STUDIES IN THE FIELD OF DIURETIC AGENTS

PART VII. 4-CHLORO-2′-METHYL-3-SULPHAMOYLBENZANILIDE

BY V. PETROW, O. STEPHENSON AND A. M. WILD

*From the British Drug Houses, Ltd., Graham Street, London, N.*1

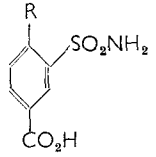
Received August 14, 1962

A new route to the anilides of 4-halogeno-3-sulphamoylbenzoic acid is described. These novel compounds, and in particular 4-chloro-2′-methyl-3-sulphamoylbenzanilide, are found to be potent orally active diuretic agents.

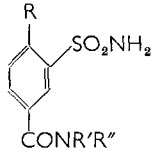
IN Part VI of this series (Jackman, Petrow, Stephenson and Wild, 1962) the preparation was described of some 4-substituted 3-sulphamoylbenzoic acids, a new class of orally active diuretic agents with only slight inhibitory activity against carbonic anhydrase. Such compounds (I) showed optimal activity when the substituent R was a fluoro-, chloro- or bromo-atom. The present study deals with some related carboxyamides (II).

Work was originally confined to the preparation of the more readily available 4-chloro-compounds (II: R = Cl), but, following early promising biological results, was later extended to analogous types.

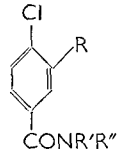
The unsubstituted amide (II; R = Cl; R′ = R″ = H) was obtained readily from 4-chloro-3-chlorosulphonylbenzoyl chloride, itself prepared by a variation of the method described by Ullmann in 1896. For the preparation of substituted carboxyamides, recourse was made to 4-chloro-3-nitrobenzoyl chloride, described by Montagne in 1900. This was condensed with the appropriate amine R′R″NH to yield the 4-chloro-3-nitrobenzamide (III; R = NO_2), which was in turn reduced to the corresponding aniline (III; R = NH_2). The last compound was then converted into the required sulphonamide (II; R = Cl) *via* the sulphonchloride (III; R = SO_2Cl) as described by Petrow, Stephenson and Wild (1960). (Data for amino and nitro-compounds are in Table I.)



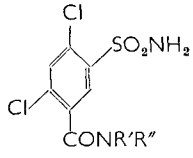
(I)



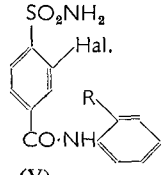
(II)



(III)



(IV)



(V)

The methyl-, ethyl-, and dimethyl-carboxyamides were all prepared by this route. They resembled the unsubstituted amide in being effective

oral diuretic agents at the 5 mg./kg. dose level in saline-loaded rats in tests carried out by Dr. A. David and his colleagues.

Extension of this work to the benzanilide derivatives (II; R = Cl, R′ = H, R″ = aryl) led to a major advance in this field. 4-Chloro-2′-methyl-3-sulphamoylbenzanilide (II; R = Cl, R′ = H, R″ = *o*-tolyl), prepared by the method described, proved to be an extremely potent oral diuretic agent with an activity fifty to one hundred times that of the parent acid (I; R = Cl). This important result led to a study of improved methods for the preparation of these compounds. The most satisfactory route discovered depends upon the greater reactivity of the carboxylyl chloride group relative to the sulphonchloride group [compare Wegscheider and Furcht (1902); Smiles and Stewart (1921) and Barr, Salminen and Weissberger (1951)]. Thus we found that 4-chloro-3-chlorosulphonylbenzoyl chloride condensed readily with one equivalent of *o*-toluidine, or its hydrochloride, in boiling toluene or chlorobenzene to give a 90 per cent yield of 4-chloro-3-chlorosulphonyl-2′-methylbenzanilide (III; R = SO_2Cl, R′ = H, R″ = *o*-tolyl). The reaction was applied to a whole range of amines including substituted anilines. The sulphonchlorides prepared in this way are summarised in Table II. Reaction of these sulphonchlorides with ammonia or amines furnished the required sulphonamides (Table III) in high yield.

Biological testing of the sulphonamides by Dr. A. David and his colleagues showed that the high oral diuretic activity of the *o*-toluidide was possessed by several other *ortho*-substituted analogues, the 4-chloro-2′-halogeno-3-sulphamoylbenzanilides (II; R = Cl, R′ = H, R″ = *o*-F-, -Cl- or -Br-C_6H_4) being especially active. The corresponding *meta*- (3′-) and *para*- (4′-) substituted compounds were much less active, as was the compound unsubstituted in the aniline ring (II; R = Cl, R′ = H, R″ = Ph). In the last compound, activity was increased by the introduction of a methyl substituent into the carboxyamide, as in 4-chloro-*N*-methyl-3-sulphamoylbenzanilide (II; R = Cl, R′ = Me, R″ = Ph), but in general an additional alkyl substituent in the carboxyamide caused no increase in diuretic activity.

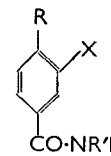
2′-Carboxy-4-chloro-3-sulphamoylbenzanilide (II; R = Cl, R′ = H, R″ = *o*-$CO_2H{\cdot}C_6H_4$), a possible metabolite of the active *o*-toluidide, was prepared by reaction of 4-chloro-3-chlorosulphonylbenzoyl chloride with anthranilic acid or with methyl anthranilate, followed in the latter case by hydrolysis of the ester. It proved to be without diuretic activity.

The introduction of further substituents into the aniline ring of the benzanilide nucleus caused no apparent increase in diuretic activity, though the more active of these types all possessed an *ortho*-substituent.

Fluoro- and bromo-analogues (II; R = F or Br, R′ = H, R″ = aryl) of the more potent compounds of the chloro-series were prepared by similar reaction techniques and proved to be highly active oral diuretic agents. The corresponding compounds (II; R = Me, R′ = H, R″ = aryl) derived from 4-methyl-3-sulphamoylbenzoic acid were somewhat less effective.

