Anticonvulsants IV: Vinylogs, Alkyl Esters of 2-Sulfamoylcinnamic Acid and Related Compounds

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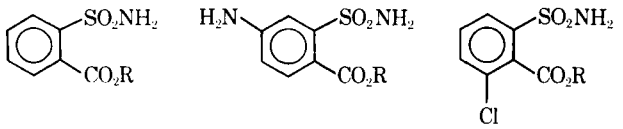
Abstract □ Alkyl *ortho*-sulfamoylbenzoates (I) and ring-substituted alkyl *ortho*-sulfamoylbenzoates (II, III) are reported to have anticonvulsant activity in mice. It is known generally that the chemical and physiological properties of a substance and its vinylog are quite similar. This correlation might be extended to the alkyl *ortho*-sulfamoylcinnamates (IV), the corresponding vinylogs of I, which were prepared and tested for anticonvulsant activity in mice. Attempts to prepare the vinylogs (IV) by the method of Loev and Kormendy failed, and the compounds obtained were identified as the alkyl esters of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxide (VII). Proof of the chemical structures was provided by spectra. Of the twelve compounds tested, one (V, R = *s*-butyl) was found to be effective against electroshock in mice at 100 mg./kg. intraperitoneally. The LD_{50}'s of these compounds were of the order of 800 mg./kg. with one exception.

Keyphrases □ 2-Sulfamoylcinnamic acid alkyl esters, related compounds—synthesis □ Anticonvulsant activity—2-sulfamoylcinnamic acid alkyl esters □ Antimalarial activity—2-sulfamoylcinnamic acid alkyl esters □ IR spectrophotometry—structure □ NMR spectroscopy—structure

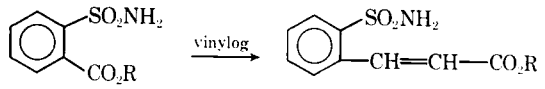
Hamor *et al.* recently reported that the alkyl esters of *ortho*-sulfamoylbenzoic acid (I), 4-amino-2-sulfamoylbenzoic acid (II), and 6-chloro-2-sulfamoylbenzoic acid (III) were capable of preventing convulsions induced by strychnine or maximal electroshock in mice (1-3). Loev and Kormendy also reported on the effectiveness of some 4-amino-2-sulfamoylbenzoates (4, 5).



I II III

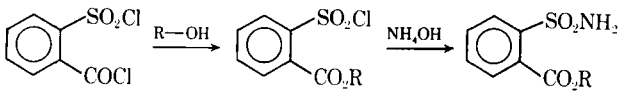
The mechanism of action of these compounds is not known precisely. It is generally believed that some drugs are adsorbed at some hypothetical receptor sites in the tissues in order to produce the pharmacological effects (6). To understand the nature of these receptor sites, one has to prepare close structural analogs of active compounds and study their pharmacological properties. Such an investigation would reveal the spatial and electronic requirements necessary for activity.

Nobles *et al.* synthesized a number of vinylogs of medicinally active compounds and reported that in some cases the vinylogs were more active than the parent compounds; in some cases the vinylogs were as active as the parent compounds and in other cases the vinylogs were inactive (7). Vinylogs of I, namely, alkyl esters of *ortho*-sulfamoylcinnamic acid (IV), were synthesized and evaluated for antielectroshock activity in mice.



I IV

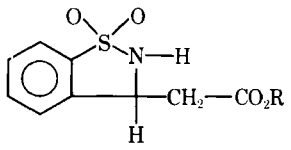
Loev and Kormendy synthesized alkyl *ortho*-sulfamoylbenzoates by taking advantage of the differences in reactivities of a sulfonyl chloride and an acid chloride toward alcohols, which is shown in Scheme I (4).



V VI I

Scheme I

Attempts to prepare IV by the procedure of Loev and Kormendy were unsuccessful as evidenced by the absence of the vinylene (—CH=CH—) group in the IR[1] and NMR[2] spectra of the compounds obtained. They were subsequently identified as the alkyl esters of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxide (VII).



VII

The synthesis of these compounds (VII) will be discussed in a later publication. The vinylogs (IV) were prepared as shown in Scheme II.

Methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, and *s*-butyl esters of *ortho*-sulfamoylcinnamic acid and 1,2-benzisothiazoline-3-acetic acid 1,1-dioxide were synthesized and tested for antielectroshock activity in mice. Figures 1 and 2 show the IR and NMR spectra, respectively, of a typical alkyl ester of *ortho*-sulfamoylcinnamic acid. Elemental analyses, melting points, solvents of crystallization, and the percentage yields of the esters (IV) are shown in Table I.

PHARMACOLOGICAL SCREENING[3]

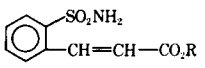
The compounds synthesized were tested for antielectroshock activity in mice. The test was patterned after that of Goodman *et al.* (8). The LD_{50}'s of the test substances were first determined in mice. They were found to be equal to or greater than 800 mg./kg. intraperitoneally in mice, with one exception (VII, R = *i*-propyl) which had an LD_{50} of 445 mg./kg. The mice were injected intraperitoneally

[1] IR spectra were taken on a Perkin-Elmer Infracord. The samples were prepared as mulls with mineral oil.

