SACCHARIN DERIVATIVES

II. SYNTHESIS AND ANTICONVULSANT ACTIVITY OF METHYL ESTERS OF 5-SUBSTITUTED 2-SULFAMIDOBENZOIC ACIDS

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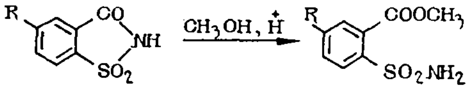
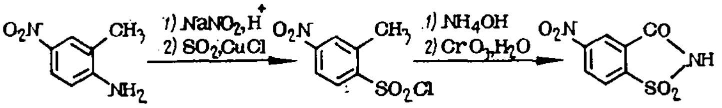
The alkyl esters of 4-amino-2-sulfamidobenzoic acids display anticonvulsant activity and have been shown to inhibit convulsions produced by electroshock and by strychnine [1, 2].

We have studied the pharmacological activity of some compounds with similar structures – the methyl esters of 5-substituted 2-sulfamidobenzoic acids; these were synthesized by methanolysis of the corresponding 3-oxo-2,3-dihydrobenzo[d]isothiazole-1,1-dioxides.



I: R = CH_3O
II: R = C_2H_5O
III: R = C_3H_7O
IV: R = C_4H_9O
V: R = $C_5H_{11}O$
VI: R = iso-C_3H_7O
VII: R = iso-C_4H_9O
VIII: R = iso-$C_5H_{11}O$
IX: R = NO_2
X: R = H

The 5-alkoxy-3-oxo-2,3-dihydrobenzo[d]isothiazole-1,1-dioxides were obtained as described in [3], and 5-nitro-3-oxo-2,3-dihydrobenzo-[d]isothiazole-1,1-dioxide [4] was obtained by the following reaction scheme:



The direct introduction of a sulfochloride group by the Meerwein method [5] and the oxidation of 2-methyl-4-nitrobenzenesulfamide with chromium anhydride [6] were also used in synthesis.

The yields and physicochemical properties of the compounds prepared are given in Table 1. R_f 0.83-0.88 in petroleum-ether (3:2).

EXPERIMENTAL

Pharmacological

Experiments were carried out on mice weighing 18-22 g, using standard methods for evaluating substances with anticonvulsant action: maximum electroshock [7], subcutaneous anticorazol [8], and antistrychnine tests. The m-cholinolytic effect was determined by the prevention of arecoline tremors [9], and the n-cholinolytic action by the prevention of nicotine convulsions [10]. The appearance of undesirable effects of the compounds was also investigated. Orientation reactions were determined by the "screen" method [11] and disturbance of motor coordination by the "rotating rod" method [12].

The compounds were injected intraperitoneally as suspensions in Tween-80; the control animal received the emulsifier alone. The data were treated statistically by probit-analysis [13].

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TABLE 1. Methyl Esters of 5-Alkoxy-2-sulfamidobenzoic Acids

Compound	R	Yield, %	Melting point, °C	Found, %				Empirical formula	Calculated, %			
				C	H	N	S		C	H	N	S
I	CH_3O	76,5	152—3	44,05	4,61	5,39	13,43	$C_9H_{11}NO_5S$	44,08	4,52	5,71	13,70
II	C_2H_5O	77,2	113—4	45,89	5,16	5,42	11,97	$C_{10}H_{13}NO_5S$	46,32	5,05	5,40	12,37
III	C_3H_7O	78,1	89—90	48,48	5,43	5,07	12,03	$C_{11}H_{15}NO_5S$	48,34	5,53	5,12	11,73
IV	C_4H_9O	77,3	79—80	50,21	6,25	4,54	10,89	$C_{12}H_{17}NO_5S$	50,16	5,96	4,87	11,16
V	$C_5H_{11}O$	74,9	92—3	51,52	6,37	4,35	10,26	$C_{13}H_{19}NO_5S$	51,81	6,35	4,65	10,64
VI	iso-C_3H_7O	64,3	99—100	48,64	5,73	4,98	11,61	$C_{11}H_{15}NO_5S$	48,34	5,53	5,12	11,73
VII	iso-C_4H_9O	75,8	102—3	50,13	5,69	4,75	11,32	$C_{12}H_{17}NO_5S$	50,16	5,96	4,87	11,16
VIII	iso-$C_5H_{11}O$	72,3	97—8	52,13	6,60	4,51	11,02	$C_{13}H_{19}NO_5S$	51,81	6,65	4,65	10,64
IX	NO_2	71,2	173—4	36,62	3,40	11,06	12,18	$C_8H_8N_2O_6S$	36,92	3,10	10,76	12,32

TABLE 2. Anticonvulsant Activity of the Methyl Esters of 5-Alkoxy-2-sulfamidobenzoic Acids, Their Mean Sedative, Myorelaxant, and Lethal Doses

Compound	Antagonism to corazol	ED_{50}, mg/kg				PI	ED_{50}, mg/kg	PI′	LD_{50}	TI
		prevention of effect of maximum electroshock	antagonism to nicotine	antagonism to arecoline	depression of orientation reaction		disturbance of motor coordination			
I	280 (233,3÷335,0)	400	300	300	1400 (1045,6÷1876,0)	5,00	1300 (722,2÷2340,0)	4,6	2000	3,5
II	245 (125,6÷477,0)	360 (205,6÷630,0)	300	300	350	1,3	300	1,1	1000	4,1
III	90 (40,9÷198,0)	120 (50,0÷288,0)	300	300	250	2,7	300	3,3	1000	11,1
IV	245 (125,6÷477,7)	245 (125,9÷477,7)	200	300	450 (231,5÷855,0)	1,8	200	—1,2	750	3,0
V	160 (124,0÷206,4)	135 (97,1÷187,6)	300	300	200	—1,2	200	—1,2	500	—3,1
VI	59 (34,7÷100,3)	94 (50,9÷170,9)	200	300	200	3,3	300	5,0	500	8,5
VII	140 (96,5÷203,0)	195 (156,5÷245,7)	300	300	200	1,4	300	2,0	1000	7,1
VIII	170 (105,5÷272,0)	200	200	300	750	4,4	500	3,0	1000	5,8
IX	250	300	300	300	1005 (905,4÷1115,5)	4,0	560 (448,2÷700,0)	2,2	1200	4,8
X	590 (245,8÷1416,0)	180 (128,5÷252,0)	300	300	300	—2,3	250	—2,3	500	—1,1