TABLE I

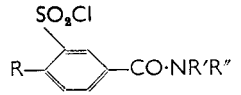
AMINO- AND NITRO-COMPOUNDS



R	X	R′	R″	m.p. °C	Formula	Found				Required			
						C	H	Cl	N	C	H	Cl	N
Cl	NH_2	H	Me	148–149	$C_8H_9ClN_2O$	52·3	4·7	18·9	15·4	52·1	4·9	19·2	15·2
Cl	NO_2	H	Et	101	$C_9H_9ClN_2O_3$	47·2	4·1	15·3	12·4	47·2	4·0	15·5	12·3
Cl	NH_2	H	Et	106–108	$C_9H_{11}ClN_2O$	54·5	5·7	17·8	14·0	54·4	5·6	17·8	14·1
Cl	NO_2	H	*o*-Me·C_6H_4	151–153	$C_{14}H_{11}ClN_2O_3$	57·9	3·8	11·9	10·0	57·8	3·8	12·2	9·6
Cl	NH_2	H	*o*-Me·C_6H_4	160–162	$C_{14}H_{13}ClN_2O$	64·4	5·1	13·7	10·9	64·5	5·0	13·6	10·7
Cl	NO_2	H	Ph·CH_2	99–101	$C_{14}H_{11}ClN_2O_3$	57·8	4·3	12·2	9·5	57·8	3·8	12·2	9·6
Cl	NH_2·HCl	H	Ph·CH_2	192–194	$C_{14}H_{14}Cl_2N_2O$	54·1	5·0	24·0	9·7	54·3	4·8	23·8	9·4
Cl	NO_2	H	Ph·CH_2·CH_2	95–97	$C_{15}H_{13}ClN_2O_3$	59·1	4·7	11·4	8·9	59·1	4·3	11·6	9·2
Cl	NH_2	H	Ph·CH_2·CH_2	134–135	$C_{15}H_{15}ClN_2O$	65·7	5·3	—	9·9	65·6	5·5	12·9	10·2
Cl	NH_2	Me	Me	73–75	$C_9H_{11}ClN_2O$	54·8	5·3	18·2	14·0	54·4	5·6	17·8	14·1
Cl	NO_2	–[CH_2]$_5$–		79–81	$C_{12}H_{13}ClN_2O_3$	—	—	13·1	10·1	—	—	13·2	10·4
Cl	NH_2	–[CH_2]$_5$–		141–143	$C_{12}H_{15}ClN_2O$	60·8	6·5	14·7	11·6	60·4	6·3	14·9	11·7
Me	NH_2·HCl	Me	Me	221–223	$C_{10}H_{15}ClN_2O$	55·7	7·3	16·4	12·8	55·9	7·0	16·5	13·1