[2] NMR spectra were taken on a Varian A-60 High Resolution NMR spectrometer, courtesy of Riker Laboratories, Northridge, Calif.

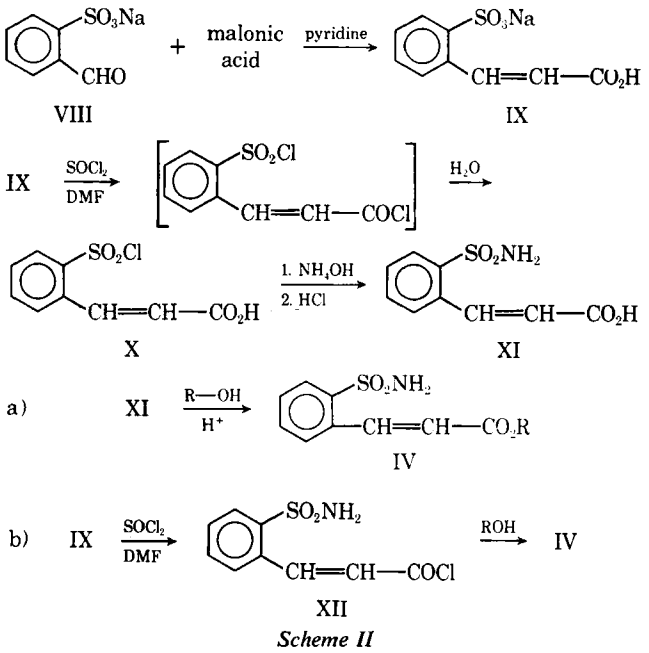
[3] The authors wish to thank Riker Laboratories, Northridge, Calif., for carrying out the pharmacological screening.

Table I—Alkyl Esters of *ortho*-Sulfamoyl-*trans*-cinnamic Acid[a]



Compd.	R	Formula	M.p.,[b] °C.	Recryst. Solvent	Yield, %	Anal., % Calcd.	Found
1	CH_3	$C_{10}H_{11}NO_4S$	134–135	MeOH	92	C, 49.78 H, 4.60	49.89 4.77
2	C_2H_5	$C_{11}H_{13}NO_4S$	100–103	EtOH	78	C, 51.75 H, 5.13	51.64 5.27
3	*n*-C_3H_7	$C_{12}H_{15}NO_4S$	117–118	EtOH	68	C, 53.51 H, 5.61	53.61 5.70
4	*i*-C_3H_7	$C_{12}H_{15}NO_4S$	141–142	i-PrOH	35	C, 53.51 H, 5.61 N, 5.20	53.38 5.60 5.06
5	*n*-C_4H_9	$C_{13}H_{17}NO_4S$	88–89	EtOH	49	C, 55.11 H, 6.05	55.13 6.06
6	*s*-C_4H_9	$C_{13}H_{17}NO_4S$	93–95	EtOH	88	C, 55.11 H, 6.05	55.12 6.21

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



Scheme II

with the test substances as aqueous suspensions, at doses of one-fifth of the LD_{50}'s. The test substances were rated for their effectiveness as antielectroshock drugs on the basis of the number of mice protected against the electroshock.

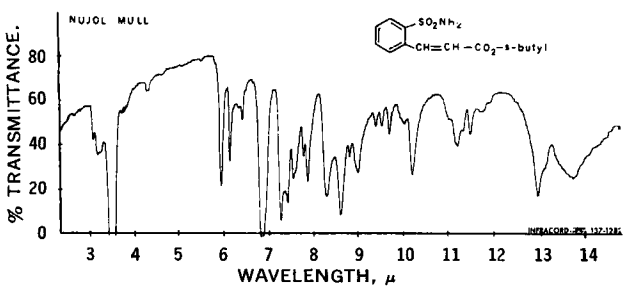


Figure 1—*IR spectra of a typical alkyl ester of* ortho-*sulfamoylcinnamic acid.*

The compounds were rated as shown here:

None of the mice protected	not effective (−)
Two to five of the ten mice protected	effective (+)
More than five mice protected	effective (+ +)

Results of Screening—Of the twelve compounds tested, one compound (VII, R = *s*-butyl) was found to be effective (+) against convulsions induced by electroshock. However, VII was found to be ineffective when administered *orally* at 250 mg./kg. dose.

Gross Observations—At low doses (20 mg./kg., i.p.) two compounds (IV, R = *n*-propyl and VII, R = methyl) produced sedation while others had no effect. At high doses (80 mg./kg., i.p.) ataxia, sedation, cyanosis, writhing, and tremors were observed with all compounds tested.

