assayed for HVA levels by HPLC. Amine **7b** or its saline vehicle was administered to the rat ip. Dialysate samples were collected for 4 h following the injection. Each rat received both saline vehicle and **7b** injections on separate days. Average, preinjection dialysate HVA levels were assigned the value of "100% base line", and changes in dialysate HVA levels following injection were compared to these levels.

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Registry No. (±)-**7a**, 121867-66-1; (±)-**7a** (free base), 121867-55-8; (±)-**7b**, 121867-67-2; (±)-**7b** (free base), 121867-56-9; (±)-**7c**, 121867-68-3; (±)-**7c** (free base), 121867-57-0; (±)-**7d**, 121867-69-4; (±)-**7d** (free base), 121867-58-1; (±)-**7e**, 121867-70-7; (±)-**7e** (free base), 121867-59-2; (±)-**7f**, 121867-71-8; (±)-**7f** (free base), 121867-60-5; (±)-**7g**, 121867-72-9; (±)-**7g** (free base), 121867-61-6; (±)-**7h**, 121867-73-0; (±)-**7h** (free base), 121867-62-7; (±)-**7i**, 121867-74-1; (±)-**7i** (free base), 121867-63-8; (±)-**7j**, 121867-75-2; (±)-**7j** (free base), 121867-64-9; (±)-**7k**, 121867-76-3; (±)-**7k** (free base), 121867-65-0; (±)-**10a**, 121868-03-9; (±)-**10a** (free base), 121867-98-9; (±)-**10b**, 121868-04-0; (±)-**10b** (free base), 121867-99-0; (±)-**10c**, 121868-05-1; (±)-**10c** (free base), 121868-00-6; (±)-**10d**, 121868-06-2; (±)-**10d** (free base), 121868-02-8; (±)-**11**, 74197-16-3; (±)-**12a**, 74197-10-7; (±)-**12b**, 121867-51-4; (±)-**12b**·2HCl, 121867-77-4; (±)-**12c**, 121867-52-5; (±)-**12d**, 121867-53-6; (±)-**12e**, 121867-54-7; (±)-**13**, 121867-78-5; (±)-**14a**, 121867-79-6; (±)-**14b**, 121867-80-9; (±)-**14c**, 121867-81-0; (±)-**14d**, 121867-82-1; (±)-**14e**, 121867-83-2; (±)-**14f**, 121867-84-3; (±)-**14g**, 121867-85-4; (±)-**14h**, 121867-86-5; (±)-**14i**, 121867-87-6; (±)-(*E*)-**14j**, 121867-88-7; (±)-(*Z*)-**14j**, 121958-22-3; (±)-**14k**, 121867-89-8; (±)-**16a**, 121867-90-1; (±)-**16b**, 121886-90-6; (±)-**16c**, 121867-91-2; (±)-**16d**, 121867-92-3; (±)-**16e**, 121867-96-7; (±)-**17a**, 121867-93-4; (±)-**17b**, 121867-94-5; (±)-**17c**, 121867-95-6; (±)-**17d**, 121868-01-7; (±)-**17e**, 121867-97-8; butyryl chloride, 141-75-3; phenylacetyl chloride, 103-80-0; 2-thienylacetyl chloride, 39098-97-0; 3-(mercaptomethyl)propionyl chloride, 7031-23-4; butyraldehyde, 123-72-8; phenylacetaldehyde, 122-78-1; propionaldehyde, 123-38-6; propionyl chloride, 79-03-8.

Quantitative Structure–Activity Relationships in Dihydropteroate Synthase Inhibition by Multisubstituted Sulfones. Design and Synthesis of Some New Derivatives with Improved Potency†

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On the bases of the linear correlation existing for a training set of homomultisubstituted 4-aminodiphenyl sulfones between the computed (INDO) electronic net charges of the SO_2 group and the enzymic inhibition data on dihydropteroate synthase from *Escherichia coli*, seven new heteromultisubstituted derivatives were designed, synthesized, and tested for their inhibition potencies. These compounds were found to be from 5–11 times more effective than 4,4′-diaminodiphenyl sulfone. The implications of the results in the drug design and in the model for the enzyme–inhibitors interaction are discussed.