TABLE II

SULPHONCHLORIDES

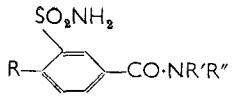


R	R′	R″	m.p. °C	Formula	Found C	Found H	Found Cl	Found N	Found S	Required C	Required H	Required Cl	Required N	Required S
Me	H	*o*-Me·C_6H_4	128–130	$C_{15}H_{14}ClNO_3S$	55·8	4·5	10·6	4·2	9·8	55·5	4·4	10·9	4·3	9·9
Me	H	*o*-Cl·C_6H_4	137–138	$C_{14}H_{11}Cl_2NO_3S$	48·8	3·1	20·6	4·1	9·5	48·7	3·2	20·5	4·1	9·3
Me	H	2,5-Cl_2·C_6H_3	136–137	$C_{14}H_{10}Cl_3NO_3S$	44·6	3·0	27·8	3·7	8·6	44·4	2·7	28·1	3·7	8·5
F	H	*o*-Me·C_6H_4	163	$C_{14}H_{11}ClFNO_3S$	51·2	3·3	10·9	4·0	10·2	51·1	3·4	10·8	4·3	9·8
F	H	*o*-F·C_6H_4	140–141	$C_{13}H_8ClF_2NO_3S$	47·1	2·6	—	4·4	9·6	47·1	2·4	—	4·2	9·7
F	H	*o*-Cl·C_6H_4	112–113	$C_{13}H_8Cl_2FNO_3S$	45·1	2·6	19·9	4·0	—	44·8	2·3	20·4	4·0	—
F	H	*o*-Br·C_6H_4	124–125	$C_{13}H_8BrClFNO_3S$	40·2	2·2	—	3·8	—	39·8	2·1	—	3·6	—
F	H	2,5-Cl_2·C_6H_3	145–146	$C_{13}H_7Cl_2FNO_3S$	40·9	2·2	—	4·1	—	40·8	1·8	—	3·7	—
Cl	H	Me	114–116	$C_8H_7Cl_2NO_3S$	—	—	—	5·1	11·7	—	—	—	5·2	12·0
Cl	H	Pr^i	117–119	$C_{10}H_{11}Cl_2NO_3S$	—	—	—	4·7	10·6	—	—	—	4·7	10·8
Cl	H	Ph	198	$C_{13}H_9Cl_2NO_3S$	47·2	2·5	—	4·0	9·7	47·3	2·8	—	4·2	9·7
Cl	H	*o*-Me·C_6H_4	161–163	$C_{14}H_{11}Cl_2NO_3S$	49·0	3·3	20·3	4·2	9·0	48·8	3·2	20·6	4·1	9·3
Cl	H	*m*-Me·C_6H_4	174–176	$C_{14}H_{11}Cl_2NO_3S$	49·3	3·0	20·7	4·3	9·6	48·8	3·2	20·6	4·1	9·3
Cl	H	*p*-Me·C_6H_4	168–169	$C_{14}H_{11}Cl_2NO_3S$	49·1	3·1	21·2	4·2	9·5	48·8	3·2	20·6	4·1	9·3
Cl	H	*o*-MeO·C_6H_4	144–146	$C_{14}H_{11}Cl_2NO_4S$	46·9	2·6	20·2	3·8	—	46·7	2·9	19·7	3·9	—
Cl	H	*o*-F·C_6H_4	156–157	$C_{13}H_8Cl_2FNO_3S$	45·2	2·5	—	4·0	9·2	44·8	2·3	—	4·0	9·2
Cl	H	*o*-Cl·C_6H_4	146–148	$C_{13}H_8Cl_3NO_3S$	—	—	29·1	3·8	9·1	—	—	29·2	3·8	8·8
Cl	H	*m*-Cl·C_6H_4	194	$C_{13}H_8Cl_3NO_3S$	43·2	2·1	28·6	3·6	8·6	42·8	2·2	29·2	3·8	8·8
Cl	H	*p*-Cl·C_6H_4	177–178	$C_{13}H_8Cl_3NO_3S$	43·2	2·1	29·6	3·7	8·8	42·8	2·2	29·2	3·8	8·8
Cl	H	*o*-Br·C_6H_4	145–146	$C_{13}H_8BrCl_2NO_3S$	38·5	2·1	37·2*	3·6	8·2	38·2	2·0	36·9*	3·4	7·8
Cl	H	*m*-CF_3·C_6H_4	144–146	$C_{14}H_8Cl_2F_3NO_3S$	41·9	2·1	—	3·8	—	42·2	2·0	—	3·5	—
Cl	H	*o*-MeO·CO·C_6H_4	149–151	$C_{15}H_{11}Cl_2NO_5S$	46·7	2·9	18·7	4·1	8·5	46·4	2·9	18·3	3·6	8·3
Cl	H	2,3-Me_2·C_6H_3	173–174	$C_{15}H_{13}Cl_2NO_3S$	50·2	3·7	—	3·9	8·6	50·3	3·7	—	3·9	9·0
Cl	H	2,4-Me_2·C_6H_3	158–160	$C_{15}H_{13}Cl_2NO_3S$	50·1	3·3	19·8	3·9	9·4	50·3	3·7	19·8	3·9	9·0
Cl	H	2,5-Me_2·C_6H_3	190–191	$C_{15}H_{13}Cl_2NO_3S$	50·5	3·5	20·0	4·3	9·3	50·3	3·7	19·8	3·9	9·0
Cl	H	2,6-Me_2·C_6H_3	185–186	$C_{15}H_{13}Cl_2NO_3S$	50·6	3·6	20·4	—	9·1	50·3	3·7	19·8	—	9·0
Cl	H	2,3-Cl_2·C_6H_3	132–134	$C_{13}H_7Cl_4NO_3S$	39·5	1·8	35·5	3·6	8·0	39·1	1·8	35·5	3·5	8·0
Cl	H	2,4-Cl_2·C_6H_3	151–153	$C_{13}H_7Cl_4NO_3S$	—	—	35·4	3·5	8·4	—	—	35·5	3·5	8·0
Cl	H	2,5-Cl_2·C_6H_3	155–156	$C_{13}H_7Cl_4NO_3S$	39·5	1·6	35·6	—	8·2	39·1	1·8	35·5	—	8·0
Cl	H	2,6-Cl_2·C_6H_3	210	$C_{13}H_7Cl_4NO_3S$	—	—	35·6	3·5	8·3	—	—	35·5	3·5	8·0
Cl	H	2,6-Br_2·C_6H_3	223–225	$C_{13}H_7Br_2Cl_2NO_3S$	32·1	1·4	47·3*	3·0	6·8	32·0	1·5	47·3*	2·9	6·6
Cl	H	2,4,5-Cl_3·C_6H_2	157–158	$C_{13}H_6Cl_5NO_3S$	36·4	1·4	40·7	3·6	7·4	36·0	1·4	40·9	3·2	7·4
Cl	H	2,4,6-Cl_3·C_6H_2	177–179	$C_{13}H_6Cl_5NO_3S$	36·5	1·2	40·3	3·2	7·4	36·0	1·4	40·9	3·2	7·4
Cl	H	Ph·CH_2	152–154	$C_{14}H_{11}Cl_2NO_3S$	49·3	3·0	20·2	4·4	9·3	48·8	3·2	20·6	4·1	9·3
Cl	Me	Me	106–108	$C_9H_9Cl_2NO_3S$	38·3	3·0	24·9	5·2	11·3	38·3	3·2	25·1	5·0	11·4
Cl	Me	Ph	120–122	$C_{14}H_{11}Cl_2NO_3S$	49·1	3·2	21·2	4·2	9·8	48·8	3·2	20·6	4·1	9·3
Cl	Me	*o*-Me·C_6H_4	119–121	$C_{15}H_{13}Cl_2NO_3S$	50·5	3·5	—	4·4	—	50·3	3·7	—	3·9	—
Cl	Et	Ph	126–128	$C_{15}H_{13}Cl_2NO_3S$	50·4	3·9	20·0	3·9	9·2	50·3	3·7	19·8	3·9	9·0
Cl	$-[CH_2]_5-$		117–119	$C_{12}H_{13}Cl_2NO_3S$	44·7	4·1	22·4	4·1	10·1	44·7	4·1	22·0	4·4	10·0
Br	H	*o*-Me·C_6H_4	170–171	$C_{14}H_{11}BrClNO_3S$	43·0	2·9	—	3·8	8·4	43·1	2·8	—	3·6	8·2
Br	H	*o*-Cl·C_6H_4	166–167	$C_{13}H_8BrCl_2NO_3S$	38·2	1·8	—	3·6	7·6	38·2	2·0	—	3·4	7·8
Br	H	2,5-Cl_2·C_6H_3	163–164	$C_{13}H_7BrCl_3NO_3S$	35·4	1·5	—	3·1	7·0	35·2	1·6	—	3·2	7·2

* Total Halogen.