Results of Antimalarial Screening[4]—Two compounds (IV, R = methyl and VII, R = *s*-butyl) were also tested for antimalarial activity against *Plasmodium berghei* in mice. The test was conducted as follows: the test substances were administered in doses of 40, 160, and 640 mg./kg. to five mice, which were injected 3 days before with a lethal dose of *Plasmodium berghei*. The compounds did not appreciably extend the survival time.

DISCUSSION

Hamor noted previously that secondary alcohol esters of *ortho*-sulfamoylbenzoic acid were more active than the esters of primary alcohols (2). In this study, the *s*-butyl ester (VII, R = *s*-butyl) was found to possess a slight antielectroshock activity in mice while

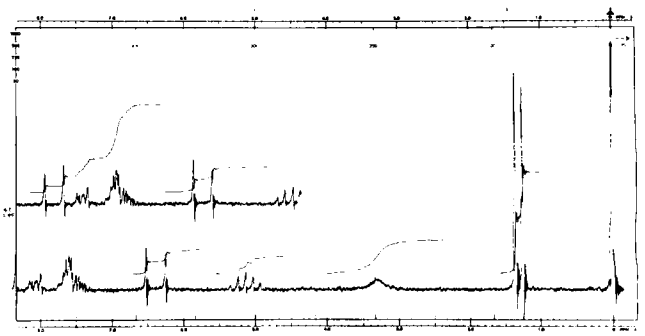


Figure 2—*NMR spectra of a typical alkyl ester of* ortho-*sulfamoylcinnamic acid.*

[4] Testing results furnished by the Walter Reed Army Medical Center, Washington, D. C.

the other esters did not have any activity. Hamor also observed that the compounds possessing antielectroshock activity had the sulfamoyl and the ester groups sterically crowding each other, especially in the case of the secondary alcohol esters (2). The sulfamoyl and the ester group in IV are not as sterically crowded as they are in I. This might account for the lack of significant activity among the compounds tested in the present study.

EXPERIMENTAL

ortho-Sulfocinnamic Acid (IX)—*ortho*-Sulfocinnamic acid (IX) was prepared as its sodium salt by the Knoevenagel reaction between *ortho*-benzaldehydesulfonic acid (VIII) and malonic acid in the presence of pyridine and piperidine (9). Compound IX was obtained in 52% yield.

ortho-Chlorosulfonylcinnamic Acid (X)—*ortho*-Sulfocinnamic acid, sodium salt (IX) (25 g., 0.1 mole) was placed in a 250 ml. three-necked flask, equipped with reflux condenser, dropping funnel, and thermometer. A drying tube containing anhydrous calcium chloride was attached to the top of the reflux condenser. The reaction was carried out under the hood. A few drops of dimethylformamide (DMF) were added to the contents of the flask. The flask was cooled in ice and thionyl chloride (25 ml., 0.3 mole) was added, drop by drop, from the dropping funnel. There was an immediate vigorous reaction with evolution of considerable heat and fumes. The contents of the flask were heated under reflux until the mixture turned homogeneous (about 2 hr.). The excess thionyl chloride was removed under reduced pressure and a bright red residue was obtained. The flask was cooled well in ice and the residue was added to ice-cold water, in small portions. There was an immediate violent reaction with the formation of an orange-yellow residue and a deep orange solution. The residue was extracted with ether in several portions (about 500 ml.). The combined ether extracts were washed with distilled water twice (2 × 10 ml.) and the ether extract was dried over anhydrous calcium sulfate[5] for 24 hr. Colorless, needle-shaped crystals were deposited at the bottom of the flask from the ether on standing overnight. The crystals were collected on a filter, washed well with water, dried, and recrystallized from ether. The product was obtained in 95% yield; m.p. 203–208° with decomposition.

Anal.—Calcd. for $C_9H_7ClO_4S$: C, 43.83; H, 2.86. Found: C, 43.95; H, 2.97.

ortho-Sulfamoylcinnamic Acid (XI)—XI was prepared by treating X with ammonium hydroxide by the standard procedure of preparing sulfonamides. Compound XI was obtained in 48% yield, m.p. 220–225° with decomposition.

[5] Drierite, W. A. Hammond Drierite Co., Xenia, Ohio.

Anal.—Calcd. for $C_9H_9NO_4S$: C, 47.57; H, 4.00. Found: C, 47.47; H, 4.21.

Alkyl ortho-Sulfamoylcinnamates (IV)—*ortho*-Sulfamoylcinnamic acid (XI) (4 g., 0.0175 mole) was placed in a 150-ml. round-bottom flask, fitted with a reflux condenser and a drying tube containing anhydrous calcium chloride. Concentrated sulfuric acid (about 10 drops) and the appropriate alcohol (50 ml.) were added to the cinnamic acid (XI) in the flask. The flask was then heated under reflux for about 3 hr. on a steam bath. The excess alcohol was allowed to evaporate slowly under the hood at room temperature. The nearly colorless crude material was collected on a filter and washed with ice-cold water. The residue was recrystallized from the appropriate alcohol (Table I).

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