Quantitation was performed, following the procedure outlined in the collaborative study of the Pharmaceutical Manufacturers Association (6).

RESULTS AND DISCUSSION

In order to demonstrate that the flame ionization detector technique was comparable to thermal conductivity detector technique, six repetitive analyses were done by each method on an experimental mouthwash product. The results obtained are summarized in Table I.

It is obvious from Table I that both methods give comparable results.

Previously during a 5-hr. period, 20 ethanol analyses could be done. Now, using a flame ionization detector, 60 analyses can be run in a 5-hr. period.

Table I.—Per Cent Ethanol Content in Experimental Mouthwash

Sample	Flame Ionization	Thermal Conductivity
1	13.0	13.1
2	13.2	13.2
3	13.1	13.1
4	13.0	13.0
5	12.9	13.0
6	13.0	13.0

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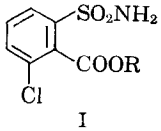
Anticonvulsants III. Alkyl Esters of 4-Bromo-2-sulfamoylbenzoic Acid and 4-Chloro-2-sulfamoylbenzoic Acid

By GLENN H. HAMOR and BERNARD L. REAVLIN

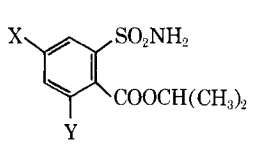
In addition to steric factors, electronic effects may also be important in the anticonvulsant activity of alkyl *o*-sulfamoylbenzoates and related compounds. To further explore the relationship between electronic properties and antielectroshock activity, three esters of 4-bromo-2-sulfamoylbenzoic acid and four esters of 4-chloro-2-sulfamoylbenzoic acid were prepared by the alcoholysis reaction of passing hydrogen chloride into a refluxing solution of 6-bromo- or 6-chlorosaccharin in the appropriate alcohol. The following alkyl 4-bromo- and 4-chloro-2-sulfamoylbenzoates were thus obtained: methyl; ethyl; *i*-propyl; and *sec*-butyl. In these compounds the bromine or chlorine atom is in the 4-position *para* to the alkoxycarbonyl group; thus, they do not possess the steric interactions between the large halogen atom and the ester moiety, which are believed to be necessary in the anticonvulsant activity of the related, potent *ortho*-substituted alkyl 6-chloro-2-sulfamoylbenzoates. Preliminary pharmacological results indicate that isopropyl 4-bromo-2-sulfamoylbenzoate lacks antielectroshock effects in mice.

Recent work has shown that alkyl esters of 2-sulfamoylbenzoic acid, 4-amino-2-sulfamoylbenzoic acid, and 6-chloro-2-sulfamoylbenzoic acid (I) possess marked anticonvulsant activity as indicated by their prevention of the effect of strychnine or maximal electroshock in mice (1–5).



I

Table I.—Anticonvulsant Activities of *ortho*- and *para*-Substituted Isopropyl Sulfamoylbenzoates[a]



Compd.	X	Y	Antielectroshock ED_{50}, Mice, mg./Kg.
1	NH_2	H	13
2	H	H	39
3	NO_2	H	240
4	Cl	H	Less active than compd. *2* above[b]
5	H	Cl	100[c]

[a] The pharmacological testing was performed by Smith Kline & French Laboratories, Philadelphia, Pa. [b] *Reference 1.* [c] Pharmacological testing was performed by Riker Laboratories, Northridge, Calif.

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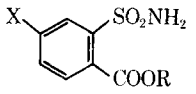
Previous paper: Hamor, G. H., and Farraj, N., *J. Pharm. Sci.*, **54**, 1265(1965).

TABLE II.—ALKYL 4-BROMO- AND 4-CHLORO-2-SULFAMOYLBENZOATES[a,b]