TABLE III

SULPHONAMIDES



R	R′	R″	m.p. °C	Formula	Found					Required				
					C	H	Cl	N	S	C	H	Cl	N	S
H	H	H	170	$C_7H_8N_2O_3S$	—	—	—	—	—	—	—	—	—	—
H	H	Me	212–214	$C_8H_{10}N_2O_3S$	45·1	4·6	—	13·1	14·7	44·9	4·7	—	13·1	15·0
H	H	*o*-Me·C_6H_4	190–191	$C_{14}H_{14}N_2O_3S$	57·9	5·1	—	9·8	10·7	57·9	4·9	—	9·7	11·0
Me	H	H	219–221	$C_8H_{10}N_2O_3S$	45·1	4·8	—	13·1	14·9	44·9	4·7	—	13·1	15·0
Me	H	Me	219–221	$C_9H_{12}N_2O_3S$	47·7	5·5	—	12·0	14·0	47·4	5·3	—	12·3	14·1
Me	H	*o*-Me·C_6H_4	230–231	$C_{15}H_{16}N_2O_3S$	59·4	5·2	—	8·9	10·3	59·0	5·3	—	9·2	10·5
Me	H	*o*-Cl·C_6H_4	192–194	$C_{14}H_{13}ClN_2O_3S$	51·5	3·9	11·0	8·9	9·7	51·6	4·0	10·9	8·6	9·8
Me	H	2,5-Cl_2·C_6H_3	189–190	$C_{14}H_{12}Cl_2N_2O_3S$	47·1	3·4	19·7	7·7	8·9	46·8	3·3	19·7	7·8	8·9
Me	Me	Me	155–157	$C_{10}H_{14}N_2O_3S$	50·0	5·7	—	11·6	13·1	49·6	5·8	—	11·6	13·2
F	H	H	212–214	$C_7H_7FN_2O_3S$	38·3	3·4	—	12·9	—	38·5	3·2	—	12·8	—
F	H	*o*-Me·C_6H_4	205–206	$C_{14}H_{13}FN_2O_3S$	54·8	4·5	—	9·2	10·7	54·4	4·2	—	9·1	10·4
F	H	*o*-F·C_6H_4	213–215	$C_{13}H_{10}F_2N_2O_3S$	49·6	3·3	—	8·5	—	50·0	3·2	—	9·0	—
F	H	*o*-Cl·C_6H_4	221–223	$C_{13}H_{10}ClFN_2O_3S$	47·7	3·3	11·3	8·6	10·0	47·5	3·1	10·8	8·5	9·8
F	H	*o*-Br·C_6H_4	219–220	$C_{13}H_{10}BrFN_2O_3S$	41·7	2·8	21·3[1]	7·6	8·5	41·8	2·7	21·4[1]	7·5	8·9
F	H	2,5-Cl_2·C_6H_3	197–198	$C_{13}H_9Cl_2FN_2O_3S$	43·4	2·6	19·7	8·0	9·1	43·0	2·5	19·5	7·7	8·8
Cl	H	H	228–230	$C_7H_7ClN_2O_3S$	—	—	—	—	—	—	—	—	—	—
Cl	H	Me	230–232	$C_8H_9ClN_2O_3S$	38·8	3·6	14·4	11·4	13·3	38·6	3·7	14·3	11·3	12·9
Cl	H	Et	208–210	$C_9H_{11}ClN_2O_3S$	40·4	4·0	13·5	11·0	12·2	41·1	4·2	13·5	10·7	12·2
Cl	H	Pr[i]	222–224	$C_{10}H_{13}ClN_2O_3S$	43·5	4·4	—	10·4	—	43·4	4·7	—	10·1	—
Cl	H	Ph	247–249	$C_{13}H_{11}ClN_2O_3S$	50·2	3·5	11·3	9·3	10·5	50·2	3·6	11·4	9·0	10·3
Cl	H	*o*-Me·C_6H_4	240–242	$C_{14}H_{13}ClN_2O_3S$	51·9	4·1	10·9	8·6	9·8	51·8	4·0	10·9	8·6	9·9
Cl	H	*m*-Me·C_6H_4	204–205	$C_{14}H_{13}ClN_2O_3S$	51·8	3·8	10·7	8·5	9·7	51·8	4·0	10·9	8·6	9·9
Cl	H	*p*-Me·C_6H_4	234–236	$C_{14}H_{13}ClN_2O_3S$	52·2	3·9	11·3	8·8	10·2	51·8	4·0	10·9	8·6	9·9
Cl	H	*o*-MeO·C_6H_4	214–215	$C_{14}H_{13}ClN_2O_4S$	49·5	4·0	10·7	8·1	9·2	49·3	3·8	10·4	8·2	9·4
Cl	H	*o*-F·C_6H_4	192–194	$C_{13}H_{10}ClFN_2O_3S$	47·6	3·3	11·2	9·0	9·4	47·5	3·1	10·8	8·5	9·8
Cl	H	*o*-Cl·C_6H_4	217–218	$C_{13}H_{10}Cl_2N_2O_3S$	45·5	3·1	20·8	8·3	9·5	45·2	2·9	20·5	8·1	9·3
Cl	H	*m*-Cl·C_6H_4	221–222	$C_{13}H_{10}Cl_2N_2O_3S$	45·6	2·8	—	8·2	9·4	45·2	2·9	—	8·1	9·3
Cl	H	*p*-Cl·C_6H_4	235–236	$C_{13}H_{10}Cl_2N_2O_3S$	45·6	3·1	20·8	8·0	9·5	45·2	2·9	20·5	8·1	9·3
Cl	H	*o*-Br·C_6H_4	209–211	$C_{13}H_{10}BrClN_2O_3S$	39·8	2·3	30·2[2]	7·1	8·5	40·1	2·6	29·6[2]	7·2	8·2
Cl	H	*m*-CF_3·C_6H_4	195–197	$C_{14}H_{10}ClF_3N_2O_3S$	44·4	3·0	—	7·0	—	44·4	2·7	—	7·4	—
Cl	H	*o*-CO_2H·C_6H_4	264–266 (*d*)	$C_{14}H_{11}ClN_2O_5S$	47·5	3·0	10·1	7·8	8·7	47·3	3·1	10·0	7·9	9·0
Cl	H	*o*-MeO·CO·C_6H_4	226–227	$C_{15}H_{13}ClN_2O_5S$	48·8	3·5	9·6	7·7	8·9	48·9	3·6	9·6	7·6	8·7
Cl	H	*p*-NH_2SO_2·C_6H_4	294–296	$C_{13}H_{12}ClN_3O_5S_2$	40·3	3·0	9·3	10·9	16·3	40·1	3·1	9·1	10·8	16·5
Cl	H	2,3-Me_2·C_6H_3	261–263	$C_{15}H_{15}ClN_2O_3S$	53·3	4·3	10·7	8·3	9·9	53·2	4·5	10·5	8·3	9·5
Cl	H	2,4-Me_2·C_6H_3	225–227	$C_{15}H_{15}ClN_2O_3S$	53·1	4·1	10·6	8·4	9·6	53·2	4·5	10·5	8·3	9·5
Cl	H	2,5-Me_2·C_6H_3	225–226	$C_{15}H_{15}ClN_2O_3S$	52·7	4·4	10·4	8·4	9·8	53·2	4·5	10·5	8·3	9·5
Cl	H	2,6-Me_2·C_6H_3	245–247	$C_{15}H_{15}ClN_2O_3S$	53·4	4·4	10·6	8·2	9·4	53·2	4·5	10·5	8·3	9·5

