STUDIES IN THE FIELD OF DIURETIC AGENTS

PART VIII. SOME MISCELLANEOUS DERIVATIVES

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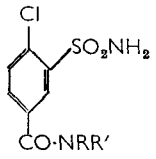
From The British Drug Houses, Ltd., Graham Street, London, N.1

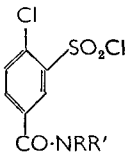
Received October 9, 1962

New derivatives of 4-chloro-3-sulphamoylbenzoic acid and of 4-chloro-3-sulphamoylaniline are described along with some formally related quinazolones.

THE preparation of alkyl, dialkyl and heterocyclic amides of 4-chloro-3-sulphamoylbenzoic acid (I; R = H or alkyl, R′ = alkyl or aralkyl or NRR′ = heterocyclic radical) (compare Petrow, Stephenson and Wild, 1963) is extended herein. It was found that 4-chloro-3-chloro-sulphonylbenzoyl chloride reacted readily with the hydrochlorides of alkyl, dialkyl and heterocyclic amines in chlorobenzene at reflux temperature to give high yields of the intermediate 4-chloro-3-chlorosulphonylbenzamides (II). Even when up to 3 moles of the amine hydrochloride was employed and the heating period extended to 5 hr. no attack upon the sulphonochloride group was found to occur. Subsequent reaction of the sulphonchloride with ammonia furnished the sulphonamides listed in Table I.



(I)



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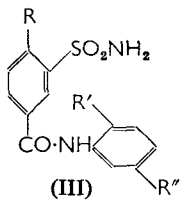
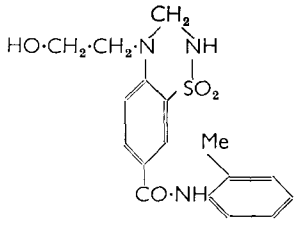
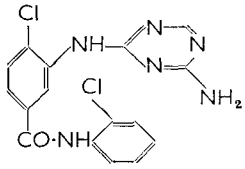


(III)

We had previously found that replacement of the chlorine atom in 5-chlorotoluene-2,4-disulphonamide by the 2-hydroxyethylamino-group yielded a water-soluble compound of equal diuretic potency. We consequently treated 4-chloro-2′-methyl-3-sulphamoylbenzanilide (III; R = Cl, R′ = Me, R″ = H) (Petrow and others, 1963) with 2-aminoethanol when smooth reaction occurred to give 4-(2-hydroxyethylamino)-2′-methyl-3-sulphamoylbenzanilide (III; R = NH·CH$_2$·CH$_2$·OH, R′ = Me, R″ = H) in high yield. This compound condensed with formaldehyde, as described earlier (Jackman, Petrow, Stephenson and Wild, 1960), to yield the 3,4-dihydrobenzothiadiazine derivative (IV).

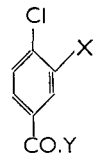


(IV)



(V)

TABLE I

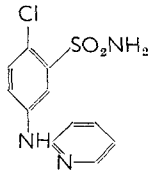


X	Y	m.p. °C	Formula	Found					Required				
				C	H	Cl	N	S	C	H	Cl	N	S
SO_2NH_2	C_4H_9·NH	171–172	$C_{11}H_{15}ClN_2O_3S$	45·2	4·7	12·1	9·7	11·2	45·4	5·2	12·2	9·6	11·0
SO_2Cl	Ph.CH_2.NH	150–152	$C_{14}H_{11}Cl_2NO_3S$	—	—	20·9	4·1	9·0	—	—	20·6	4·1	9·3
SO_2NH_2	Ph.CH_2.NH	185–187	$C_{14}H_{15}ClN_2O_3S$	51·7	4·2	10·9	8·8	10·1	51·8	4·0	10·9	8·6	9·9
SO_2NH_2	Me_2N	134–136	$C_9H_{11}ClN_2O_3S$	41·0	4·2	13·6	10·8	12·3	41·1	4·2	13·5	10·7	12·2
SO_2NH_2	Et_2N	174–176	$C_{11}H_{16}ClN_2O_3S$	45·5	5·3	12·3	9·6	10·7	45·4	5·2	12·2	9·6	11·0
SO_2Cl	Pyrrolidin-1-yl	153–155	$C_{11}H_{11}Cl_2NO_3S$	42·5	3·6	—	4·8	—	42·9	3·6	—	4·5	—
SO_2NH_2	Pyrrolidin-1-yl	191–192	$C_{11}H_{13}ClN_2O_3S$	45·6	4·5	—	9·7	11·3	45·8	4·5	—	9·7	11·1
SO_2Cl	1,2,3,6-Tetrahydropyrid-1-yl	115	$C_{12}H_{11}Cl_2NO_3S$	—	—	21·7	4·4	10·0	—	—	22·2	4·4	10·0
SO_2NH_2	1,2,3,6-Tetrahydropyrid-1-yl	157–159	$C_{12}H_{13}ClN_2O_3S$	47·6	4·3	—	8·8	—	47·9	4·4	—	9·3	—
SO_2Cl	Morpholino	131–133	$C_{11}H_{11}Cl_2NO_4S$	40·9	3·1	—	4·6	—	40·8	3·4	—	4·3	—
SO_2NH_2	Morpholino	230–231	$C_{11}H_{13}ClN_2O_4S$	43·1	4·2	11·2	—	—	43·4	4·3	11·6	—	—
SO_2Cl	Hexamethyleneimino-(Perhydroazepin-1-yl)	100	$C_{13}H_{15}Cl_2NO_3S$	—	—	—	4·5	—	—	—	—	4·2	—
SO_2NH_2	Hexamethyleneimino (Perhydroazepin-1-yl)	160–162	$C_{13}H_{17}ClN_2O_3S$	48·8	5·5	11·4	8·7	10·2	49·3	5·4	11·2	8·8	10·1