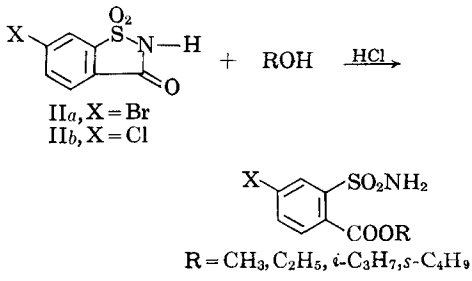


Compd.	X	R	Formula	M.p.,[c] °C.	Recrystallizing Solvent	Yield, %	Anal., % Calcd.	Found
6	Cl	CH_3	$C_8H_8ClNO_4S$	178–180	Methanol	60	C, 38.49 H, 3.20	38.51 3.34
7	Cl	C_2H_5	$C_9H_{10}ClNO_4S$	148–150	Ethanol	55	C, 41.04 H, 3.83	41.18 3.88
8	Cl	*i*-C_3H_7	$C_{10}H_{12}ClNO_4S$	125–127[d]	2-Propanol	31	C, 43.26 H, 4.36	43.44 4.45
9	Cl	*s*-C_4H_9	$C_{11}H_{14}ClNO_4S$	169–171	2-Butanol	28	C, 45.30 H, 4.80	45.26 5.03
10	Br	C_2H_5	$C_9H_{10}BrNO_4S$	152–154	Ethanol	70	C, 35.08 H, 3.24	35.06 3.38
11	Br	*i*-C_3H_7	$C_{10}H_{12}BrNO_4S$	151–153	2-Propanol	29	C, 37.29 H, 3.73	37.22 3.81
12	Br	*s*-C_4H_9	$C_{11}H_{14}BrNO_4S$	129–131	2-Butanol	29	C, 39.38 H, 4.16	39.31 4.31

[a] Analyses were performed by Elek Microanalytical Laboratories, Torrance, Calif. [b] Infrared analysis of selected compounds corresponded to the indicated structures. [c] Melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected. [d] Reported m.p. 142–144° (1).

It has been proposed that the activity of these sulfamoylbenzoates is related to their resistance to hydrolysis (5). To support this concept, data correlating anticonvulsant potency with increased chain branching of the alkyl portion of the ester were presented (5). Apart from the steric factors noted, a relationship also appears to exist between the anticonvulsant activity of these esters and the electronic effects of substituents attached to the benzene ring. The pharmacological properties reported in Table I for five previously synthesized isopropyl sulfamoylbenzoates show that the presence of electron-donating substituents *para* to the alkoxycarbonyl group tend to increase the activity, while electron-withdrawing substituents tend to decrease it. Thus, the *para* amino analog (compound *1*, Table I) possesses greater antielectroshock activity than does the desamino compound *2*, with the *para* nitro compound *3* being considerably less active.

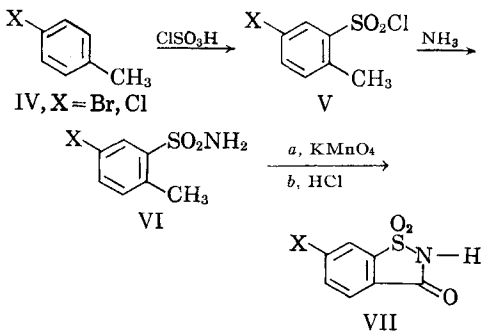
In an effort to further explore the relationship between electronic effects and anticonvulsant activity, a number of esters containing a bromine or a chlorine atom *para* to the alkoxycarbonyl group were prepared. The three alkyl 4-bromo-2-sulfamoylbenzoates and the four alkyl 4-chloro-2-sulfamoylbenzoates synthesized are listed and their properties given in Table II, and have the formula shown



IIa, X = Br
IIb, X = Cl

III

Scheme I



IV, X = Br, Cl

V

VI

VII

Scheme II

below (III). These compounds were prepared by the alcoholysis reaction of passing hydrogen chloride into a refluxing solution of 6-bromosaccharin or 6-chlorosaccharin in the appropriate alcohol, as pictured in Scheme I (4, 5).

6-Bromosaccharin (II*a*) and 6-chlorosaccharin (II*b*) were synthesized by the reaction sequence shown in Scheme II. Chlorosulfonation of the *p*-halotoluene (IV) by the procedure of Huntress (6) followed by treatment with aqueous ammonia gives 5-halo-2-methylbenzenesulfonamide (VI). Alkaline potassium permanganate oxidation of VI by the method of Noyes (7) gives the known 6-bromosaccharin (VII) (8) and 6-chlorosaccharin (VII) (8).

