STUDIES IN THE FIELD OF DIURETICS

PART III. SOME SYMMETRICAL BENZENE-1,3-DISULPHONALKYLAMIDES

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The symmetrical benzene-1,3-disulphonalkylamides described herein are found to be virtually devoid of carbonic anhydrase inhibiting activity. Certain dialkylamides nevertheless retain significant diuretic activity, which is consequently regarded as an intrinsic property of the 1,3-disulphamylbenzene ring system and not as solely an expression of carbonic anhydrase inhibiting activity.

IN Part II of this series[1] the preparation of a number of 1,3-disulphamyl derivatives of benzene was reported. Most of these compounds were found to show some diuretic activity in the saline-loaded rat when administered by mouth. For reasons outlined in the earlier publication, 5-chloro-2,4-disulphamyltoluene (disulphamide) was selected for further study.

In the course of this work it was found that diuretic activity in this series was not related in simple manner to the carbonic anhydrase inhibiting activity *in vitro*. This observation seemed to indicate that their diuretic properties stemmed from structural features active in their own right as well as from ability to inhibit the enzyme carbonic anhydrase. To test this hypothesis attention was directed to the related benzene-1,3-disulphonalkylamides; which group of compounds was expected to possess negligible carbonic anhydrase inhibiting activity by virtue of the substituents on their sulphamyl groups[2].

The benzene-1,3-disulphonalkylamides recorded in Table I were prepared by standard methods involving reaction of the appropriate disulphonchloride (cf.[1]) with the amine in aqueous or aqueous: ethanolic solution, or under anhydrous conditions in a variety of solvents. In most instances the use of a two-phase system, e.g., carbon tetrachloride or chloroform and water, led to readier control of the reaction and improved yields. Precautions were necessary in those reactions in which a halogen atom, particularly bromine or fluorine, was situated *o*- to a sulphonchloride group, when the reaction had to be performed at low temperatures using only theoretical amounts of amine, otherwise replacement of the halogen atom by substituted amine readily occurred.

The alkylamides listed in Table I proved to be, without exception, essentially inactive ($<$ than 1/5000 $\times$ acetazolamide) as inhibitors of carbonic anhydrase. Their diuretic study kindly made by Dr. A. David and his colleagues, in saline-loaded rats, showed clearly the retention of significant activity in the methylamides and dimethylamides. Increase in the size of the sulphonamide alkyl substituent beyond methyl led to rapid diminution of diuretic activity, which had essentially disappeared in the 2,4-disulphonbutylamides. Replacement of the $^{-}NH_2$ moiety of the