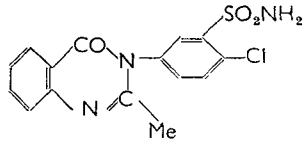
The effect of replacing the sulphamoyl group in the benzanilides (I; R = H, R′ = *o*-tolyl, *o*-chlorophenyl or 2,5-dichlorophenyl) by basic residues was next examined. The starting material in each case was the appropriate 3-amino-4-chlorobenzanilide (Petrow and others, 1963). The amino-group was replaced by an alkyl-ureido-group or by a biguanido-group, and in one case the biguanide was converted into the triazine (V) by reaction with formic acid.

The noteworthy diuretic activity possessed by 4-chloro-3-sulphamoylbenzoic acid (Jackman, Petrow, Stephenson and Wild, 1962) prompted further study of the effect of replacing the carboxyl group in this compound by other groups. With this object in view, 4-chloro-3-sulphamoylaniline (Petrow and others, 1960) was converted into acyl, aroyl [including 2-substituted aroyl derivatives which bear strong formal resemblance to the active benzanilide diuretics (III; R = Cl, R′ = Cl or Me and R″ = H or Cl)], succinoyl, phthaloyl, arylsulphonyl and ethoxycarbonyl derivatives. In addition the amino-group in 4-chloro-3-sulphamoylaniline was replaced by ureido-, substituted ureido-carbamoylureido-, and biguanido-groups. The latter derivative was converted into an amino-*s*-triazine by reaction with formic acid. Reaction of the amine with 2-bromo- or 2-chloro-pyridine furnished the 4-(2-aminopyridyl) derivative (VI).

Extending our earlier work on quinazolones (Jackman, Petrow and Stephenson, 1960) the synthesis of 2-methyl-3-(4-chloro-3-sulphamoylphenyl)-3*H*-4-quinazolone (VII) was carried out by reaction of acetanthranil with 4-chloro-3-sulphamoylaniline. The related 2-methyl-3-(4-sulphamoylphenyl)-3*H*-4-quinazolone was also prepared by reaction of *o*-acetamidobenzoic acid with 4-aminobenzenesulphonamide in pyridine, using benzenesulphonyl chloride as condensing agent (Jackman, Petrow and Stephenson, 1960).



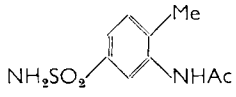
(VI)



(VII)

Quinazolone derivatives containing a sulphamoyl group in the aromatic nucleus were next studied. 2-Methyl-7-sulphamoyl-3*H*-4-quinazolone (VIII) was prepared *via* acet-*o*-toluidide. This was chlorosulphonated and thence converted into the 4-sulphonamide (IX). The structure of the latter was proved by (*a*) hydrolysis and deamination to toluene-*p*-sulphonamide and (*b*) identity with the compound prepared by an unambiguous route (Petrow, Stephenson and Wild, 1960). Oxidation of the sulphonamide with alkaline potassium permanganate gave 2-acetamido-4-sulphamoylbenzoic acid (X), converted by acetic anhydride-acetic acid into 2-methyl-7-sulphamoyl-4*H*-3,1-benzoxaz-4-one (XI), which yielded the required quinazolone (VIII) on treatment with ammonia.