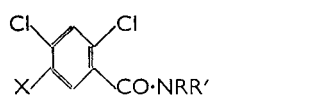
TABLE III *continued*

R	R′	R″	m.p. °C	Formula	Found C	Found H	Found Cl	Found N	Found S	Required C	Required H	Required Cl	Required N	Required S
Cl	H	2,3-Cl_2·C_6H_3	218–220	$C_{13}H_9Cl_3N_2O_3S$	41·2	2·4	27·8	7·2	8·5	41·1	2·4	28·0	7·4	8·4
Cl	H	2,4-Cl_2·C_6H_3	202–204	$C_{13}H_9Cl_3N_2O_3S$	41·3	2·1	28·1	7·4	8·5	41·1	2·4	28·0	7·4	8·4
Cl	H	2,5-Cl_2·C_6H_3	218	$C_{13}H_9Cl_3N_2O_3S$	41·0	2·5	—	7·3	8·4	41·1	2·4	—	7·4	8·4
Cl	H	2,6-Cl_2·C_6H_3	219–220	$C_{13}H_9Cl_3N_2O_3S$	41·1	2·1	28·0	7·3	8·5	41·1	2·4	28·0	7·4	8·4
Cl	H	2,6-Br_2·C_6H_3	246–248	$C_{13}H_9Br_2ClN_2O_3S$	33·1	1·6	42·3[2]	6·0	7·3	33·3	1·9	41·7[2]	6·0	6·8
Cl	H	2,4,5-Cl_3·C_6H_2	262–264	$C_{13}H_8Cl_4N_2O_3S$	37·4	1·8	34·8	6·5	7·5	37·7	2·0	34·3	6·8	7·7
Cl	H	2,4,6-Cl_3·C_6H_2	205–206	$C_{13}H_8Cl_4N_2O_3S$	38·1	1·9	34·8	6·7	7·9	37·7	2·0	34·3	6·8	7·7
Cl	H	Ph·CH_2	186–187	$C_{14}H_{13}ClN_2O_3S$	52·1	3·6	11·3	9·0	10·2	51·8	4·0	10·9	8·6	9·9
Cl	H	Ph·CH_2·CH_2	172–174	$C_{15}H_{15}ClN_2O_3S$	53·3	4·5	10·1	7·8	9·4	53·2	4·5	10·5	8·3	9·5
Cl	Me	Me	135–136	$C_9H_{11}ClN_2O_3S$	41·2	4·3	13·3	10·8	12·0	41·2	4·2	13·5	10·7	12·2
Cl	Me	Ph	194–196	$C_{14}H_{13}ClN_2O_3S$	52·2	3·9	—	—	10·3	51·8	4·0	—	—	9·9
Cl	Me	*o*-Me·C_6H_4	188–190	$C_{16}H_{15}ClN_2O_3S$	53·2	4·2	10·6	8·2	9·3	53·2	4·5	10·5	8·3	9·5
Cl	Et	Ph	167–168	$C_{15}H_{15}ClN_2O_3S$	53·8	4·3	10·6	7·9	9·3	53·2	4·5	10·5	8·3	9·5
Cl	Et	*o*-Me·C_6H_4	178–180	$C_{16}H_{17}ClN_2O_3S$	54·7	5·0	10·2	8·0	8·9	54·5	4·9	10·1	7·9	9·1
Cl	Et	*o*-Cl·C_6H_4	173–175	$C_{15}H_{14}Cl_2N_2O_3S$	48·4	3·9	18·9	7·6	8·9	48·3	3·8	19·0	7·5	8·6
Cl	$-[CH_2]_5-$		178–180	$C_{12}H_{15}ClN_2O_3S$	47·4	4·7	11·9	9·4	10·6	47·6	5·0	11·7	9·3	10·6
Br	H	*o*-Me·C_6H_4	245–246	$C_{14}H_{13}BrN_2O_3S$	45·1	3·5	—	8·0	9·1	45·4	3·5	—	7·6	8·7
Br	H	*o*-Cl·C_6H_4	228–230	$C_{13}H_{10}BrClN_2O_3S$	40·0	2·4	—	7·4	8·5	40·1	2·6	—	7·2	8·2
Br	H	2,5-Cl_2·C_6H_3	226–228	$C_{13}H_9BrCl_2N_2O_3S$	37·1	2·2	35·0[2]	6·4	7·4	36·8	2·1	35·6[2]	6·6	7·6