TABLE I

SYMMETRICAL BENZENE-1,3-DISULPHONALKYLAMIDES

No.	R	Substituent at position				m.p. °C	Formula	Found					Required				
		2	4	5	6			C	H	N	S	Cl	C	H	N	S	Cl
1	MeNH	—	Me	—	—	127–129	$C_9H_{14}O_4N_2S_2$	38·7	4·6	10·0	—	—	38·6	5·0	10·1	—	—
2	,,	—	Et	—	—	120–121	$C_{10}H_{16}O_4N_2S_2$	41·4	5·2	9·6	21·7	—	41·1	5·5	9·6	21·9	—
3	,,	—	Me_2CH	—	—	136–137	$C_{11}H_{18}O_4N_2S_2$	43·3	5·7	8·8	20·6	—	43·1	5·9	9·1	20·9	—
4	,,	—	F	—	—	144–145	$C_8H_{11}O_4N_2S_2F$	33·7	3·8	9·8	22·7	—	34·0	3·9	9·9	22·7	—
5	,,	—	Cl	—	—	141–143	$C_8H_{11}O_4N_2S_2Cl$	32·4	3·8	9·1	21·2	11·7	32·2	3·7	9·4	21·5	11·9
6	,,	—	Br	—	—	139–141	$C_8H_{11}O_4N_2S_2Br$	27·8	3·4	8·7	—	—	28·0	3·2	8·2	—	—
7	,,	—	Me	Me	—	178–180	$C_{10}H_{16}O_4N_2S_2$	41·0	5·2	9·5	—	—	41·1	5·5	9·6	21·9	—
8	,,	—	Me	—	Me	176–178	,,	41·2	5·5	9·4	21·2	—	41·1	5·5	9·6	21·9	—
9	,,	—	Me	—	F	144–146	$C_9H_{13}O_4N_2S_2F$	37·0	4·4	9·6	21·5	—	36·5	4·4	9·5	21·6	—
10	,,	—	Me	—	Cl	194–195	$C_9H_{13}O_4N_2S_2Cl$	34·9	4·5	9·0	20·1	11·0	34·6	4·2	9·0	20·5	11·4
11	EtNH	—	Me	—	Cl	125	$C_{11}H_{17}O_4N_2S_2Cl$	38·7	4·9	8·1	—	10·1	38·8	5·0	8·2	—	10·4
12	n-PrNH	—	Me	—	Cl	107–108	$C_{13}H_{21}O_4N_2S_2Cl$	42·1	5·6	8·0	—	10·1	42·3	5·7	7·6	17·4	9·6
13	iso-PrNH	—	Me	—	Cl	220	,,	42·3	5·5	7·6	17·3	—	42·3	5·7	7·6	17·4	9·6
14	n-BuNH	—	Me	—	Cl	97–98	$C_{15}H_{25}O_4N_2S_2Cl$	45·2	6·0	7·4	16·1	—	45·4	6·3	7·1	16·1	—
15	C_5H_4NH	—	Me	—	Cl	129–130	$C_{19}H_{17}O_4N_2S_2Cl$	42·6	4·6	—	17·6	—	42·8	4·7	—	17·6	—
16	$C_5H_4(Me)NH$	—	Me	—	Cl	124–125	$C_{15}H_{21}O_4N_2S_2Cl$	45·4	5·1	6·9	15·9	—	45·9	5·4	7·1	16·3	—
17	Me_2N	—	Me	—	Cl	150–152	$C_{11}H_{17}O_4N_2S_2Cl$	39·3	5·2	8·3	19·1	10·6	38·7	5·0	8·2	18·8	10·4
18	MeNH	—	Me	Cl	—	153–155	$C_9H_{13}O_4N_2S_2Cl$	34·7	4·0	9·1	20·7	11·3	34·6	4·2	9·0	20·5	11·4
19	Me_2N	—	Me	Cl	—	128–130	$C_{11}H_{17}O_4N_2S_2Cl$	38·8	5·0	8·0	19·1	—	38·8	5·0	8·2	18·8	—
20	MeNH	—	Cl	Me	—	157–160	$C_9H_{13}O_4N_2S_2Cl$	34·9	4·2	—	—	—	34·6	4·2	—	—	—
21	Me_2N	—	Cl	Me	—	127–129	$C_{11}H_{17}O_4N_2S_2Cl$	38·7	5·0	8·4	18·5	10·4	38·8	5·0	8·2	18·8	10·4
22	$N<(CH_2)_5$	—	Cl	Me	—	135–136	$C_{17}H_{25}O_4N_2S_2Cl$	48·7	5·6	6·5	—	8·3	48·6	6·0	6·7	—	8·4