Inter alia 7-sulphamoylquinazol-2,4-dione (XII) was prepared by reaction of 2-amino-4-sulphamoylbenzoic acid with potassium cyanate in acid medium.



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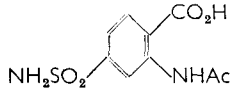
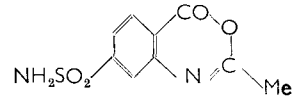


(X)



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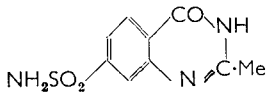

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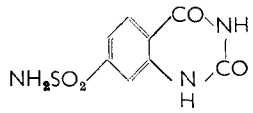
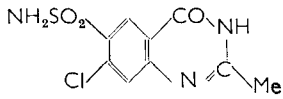
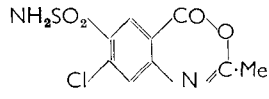


(XII)

Finally, we synthesised 7-chloro-2-methyl-6-sulphamoyl-3*H*-4-quinazolone (XIII), a compound more closely related to chlorothiazide. The synthesis employed 2-acetamido-4-chloro-5-sulphamoylbenzoic acid as starting material and proceeded *via* 7-chloro-2-methyl-6-sulphamoyl-4*H*-3,1-benzoxaz-4-one (XIV). Whilst this work was in progress the preparation of the quinazolone (XIII) by a similar process was reported by Cohen, Klarberg and Vaughan (1959, 1960).



(XIII)



(XIV)

Biological study of the above compounds by Dr. A. David and his colleagues failed to reveal a product superior to 4-chloro-2′-methyl-3-sulphamoylbenzanilide in diuretic potency.

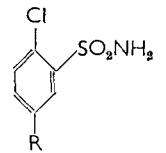
Experimental

A few of the compounds described below are included in the Tables (I and II) and in these cases analytical data is omitted.

4-*Chloro*-3-*sulphamoylbenzdiethylamide.* (*a*) A solution of 4-chloro-3-chlorosulphonylbenzoyl chloride (18·2 g.) in chlorobenzene (60 ml.) was treated with diethylamine hydrochloride (7·3 g.) and the mixture boiled under reflux for 2·5 hr.; the excess of chlorobenzene was then distilled off at reduced pressure. The residual oil was dissolved in chloroform (50 ml.) and the solution added with stirring to liquid ammonia (200 ml.). The ammonia and chloroform were boiled off, the residue dissolved in water (200 ml.) and the solution acidified with hydrochloric acid. The *product* (16·5 g.) had m.p. 174–176° (from ethanol).

(*b*) A solution of 4-chloro-3-chlorosulphonylbenzoyl chloride (18·2 g.) in chlorobenzene (60 ml.) was treated with diethylamine hydrochloride (21·9 g. = 3 mole. equivs.) and the mixture boiled under reflux for 5 hr. The reaction was then completed as in (*a*) to yield the same *product* (16·7 g.), m.p. 174 to 176° (from ethanol).