The diaryl sulfone derivatives (SO), like sulfanilamides (SA), exert their biological action by inhibiting the enzyme dihydropteroate synthase (DHPS) competitively with respect to the substrate 4-aminobenzoate.[1] The important role of these compounds as antibacterial,[1] antimalarial,[2] and antileprotic[3] agents is well-recognized. Moreover, the urgent need for potent antimalarials,[2] the increased incidence of the so-called atypical mycobacterial infections,[3] and the representative role assumed by SO and SA in the development of some aspects of quantitative structure–activity relationship (QSAR) methodologies[1] have led to a renewed interest in this class of drugs.

On the basis of QSAR analysis of a large series of SO using both empirical and quantum chemical descriptors of the molecular structure, we concluded[4,5] that, like in the case of SA, the electronic structure of the common moiety 4-$NH_2C_6H_4SO_2$, modulated by the substituents, is the determining factor connected with inhibitory potency. In particular, the more electron-rich the common moiety is, the more active the compounds are. This situation is at its best realized by the design and synthesis of multisubstituted SO bearing electron-donor substituents, the most efficient one being the hydroxy group, which can dissociate, giving the hydroxylate anion.

In the present work, the inhibitory effect exerted by some newly synthesized 2′,4′- and 2′,4′,6′-substituted SO on the enzymic activity has been studied and correlated with theoretical electronic features of the SO_2 group. The 2′-CH_3, 4′-OH; 2′,6′-$(CH_3)_2$, 4′-OH; and 2′-Cl, 4′-OH derivatives are about 1 order of magnitude more effective than the 4,4′-diaminodiphenyl sulfone (DDS). The equations found allow us, on a simple basis, to design multisubstituted SO and predict their biological activity prior to synthesis.

Results and Discussion

Table I reports the measured ap_E values, giving the inhibitory effect on DHPS from *E. coli* of 11 new SO derivatives (compounds **14–24**), together with the previously

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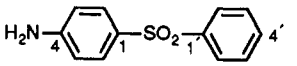
Table I. Experimental and Theoretical Descriptors of Sulfones



no.	substituents	EII_{50}[a]	ap_E obsd[b]	ap_E calcd[c]	pK_{a_1}[d]	pK_{a_2}[d]	% A^-[e]	$q(SO_2)$[f]
1	4′-NH_2 (DDS)	2.64 (±0.76)	−0.42	−0.44				−0.5603
2	2′,4′-$(NO_2)_2$	36.31 (±13.72)	−1.56	−1.28				−0.5204
3	2′,4′-$(CH_3)_2$	1.89 (±0.54)	−0.28	−0.31				−0.5668
4	2′,4′-$(Cl)_2$	2.24 (±0.60)	−0.35	−0.36				−0.5356
5	2′,4′-$(NH_2)_2$	1.59 (±0.20)	−0.20	−0.52				−0.5567
6	2′,4′-$(OCH_3)_2$	3.21 (±1.13)	−0.51	−0.72				−0.5472
7	2′,4′-$(OH)_2$	0.71 (±0.17)	0.15	−[g]	7.67	10.14		−0.5480
8	2′-OH, 4′-O^-	0.51 (±0.14)	0.29[h]	0.22			77.2	−0.5921
9	2′,4′,6′-$(CH_3)_3$	1.69 (±0.55)	−0.23	−0.09				−0.5772
10	2′,4′,6′-$(Cl)_3$	3.31 (±1.18)	−0.52	−0.68				−0.5204
11	2′,4′,6′-$(OCH_3)_3$	12.88 (±4.57)	−1.11	−0.90				−0.5382
12	2′,4′,6′-$(OH)_3$	1.91 (±0.34)	−0.28	−[g]	7.69	9.62		−0.5397
13	2′,6′-$(OH)_2$, 4′-O^-	1.46 (±0.27)	−0.16[h]	0.01			76.4	−0.5824
14	2′-CH_3, 4′-OCH_3	1.77 (±0.63)	−0.25	−0.33				−0.5658
15	2′-CH_3, 4′-OH	0.34 (±0.32)	0.47	−[g]	7.94			−0.5659
16	2′-CH_3, 4′-O^-	0.23 (±0.21)	0.66[h]	0.55			64.5	−0.6083
17	2′-Cl, 4′-OH	0.26 (±0.01)	0.58	−[g]	6.70			−0.5423
18	2′-Cl, 4′-O^-	0.26 (±0.01)	0.59[h]	0.76			96.9	−0.5895
19	2′,4′-$(CH_3)_2$, 6′-OCH_3	3.02 (±0.10)	−0.48	−0.48				−0.5588
20	2′,4′-$(CH_3)_2$, 6′-OH	1.78 (±0.08)	−0.25	−[g]	8.61			−0.5596
21	2′,4′-$(CH_3)_2$, 6′-O^-	0.50 (±0.02)	0.30[h]	0.11			28.0	−0.5871
22	2′,6′-$(CH_3)_2$, 4′-OCH_3	1.77 (±0.15)	−0.25	−0.13				−0.5755
23	2′,6′-$(CH_3)_2$, 4′-OH	0.51 (±0.09)	0.29	−[g]	8.20			−0.5757
24	2′,6′-$(CH_3)_2$, 4′-O^-	0.25 (±0.05)	0.59[h]	0.69			50.0	−0.6149