23	MeNH	—	Me	—	Br	189–190	$C_9H_{13}O_4N_2S_2Br$	30·5	3·7	7·7	18·1	—	30·3	3·6	7·8	17·9	—
24	EtNH	—	Me	—	Br	117–118	$C_{11}H_{17}O_4N_2S_2Br$	33·8	4·3	7·0	16·7	—	34·3	4·4	7·3	16·6	—
25	n-PrNH	—	Me	—	Br	128–129	$C_{13}H_{21}O_4N_2S_2Br$	37·5	5·0	6·7	—	19·2*	37·8	5·1	6·8	—	19·4*
26	iso-PrNH	—	Me	—	Br	222–223	,,	38·0	5·0	7·2	—	—	37·8	5·1	6·8	—	19·4*
27	n-BuNH	—	Me	—	Br	96–97	$C_{15}H_{25}O_4N_2S_2Br$	—	—	6·4	14·8	—	40·8	5·7	6·4	14·5	—
28	C_5H_4NH	—	Me	—	Br	125–126	$C_{19}H_{17}O_4N_2S_2Br$	38·4	4·2	6·6	15·8	—	38·1	4·2	6·9	15·7	—
29	$C_5H_4(Me)NH$	—	Me	—	Br	128	$C_{16}H_{21}O_4N_2S_2Br$	41·6	4·6	6·5	—	18·5*	40·2	4·8	6·4	—	18·3*
30	MeNH	—	Cl	Cl	—	147–149	$C_9H_{16}O_4N_2S_4Cl_2$	28·8	3·4	7·9	—	20·7	28·9	3·0	8·4	—	21·3
31	,,	—	Cl	—	Cl	192–194	,,	28·7	3·3	8·6	—	—	28·9	3·0	8·4	—	21·3
32	,,	—	Cl	—	NH_2	180–183	$C_8H_{12}O_4N_3S_2Cl$	31·1	4·1	13·5	—	11·3	30·6	3·9	13·4	—	11·3
33	,,	—	MeNH	—	—	166–168	$C_9H_{15}O_4N_3S_2$	30·6	5·1	14·5	—	—	36·8	5·2	14·3	—	—
34	,,	—	MeNH	—	Me	206–207	$C_{10}H_{17}O_4N_3S_2$	39·0	5·7	13·9	21·0	—	39·1	5·6	13·7	20·8	—
35	,,	—	MeNH	—	Cl	213–124	$C_9H_{14}O_4N_3S_2Cl$	32·7	4·3	12·4	—	—	32·9	4·3	12·8	—	—
36	,,	—	$N<(CH_2)_5$	—	Me	208–209	$C_{14}H_{23}O_4N_3S_2$	46·4	6·3	12·0	—	—	46·5	6·4	11·6	—	—
37	n-BuNH	—	n-BuNH	—	Me	107	$C_{19}H_{35}O_4N_3S_2$	52·8	8·4	9·7	—	—	52·6	8·2	9·7	—	—
38	$N<(CH_2)_6$	—	$N<(CH_2)_5$	—	Me	139–140	$C_{23}H_{35}O_4N_3S_2$	56·6	7·3	9·2	—	—	56·3	7·5	9·0	—	—
39	$NH.NH_2$	—	Me	—	—	147 (d)	$C_7H_{12}O_4N_4S_2$	30·1	4·5	20·3	22·8	—	30·0	4·3	20·0	22·9	—
40	MeNH	—	OH	Cl	—	152–154	$C_8H_{11}O_5N_2S_2Cl$	30·7	3·5	9·4	—	—	30·6	3·5	8·9	—	—
41	,,	OH	—	SO_2NHMe	—	217–218	$C_8H_{14}O_7N_3S_3$	29·5	4·3	10·8	—	—	28·9	4·1	11·3	—	—
42	,,	Me	OH	SO_2NHMe	—	222–224	$C_{10}H_{17}O_7N_3S_3$	31·5	4·6	10·8	—	—	31·0	4·4	10·9	—	—
43	,,	OH	Me	Cl	Me	198–200	$C_{10}H_{15}O_5N_2S_2Cl$	35·4	4·5	8·2	18·3	10·3	35·0	4·4	8·2	18·7	10·4
44	Et.O.CO.NH	—	Me	—	—	103–105	$C_{15}H_{23}O_5N_3S_2$	42·5	5·5	6·6	—	—	42·6	5·2	6·6	—	—
45	MeNH	MeNH	—	SO_2NHMe	—	159–160	$C_{10}H_{18}O_6N_4S_3$	31·3	4·7	14·3	—	—	31·1	4·7	14·5	—	—
46	,,	—	Br	—	MeNH	228–229	$C_9H_{14}O_4N_3S_2Br$	29·1	3·6	10·8	—	22·1*	29·1	3·8	11·3	—	21·5*