TABLE II



R	m.p. ° C	Formula	Found					Required				
			C	H	Cl	N	S	C	H	Cl	N	S
NH_2·HCl	236 (*d*)	$C_6H_8Cl_2N_2O_2S$	29·7	3·5	—	—	—	29·6	3·3	—	—	—
N:CH·Ph	146–148	$C_{13}H_{11}ClN_2O_2S$	53·0	3·9	12·2	9·6	—	52·9	3·8	12·0	9·5	—
NH·Ac	252–253	$C_8H_9ClN_2O_3S$	38·6	3·4	—	11·4	12·9	38·6	3·7	—	11·3	12·9
NH·CO·$CHCl_2$	199–200	$C_8H_7Cl_3N_2O_3S$	30·6	2·4	33·6	9·1	—	30·2	2·2	33·5	8·8	—
NH·CO·Ph	281(*d*)	$C_{13}H_{11}ClN_2O_3S$	50·5	3·6	11·6	9·1	10·6	50·2	3·6	11·4	8·8	10·3
NH·CO·C_6H_4·Me(*o*)	181–182	$C_{14}H_{13}ClN_2O_3S$	51·6	4·2	—	9·0	10·3	51·8	4·0	—	8·6	9·9
NH·CO·C_6H_4·Cl(*o*)	210	$C_{13}H_{10}Cl_2N_2O_3S$	45·2	2·7	—	8·1	9·4	45·2	2·9	—	8·1	9·3
NH·CO·C_6H_4·Cl(*p*)	288–289	$C_{13}H_{10}Cl_2N_2O_3S$	45·0	2·6	20·2	7·8	—	45·2	2·9	20·6	8·1	—
NH·CO·CH_2·CH_2·COOH	214(*d*)	$C_{10}H_{11}ClN_2O_5S$	39·4	3·9	11·7	9·2	—	39·1	3·6	11·6	9·1	—
Phthalimido	264–265	$C_{14}H_9ClN_2O_4S$	49·8	3·1	10·7	8·3	—	49·9	2·7	10·5	8·3	—
NH·SO_2·Ph	184–185	$C_{12}H_{11}ClN_2O_4S_2$	41·6	3·0	10·5	8·1	18·1	41·5	3·2	10·2	8·1	18·5
NH·CO·OEt	199–201	$C_9H_{11}ClN_2O_4S$	39·2	4·3	—	10·3	11·5	38·8	4·0	—	10·1	11·5
NH·CO·NH_2	195–196(*d*)	$C_7H_8ClN_3O_3S$	33·4	3·3	—	16·8	13·1	33·7	3·2	—	16·8	12·8
NH·CO·NH·Pr(n)	218	$C_{10}H_{14}ClN_3O_3S$	41·3	4·9	12·2	14·1	—	41·2	4·8	12·2	14·4	—
NH·CO·NH·Bu(n)	189–190	$C_{11}H_{16}ClN_3O_3S$	43·4	5·3	11·4	13·7	—	43·2	5·3	11·6	13·7	—
NH·CO·NH·Bu(s)	181–182	$C_{11}H_{16}ClN_3O_3S$	43·1	4·9	11·6	13·9	—	43·2	5·3	11·6	13·7	—
NH·CO·NH·C_6H_{11}	203–204	$C_{13}H_{18}ClN_3O_3S$*	46·7	5·6	10·6	12·4	—	47·0	5·5	10·7	12·7	—
NH·CO·NH·Ph	222–223	$C_{13}H_{12}ClN_3O_3S$	48·0	3·6	—	12·8	—	47·9	3·7	—	12·9	—
NH·CO·NH·CO·NH_2	232–233(*d*)	$C_8H_9ClN_4O_4S$	32·7	2·8	12·0	19·4	—	32·8	3·1	12·1	19·1	—
NH·C(:NH)·NH·C(:NH)·NH_2·HCl	226	$C_8H_{13}Cl_2N_6O_2S$	29·2	4·0	21·6	25·8	—	29·4	3·7	21·7	25·7	—
4-Amino-1,3,5-triazin-2-yl hydrochloride	297(*d*)	$C_9H_{10}Cl_2N_4O_2S$	32·0	2·9	20·9	—	9·6	32·0	3·0	21·1	—	9·5
Pyrid-2-ylamino	252–253	$C_{11}H_{10}ClN_3O_2S$	46·4	3·3	12·8	14·9	11·5	46·5	3·6	12·5	14·8	11·3

* Compound readily forms a monohydrate.

4-*Chloro*-3-*chlorosulphonylbenzmorpholide.* A solution of 4-chloro-3-chlorosulphonylbenzoyl chloride (18·2 g.) in chlorobenzene (60 ml.) was treated with morpholine hydrochloride (8·25 g.) and the mixture heated under reflux for 2 hr.; the excess of chlorobenzene was then distilled off at reduced pressure. Crystallisation of the residue from 1,2-dichloroethane-light petroleum (b.p. 60 to 80°) yielded the *product* (19·0 g.), m.p. 131–133°.

4-*Chloro*-3-*sulphamoylbenzmorpholide.* The foregoing sulphonchloride (17 g.) was added with stirring to liquid ammonia (200 ml.) and the excess of ammonia was boiled off. The residue was dissolved in water and the solution acidified with hydrochloric acid to yield the *product* (15·3 g.), m.p. 230–231° (from aqueous ethanol).

4-*Chloro*-3-*dimethylsulphamoylbenzdimethylamide.* 4-Chloro-3-chlorosulphonylbenzoyl chloride (9·1 g.) was added in portions to aqueous dimethylamine (36 ml., 25 per cent w/v) and, after the addition was complete, excess of amine was boiled off. Crystallisation of the residue from acetone–light petroleum (b.p. 60–80°) yielded the *product* (7·25 g.), m.p. 92–93°. Found: C, 45·4; H, 5·1; Cl, 12·3; N, 9·6; S, 10·6. $C_{11}H_{15}ClN_2O_3S$ requires C, 45·4; H, 5·2; Cl, 12·2; N, 9·6; S, 11·0 per cent.