[a] Enzyme inhibition index values: SO concentration giving 50% inhibition of enzyme activity divided by 4-aminobenzoate concentration.[5] Standard deviations are given in parentheses. [b] $ap_E = \log (1/EII_{50})$. [c] Calculated with eq 3. [d] Acidic dissociation constants of the hydroxy substituents. [e] Percentage of monoanionic forms. [f] Electronic total net charges computed in the INDO approximation.[10] [g] See the corresponding anionic forms: **8**, **13**, **16**, **18**, **21**, and **24**. [h] By ascribing the whole inhibitory effect of the acidic compounds to their monoanionic forms only,[5] the ap_E values measured for compounds **7**, **12**, **15**, **17**, **20**, and **23** were corrected to obtain the values assigned to the anionic forms **8**, **13**, **16**, **18**, **21**, and **24**.

measured[5] ap_E values of the 4′-NH_2 substituted (DDS) and 2′,4′-, and 2′,4′,6′-substituted SO (compounds **1–13**), for comparison. Table I also reports the pK_a values of SO bearing acidic hydroxy substituents, the percentage of the monoanionic forms, and the total net charges of the SO_2 group computed in the INDO approximation.

The following equation summarizes the results of QSAR analysis for the training set (compounds **1–3**, **5**, **6**, **8**, **9**, **11**, and **13**):

$$ap_E = -22.8\ (\pm 5.8)q(SO_2) - 13.3\ (\pm 3.2) \qquad (1)$$

$$n = 9 \quad r = 0.940 \quad s = 0.195 \quad F = 49.2$$

where n represents the number of SO considered, r is the correlation coefficient, s is the standard deviation from the regression, F is the significance F test, and the values in parentheses give the 95% confidence intervals.

The above equation clearly indicates that the more electron-rich (nucleophilic) the SO_2 group is, the more active the compounds are.

Based upon previous results[2,4–6] and eq 1, some di- and trisubstituted derivatives, designed to increase the electronic charge on the SO_2 group, and, in general, on all the common moiety, were synthesized and tested (compounds **14–24**). By including compounds **14**, **16**, **19**, **21**, **22**, and **24** in the regression, we obtain the following equation:

$$ap_E = -22.1\ (\pm 3.1)q(SO_2) - 12.8\ (\pm 1.8) \qquad (2)$$

$$n = 15 \quad r = 0.958 \quad s = 0.166 \quad F = 146$$

which shows an improvement of the statistical significance.

In this correlation the anionic forms of the acidic compounds have been considered.[5]

The chloro derivatives were discarded from eq 2 because of their large deviations from linearity. However, as suggested by Seydel and co-workers,[2] the use of an indicator variable I ($I = 1$ when the 2′-Cl substituent is present, and $I = 0$ in all the other cases) allows us to include these compounds in the regression, obtaining the following equation:

$$ap_E = -20.8\ (\pm 2.8)q(SO_2) + 0.60\ (\pm 0.20)I - 12.1\ (\pm 1.6) \qquad (3)$$

$$n = 18 \quad r = 0.958 \quad s = 0.171 \quad F = 83.1$$

which is comparable with eq 2 and confirms that the inhibitory activity is positively influenced by electron-donor substituents and by the *o*-chloro substitution,[2,5,6] which enhances the activity by a factor of 2. The increase in the inhibitory potency due to the *o*-chloro substituents may be associated with a peculiar hydrophobic interaction with the enzymic site and/or to a specific *o*-chloro electronic phenomenon. Further investigation on this point is in progress.

