2-chloroethyl)amino]phenoxy}-2-methylpropionate (VI). To V (8.7 g, 0.028 mole) was added 65 ml of $POCl_3$ and the mixt heated on a steam bath for 0.5 hr. The soln was poured on 800 ml of crushed ice while stirring, neutralized to pH 5 with NaOAc, and extd (CH_2Cl_2, 3 × 200 ml). The combined exts were washed (H_2O, 2 × 200 ml), dried ($MgSO_4$), and treated with activated C. The solvent was evapd under reduced pressure. The remaining oily material was dissolved in CH_2Cl_2–PhMe (30:200 ml) and the soln evapd to dryness at 50° under reduced pressure. A brown oily product (9.8 g, 98%) was obtd which was used without further purification in the subsequent reaction.

Dicyclohexylammonium 2-{4-[*N*,*N*-Bis(2-chloroethyl)amino]-phenoxy}-2-methylpropionate (II). VI (8.6 g, 0.024 mole) was heated on a steam bath in 150 ml of concd HCl for 0.5 hr, cooled, neutralized with NaOAc to pH 5, and extd with CH_2Cl_2 (3 × 200 ml). The combined exts were washed (H_2O, 2 × 200) and dried ($MgSO_4$). The solvent was then evapd under reduced pressure. The remaining oily material was dissolved in PhMe and the soln evapd to dryness under reduced pressure. A viscous oily product (4.2 g, 55%) was obtd. *Anal.* ($C_{14}H_{19}Cl_2NO_3$), C, H, N, O.

The dicyclohexylamine salt was made by add of dicyclohexylamine in Et_2O and subsequent pptn with petr ether (bp 30–60°), mp 139–141°. The recrystd salt (Et_2O–petr ether) melted at 141–143°. *Anal.* ($C_{26}H_{42}Cl_2N_2O_3$) C, H, Cl.

Antitumor Test. The tests against lymphoid leukemia L-1210 were carried out by CCNSC, National Cancer Institute, according to test procedures described in ref 6.

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Structure–Activity Studies on Sulfamyl Diuretics

Peter W. Feit,* Ole B. Tvaermose Nielsen, and Herta Bruun

Leo Pharmaceutical Products, 2750 Ballerup, Denmark.
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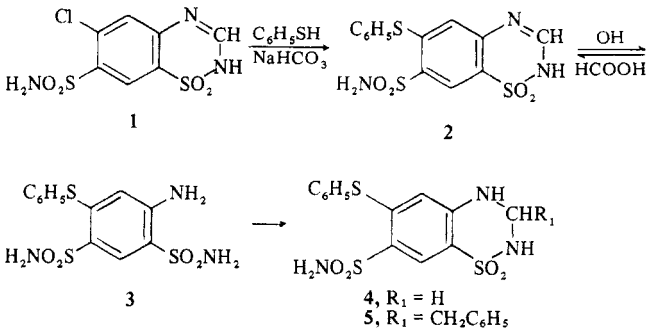
An examination of the structure-activity relationship of thiazide and hydrothiazide diuretics led to the conclusion that apart from other factors a substituent in neighboring position to the sulfonamide group must be present and that compounds having Cl, Br, NO_2, and CF_3 groups in this position are highly active.[1] In generalizations about structural features that lead to diuretic activity in both the aromatic disulfonamides and the thiazides and their related structures this substituent was designated the "activating group."[2] It was suggested that the outstanding activating groups are halogen or a "pseudohalogen" as CF_3. Even the non-thiazide-type high-ceiling diuretic 4-chloro-*N*-(2-furylmethyl)-5-sulfamylanthranilic acid[3,4] (furosemide) could be reduced to the empirical rules.[2] The recently described diuretic activity of 3-*n*-butylamino-4-chloro-5-sulfamylbenzoic acid[5] seemed to provide further support for the predicted structural requirements. On the other hand recent reports[6,7] disclosed that certain 4-substituted 3-amino-5-sulfamylbenzoic and 5-sulfamylanthranilic acid derivatives are greatly superior in potency to the corresponding 4-Cl compounds. Both similarities and differences in the influence of the different 4 substituents on the diuretic activity of these 2 series were seen. In the 4-RNH-3-amino-5-sulfamylbenzoic acid series, highly potent compounds were found while among the anthranilic acid derivatives the 4-RNH group afforded less active agents. C_6H_5O and C_6H_5S in the 4 position, however, provided increased activity in both series.