1 = Bromine
2 = Total Halogen

TABLE IV

DERIVATIVES OF 2,4-DICHLOROBENZOIC ACID



R	R′	X	m.p. °C	Formula	Found C	Found H	Found Cl	Found N	Found S	Required C	Required H	Required Cl	Required N	Required S
H	H	NH_2·SO_2	216–217	$C_7H_6Cl_2N_2O_3S$	—	—	26·0	10·2	12·1	—	—	26·3	10·4	11·9
H	Me	NO_2	144–145	$C_8H_6Cl_2N_2O_3$	38·7	2·5	—	—	—	38·6	2·4	—	—	—
H	Me	NH_2	137–138	$C_8H_8Cl_2N_2O$	43·6	3·8	—	12·8	—	43·9	3·7	—	12·8	—
H	Me	Cl·SO_2	174–175	$C_8H_6Cl_3NO_3S$	32·2	2·2	34·9	4·6	10·3	31·8	2·0	35·1	4·6	10·6
H	Me	NH_2·SO_2	223–225	$C_8H_8Cl_2N_2O_3S$	34·2	2·8	25·0	10·1	11·8	33·9	2·9	25·0	9·9	11·3
Me	Me	NO_2	155–157	$C_9H_8Cl_2N_2O_3$	41·4	3·1	—	—	—	41·0	3·1	—	—	—
Me	Me	NH_2	149–150	$C_9H_{10}Cl_2N_2O$	46·6	4·4	30·2	12·5	—	46·3	4·3	30·4	12·0	—
Me	Me	Cl·SO_2	156–158	$C_9H_8Cl_3NO_3S$	—	—	33·8	4·2	10·1	—	—	33·6	4·4	10·1
Me	Me	NH_2·SO_2	243–245	$C_9H_{10}Cl_2N_2O_3S$	36·8	3·4	23·5	—	11·1	36·4	3·4	23·9	—	10·8

A few amides (cf. IV) of 2,4-dichloro-5-sulphamoylbenzoic acid were also prepared (cf. Table IV), but these had no diuretic activity at a dose level of 10 mg./kg. in saline-loaded rats.

Finally, three analogues of the most active benzanilides but with the halogen and sulphamoyl groups interchanged (cf. V; R = Me or Cl) were prepared by heating the 3-halogeno-4-sulphamoylbenzoic acid with *o*-toluidine or *o*-chloroaniline at reflux temperature in an atmosphere of nitrogen. They had no diuretic activity when administered to saline-loaded rats at doses of 10 mg./kg.

Most of the compounds described were less potent inhibitors of carbonic anhydrase than acetazolamide. There was again no apparent connection between inhibitory activity* against carbonic anhydrase and oral diuretic activity. Thus the carbonic anhydrase inhibitory activity of 4-chloro-2′-methyl-3-sulphamoylbenzanilide was 0·32 relative to acetazolamide (= 1·0), whilst that of the corresponding 4,2′-dichloro-3-sulphamoylbenzanilide was only 0·04. Both compounds were nevertheless approximately equi-effective oral diuretic agents and more potent than the other compounds listed in Table III.

EXPERIMENTAL

Most of the following examples illustrate methods of preparation used for the products listed in the tables, which also include the analyses.

N-4-*Dimethyl*-3-*sulphamoylbenzamide.* A solution of methyl 4-methyl-3-sulphamoylbenzoate (6·8 g.) in 33 per cent ethanolic methylamine (50 ml.) was kept at room temperature for 6 days when excess of amine was boiled off. The residue was dissolved in water and acidified with hydrochloric acid. The *product* (5·2 g.) had m.p. 219–221° after crystallisation from methanol.

4-*Chloro*-NN-*dimethyl*-3-*sulphamoylbenzamide.* (*a*) 3-*Amino*-4-*chloro*-NN-*dimethylbenzamide.* A mixture of 4-chloro-*NN*-dimethyl-3-nitrobenzamide (34·9 g.) and iron powder (35 g.) in 20 per cent ethanol (300 ml.) containing glacial acetic acid (3 ml.) was heated with stirring under reflux for 5 hr., and was then filtered hot. The oily product which separated was isolated with chloroform and purified by distillation. It (22 g.) had b.p. 174° at 1·0 mm. and m.p. 73–75° (from benzene).

(*b*) 4-*Chloro*-3-*chlorosulphonyl*-NN-*dimethylbenzamide.* A solution of the foregoing amine (17 g.) in 24 per cent hydrochloric acid (200 ml.) was diazotised at 5 to 10° by the addition of a solution of sodium nitrite (7 g.) in water (20 ml.) and the diazo solution added slowly with stirring to a saturated solution of sulphur dioxide in acetic acid (160 ml.) containing cupric chloride dihydrate (8·5 g.). Stirring was continued for 30 min. after the addition was complete. The solution was then diluted with ice-water and the sulphonchloride collected and drained. A portion, crystallised from benzene-light petroleum (b.p. 60–80°) had m.p. 106–108°.

* Determined with Mr. B. G. Overell, M.Sc., and Mrs. S. Ray.

(*c*) A solution of the foregoing sulphonchloride in chloroform (100 ml.) was added with stirring to ammonia solution (170 ml., d = 0·880) and stirring was continued for 30 min. after the addition was complete. Excess of ammonia and chloroform were then boiled off and the residue acidified with hydrochloric acid. The sulphonamide which separated had m.p. 145–146° after crystallisation from water.

4-*Chloro*-N-*isopropyl*-3-*sulphamoylbenzamide.* (*a*) 4-*Chloro*-3-*chlorosulphonylbenzoyl chloride.* A mixture of *p*-chlorobenzoic acid (156 g.), pentachloroethane (120 ml.) and chlorosulphonic acid (266 ml.) was heated under reflux for 4 hr., cooled and poured with stirring on to crushed ice. The solid was collected, washed with ice-cold water, dissolved in 1,2-dichloroethane, washed again with water and the organic layer dried with calcium chloride. The solution so obtained was added to thionyl chloride (140 ml.), dimethylformamide (10 ml.) added as catalyst, and the mixture heated under reflux for 2 hr. Excess of solvent was boiled off and the residual oil distilled at 1·5 mm. to yield the *diacid chloride* (80 per cent yield), b.p. 136–138° and m.p. 42–43° (from ether).