Legend. PI is the index of protection (ED_{50} for sedative effect/ED_{50} for antagonism to corazol); TI is the therapeutic index (LD_{50}/ED_{50} for antagonism to corazol); PI′ is the protection index (ED_{50} for myorelaxant effect/ED_{50} for antagonism to corazol). Figures in parentheses give confidence interval for $P = 0.05$.

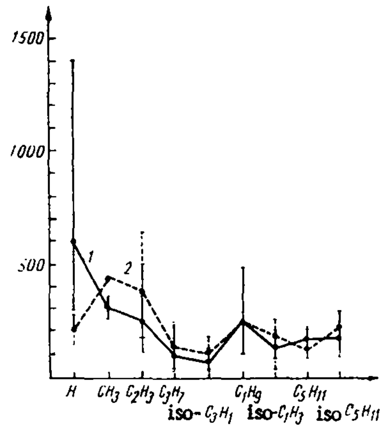

Fig. 1. Relationship between anticorazol and antielectroshock activity of methyl 5-alkoxy-2-sulfamidobenzoates and the size of the alkoxy group. Alkyl groups are plotted along the x axis; ED_{50} (in mg/kg) along the y axis. 1) anticorazol activity; 2) antielectroshock activity.

The tests showed that none of the ten compounds prevented nicotine or strychnine convulsions, or arecoline tremor. However, some of the compounds showed antagonism to corazol and inhibited electroshock convulsions; a relationship between the size of the alkoxy group and the pharmacological action of the compound was noted, particularly in the anticorazol test. The unsubstituted derivative X (R = H) was the least active. The introduction of an alkoxy group led to an increase in activity and this activity increased with the size of the alkoxy group. Compounds III and VI showed the maximum activity (Table 2); a further increase in the size of the alkoxy group led to an increase in anticorazol activity. Compounds containing an isoalkoxy group were somewhat more active than those with a normal alkoxy group (see Fig. 1).

In the maximum electroshock test, the relationship between structure and activity is not so marked, and compound VI (R = iso-C_3H_7O) was the most active.

From Table 2 it can be seen that compound VI had a negligible effect on motor coordination, produced only slight myorelaxation, ataxia, and depression of the orientation reaction, and was only weakly toxic. Compounds I, VIII, and IX displayed similar secondary properties. Thus, in spite of their low anticonvulsant activity, these compounds have considerable protective and therapeutic properties.

Chemical

The IR spectra of the compounds were measured in mineral oil using a UR-20 spectrometer. Thin-layer chromatography was carried out on Silufol UV-254 plates.

Methyl Esters of 5-Substituted 2-Sulfamidobenzoic Acids (I-IX). A current of dry hydrogen chloride was passed into a suspension of 0.02 mole of the appropriate 3-oxo-2,3-dihydrobenzo[d] isothiazole-1,1-dioxide in 50 ml of boiling absolute methanol. The mixture was refluxed for 3 hours until the starting material had dissolved, the methanol distilled off at reduced pressure, and the viscous residue dissolved in hot 70% ethanol. On cooling, white crystals (golden where R = NO_2) separated out. Compound X was prepared by the same method [14].

The IR spectra of compounds I-X show absorption at 1710-1715 cm^{-1} (ester carbonyl group), at 1140 and 1350 cm^{-1} (sulfonyl group) and at 3260-3270 cm^{-1} and 3350-3360 cm^{-1} (N—H bond).

2-Methyl-4-nitrobenzenesulfonamide. A suspension of 38.03 g (0.25 mole) of 2-methyl-4-nitroaniline in 250 ml of concentrated hydrochloric acid at 0-5°C was diazotized with a solution of 17.25 g of sodium nitrite. The solution of the diazonium salt was warmed to 30-40°C and added to a mixture of 200 ml of benzene containing 21.3 g of copper dichloride dihydrate; the rate of addition was such that a vigorous evolution of nitrogen occurred and the reaction proceeded fairly quickly. The reaction mixture was held at a constant temperature until the evolution of nitrogen stopped and was then poured into 1.5 liters of water. The organic layer was separated, washed with 1-2% solution of sodium hydroxide and water, and the benzene distilled off.

An ethereal solution of the residue was added to 100 ml of 25% aqueous ammonia at room temperature, and the excess ammonia and ether removed by heating on a water bath. The precipitate was filtered off, washed on the filter with water and ether, and recrystallized from aqueous ethanol to give a product having mp 155-157°C (literature value 157°C [4]).

5-Nitro-3-oxo-2,3-dihydrobenzo[d]isothiazole-1,1-dioxide. To a solution of 4.3 g (0.02 mole) of 2-methyl-4-nitrobenzenesulfonamide in 25 ml of concentrated sulfuric acid at 65°C was added portionwise with mixing 6 g of technical chromium trioxide; the temperature was maintained at 65-70°C throughout the addition, and for a further 15-20 min until the evolution of gas had ceased. The reaction mixture was poured into 100 ml of water and the precipitated material was filtered off and recrystallized from water to give a 50.5% yield of product, mp 212-214°C.

The same result was obtained when 8.8 g of potassium dichromate was used.

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