4-(2-*Hydroxyethylamino*)-2′-*methyl*-3-*sulphamoylbenzanilide.* A solution of 4-chloro-2′-methyl-3-sulphamoylbenzanilide (20 g.) in 2-hydroxyethylamine (20 ml.) was heated at 120° for 4 hr. and the excess of amine was then distilled off at reduced pressure. The residue was dissolved in aqueous ethanol and acidified with dilute hydrochloric acid. The *product* (19·35 g.) had m.p. 171–172° (from aqueous ethanol). Found: C, 54·6; H, 5·1; N, 12·0; S, 8·8. $C_{16}H_{19}N_3O_4S$ requires C, 55·0; H, 5·5; N, 12·0; S, 9·2 per cent.

3,4-*Dihydro*-4-(2-*hydroxyethyl*)-7-o-*tolylcarbamoyl*-1,2,4-*benzothiadiazine* 1,1-*dioxide.* A solution of the foregoing compound (7 g.) in 2-ethoxyethanol (50 ml.) was treated with 40 per cent formaldehyde solution (2 ml.) and a saturated solution of hydrogen chloride in 2-ethoxyethanol (1 ml.) added as catalyst. The mixture was heated under reflux for 1 hr., and the excess of solvent was then distilled off at reduced pressure. The residual solid was crystallised from 25 per cent ethanol to yield the *product*, m.p. 242–243°. Found: C, 56·5; H, 5·3; N, 11·6; S, 8·9. $C_{17}H_{19}N_3O_4S$ requires C, 56·4; H, 5·3; N, 11·6; S, 8·9 per cent.

4,2′-*Dichloro*-3-*nitrobenzanilide.* A solution of 4-chloro-3-nitrobenzoyl chloride (40 g.) in chloroform (250 ml.) was stirred and treated with a solution of *o*-chloroaniline (51 g.) in chloroform (100 ml.) during 20 min. with cooling below 15°. After 1 hr. water was added to dissolve the *o*-chloroaniline hydrochloride and the *product* (43·6 g.) was collected. Concentration of the chloroform layer yielded a further crop of 16·2 g. It had m.p. 140° (from aqueous ethanol). Found: C, 50·4; H, 2·4; Cl, 22·8; N, 8·9. $C_{13}H_8Cl_2N_2O_3$ requires C, 50·2; H, 2·6; Cl, 22·8; N, 9·0 per cent.

3-*Amino*-4,2′-*dichlorobenzanilide.* A solution of the foregoing nitrocompound (54 g.) in ethanol (100 ml.), water (400 ml.) and acetic acid

(3 ml.) was heated with stirring under reflux and iron powder (50 g.) added in portions during 30 min. The mixture was heated for 5 hr. and filtered hot. The product (29·4 g.) separated on cooling and had m.p. 144° (from aqueous ethanol). Found: C, 55·3; H, 3·8; N, 9·9. $C_{13}H_{10}Cl_2N_2O$ requires C, 55·5; H, 3·6; N, 10·0 per cent.

4,2′,5′-*Trichloro*-3-*nitrobenzanilide* was obtained in 90 per cent yield by reaction of 4-chloro-3-nitrobenzoyl chloride with 2,5-dichloroaniline in chloroformic solution. It had m.p. 177–178° (from aqueous ethanol). Found: C, 45·3; H, 1·9; Cl, 30·8; N, 8·1. $C_{13}H_7Cl_3N_2O_3$ requires C, 45·2; H, 2·0; Cl, 30·8; N, 8·1 per cent.

3-*Amino*-4,2′,5′-*trichlorobenzanilide*, obtained by reduction of the foregoing nitro-compound, had m.p. 167–168° (from aqueous ethanol). Found: Cl, 33·5; N, 8·6. $C_{13}H_9Cl_3N_2O$ requires Cl, 33·7; N, 8·9 per cent.

3-(3-*Butylureido*)-4-*chloro*-2′-*methylbenzanilide*. A mixture of 3-amino-4-chloro-2′-methylbenzanilide (5·2 g.) and butyl *iso*cyanate (5 g.) in dioxan (10 ml.) was heated on the steam-bath for 10 hr. The dioxan was distilled off under reduced pressure and the residual solid crystallised from aqueous methanol to yield the *product*, m.p. 192–194°. Found: C, 63·1; H, 5·8; Cl, 10·3; N, 11·7. $C_{19}H_{22}ClN_3O_2$ requires C, 63·4; H, 6·2; Cl, 9·9; N, 11·7 per cent.