These facts prompted us to synthesize analogs of selected thiazide-type diuretics[4,8] of different structures bearing C_6H_5O or C_6H_5S groups instead of Cl or CF_3 ortho to the sulfonamide group. Furthermore, we investigated the corresponding analogs of 4-chloro-5-sulfamylsalicylic acid[9] (**21**), which had been shown in a preclinical study,‡ to be a high-ceiling diuretic although about 0.1 as potent as furosemide.

Chemistry. As analogs to chlorothiazide (**1**) and flumethiazide, hydrochlorothiazide and hydroflumethiazide, and bendroflumethiazide, 6-phenylthio-7-sulfamyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**2**), 6-phenylthio-7-sulfamyl-2,3-dihydro-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**4**), and the corresponding 3-benzyl compound **5** were synthesized according to Scheme I. The preparation of the disulfamylaniline **3** by halogen exchange in 3-chloro-4,6-disulfamylaniline failed in our hands. However, ring closure to chlorothiazide (**1**) increased the reactivity of the Cl to such a degree as to allow the exchange reaction with the thiophenoxide ion to form **2**. For purification crude **2** is conveniently hydrolyzed to **3**. Ring-closure reactions to **2**, **4**, and **5** were performed by established methods.[4]

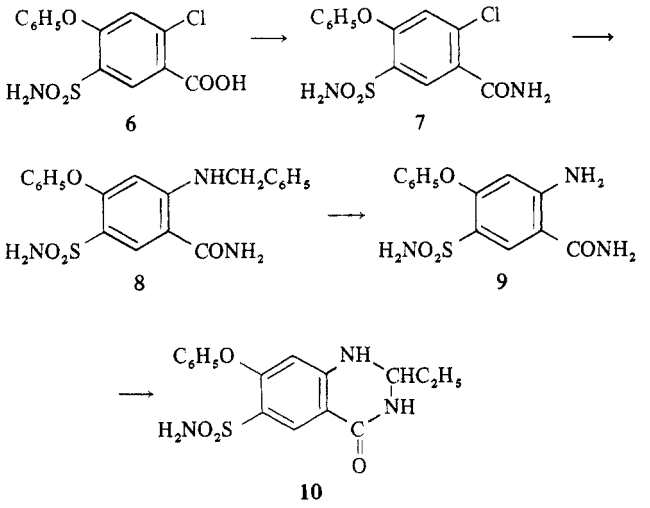
‡Personal communication from Dr. K. H. Olesen, Medical Department B, Rigshospital, University of Copenhagen, Medical School.

Scheme I



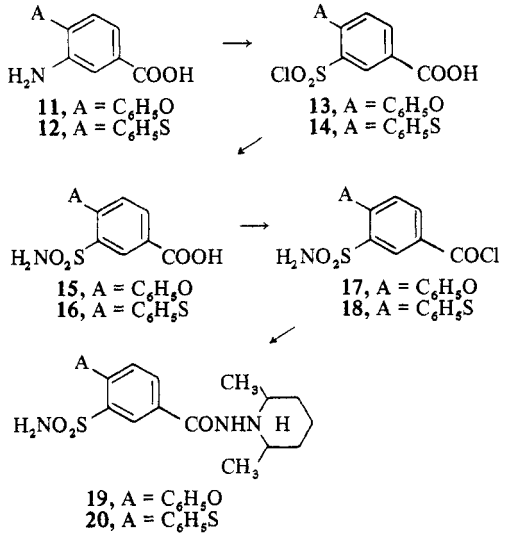
The preparation of the quinethazone analog, 2-ethyl-7-phenoxy-6-sulfamyl-1,2-dihydroquinazol-4-one (**10**), is given in Scheme II. The ring closure was performed by a method analogous to the synthesis of quinethazone.[10]