It is worth stressing that some compounds (**16**, **18**, **21**, and **24**) are from 5–11.5 times more effective than DDS (compound **1**). The 2′-CH_3, 4′-OH and 2′-Cl, 4′-OH derivatives are the most active compounds of this class of drugs.

Conclusions

The good correlations found are encouraging in view of the design of new multisubstituted SO on the basis of a simple calculation of the electronic net charge of the SO_2 prior to synthesis. In this context, the superiority of quantum chemical descriptors clearly emerges when compared with empirical substituent constants (like σ), in which the additivity criterion is generally assumed and relevant changes of the molecular geometry cannot be

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Table II. Aryl 4-Nitrophenyl Sulfides (4-$NO_2C_6H_4MC_6H_2$-2′-X,4′-Y,6′-Z) and Sulfones

no.	X	Y	Z	M	synth meth	time, h	% yield[a]	mp, °C	recrystn solv[b]	formula[c]
14a	CH_3	OCH_3	H	S			89	69–70	C	$C_{14}H_{13}NO_3S$
17a	Cl	OH	H	S			82	185–187[d]	A	$C_{12}H_8ClNO_3S$
19a	CH_3	CH_3	OCH	S			69	103–104	C	$C_{15}H_{15}NO_3S$
20a	CH_3	CH_3	OH	S			82	133–134	A	$C_{14}H_{13}NO_3S$
22a	CH_3	OCH_3	CH_3	S			83	115–117	B	$C_{15}H_{15}NO_3S$
23a	CH_3	OH	CH_3	S			80	170–172	A	$C_{14}H_{13}NO_3S$
14b	CH_3	OCH_3	H	SO_2	A	4	92	130–130.5	*e*	$C_{14}H_{13}NO_5S$
17b	Cl	OH	H	SO_2	A	5	96	202–204[f]	A	$C_{12}H_8ClNO_5S$
19b	CH_3	CH_3	OCH_3	SO_2	B	24	79	202–203	*g*	$C_{15}H_{15}NO_5S$
20b	CH_3	CH_3	OH	SO_2	B	24	81	149–150	*h*	$C_{14}H_{13}NO_5S$
22b	CH_3	OCH_3	CH_3	SO_2	B	48	82	147–147.5	*i*	$C_{15}H_{15}NO_5S$
23b	CH_3	OH	CH_3	SO_2	A	3	67	177–178	*j*	$C_{14}H_{13}NO_5S$

[a] No attempt was made to maximize yield. [b] A = ethanol–water, B = ethanol, C = 2-propanol. [c] Analyzed for C, H, N, and S; analytical results were within ±4% of the theoretical values. [d] The crude product was precipitated from ice–water solution adjusting the pH to 8 (lit.[20] mp 190 °C). [e] The product was crystallized on cooling the reaction mixture and was chromatographed on silica gel with CH_2Cl_2 as eluant. [f] Literature[20] mp 207 °C. [g] Crude product was chromatographed on silica gel with $CHCl_3$ as eluant. [h] The crude product was purified by chromatography on silica gel with $CHCl_3$ as eluant and recrystallized from 2-propanol. [i] Crude product was recrystallized from C_2H_5OH–CH_3COOH and chromatographed on silica gel with CH_2Cl_2 as eluant. [j] The crude product was chromatographed on silica gel with 30% petroleum ether in ether as eluant and recrystallized from ethanol–water.

directly accounted for. In fact, no significant correlations were found when classical physicochemical parameters (σ, π, MR, V_W, etc.) were considered.