3-(3-*s*-*Butylureido*)-4-*chloro*-2′-*methylbenzanilide* had m.p. 215° (from aqueous ethanol). Found: C, 63·2; H, 6·1; N, 11·9 per cent.

3-(3-*Butylureido*)-4,2′-*dichlorobenzanilide*, obtained by reaction of 3-amino-4,2′-dichlorobenzanilide with butyl *iso*cyanate in dioxan, had m.p. 171–172° (from aqueous methanol). Found: C, 56·4; H, 5·0; Cl, 18·4; N, 11·0. $C_{18}H_{19}Cl_2N_3O_2$ requires C, 56·9; H, 5·0; Cl, 18·6; N, 11·1 per cent.

3-*Biguanido*-4,2′-*dichlorobenzanilide hydrochloride*. A solution of 3-amino-4,2′-dichlorobenzanilide (28·1 g.) in ethanol (50 ml.) was treated with dicyandiamide (8·4 g.), followed by a solution of hydrogen chloride (4 g.) in ethanol (20 ml.). The mixture was heated under reflux for 90 min. After cooling, the *product* (22 g.) was collected. It had m.p. 245–247° (from ethanol). Found: C, 45·3; H, 3·7; Cl, 26·7; N, 20·9. $C_{15}H_{15}Cl_3N_6O$ requires C, 44·8; H, 3·8; Cl, 26·5; N, 20·9 per cent.

3-(4-*Amino*-1,3,5-*triazin*-2-*ylamino*)-4,2′-*dichlorobenzanilide*. A solution of the foregoing biguanide hydrochloride (10·05 g.) in formic acid (40 ml.) was heated under reflux for 2 hr., and the excess of formic acid was then distilled off at reduced pressure. The *product* (9·8 g.) had m.p 214–215° (from aqueous methanol). Found: C, 51·3; H, 3·0; N, 22·2. $C_{16}H_{12}Cl_2N_6O$ requires C, 51·2; H, 3·2; N, 22·4 per cent.

N-(4-*Chloro*-3-*sulphamoylphenyl*)*phthalimide*. Phthalic anhydride (7·4 g.) was added during 10 min. to a stirred suspension of 4-chloro-3-sulphamoylaniline (10·3 g.) in water (200 ml.) at 80–90°, and the heating was continued for 6 hr. After cooling, the *product* (12·5 g.) was collected. It had m.p. 264–265° (from aqueous acetone).

4′-*Chloro*-3′-*sulphamoylbenzenesulphonanilide*. Benzenesulphonyl chloride (7·1 g.) was added in portions with cooling to a solution of 4-chloro-3-sulphamoylaniline (8·3 g.) in pyridine (30 ml.). The mixture was

warmed for 15 min. then cooled, diluted with ice-water and acidified with hydrochloric acid. The *product* (10·6 g.) had m.p. 184–185° (from ethanol-benzene).

1-(4-*Chloro*-3-*sulphamoylphenyl*)*biuret*. A solution of 4-chloro-3-sulphamoylaniline (10·3 g.) in water (100 ml.) and ethanol (70 ml.) was heated to 90° and treated with nitrobiuret (10 g.), added during 5 min. Heating was continued for 2 hr. and most of the ethanol was allowed to evaporate. The *product* (10 g.) separated out on cooling. It had m.p. 232–233° (decomp.) (from aqueous ethanol).

2-(4-*Chloro*-3-*sulphamoylanilino*)*pyridine*. A mixture of 4-chloro-3-sulphamoylaniline (10·3 g.) and 2-chloropyridine (5·7 g.) was heated at 165° for 2 hr. The dark residue was dissolved in 80 per cent ethanol and buffered with sodium acetate. The *product* (12 g.) had m.p. 252–253° (from ethanol containing a trace of acetone). Use of 2-bromopyridine in place of 2-chloropyridine gave a somewhat lower yield of product.

3-(4-*Chloro*-3-*sulphamoylphenyl*)-2-*methyl*-3H-4-*quinazolone*. A mixture of 4-chloro-3-sulphamoylaniline (5·17 g.) and acetanthranil (4 g.) was heated at 130° for 3 hr. The resinous residue solidified on boiling with ethanol. The *product* had m.p. 295–296° (from aqueous ethoxyethanol). Found: C, 51·5; H, 3·4; Cl, 10·4; N, 12·2; S, 9·5. $C_{15}H_{12}ClN_3O_3S$ requires C, 51·5; H, 3·5; Cl, 10·1; N, 12·0; S, 9·2 per cent.