Scheme II



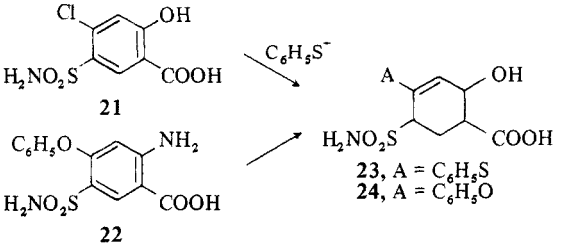
The preparation of the clopamide analogs *cis*-*N*-(2,6-dimethyl-1-piperidyl)-3-sulfamyl-4-phenoxybenzamide (**19**) and the corresponding 4-phenylthiobenzamide (**20**) was performed as outlined in Scheme III. The 3-aminobenzoic acids **11** and **12** were prepared by hydrogenation of the corresponding NO_2 acids. The 3-nitro-4-phenoxybenzoic acid is known,[11] while the 3-nitro-4-phenylthiobenzoic acid was produced by an analogous method.

Scheme III



The most direct approach for the preparation of the C_6H_5O and C_6H_5S analogs of the 4-chloro-5-sulfamyl salicylic acid (**21**) diuretic appeared to be based on halogen exchange in **21**. However, this reaction could be performed only by using the highly nucleophilic thiophenoxide ion to give **23**. The phenoxy compound **24** was, therefore, prepared from the anthranilic acid derivative **22** *via* the diazonium sulfate in a usual manner (Scheme IV). Further details are given in the Experimental Section.

Scheme IV



Diuretic Screening and Discussion. The benzothiadiazine **2**, the dihydrobenzothiadiazines **4** and **5**, the dihydroquinazolone **10**, the benzoic acid derivatives **19** and **20**, and the salicylic acids **23** and **24** prepared in this study were screened for their diuretic effect in dogs by a described[5] procedure. Compounds **2**, **4**, **5**, **19**, and **20** were administered at a dose of 1 mg/kg and **10**, **23**, and **24** at a dose of 10 mg/kg iv. No diuretic effect could be detected except for **23**, which showed the following urinary excretion per kilogram in the 3-hr test period: 6 ml of urine, 0.5 mequiv of Na^+, 0.3 mequiv of K^+, and 0.6 mequiv of Cl^-. (Values of controls: 2 ml of urine, 0.2 mequiv of Na^+, 0.1 of K^+, and 0.1 of Cl^-). When one considers the high screening dose and the results obtained with the corresponding 4-chlorosalicylic acid **21** (10 mg/kg iv: 12 ml of urine, 1.5 mequiv of Na^+, 0.5 mequiv of K^+, 1.4 mequiv of Cl^-) the diuretic potency of **23** is extremely low. Compounds **2** and **4** were also investigated in water-loaded rats. Oral administration of 10 and 20 mg/kg of **2** and 1 mg/kg of **4** exhibited no diuretic activity.

The striking feature of the present investigation is the lack of activity of compounds in which the Cl or the CF_3 group of several thiazide type diuretics of different structures are replaced by C_6H_5O or C_6H_5S. This is contrary to the results obtained with the high-ceiling diuretics of the anthranilic and 3-aminobenzoic acid series where a similar replacement gave the compounds a several tenfold increase in potency. When one considers the diuretic activity of 4-chloro-5-sulfamylsalicylic acid, which is closely related both in chemical structure and type of diuretic action to the anthranilic and 3-aminobenzoic acid diuretics, the absence or negligible activity of **23** and **24** is of interest.

