the addition of water gave 0.780 Gm. (62%), m.p. 167–169°. Another recrystallization from the same solvent system gave 0.704 Gm. (56%), m.p. 169–171°; $\nu_{max.}$ 3500, 3350, 3200 (NH); 1645, 1620, 1570 (NH, C=N, C=C); 750, 695 cm.$^{-1}$ (C_6H_5); $\lambda_{max.}$ (pH 1) 277 mμ (ε 7600); $\lambda_{max.}$ (pH 7) 280 mμ (ε 5800); $\lambda_{max.}$ (pH 13) 289 mμ (ε 6800).

Anal.—Calcd. for $C_{15}H_{20}N_4$: C, 70.3; H, 7.86; N, 21.9. Found: C, 70.5; H, 7.80; N, 21.7.

REFERENCES

(1) Baker, B. R., Ho, B.-T., and Chheda, G. B., *J. Heterocyclic Chem.*, **1**, 88(1964).
(2) Baker, B. R., and Jordaan, J. H., *J. Med. Chem.*, **8**, 35(1965).
(3) Albert, A., *Quart. Rev.*, **1952**, 197.
(4) Linstead, R. P., *J. Chem. Soc.*, **1937**, 812.
(5) Linstead, R. P., and Wang, A. B.-L., *ibid.*, **1937**, 807.
(6) Hyde, K. A., *et al.*, *J. Org. Chem.*, **27**, 1717(1962).
(7) Smith, J. M., Jr., *et al.*, *J. Am. Chem. Soc.*, **70**, 3997 (1948).
(8) Seeger, D. R., *et al.*, *ibid.*, **71**, 1753(1949).
(9) Dakin, H. D., and Dudley, H. W., *J. Chem. Soc.*, **105**, 2453(1914).
(10) Fairburn, E. I., *et al.*, *J. Am. Chem. Soc.*, **76**, 676 (1954).
(11) Mowat, J. H., *et al.*, *ibid.*, **70**, 14(1948).
(12) Taylor, E. C., and Cain, C. K., *ibid.*, **71**, 2538(1949).
(13) Bertino, J., *et al.*, *J. Biol. Chem.*, **239**, 479(1964).
(14) Baker, B. R., Ho, B.-T., and Neilson, T., *J. Heterocyclic Chem.*, **1**, 79(1964).
(15) Zakrzewski, S. F., *J. Biol. Chem.*, **238**, 1485(1963).
(16) Hammett, L. P., "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 184–207.
(17) Baker, B. R., Shapiro, H. S., and Werkheiser, W. C., *J. Med. Chem.*, **8**, 283(1965).
(18) Baker, B. R., and Novotny, J., unpublished data.
(19) Baker, B. R., Ho, B.-T., and Santi, D. V., *J. Pharm. Sci.*, to be published.
(20) Baugh, C. M., and Shaw, E., *J. Org. Chem.*, **29**, 3610 (1964).
(21) Renfrew, A. G., and Piatt, P. C., *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 657(1950).

Synthesis and Anticonvulsant Activity of Some Alkyl Esters of 6-Chloro-2-sulfamoylbenzoic Acid

By GLENN H. HAMOR and NAIM FARRAJ

The application of the Rule of Six for the estimation of steric effects to a series of alkyl esters of 4-amino-2-sulfamoylbenzoic acid possessing pronounced anticonvulsant activity shows the highly hindered isopropyl and *sec*-butyl esters to be much more potent than the less hindered methyl, ethyl, and *n*-propyl compounds. In order to provide further information concerning steric factors and anticonvulsant properties, four alkyl 6-chloro-2-sulfamoylbenzoates, which contain the chlorine atom in the shielding position adjacent to the alkoxycarbonyl group, were synthesized: the methyl, ethyl, *n*-propyl, and isopropyl esters. Preliminary pharmacological results indicate that the isopropyl 6-chloro-2-sulfamoylbenzoate produces strong antielectroshock effects in mice which are quite specific, with no other CNS activity except at high doses in the gross observations.

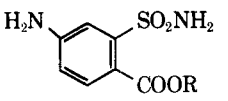
RECENT work has shown that alkyl esters of 2-sulfamoylbenzoic acid and 4-amino-2-sulfamoylbenzoic acid (I) possess marked anticonvulsant activity as indicated by their prevention of the effect of strychnine or maximal electroshock in mice (1–3).