(*b*) 4-*Chloro*-3-*chlorosulphonyl*-N-*isopropylbenzamide.* A solution of the foregoing compound (13·7 g.) in toluene (130 ml.) was cooled to −20° and treated with stirring with a solution of isopropylamine (6·0 g.) in toluene (60 ml.). The mixture was allowed to warm up to 10°, and was then filtered to remove isopropylamine hydrochloride. Dilution of the filtrate with light petroleum furnished the *product* (10·8 g.), m.p. 117–119° after crystallisation from toluene-light petroleum (b.p. 60–80°).

(*c*) A solution of the foregoing sulphonchloride (9 g.) in chloroform (90 ml.) was added with stirring to ammonia solution (90 ml., d = 0·880) and stirring was continued for 30 min. after the addition was complete. Then the excess of chloroform and ammonia was boiled off. The residual *product* (7·6 g.) had m.p. 222–224° after crystallisation from aqueous methanol.

2′-*Methyl*-3-*sulphamoylbenzanilide.* A solution of *m*-sulphamoylbenzoic acid (40 g.) in *o*-toluidine (40 ml.) was heated at reflux temperature, with slow removal of the water formed, for 2 hr. After cooling, the residue was extracted with 10 per cent aqueous potassium hydroxide solution (100 ml.), the extract was diluted to 800 ml., boiled with charcoal and filtered hot. The filtrate was acidified and filtered hot. The residual *product* (39 g.) had m.p. 190–191° after crystallisation from aqueous ethanol.

4-*Chloro*-2′-*methyl*-3-*sulphamoylbenzanilide.* 1. (*a*) 4-*Chloro*-2′-*methyl*-3-*nitrobenzanilide.* A solution of *o*-toluidine (42·8 g.) in chloroform (50 ml.) was added below 15°, with stirring and cooling, to a solution of 4-chloro-3-nitrobenzoyl chloride (39·6 g.) in chloroform (250 ml.). The *product* was collected after a further 15 min.; it had m.p. 151–153° (after crystallisation from benzene). A small second crop of material

was obtained by concentration of the chloroform liquors (total yield, 47 g.).

(*b*) 3-*Amino*-4-*chloro*-2'-*methylbenzanilide*. A mixture of the foregoing nitro-compound (36·2 g.), iron powder (34 g.), water (250 ml.), ethanol (50 ml.) and acetic acid (2·5 ml.) was heated with stirring, under reflux, for 6 hr., and then filtered hot. The residual solid was extracted with boiling ethanol and the extract added to the filtrate. Concentration of the filtrate yielded the amine (24·2 g.), m.p. 160–162° after crystallisation from aqueous ethanol.

(*c*) 4-*Chloro*-3-*chlorosulphonyl*-2'-*methylbenzanilide*. A solution of the foregoing amine (23·8 g.) in 24 per cent hydrochloric acid (200 ml.) was diazotised at 0–5° by the addition of a solution of sodium nitrite (6·3 g.) in water (15 ml.), and the solution added dropwise, with stirring, at 20–25° to a saturated solution of sulphur dioxide in acetic acid (250 ml.) containing cupric chloride dihydrate. Stirring was continued for a further 30 min. and precipitation of the sulphonchloride was completed by dilution with ice-water. It was collected, washed with ice-water and drained. A sample, crystallised from chloroform-light petroleum (b.p. 60–80°), had m.p. 161–163°.

(*d*) A suspension of the foregoing sulphonchloride (40 g.) in chloroform (200 ml.) was added with stirring to aqueous ammonia (400 ml., d = 0·880) and the stirring continued for 1 hr. after the addition was complete. The sulphonamide separated and was collected. It had m.p. 240–242° after crystallisation from aqueous ethanol. The overall yield in the last two stages was 55 per cent.

2. 4-*Chloro*-3-*chlorosulphonyl*-2'-*methylbenzanilide*. (*a*) *o*-Toluidine (107 g.) was added gradually with stirring to a solution of 4-chloro-3-chlorosulphonylbenzoyl chloride (273 g.) in chlorobenzene (1,650 ml.) and the mixture heated under reflux for about 45 min. The solution was cooled slightly and diluted with light petroleum (b.p. 80–100°) until crystallisation began. The *product* (296 g.) had m.p. 162–163° after crystallisation from chlorobenzene-light petroleum (b.p. 60–80°). It was identical with the product described in 1 (*c*).

(*b*) *o*-Toluidine hydrochloride (7·1 g.) was mixed with 4-chloro-3-chlorosulphonylbenzoyl chloride (13·6 g.) in chlorobenzene (200 ml.), and the mixture was heated at reflux temperature for 40 min. The sulphonchloride (14·6_6 g.), isolated by dilution with light petroleum, had m.p. 162–163°.

3. 4-*Chloro*-2'-*methyl*-3-*sulphamoylbenzanilide*. A solution of 4-chloro-3-sulphamoylbenzoic acid (11·8 g.) in *o*-toluidine (20 ml.) was heated in an atmosphere of nitrogen at 190–200° for 1·5 hr., and poured with stirring into 2N hydrochloric acid. The solid was purified by recrystallisation from 50 per cent ethanol to yield the product (7 g.), m.p. 238–239°, which was not depressed on admixture with the material described under 1 (*d*).