One conclusion to be drawn is that at least the C_6H_5O and C_6H_5S substituents cannot be regarded as "activating groups" in the sense of earlier predicted[2] structural requirements for sulfamyl diuretics. The results presented emphasize the difficulties in finding general rules for the structural requirements of high-ceiling diuretics. However, one common features of all short-acting, high-ceiling diuretics evaluated to date (including ethacrynic acid and triflocine) is the presence of a carboxyl group ionized at physiological pH. The influence of this on both the distribution in the

organism and on the mode of excretion of the compounds cannot be overlooked.

Experimental Section§

4,6-Disulfamyl-3-phenylthioaniline (3). A stirred mixt of 6-chloro-7-sulfamyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**1**) (5.92 g), C_6H_5SH (2.76 g), and 1 *N* $NaHCO_3$ (50 ml) was heated in an oil bath at 100° for 24 hr. After cooling 1 *N* HCl was added until pH 8 and the pptd mixt# of **2** and **3** (5.83 g) collected. The crude material was dissolved in 1 *N* NaOH (100 ml) and the filtered soln heated on a steam bath for 90 min. Addn of 4 *N* HCl (30 ml) to the cooled reaction mixt pptd crude **3** (4.76 g). It was twice recrystd from hot MeOH–H_2O with the aid of decolorizing C and dried *in vacuo* at 115° for 3 hr; yield 2.84 g, mp 213–214°. *Anal.* ($C_{12}H_{13}N_3O_4S_3 \cdot 0.5CH_3OH$) C, H, N.

6-Phenylthio-7-sulfamyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (2). A mixt of **3** (0.5 g) and HCOOH (5 ml) was refluxed for 1 hr. Pptd **2** was collected after cooling and washed with HCOOH and Et_2O; yield 0.46 g, mp 300°. *Anal.* ($C_{13}H_{11}N_3O_4S_3$) C, H, N.

6-Phenylthio-7-sulfamyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (4). A mixt of **3** (0.8 g), $(CH_2O)_x$ (0.065 g), and aq MeOH (10 ml, 50%) was refluxed for 1 hr after addn of TsOH (approx 0.05 g). After cooling pptd crude **4** (0.58 g) was collected and recrystd from aq MeOH; yield 0.41 g, mp 271–272°. *Anal.* ($C_{13}H_{13}N_3O_4S_3$) C, H, N.

3-Benzyl-6-phenylthio-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (5). A mixt of **3** (2.4 g), $C_6H_5CH_2CH(OMe)_2$ (1 g), aq MeOH (20 ml, 50%), and AcOH (0.2 ml) was refluxed for 1 hr. After cooling crude **5** (2.35 g) was collected and twice recrystd from warm MeOH–H_2O; yield 1.57 g, mp 241–242°. *Anal.* ($C_{20}H_{19}N_3O_4S_3$) C, H, N.

2-Chloro-4-phenoxy-5-sulfamylbenzamide (7). A mixt of 2-chloro-4-phenoxy-5-sulfamylbenzoic acid[7] (**6**) (5.0 g) and $SOCl_2$ (10 ml) was refluxed for 1 hr. Excess of $SOCl_2$ was removed *in vacuo* and the crude 2-chloro-4-phenoxy-5-sulfamylbenzoyl chloride obtained was dissolved in CH_2Cl_2 (15 ml) and added dropwise to aq NH_3 (50 ml, 25%) while stirring at room temp. After addnl stirring for 1 hr, CH_2Cl_2 was distd off by heating on a steam bath and, after cooling, the pptd crude **7** was collected, washed with H_2O, and dried. It was recrystd from EtOH; yield 2.0 g, mp 232–233°. *Anal.* ($C_{13}H_{11}ClN_2O_4S$) C, H, Cl, N, S.

2-Benzylamino-4-phenoxy-5-sulfamylbenzamide (8). A stirred mixt of **7** (3.0 g) and $C_6H_5CH_2NH_2$ (10 ml) was heated to 110–120° for 2 hr and was then poured into 2 *N* HCl (40 ml) to ppt crude **8.** It was recrystd from EtOH; yield 1.4 g, mp 231–232°. *Anal.* ($C_{20}H_{19}N_3O_4S$) H, Cl, N, S; calcd C: 60.43; found 60.00.