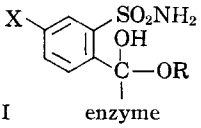
Preliminary pharmacological results indicate isopropyl 4-bromo-2-sulfamoylbenzoate,[1] (compound *11*, Table II), lacks antielectroshock effects when administered intraperitoneally, in suspension form, to mice at a dose of 100 mg./Kg. (0/10 mice protected). The compound was also inactive at doses of 200 mg./Kg. i.p. and 250 mg./Kg. p.o. The LD_{50} is greater than 800 mg./Kg. (0/10 mice i.p.). It is of interest to note that isopropyl 4-chloro-2-

[1] The authors thank Riker Laboratories, Northridge, Calif. for performing the pharmacological testing.

sulfamoylbenzoate has previously been reported to be less active than the deschlorocompound isopropyl 2-sulfamoylbenzoate, but no pharmacological data were given (1).

DISCUSSION

One possible explanation for the greatly reduced activity of the *p*-bromo-, *p*-chloro-, and *p*-nitro-substituted *o*-sulfamoylbenzoates when compared with the *p*-amino and desamino compounds may be obtained by considering that these esters are undergoing nucleophilic attack in a manner that approximates alkaline hydrolysis ($B_{AC}2$) in a chemical system (9). Alkaline hydrolysis of esters has been shown to be quite sensitive to the electronic effects of substituents on a benzene ring. One might then postulate that during the hydrolytic process these sulfamoylbenzoates are forming an enzyme–ester intermediate analogous to the tetrahedral intermediate demonstrated in $B_{AC}2$ hydrolysis (10). If this is the case, then electron-attracting substituents by increasing the polarization at the ester carbonyl group promote the formation of the enzyme–ester complex (VIII) and thus increase the rate of hydrolysis leading to pharmacologically inactive compounds.



VIII

Isopropyl 6-chloro-2-sulfamoylbenzoate (Table I, compound *5*), in which the chlorine atom is *ortho* to the ester moiety, has antielectroshock activity intermediate between that of the unsubstituted compound isopropyl *o*-sulfamoylbenzoate (compound *2*) and the compounds with electron-attracting group *para* to the alkoxycarbonyl group. The electron-withdrawing properties of the *ortho* chlorine atom, which would tend to labilize the ester to hydrolysis, are opposed by a steric hindrance to hydrolysis as a result of the steric effects of the chlorine atom. It may be of interest to note that correlation of antielectroshock activity of some 12 selected sulfamoylbenzoates with substituent effects by subjection to regression analysis according to the method of Hansch[2] (11), shows that electronic, steric, and hydrophobic factors are all important.

EXPERIMENTAL

4-Bromo- and 4-Chloro-2-sulfamoylbenzoic Acid Esters.—These esters were prepared by acidic alcoholysis of 6-bromosaccharin (II*a*) and 6-chlorosaccharin (II*b*). The known saccharins were synthesized by chlorosulfonation of the corresponding *p*-halotoluene (IV) (6), followed by treatment with aqueous ammonia which gave the 5-halo-2-methylbenzenesulfonamide (VI). The subsequent alkaline potassium permanganate oxidation of (VI) by the method of Noyes (7) yielded the desired 6-bromo- and 6-chlorosaccharins.

The esters synthesized are listed and their properties given in Table II. The alcoholysis procedure used will be illustrated by the following account of the preparation of isopropyl 4-bromo-2-sulfamoylbenzoate (compound *11*). Five grams (0.02 mole) of 6-bromosaccharin [m.p. 213–214°; reported m.p. 217° (12)] was placed in a two-necked flask fitted with a reflux condenser protected by a calcium chloride tube, and a gas inlet tube. To this was added 100 ml. of dry 2-propanol; the saccharin dissolved at the reflux temperature. The refluxing was continued while a continuous current of dry hydrogen chloride gas was passed through the solution for 2.5 hr. The passage of hydrogen chloride gas was discontinued and the reflux condenser removed; the solution was then heated for several minutes to expel hydrogen chloride. After partial evaporation, the cooled solution gave 1.8 Gm. (28.5%) of crystalline isopropyl 4-bromo-2-sulfamoylbenzoate (compound *11*), m.p. 151–153°.

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[2] The authors are grateful to Dr. Corwin Hansch, Chemistry Department, Pomona College, Claremont, Calif., for performing this analysis.