4-*Chloro*-3,4′-*disulphamoylbenzanilide.* To a stirred mixture of sulphanilamide (8·6 g.) and anhydrous sodium acetate (4·0 g.) in glacial acetic acid (50 ml.) at 70–80° was slowly added a solution of 4-chloro-3-chlorosulphonylbenzoyl chloride (13·6 g.) in acetic acid (27 ml.). Enough water was added to dissolve sodium chloride and the *sulphonchloride* crystallised on cooling. It was collected, washed with cold water, and added in portions with stirring to ammonia solution (300 ml., d = 0·880). When the addition was complete, excess of ammonia was boiled off; the disulphonamide then separated on cooling. It had m.p. 294–296° after crystallisation from aqueous ethanediol.

2′-*Carboxy*-4-*chloro*-3-*sulphamoylbenzanilide.* (*a*) A mixture of anthranilic acid (6·9 g.) and anhydrous sodium acetate (4·1 g.) in acetic acid (70 ml.) was heated to 80°, treated with a solution of 4-chloro-3-chlorosulphonylbenzoyl chloride (13·6 g.) in acetic acid (20 ml.), and the whole heated to 110° to complete the reaction.The crude *sulphonchloride*, isolated by dilution, was added to ammonia solution (150 ml., d = 0·880) and excess of ammonia was then boiled off. Acidification of the residual liquid yielded the product (10 g.), m.p. 264–266° (decomp.) after crystallisation from aqueous ethanediol.

(*b*) 4-Chloro-2′-methoxycarbonyl-3-sulphamoylbenzanilide (13·8 g.) was dissolved in warm 0·5N sodium hydroxide (200 ml.) and the solution left overnight at room temperature. Acidification furnished the product (12 g.). It had m.p. 264–266° (decomp.) after crystallisation from 30 per cent aqueous dimethylformamide. The m.p. was not depressed on admixture with the compound prepared in (*a*).

4-*Chloro*-2′-*methyl*-3-*methylsulphamoylbenzanilide.* A solution of 4-chloro-3-chlorosulphonyl-2′-methylbenzanilide (11·2 g.) in chloroform (180 ml.) was added with stirring and cooling below 10° to 10 per cent aqueous methylamine solution (100 ml.) and stirring was continued for 30 min. after the addition was complete. The product (8·4 g.) was collected and had m.p. 223–224° after crystallisation from aqueous methanol. Found: C, 53·2; H, 4·3; N, 8·2; S, 9·8. $C_{15}H_{15}ClN_2O_3S$ requires C, 53·2; H, 4·5; N, 8·3; S, 9·5 per cent.

4-*Chloro*-3-*ethylsulphamoyl*-2′-*methylbenzanilide* had m.p. 161–162° after crystallisation from toluene. Found: C, 54·5; H, 4·8; Cl, 9·9; N, 8·1; S, 9·2. $C_{16}H_{17}ClN_2O_3S$ requires C, 54·5; H, 4·9; Cl, 10·1; N, 7·9; S, 9·1 per cent.

4-*Chloro*-3-*dimethylsulphamoyl*-2′-*methylbenzanilide* had m.p. 134–136° after crystallisation from methanol. Found: C, 54·7; H, 4·7; Cl, 10·0; N, 8·1; S, 9·1. $C_{16}H_{17}ClN_2O_3S$ requires C, 54·5; H, 4·9; Cl, 10·1; N, 7·9; S, 9·1 per cent.

3-*Bromo*-2′-*methyl*-4-*sulphamoylbenzanilide.* A solution of 3-bromo-4-sulphamoylbenzoic acid (4 g.) in *o*-toluidine (10 ml.) was heated under reflux in an atmosphere of nitrogen for 2 hr., the mixture cooled somewhat and poured with stirring into dilute hydrochloric acid. The resultant

solid was dissolved in dilute sodium hydroxide solution, brought to pH 10 with acetic acid and filtered hot. The insoluble *product* was washed with hot water. It (2 g.) had m.p. 220–222° after crystallisation from aqueous methanol. Found: C, 45·5; H, 3·7; Br, 21·6; N, 7·3. $C_{14}H_{13}BrN_2O_3S$ requires C, 45·5; H, 3·5; Br, 21·7; N, 7·6 per cent.

3-*Bromo*-2′-*chloro*-4-*sulphamoylbenzanilide* had m.p. 226–228° after crystallisation from aqueous ethanol. Found: C, 40·4; H, 2·9; N, 6·8; S, 7·9. $C_{13}H_{10}BrClN_2O_3S$ requires C, 40·1; H, 2·6; N, 7·2; S, 8·2 per cent.

3-*Chloro*-2′-*methyl*-4-*sulphamoylbenzanilide.* A solution of 3-chloro-4-sulphamoylbenzoic acid (10 g.) in *o*-toluidine (45 ml.) was distilled over 1 hr. under nitrogen to remove most of the base, last traces of which were distilled off at reduced pressure. The residual solid was dissolved in 0·5N sodium hydroxide solution (500 ml.), heated to near boiling and filtered hot. The insoluble *product* (4·1 g.) had m.p. 218–220° after crystallisation from aqueous ethanol. Found: C, 52·1; H, 4·3; N, 9·1; S, 10·1. $C_{14}H_{13}ClN_2O_3S$ requires C, 51·8; H, 4·0; N, 8·6; S, 9·9 per cent.

REFERENCES

Barr, C. R., Salminen, I. F. and Weissberger, A. (1951). *J. Amer. chem. Soc.*, **73**, 4131–4133.
Jackman, G. B., Petrow, V., Stephenson, O. and Wild, A. M. (1962). *J. Pharm. Pharmacol.*, **14**, 679–686.
Montagne, P. J. (1900). *Rec. Trav. chim.*, **19**, 46–78.
Petrow, V., Stephenson, O. and Wild, A. M. (1960). *J. Pharm. Pharmacol.*, **12**, 705–719.
Smiles, S. and Stewart, J. (1921). *J. chem. Soc.*, **119**, 1792–1798.
Ullmann, H. M. (1894). *Amer. chem. J.*, **16**, 530–543.
Wegscheider, R. and Furcht, M. (1902). *Monatsh.*, **23**, 1093–1146.