2-Amino-4-phenoxy-5-sulfamylbenzamide (9). A soln of **8** (1.3 g) in methylcellosolve (20 ml) was hydrogenated at room temp after addn of 10% Pd/C (0.3 g). After 20 min the theor amt of H_2 had been absorbed and the uptake became negligible. The catalyst was removed by filtration and the filtrate was evapd *in vacuo.* The residue was triturated with H_2O (10 ml) to give crude **9.** It was recrystd from aq EtOH; yield 0.7 g, mp 240–241°. *Anal.* ($C_{13}H_{13}N_3O_4S$) C, H, N, S.

2-Ethyl-7-phenoxy-6-sulfamyl-1,2-dihydroquinazol-4-one (10). A soln of **9** (0.75 g) and C_2H_5CHO (0.5 ml) in EtOH (25 ml) acidified with concd HCl (0.05 ml) was refluxed for 1.5 hr and was then evapd *in vacuo.* The residue was triturated with H_2O (10 ml) to give crude **10.** It was recrystd twice from aq EtOH; yield 0.23 g, mp 245–247° dec. *Anal.* ($C_{16}H_{17}N_3O_4S$) C, H, N. S.

3-Amino-4-phenoxybenzoic Acid (11). A soln of 3-nitro-4-phenoxybenzoic acid[11] (3.1 g) in EtOH (100 ml) was hydrogenated at room temp after addn of 10% Pd/C (0.3 g). When the H_2 uptake became negligible the catalyst was removed by filtration, and the filtrate was evapd *in vacuo.* The residue was recrystd from aq EtOH; yield 2.3 g, mp 154–156°. *Anal.* ($C_{13}H_{11}NO_3$) C, H, N.

3-Chlorosulfonyl-4-phenoxybenzoic Acid (13). **11** (6.9 g) was treated with warm concd HCl (75 ml) and after cooling diazotized at 0–5° by addn of a soln of $NaNO_2$ (2.5 g) in H_2O (6 ml). A soln of $CuCl_2 \cdot 2H_2O$ (1.1 g) in H_2O (6 ml) was mixed with a cooled satd soln of SO_2 in AcOH (50 ml) and the diazonium salt soln added while stirring and cooling. After 15 min the stirred reaction mixt was allowed to reach room temp. When the N_2 evoln had ceased the stirring was contd at 30–40° for 45 min. After addnl stirring at room temp for 16 hr pptd crude **13** was collected, washed with petr ether and dried in air; yield 4.6 g, mp 188–189°.

4-Phenoxy-3-sulfamylbenzoic Acid (15). **13** (4.6 g) was added in portions to stirred and ice-cooled aq NH_3 (100 ml, 25%) during 1 hr. After the reaction mixt had been left for 18 hr at room temp acidification with 4 *N* HCl liberated oily **15,** crystd on rubbing. It was recrystd from aq EtOH; yield 2.7 g, mp 189–190°. *Anal.* ($C_{13}H_{11}NO_5S \cdot 0.5H_2O$) C, H, N.

4-Phenoxy-3-sulfamylbenzoyl Chloride (17). A mixt of **15** (1.5 g) and $SOCl_2$ (2.2 g) was refluxed for 1 hr. Excess of $SOCl_2$ was removed *in vacuo* and the residue dissolved in EtOAc (10 ml). The soln was treated with decolorizing C and **17** pptd by addn of petr ether; yield 1.2 g, mp 97–98°. *Anal.* ($C_{13}H_{10}ClNO_4S$) C, H, Cl, N.