The results (heretofore unpublished) of pharmacological testing of a series of alkyl 4-amino-2-sulfamoylbenzoates are shown in Table I. The property of these compounds in preventing strychnine-induced convulsions is quite unusual. In fact, Horrom and Lynes in 1963, reporting the anticonvulsant potency of two benzamide compounds, stated: "to our knowledge no other compounds are known to antagonize strychnine-induced convulsions at doses which produce little or no neurological symptoms" (4). The methyl, ethyl, and *n*-propyl esters in Table I are considerably less potent than the isopropyl compound.

If the intact ester group is necessary for anticonvulsant activity, then steric effects in the

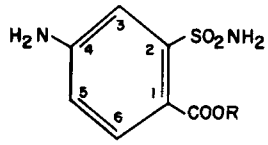
Received April 1, 1965, from the School of Pharmacy, University of Southern California, Los Angeles.
Accepted for publication June 30, 1965.
Presented to the Scientific Section, A.PH.A., Detroit meeting, March 1965.
This investigation was supported in part by research grant NB 03328-04 from the National Institute of Neurological Diseases and Blindness, U. S. Public Health Service, Bethesda, Md.

TABLE I.—ANTICONVULSANT ACTIVITIES OF ALKYL 4-AMINO-2-SULFAMOYLBENZOATES[a]



Compd.	R	Antielectroshock ED_{50}, Mice, mg./Kg.	Antistrychnine ED_{50}, Mice, mg./Kg.
XIII	CH_3	48	115
XIV	C_2H_5	34	80
XV	*n*-C_3H_7	45	125
II	*i*-C_3H_7	13	46
XVI	*n*-C_4H_9	70	130
XVII	*s*-C_4H_9	13.8	83
XVIII	*n*-C_5H_{11}	30	122
XIX	$CH(C_2H_5)_2$	82	142
XX	*n*-C_6H_{13}	95	175
XXI	Mephenesin	140	355

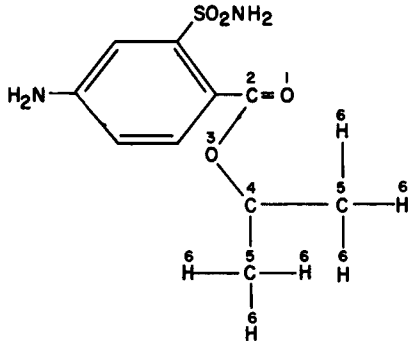
[a] The pharmacological testing was performed by Smith Kline & French Laboratories, Philadelphia, Pa.



R = CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, n-C_4H_9, s-C_4H_9, n-C_5H_{11}, $CH(C_2H_5)_2$, n-C_6H_{13}

I

isopropyl ester, by causing an increased resistance to hydrolysis, may be a factor in this augmented activity. A qualitative estimation of the amount of steric hindrance is given by the Rule of Six which states: "In reactions involving addition to an unsaturated function containing a double bond, the greater the number of atoms in the six-position the greater will be the steric effects" (5). The six-number, then, is the number of atoms in the 6-position, with the carbonyl oxygen atom being the number 1-position. Isopropyl 4-amino-2-sulfamoylbenzoate (II) thus has a six-number of 6.

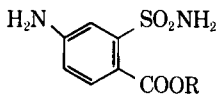


II

The most highly hindered acids resist esterification and possess the highest six-numbers (5). Whitfield has recently reported that dipeptides and polypeptides with a six-number of 0 hydrolyze fastest; those with a six-number of 3 at intermediate rates; and those with a six-number of 6, slowest (6). The Rule of Six may be applied to the enzyme-catalyzed hydrolysis of esters. The rate of lipase-catalyzed hydrolysis of stearic acid esters decreases with increasing of the number of atoms in the 6-position, the secondary butyl ester hydrolyzing more slowly than the *n*-butyl compound (7).

The six-numbers are especially useful for those reactions in which the intermediate or activated complex has a tetrahedral configuration. The α-chymotrypsin-catalyzed hydrolysis of esters has been reported to involve a tetrahedral intermediate (8). Table II shows the correlation of the Rule of Six with anticonvulsant activity of certain alkyl 4-amino-2-sulfamoylbenzoates.