2-*Acetamido*-4-*sulphamoyltoluene*. Acet-*o*-toluidide (292 g.) was added slowly with stirring to chlorosulphonic acid (1165 g.) with cooling to keep reaction temperature below 80° and the mixture was kept at 70–75° for 3 hr. It was then cooled and poured into ice water. The crude sulphonchloride was washed with water, drained and added to liquid ammonia (2 litres). After the ammonia had evaporated the residue was dissolved in water (1 litre) and the solution acidified to pH 4 with hydrochloric acid. The *product* (124 g.) was crystallised from water and then from glacial acetic acid; it had m.p. 230–232° (decomp.).

The foregoing compound (4·6 g.) was refluxed with acetic anhydride (14 ml.) for 1 hr. The solid *triacetyl* derivative (4·9 g.) had m.p. 223–225° after crystallisation from a large volume of water. Found: C, 49·6; H, 5·0; N, 9·1; S, 10·0. $C_{13}H_{16}N_2O_5S$ requires C, 50·0; H, 5·2; N, 9·0; S, 10·3 per cent. The *diacetyl* derivative, m.p. 231–233° (from water) was obtained by refluxing the *monoacetyl* derivative (4·6 g.) with acetic acid (22 ml.) and acetic anhydride (5·5 ml.) for 30 min. or by boiling the triacetyl derivative (1·5 g.) with water (450 ml.) for 4 hr. Found: C, 48·5; H, 5·0; N, 10·5; S, 12·2. $C_{11}H_{14}N_2O_4S$ requires C, 48·9; H, 5·2; N, 10·3; S, 11·9 per cent. Hydrolysis of 2-acetamidotoluene-4-sulphonamide (46 g.) with 5N sodium hydroxide solution (500 ml.) for $2\frac{1}{2}$ hr. yielded 2-aminotoluene-4-sulphonamide (26 g.), m.p. 177–179° (from water). A solution of the amine (4·6 g.) in water (50 ml.) and concentrated hydrochloric acid (7 ml.) was diazotised at 5° by the addition of a solution of sodium nitrite (1·8 g.) in water (10 ml.). The diazo-solution was cooled to 0–5° and treated with 40–50 per cent hypophosphorous acid (44 ml.). After several hours the solid (3·4 g.) which had separated was

collected. It had m.p. 135–137°, not depressed on admixture with *toluene*-p-*sulphonamide*.

2-*Acetamido*-4-*sulphamoylbenzoic acid*, prepared in 45 per cent yield by oxidation of 2-acetamidotoluene-4-sulphonamide with potassium permanganate (6·7 mole) in aqueous alkaline solution at below 80°, had m.p. 230° (decomp.) (from water). Found: N, 10·9; S, 12·5. Calc. for $C_9H_{10}N_2O_5S$: N, 10·8; S, 12·4 per cent.

2-*Methyl*-7-*sulphamoyl*-4H-3,1-*benzoxaz*-4-*one*. The foregoing acid (2·6 g.) was heated under reflux with acetic acid (8 ml.) and acetic anhydride (1·9 ml.) for 20 min. The *product* had m.p. 218° (decomp.) (from acetic acid-acetic anhydride [4:1]). Found: C, 44·8; H, 3·6; S, 13·0. $C_9H_8N_2O_4S$ requires C, 45·0; H, 3·4; S, 13·3 per cent.

2-*Methyl*-7-*sulphamoyl*-3H-4-*quinazolone*. The foregoing compound (8 g.) was added to 10N ammonia (64 ml.) and the mixture warmed on the steam-bath until the solid was almost dissolved. A solution of sodium hydroxide (10 g.) in water (136 ml.) was then added and the mixture heated under reflux for 30 min. The mixture was cooled slightly, saturated with carbon dioxide, and the *product* (5·6 g.) collected; it had m.p. 315° (decomp.) (from a large volume of water). It was soluble in sodium carbonate solution but insoluble in sodium bicarbonate solution. Found: C, 45·3; H, 3·6; N, 18·2; S, 13·3. $C_9H_9N_3O_3S$ requires C, 45·2; H, 3·8; N, 17·6; S, 13·4 per cent.