***N*-[*cis*-2,6-Dimethyl-1-piperidyl]-4-phenoxy-3-sulfamylbenzamide (19).** A soln of **17** (2.7 g) in dry $CHCl_3$ (30 ml) was added to a stirred mixt of 1-amino-*cis*-2,6-dimethylpiperidine[12] (1.12 g), Et_3N (0.87 g), and dry $CHCl_3$ (30 ml) keeping the temp at 30° by cooling. After addnl stirring at room temp for 48 hr the reaction mixt was evapd *in vacuo,* and the residue dissolved in a mixt of EtOAc (100 ml) and H_2O (100 ml). The organic layer was washed twice with H_2O, dried ($MgSO_4$), and chromatogd on neutral Al_2O_3 (Woelm, activity I). Elution with $CHCl_3$–MeOH (9:1) and evapn of the eluate gave crude **19.** It was recrystd from aq MeOH; yield 0.3 g, mp 154–156°. *Anal.* ($C_{20}H_{25}N_3O_4S \cdot H_2O$) C, H, N; calcd H_2O 4.27, found 5.05.

3-Nitro-4-phenylthiobenzoic Acid. To a warm soln (70°) of 4-chloro-3-nitrobenzoic acid (20.2 g) in DMF (75 ml), K_2CO_3 (17.3 g) was added, followed by Cu powder (0.5 g) and C_6H_5SH (12.2 g). After the exothermic reaction had ceased, the resultant soln was refluxed for 6 hr. After evapn *in vacuo,* the residue was extd with H_2O (100 ml). After filtration the crude acid was pptd from the filtrate by acidification with 4 *N* HCl. It was recrystd from EtOH; yield 19.2 g, mp 226–227°. *Anal.* ($C_{13}H_9NO_4S$) C, H, N.

3-Amino-4-phenylthiobenzoic Acid (12). To a stirred suspension of 3-nitro-4-phenylthiobenzoic acid (13.4 g) in boiling aq EtOH (100 ml, 70% H_2O) a soln of $NaHSO_3$ (25.4 g) in H_2O (100 ml) was added during 30 min. After addnl refluxing for 1 hr, 4 *N* HCl was added until pH 3–4 and the reaction mixt refluxed for another 16 hr. After cooling the pptd crude **12** was collected and recrystd from aq EtOH; yield 5.8 g, mp 141–143°. *Anal.* ($C_{13}H_{11}NO_2S \cdot 0.25H_2O$) C, H, N.

3-Chlorosulfonyl-4-phenylthiobenzoic acid (14) was prepd from **12** according to the same procedure as **13,** except that the reaction mixt after the N_2 evoln had ceased was stirred at 40–50° for 2 hr, whereafter **14** was isolated without addnl stirring; yield 73%, mp 178–185°.

4-Phenylthio-3-sulfamylbenzoic acid (16) was prepd from **14** according to the same procedure as **13,** except that most of the excess of NH_3 was removed by distn before acidification; yield 27%, mp 242–243°. *Anal.* ($C_{13}H_{11}NO_4S_2$) C, H, N.

4-Phenylthio-3-sulfamylbenzoyl chloride (18) was prepd from **16** according to the same procedure as **17;** yield 41%, mp 145–146°. *Anal.* ($C_{13}H_{10}ClNO_3S_2$) C, H, N, Cl.

***N*-[*cis*-2,6-Dimethyl-1-piperidyl]-4-phenylthio-3-sulfamylbenzamide (20)** was prepd from **18** according to the same procedure as **19,** except that the compd was eluted with CH_2Cl_2–MeOH (9:1); yield 12%, mp 168–169°. *Anal.* ($C_{20}H_{25}N_3O_3S_2 \cdot 0.5H_2O$) C, H, N, H_2O.