* Bromine

sulphamyl groups by a heterocyclic radical likewise led to almost complete loss of diuretic potency.

Comparison of the diuretic activities of the 1,3-disulphamyl benzene derivatives described in Part II with their alkylated analogues recorded herein showed that alkylation was accompanied always by loss of potency and by virtual disappearance of carbonic anhydrase inhibiting activity. Significant diuretic activity was retained, however, by certain methylamides and dimethylamides (Nos. 5, 6, 9, 17, 18 and 46). The hypothesis that 1,3-disulphamylbenzene derivatives may be diuretically active *per se* and independently of their carbonic anhydrase inhibiting properties may consequently be regarded as proven.

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Experimental

The following illustrate the preparative methods involved.

5-Chlorotoluene-2,4-disulphonmethylamide. 5-Chlorotoluene-2,4-disulphonchloride (20 g.) was added in portions with stirring and cooling below 20° to a mixture of 25 per cent w/v aqueous methylamine (100 ml.) and carbon tetrachloride (100 ml). After the addition was complete, stirring was continued for 15 minutes at room temperature. The product (19 g.) was collected and crystallised from ethanol; m.p. 194–195°.

5-Methylaminotoluene-2,4-disulphonmethylamide. (*a*) The foregoing compound (15·6 g.) was dissolved in 33 per cent ethanolic methylamine (50 ml.) and the solution heated at *ca.* 60° for 10 hours when excess of amine and solvent was boiled off. The residual *product* had m.p. 205–206° after crystallisation from aqueous ethanol.

(*b*) 5-Fluorotoluene-2,4-disulphonchloride (20 g.) was added in portions with stirring and cooling to liquid methylamine (100 ml.). The excess of amine was allowed to evaporate overnight at room temperature. The viscous residue was dissolved in hot water and the solution acidified with hydrochloric acid. The *product* which separated had m.p. 206–207° after crystallisation from aqueous ethanol and was identical with that described in (*a*).

Toluene-2,4-disulphonylaminoacetate diethyl ester. A solution of toluene-2,4-disulphonchloride (28·8 g.) in chloroform (150 ml.) was added with stirring and cooling below 10° to a mixture of ethyl aminoacetate hydrochloride (35 g.) and triethylamine (50·5 g.) in chloroform (500 ml.) Stirring was continued for 30 minutes after the addition was complete then excess of triethylamine was extracted with dilute hydrochloric acid. Concentration of the chloroform furnished the solid *product* which had m.p. 103°—105° after crystallisation from aqueous ethanol.

Fluorobenzene-2,4-disulphonmethylamide. To a stirred solution of fluorobenzene-2,4-disulphonyl chloride (29·3 g.) in carbon tetrachloride (120 ml.) was added slowly, with cooling to 0°, a 10 per cent aqueous solution of methylamine (125 ml.). After the addition was complete stirring was continued at 0° for 4 hours when the aqueous layer was

separated and acidified with concentrated hydrochloric acid. The *product* which separated on cooling had m.p. 144–145° after crystallisation from water.

5-*Methylaminochlorobenzene*-2,4-*disulphonmethylamide*. 1,5-Dichlorobenzene-2,4-disulphonchloride (20 g.) was added in portions with stirring and cooling below 30° to a 30 per cent aqueous solution of methylamine (150 ml.). Stirring was continued for 30 minutes and excess of methylamine was boiled off. The residual liquors were cooled and acidified with hydrochloric acid. The *product* (70 per cent yield), had m.p. 213° after crystallisation from aqueous ethanol.

REFERENCES

1. Boggiano, Condon, Davies, Jackman, Overell, Petrow, Stephenson and Wild, *J. Pharm. Pharmacol.* 1960, **12**, 419.
2. Krebs, *Biochem. J.*, 1948, **43**, 525.