2-*Amino*-4-*sulphamoylbenzoic acid*, obtained by hydrolysis of the acetamido-compound with concentrated hydrochloric acid, had m.p. 233° (decomp.) (from water). Found: C, 38·5; H, 3·9; N, 12·7. Calc. for $C_7H_8N_2O_4S$: C, 38·9; H, 3·7; N, 13·0 per cent.

7-*Sulphamoylquinazol*-2,4-*dione*. The foregoing compound (21·6 g.) was dissolved in a mixture of water (400 ml.) and acetic acid (30 ml.) at 60° and treated with a solution of potassium cyanate (10 g.) in water (50 ml.). Concentrated sulphuric acid (50 ml.) was then added and the mixture heated under reflux for 30 min. After cooling, the product (15 g.) was collected. It had m.p. *ca.* 400° (decomp.) after crystallisation from a large volume of water. Found: C, 40·2; H, 3·2; N, 17·1; S, 13·2. $C_8H_7N_3O_4S$ requires C, 39·8; H, 2·9; N, 17·4; S, 13·3 per cent.

2-*Acetamido*-4-*chlorotoluene*-5-*sulphonamide*. 2-Acetamido-4-chlorotoluene (61 g.) was added with stirring to chlorosulphonic acid (195 g.) at 75–80° and the mixture was heated at 95–100° for 3 hr. After cooling the mixture was poured on to crushed ice and the solid sulphonchloride collected, washed with cold water and added to liquid ammonia (1 litre). The *product* (58 g.), isolated in the usual way, had m.p. 250° (decomp.) (from water). Found: C, 41·5; H, 4·2; Cl, 13·1; N, 10·5; S, 12·1. Calc. for $C_9H_{11}ClN_2O_3S$: C, 41·2; H, 4·2; Cl, 13·5; N, 10·7; S, 12·2 per cent.

2-*Acetamido*-4-*chloro*-5-*sulphamoylbenzoic acid* was obtained in 45 per cent yield by oxidation of the foregoing compound with potassium permanganate (6·7 mole.) in aqueous alkaline solution at below 70°. It had m.p. 257° (decomp.) (from water). Found: C, 37·1; H, 3·3; Cl, 12·0; S, 10·8. $C_9H_9ClN_2O_5S$ requires C, 36·9; H, 3·1; Cl, 12·1; S, 10·9 per cent.

7-Chloro-2-methyl-6-sulphamoyl-4H-3,1-*benzoxaz-4-one.* The foregoing acid (8·8 g.) was heated under reflux for 20 min. with a mixture of acetic acid (24 ml.) and acetic anhydride (5·7 ml.), and after cooling the *product* (5·4 g.) was collected. It had m.p. 240° (decomp.) from acetic acid-acetic anhydride (4:1). Found: C, 39·2; H, 2·3; Cl, 12·7; S, 11·9. $C_9H_7ClN_2O_4S$ requires C, 39·4; H, 2·6; Cl, 12·9; S, 11·7 per cent.

7-Chloro-2-methyl-6-sulphamoyl-3H-4-*quinazolone.* The foregoing benzoxazone (5·4 g.) was added to 10N ammonia (48 ml.) and the mixture warmed until most of the solid was dissolved. A solution of sodium hydroxide (10 g.) in water (136 ml.) was then added and the mixture heated under reflux for 30 min. It was then cooled slightly and saturated with carbon dioxide. The *product* (3·7 g.) was collected. It had m.p. 345° (decomp.) after crystallisation from a large volume of water. Found: C, 40·0; H, 2·7; Cl, 13·2; S, 11·9. Calc. for $C_9H_8ClN_3O_3S$: C, 39·5; H, 2·9; Cl, 13·0; S, 11·7 per cent.

2-*Methyl*-3-p-*sulphamoylphenyl*-3H-4-*quinazolone.* Benzenesulphonyl chloride (17·8 g.) was added during 5 min. to a solution of *o*-acetamidobenzoic acid (17·9 g.) in pyridine (35 ml.) without cooling. A suspension of *p*-aminobenzenesulphonamide (17·1 g.) in pyridine (15 ml.) was then added to the mixture, which was heated on the steam-bath for 1 hr. It was then cooled, poured into ice water and the *product* (14·5 g.) crystallised from ethanol. It had m.p. 256°. Found: C, 57·2; H, 4·1; N, 13·0; S, 10·3. $C_{15}H_{13}N_3O_3S$ requires C, 57·1; H, 4·2; N, 13·3; S, 10·2 per cent.

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