4-Phenylthio-5-sulfamylsalicylic Acid (23). A stirred mixt of 4-chloro-5-sulfamylsalicylic acid (**21**) (7.53 g), C_6H_5SH (6.7 g), $NaHCO_3$ (10.2 g), and H_2O (60 ml) was kept at approx 85° for 5 days. After cooling, the reaction mixt was extd with Et_2O, and the aq soln adjusted to pH 8 by addn of 4 *N* HCl. The pptd Na salt of **23** (3.2 g) was collected and washed with cold H_2O. The sodium salt (1.6 g) was recrystd from H_2O; yield 1.15 g. *Anal.* ($C_{13}H_{10}NNaO_5S_2 \cdot 3H_2O$) C, H, N, H_2O. The Na salt of **23** (1 g) was dissolved in boiling H_2O (30 ml), and **23** was liberated by addn of 1 *N* HCl (6 ml). After cooling **23** was collected, recrystd from aq EtOH, and dried *in vacuo* at 100°; yield 0.63 g, mp 252–253° dec. *Anal.* ($C_{13}H_{11}NO_5S_2$) C, H, N.

4-Phenoxy-5-sulfamylsalicylic Acid (24). A soln of 4-phenoxy-5-sulfamylanthranilic acid[7] (**22**) (1.5 g) and $NaNO_2$ (0.34 g) in 1 *N* NaOH (10 ml) was dropwise added to 4 *N* H_2SO_4 (150 ml) while stirring at 0–5°. The resulting diazonium soln was heated on a steam bath until the evoln of N_2 had ceased (about 24 hr). After cooling, the pptd crude **24** was collected, washed with H_2O, and dried. It was recrystd twice from aq EtOH; yield 0.27 g, mp 240–241°. *Anal.* ($C_{13}H_{11}NO_6S$) C, H, N, S.

§ Analyses were performed by G. Cornali and W. Egger of these labs. When not otherwise stated analyses are indicated only by symbols of the elements; analytical results for those elements were within ±0.4% of the calcd values. Mp were cor and taken in open glass capillaries using a Hershberg apparatus.

#Controlled by tlc: silica gel (HF_{254}, Merck); Et_2O (100), AcOH (0.5); detection by uv.

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†In this reference the term metanilic acid has been used erroneously for 3-aminobenzoic acid throughout.

4-Anilino-1-phenyl-3-pyrrolecarboxylic Acids. Analogs of the Fenamic Acids

Victor J. Bauer and S. R. Safir*

CNS Disease Therapy Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965.
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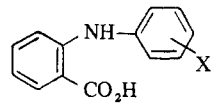
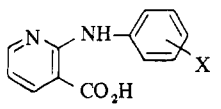
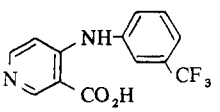
Substitution of a pyridine ring for the benzene ring of the antiinflammatory fenamic acids–flufenamic acid (**1a**), mefenamic acid (**1b**), and meclofenamic acid (**1c**)[1]–has given niflumic acid (**2a**, antiinflammatory),[2] clonixin (**2b**, antiinflammatory),[3] and triflocin (**3**, diuretic).[4] Incorporation of a thiophene ring in the molecule has produced the antiinflammatory analogs **4a–c**.[5] We now report the synthesis of several pyrrole analogs **9** of the fenamic acids.



1a, X = 3-CF_3
b, X = 2,3-$(CH_3)_2$
c, X = 2,6-Cl_2-3-CF_3

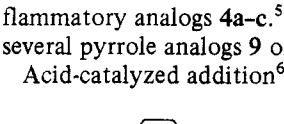


2a, X = 3-CF_3
b, X = 3-Cl-2-CH_3

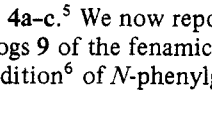


3

Acid-catalyzed addition[6] of *N*-phenylglycine ethyl ester to ethyl acrylate gave the diester **5**, which underwent Dieckmann cyclization to the known[7] β-keto ester **6**. Treatment of **6** with the appropriate anilines provided the enamino esters **7** (Table I). S dehydrogenation of **7** yielded the ethyl anilinopyrrolecarboxylates **8** (Table II), which were saponified to the desired acids **9** (Table III).