Finally, these results are consistent with the model[1] proposed recently for the interaction between both SA and SO inhibitors and the active site of DHPS. In fact, because of the long range of action of electrostatic forces, the SO_2 group (like the CO_2^- group of the substrate 4-aminobenzoate) appears to be the first to interact, anchoring the molecule loosely and increasing the probability of a correct and close fitting. This allows other forces with a small range of action to become operative.

Experimental Section

Enzymic Inhibition Measurements. The enzyme preparation, containing *E. coli* dihydropteroate synthase (EC 2.5.1.15), was obtained essentially by the method of Richey and Brown,[7] as described previously.[5]

The enzyme substrate 2-amino-4-hydroxy-6-(hydroxymethyl)-7,8-dihydropteridine pyrophosphate (dihydropteridine-PP) was prepared by a modified[5] version of the method proposed by Ho et al.[8]

4-Amino[7-^{14}C]benzoic acid (sp act. 53 μCi/mg) was purchased from the Radiochemical Centre, Amersham, U.K.

The assays were performed as described in our previous study.[5] The complete reaction mixture contained the following in a final volume of 1 mL: 0.1 M Tris-HCl buffer, pH 8.6; 0.01 M $MgCl_2$; 0.05 M mercaptoethanol; 0.12 mM dihydropteridine-PP; 5 μM 4-amino[7-^{14}C]benzoic acid (16 000 cpm); and different concentrations of SO, when present. The reaction was started by addition of 0.05 mL of the enzyme preparation.

The values of the SO concentrations giving 50% inhibition of enzyme activity were calculated by interpolation from linear regressions of 1/dpm vs SO concentrations. These values divided by PAB concentration give the enzyme inhibition indices, EII_{50}, which, in turn, are expressed as $ap_E = \log (1/EII_{50})$. Each reported ap_E value represents the mean of at least three independent measures.

The pH values of the different reaction mixture (with or without the inhibitors) were measured in separate experiments and resulted to be 8.2 ± 0.1, throughout the duration of the experiment.

pK_a Measurements. The pK_a values of the acidic derivatives (compounds **7**, **12**, **15**, **17**, **20**, and **23**) were measured spectrophotometrically, with a Beckman DU8 spectrophotometer, at 25 ± 2 °C, according to the method outlined by Albert and Serjant.[9] The measured values of pK_a are given in Table I together with the percentage values of the monoanionic forms (**8**, **13**, **16**, **18**, **21**, and **24**) present in the solution at pH 8.2.

By ascribing the whole inhibitory effect of the acidic compounds to their monoanionic forms only,[5] the ap_E values measured for compounds **7**, **12**, **15**, **17**, **20**, and **23** were corrected to obtain the values assigned in Table I to the anions **8**, **13**, **16**, **18**, **21**, and **24**.

Calculations. LCAO-MO results were performed by making use of a modified version of the INDO method[10] (QCPE 141). The two center repulsion integrals were computed from the Nishimoto–Mataga formula.[11] The calculations were performed at the Centro Interdipartimentale di Calcolo Automatico e Informatica Applicata of the University of Modena.

Standard geometries were used for the common moiety 4-$NH_2C_6H_4SO_2$ a constant geometry was assumed[12] for all the derivatives of Table I.

Chemistry. Melting points were determined on Büchi apparatus and are uncorrected. Microanalyses were within ±0.4% of the theoretical values.

2,6-Dimethyl-4-methoxythiophenol. The thiol was prepared from 4-thiocyano-3,5-dimethylanisole according to a literature method,[13] modified in order to isolate the compound: 84%, bp 94–95 °C (2 mm) [lit.[14] bp 126–130 °C (10 mm), lit.[15] bp 270–272 °C (760 mm)].

2,6-Dimethyl-4-hydroxythiophenol. A mixture of 2,6-dimethyl-4-hydroxyaniline[16] (27.4 g, 200 mmol), concentrated hydrochloric acid (36.4 mL), and ice (50 g) was cooled at −5 °C and slowly treated with a solution of sodium nitrite (13.8 g, 200 mmol) in water (75 mL), the temperature being maintained below 0 °C. The cold solution of the diazonium salt was added dropwise (1 h) under stirring to an aqueous (75 mL) solution of potassium ethyl xantate (64 g, 400 mmol) maintained at 70–78 °C. After stirring for 1 h further, the mixture was cooled at room temperature, adjusted to pH 8, and extracted with ether, and the extracts were washed with water, dried, and evaporated. The residue was hydrolyzed for 12 h under a nitrogen atmosphere, by refluxing with a solution of 50.4 g of KOH in 250 mL of ethanol. After evaporation of the solvent, the reaction mixture was diluted with water and the solution was washed with ether. The aqueous layer was acidified by the slow addition of dilute sulfuric acid and