TABLE II.—CORRELATION OF THE RULE OF SIX WITH ANTICONVULSANT ACTIVITY[a]

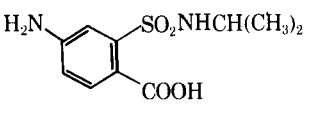


Compd.	R	Antielectroshock ED_{50}, Mice, mg./Kg.	Antistrychnine ED_{50}, Mice, mg./Kg.	Six Number[b]
XIII	CH_3	48	115	0
XIV	C_2H_5	34	80	3
XV	*n*-C_3H_7	45	125	3
II	*i*-C_3H_7	13	46	6
XVI	*n*-C_4H_9	70	130	3
XVII	*s*-C_4H_9	13.8	83	6

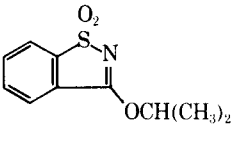
[a] The pharmacological testing was performed by Smith Kline & French Laboratories, Philadelphia, Pa. [b] The number of atoms in position six is given by counting the carbonyl oxygen atom as position 1.

DISCUSSION

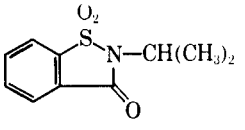
There are some further reasons to believe that steric effects may be implicated in the anticonvulsant activity of alkyl esters of 4-amino-2-sulfamoylbenzoic acid. Because a compound (III) possessing a free carboxyl group was inactive (9), the intact ester group seems to be necessary for potency. The closed ring analogs (IV,V) of the open ring 2-sulfamoylbenzoates were also inactive (9). For maximum activity in the isopropyl sulfamoylbenzoate series (VI) the isopropoxycarbonyl and sulfamoyl



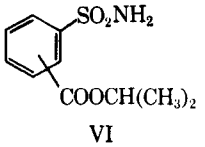
III



V



IV



VI

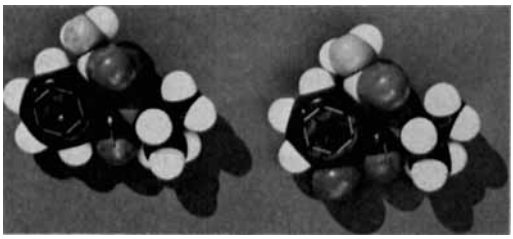
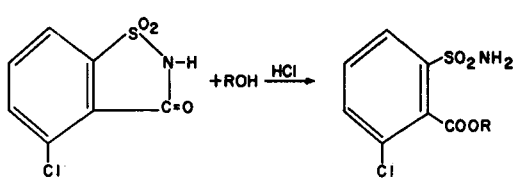


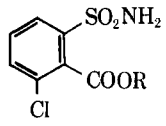
Fig. 1.—Stuart-Briegleb molecular models of isopropyl 2-sulfamoylbenzoate (left) and isopropyl 6-chloro-2-sulfamoylbenzoate (right). See structural formula VIII (R = *i*-C_3H_7).