4a, X = 3-CF_3
b, X = 3-Cl-2-CH_3
c, X = 2,6-Cl_2



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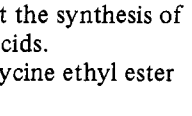
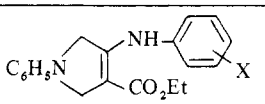


6

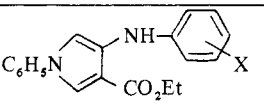
Compounds **9** were found† to be without activity in the rat paw carrageenin edema antiinflammatory assay,[8] the adjuvant-induced rat polyarthritis test,[9] and the phenyl-*p*-quinone writhing analgetic screen.[10]

Table I. Ethyl 4-Anilino-1-phenyl-3-pyrroline-3-carboxylates (**7**)



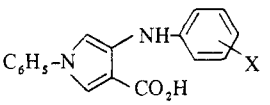
X	Mp, °C	Recrystn solv	Formula
H	129–130	Hexane	$C_{19}H_{20}N_2O_2$
3-CF_3	112–113	Hexane	$C_{20}H_{19}F_3N_2O_2$
2,3-$(CH_3)_2$	150–151	Hexane	$C_{21}H_{24}N_2O_2$
4-F	167–168	Hexane–C_6H_6	$C_{19}H_{19}FN_2O_2$

Table II. Ethyl 4-Anilino-1-phenyl-3-pyrrolecarboxylates (**8**)



X	Mp, °C	Recrystn solv	Formula
H	83	EtOH	$C_{19}H_{18}N_2O_2$
3-CF_3	81–82	EtOH	$C_{20}H_{17}F_3N_2O_2$
2,3-$(CH_3)_2$	80–81	EtOH	$C_{21}H_{22}N_2O_2$
4-F	100–101	EtOH	$C_{19}H_{17}FN_2O_2$

Table III. 4-Anilino-1-phenyl-3-pyrrolecarboxylic Acids (**9**)



X	Mp, °C	Recrystn solv	Formula
H	208	MeCN	$C_{17}H_{14}N_2O_2$
3-CF_3	189	MeCN	$C_{18}H_{13}F_3N_2O_2$
2,3-$(CH_3)_2$	192–193	MeCN	$C_{19}H_{18}N_2O_2$
4-F	212–213	MeCN	$C_{17}H_{13}FN_2O_2$

Experimental Section‡

***N*-(Carboxymethyl)-*N*-phenyl-β-alanine Diethyl Ester (5).** A mixt of 500 g (2.8 moles) of *N*-phenylglycine ethyl ester, 500 ml of ethyl acrylate, and 50 ml of HOAc was heated at 160° for 4 days in a bomb, cooled, dild with Et_2O, and filtered. The filtrate was washed with NaOH soln, dried ($MgSO_4$), and concd. The liquid was distd to provide, after collection of unreacted *N*-phenylglycine ethyl ester, 260 g (33%) of yellow liq, bp 195–210° (15–20 mm). Redistn of a small portion gave a colorless liquid, bp 200–204° (12 mm) [lit.[7] bp 210–211° (16 mm)]. *Anal.* ($C_{15}H_{21}NO_4$) C, H, N.

Ethyl 4-Oxo-1-phenyl-3-pyrrolidinecarboxylate (6). To a stirred mixt of 70 g (0.62 mole) of KO-*tert*-Bu and 3 l. of C_6H_6 was added dropwise during 1 hr 169 g (0.61 mole) of **5**. The mixt was heated under reflux for 3 hr, cooled, and filtered. The collected solid was suspended in 2 l. of H_2O, acidified with 45 ml of HOAc, and extd with $CHCl_3$. The $CHCl_3$ soln was dried ($MgSO_4$) and concd to an oily solid. Recrystn (EtOH) gave 73 g (51%) of off-white crystals, mp 77–78°. Several recrystns gave colorless crystals, mp 97–98° (lit.[7]

†Animal testing was carried out by Drs. A. E. Sloboda and A. C. Osterberg of these laboratories.

‡Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff. All compounds were analyzed for C, H, N, and F; found values were within ±0.4% of theoretical.