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the product was isolated by extraction with ether. The organic layer was washed with water, dried, and evaporated. The solid residue was washed with hot cyclohexane, the solvent was removed, and the product was chromatographed on silica gel ($CHCl_3$ as eluant) to give 2,6-dimethyl-4-hydroxythiophenol (15.5 g, 50%), mp 105–106 °C. Anal. ($C_8H_{10}OS$) C, H, N, S.

2,4-Dimethyl-6-hydroxythiophenol. 2,4-Dimethyl-6-hydroxyaniline was obtained [78%, mp 158–159 °C (lit.[16] mp 163 °C)] by catalytic hydrogenation (Raney Ni catalyst, 1 atm) of the corresponding nitro derivative,[17] and it was converted to 2,4-dimethyl-6-hydroxythiophenol by the procedure described for the preparation of 2,6-dimethyl-4-hydroxythiophenol: yield, 65%; bp 84 °C (1.5 mm); mp 39–40.5 °C [lit.[18] bp 126–127 °C (19 mm)].

4-Nitrophenyl 2-Methyl-4-methoxyphenyl Sulfide (14a) (Table II). To a stirred solution of sodium hydroxide (0.6 g, 15 mmol) in water (20 mL) were added 4-nitrophenyl 2-methyl-4-hydroxyphenyl sulfide[19] (2.6 g, 10 mmol) and dimethyl sulfate (1.9 g, 15 mmol). The mixture was heated at 100 °C for 24 h, diluted with water, and extracted with ether. The organic layer was washed with 5% aqueous NaOH and with water, dried, and evaporated. The residue was chromatographed on silica gel (benzene as eluant) and recrystallized from 2-propanol to give **14a** (2.4 g, 89%).

Synthesis of Aryl 4-Nitrophenyl Sulfide (17a, 20a, and 23a) (Table II). To a solution of the appropriate thiophenol (50 mmol) in dry acetone (80 mL) were added dry potassium carbonate (60 mmol) and a solution of 4-chloronitrobenzene (50 mmol) in dry acetone (80 mmol). The mixture was refluxed under a nitrogen atmosphere for 7 h and the solvent was removed. Ice and water were added and the crude product was collected by filtration, washed with water, and recrystallized.

4-Nitrophenyl 2,4-Dimethyl-6-methoxyphenyl Sulfide (19a) (Table II). A mixture of 4-nitrophenyl 2,4-dimethyl-6-hydroxyphenyl sulfide (5.5 g, 20 mmol), dimethyl sulfate (10 g, 79 mmol), and 45 mL of 8% aqueous NaOH was stirred at 100 °C for 24 h. After cooling, water was added and the mixture was extracted with benzene. The extracts were washed with 8% NaOH and water, dried, and evaporated to give a solid residue, which was recrystallized from 2-propanol to yield sulfide **19a** (4 g, 69%).

4-Nitrophenyl 2,6-Dimethyl-4-methoxyphenyl Sulfide (22a) (Table II). To a solution of sodium (2.5 g) in absolute ethanol (70 mL) was added 2,6-dimethyl-4-methoxythiophenol (16.8 g, 100 mmol) followed by 15.7 g (100 mmol) of 4-nitrochlorobenzene dissolved in 100 mL of absolute ethanol. The mixture was refluxed under a nitrogen atmosphere for 3 h and was allowed to stand overnight at room temperature. The precipitate obtained was collected by filtration, washed with cold ethanol and water, and recrystallized from ethanol to afford **22a** (24 g, 83%).