VII VIII

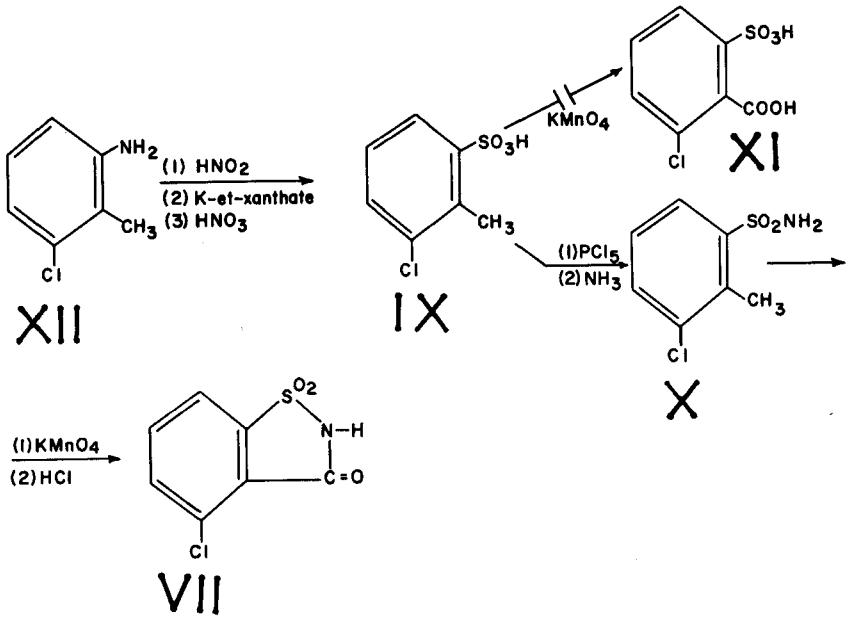
Scheme I

TABLE III.—ALKYL 6-CHLORO-2-SULFAMOYLBENZOATES[a]



Compd.	R	Formula	M.p.,[b] °C.	Recrystallizing Solvent	Yield, %	Anal., % Calcd.	Found
XXII	CH_3	$C_8H_8ClNO_4S$	137–138	Methanol–H_2O	68	C, 38.87 H, 3.20	C, 38.76 H, 3.44
XXIII	C_2H_5	$C_9H_{10}ClNO_4S$	96	Ethanol–H_2O	76	C, 40.98 H, 3.78	C, 40.74 H, 3.84
XXIV	*n*-C_3H_7	$C_{10}H_{12}ClNO_4S$	100–101	1-Propanol–H_2O	75	C, 43.24 H, 4.32	C, 43.30 H, 4.50
XXV	*i*-C_3H_7	$C_{10}H_{12}ClNO_4S$	131	2-Propanol–H_2O	68	C, 43.24 H, 4.32	C, 43.63 H, 4.40

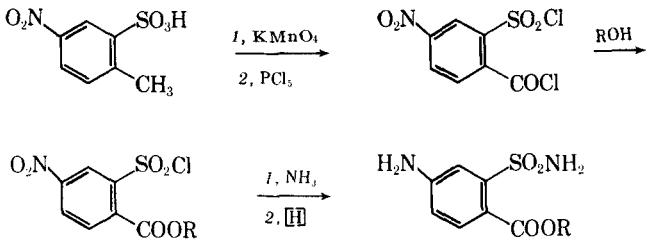
[a] Analyses were performed by Elek Microanalytical Laboratories, Torrance, Calif. [b] Melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected.



Scheme II

groups must be vicinal. The *meta* isomer was much less potent, and the *para* isomer was essentially devoid of activity (2).

In an effort to provide further information concerning the effect of steric hindrance on pharmacological activity, a number of esters containing a shielding chlorine atom adjacent to the alkoxycarbonyl group were prepared. Figure 1 shows Stuart-Briegleb molecular models of isopropyl 2-sulfamoylbenzoate and isopropyl 6-chloro-2-sulfamoylbenzo-



Scheme III

ate. The greater shielding effect of the chlorine atom in the 6-position as compared with hydrogen is readily visible.

The four alkyl 6-chloro-2-sulfamoylbenzoates synthesized are listed and their properties given in Table III and have the formula shown below (VIII). These compounds were prepared by the alcoholysis reaction of passing hydrogen chloride into a refluxing solution of 4-chlorosaccharin (VII) in the appropriate alcohol, as pictured in Scheme I (1, 10).

4-Chlorosaccharin (VII) was synthesized by the reaction sequence shown in Scheme II. Commercially available 3-chloro-2-methylaniline (XII) was converted to the corresponding xanthate by Leckart's method (11). Oxidation of the intermediate xanthate by the Masuda and Hamor procedure (13) gave 3-chloro-2-methylbenzenesulfonic acid (IX). 3-Chloro-2-methylbenzenesulfonamide (X) was prepared by conventional reactions and converted to 4-chlorosaccharin[1] (VII) according to the procedure of Davies (12).

The attempted preparation of alkyl 6-chloro-2-sulfamoylbenzoates by the procedure of Loev and Kormendy (3) for the synthesis of alkyl 4-amino-2-sulfamoylbenzoates (Scheme III) was unsuccessful, because the permanganate oxidation of 3-chloro-2-methylbenzenesulfonic acid (X) gave only unchanged starting material.