Table III. Aryl 4-Aminophenyl Sulfones ($4\text{-}NH_2C_6H_4SO_2C_6H_2\text{-}2'\text{-}X,4'\text{-}Y,6'\text{-}Z$)

no.	X	Y	Z	% yield[a]	mp, °C	recrystn solv[b]	formula[c]
14	CH_3	OCH_3	H	89	144–145	A	$C_{14}H_{15}NO_3S$
15	CH_3	OH	H	76	163–164	B	$C_{13}H_{13}NO_3S$
17	Cl	OH	H	95	205–207[d]	C–B	$C_{12}H_{10}ClNO_3S$
19	CH_3	CH_3	OCH_3	83	191–192	C	$C_{15}H_{17}NO_3S$
20	CH_3	CH_3	OH	74	170–171	D	$C_{14}H_{15}NO_3S$
22	CH_3	OCH_3	CH_3	77	202–203	A	$C_{15}H_{17}NO_3S$
23	CH_3	OH	CH_3	96	178–179	C–B	$C_{14}H_{15}NO_3S$

[a,c] See corresponding footnotes in Table II. [b] A = 2-propanol, B = water, C = ethanol, D = benzene. [d] Literature[20] mp 209–216 °C.

Synthesis of Aryl 4-Nitrophenyl Sulfones (Table II). The sulfones were prepared according to the following methods.

Method A. A solution of the sulfide (10 mmol) in acetic acid was heated at 100 °C and hydrogen peroxide (30% v/v, 25 mmol) was added dropwise. The solution was concentrated and diluted with ice–water. The crude product was collected by filtration, washed with water, and purified by crystallization or column chromatography on silica gel.

Method B. To a stirred solution of the sulfide (10 mmol) in chloroform was added slowly 3-chloroperbenzoic acid (85%, 25 mmol) in 70 mL of chloroform at 0 °C. The 3-chlorobenzoic acid and unchanged peroxy acid were removed by washing with dilute alkali and dilute aqueous sodium sulfite. Removal of the solvent gave the crude product, which was purified by crystallization or column chromatography on silica gel.

Synthesis of Aryl 4-Aminophenyl Sulfones (14, 17, 19, 20, 22, and 23) (Table III). The amino derivatives were prepared by catalytic hydrogenation (Raney Ni catalyst, 1 atm, room temperature) of the corresponding nitro compounds in methanol. When the calculated amount of H_2 had been absorbed, the catalyst was removed by filtration. Crude products obtained after removal of the solvent were purified by crystallization.

4-Aminophenyl 4-Hydroxy-2-methylphenyl Sulfone (15). A solution of sulfone **14** (2.5 g) in 22 mL of 48% hydrobromic acid was stirred at 130 °C for 36 h. Excess of hydrobromic acid was evaporated and the residue was dissolved in water (100 mL), basified with aqueous sodium hydroxide, and filtered with charcoal. The solution was neutralized with dilute hydrochloric acid, and the crude product was collected by filtration and recrystallized from water to afford sulfone **15** (1.8 g, 76%).

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Dihydropyrimidines: Novel Calcium Antagonists with Potent and Long-Lasting Vasodilative and Antihypertensive Activity

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The novel calcium antagonists 3-*N*-substituted-3,4-dihydropyrimidines **1** and **9** and 3-*N*-substituted-dihydropyrimidin-2(1*H*)-ones **8** were regioselectively synthesized in good yields. Compounds **1** [especially **1s** [R^1 = $(CH_2)_2N$(benzyl)(2-naphthylmethyl), R^2 = *i*-Pr, X = *o*-NO_2] and **1t** [R^1 = $(CH_2)_2N$(benzyl)(3,4-dichlorobenzyl), R^2 = *i*-Pr, X = *o*-NO_2]] exhibited not only more potent and longer lasting vasodilative action but also a hypotensive activity with slow onset as compared with dihydropyridines. Moreover, some dihydropyrimidines [**1q** [R^1 = $(CH_2)_2N$(benzyl)(3-phenylpropyl), R^2 = CH_2(cyclopropyl), X = *o*-NO_2], **1s**, and **1t**] were weaker in blocking atrioventricular conduction in anesthetized open-chest dogs and less toxic than the dihydropyridines.

1,4-Dihydropyridine derivatives possessing calcium antagonistic action in the cardiovascular system have attracted much synthetic attention over the past 20 years. Calcium antagonists inhibit the influx of calcium ions

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