Preliminary pharmacological results indicate isopropyl 6-chloro-2-sulfamoylbenzoate[2] (XXV) produces strong antielectroshock effects when administered intraperitoneally, in suspension form, to mice at a dose of 100 mg./Kg. This anticonvulsant activity, as shown by the electroshock test, is quite specific because no other CNS effects were noted except at high doses in the gross observations. The approximate LD_{50} is >800 mg./Kg. (4/10 mice, i.p.). No antipyresis properties were seen at 267 mg./Kg. i.p., rat. No hypoglycemic effect was noted at 500 mg./Kg. orally in the rat. The isopropyl 4-chloro-2-sulfamoylbenzoate reported by Loev and Kormendy (3), which contains the chlorine atom in the steric-free position *para* to the isopropoxycarbonyl group, is much less active than the *ortho*-substituted, isopropyl 6-chloro-2-sulfamoylbenzoate (XXV).

EXPERIMENTAL

3-Chloro-2-methylbenzenesulfonic Acid (IX).—The diazonium solution (adjusted to pH 5 by use of a saturated sodium acetate solution) was added in portions with stirring to the potassium ethyl xanthate solution maintained at a temperature of 65–70° to prevent the xanthate oil from floating and reacting explosively. The product, 6-chlorotoluene-2-ethyl xanthate, a dark brown oil, was separated from the reaction mixture and the aqueous layer extracted with ether to give a yield of 90%.

Oxidation of the xanthate oil by nitric acid using the method of Masuda and Hamor (13) gave 3-chloro-2-methylbenzenesulfonic acid (IX) as a hygroscopic solid, m.p. 60–65°. [Reported m.p. 60–70°; anhydrous, m.p. 72° (12).] The sulfonic acid was converted to the sodium salt by use of sodium carbonate to give a yield of 55% from the xanthate.

4-Chlorosaccharin (VII).—Reaction of sodium 3-chloro-2-methylbenzenesulfonate with phosphorus pentachloride, followed by treatment with ammonia water (Scheme II) gave 3-chloro-2-methylbenzenesulfonamide (X) (58% yield), m.p. 179°. [Reported m.p. 180° (12).] Permanganate oxidation of the sulfonamide according to Davies yields 4-chlorosaccharin (VII) (45%), m.p. 210°. [Reported m.p. 210–212° (12).]

Isopropyl 6-Chloro-2-sulfamoylbenzoate (XXV).—Six grams (0.028 mole) of 4-chlorosaccharin was dissolved in 100 ml. of dry isopropyl alcohol and poured into a dry 250-ml. two-necked flask. The solution was heated under reflux for 2 hr. with continuous passage of dry hydrogen chloride gas through the solution. The current 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 solution on cooling yielded crystals. Recrystallization from a mixture of isopropyl alcohol and water gave 5.2 Gm. (58%) of white, crystalline solid, m.p. 131°. The remaining esters listed in Table III were prepared by this procedure.

[1] Davies names this compound 6-chlorosaccharin.

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

REFERENCES

(1) Hamor, G. H., and Janfaza, M., *J. Pharm. Sci.*, **52**, 102(1963).
(2) Loev, B., and Kormendy, M., *J. Org. Chem.*, **27**, 1703 (1962).
(3) *Ibid.*, **27**, 2177(1962).
(4) Horrom, B. W., and Lynes, T. E., *J. Med. Chem.*, **6**, 528(1963).
(5) Newman, M. S., ed., "Steric Effects in Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1956, p. 206.
(6) Whitfield, R. E., *Science*, **142**, 577(1963).
(7) Balls, A. K., and Matlack, M. B., *J. Biol. Chem.*, **123** 679(1938).
(8) Bender, M. L., *J. Am. Chem. Soc.*, **84**, 2582(1962).
(9) Hamor, G. H., unpublished data.
(10) Jesurun, J. A., *Ber.*, **26**, 2286(1893).
(11) Leuckart, R., *J. Prakt. Chem.*, **41** (No. 2), 179(1890).
(12) Davies, W., *J. Chem. Soc.*, **119**, 876(1921).
(13) Masuda, J. Y., and Hamor, G. H., *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 61(1957).