STUDIES IN THE FIELD OF DIURETICS

PART IV. THE CONDENSATION OF SOME HALOGENO-2,4-DISULPHAMYLBENZENE DERIVATIVES WITH BASIC REAGENTS

BY G. B. JACKMAN, V. PETROW, O. STEPHENSON AND A. M. WILD

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

Received May 13, 1960

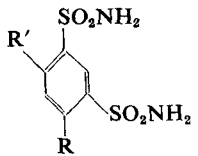
The condensation of some halogeno-2,4-disulphamylbenzenes with basic reagents has been examined. Some of the resulting products have been converted into 1,2,4-benzothiadiazine-1,1-dioxide derivatives. By using 2-aminopyridine in the reaction the novel azaphenthiazines (VII) were obtained.

AFTER the discovery of the diuretic properties of 5-chloro-2,4-disulphamyltoluene[1] (disulphamide) (I; R = Me, R′ = Cl), the stability of this product towards various reagents was examined as a matter of routine. Observations made in the course of this work upon the reactivity of the halogen atom towards basic reagents (cf.[2]) are described herein, together with collateral studies on the ring closure of some basic derivatives to novel thiadiazine types.

5-Chloro-2,4-disulphamyltoluene surprisingly proved stable to heating with strongly alkaline reagents such as aqueous potassium hydroxide, ethanolic sodium ethoxide, or sodium formate in ethanediol (cf.[3]). In striking contrast, its fully methylated derivative, 5-chloro-2,4-bisdimethylsulphamyltoluene (II; R = Cl, R′ = R″ = Me), reacted readily with ethanolic sodium ethoxide or with aqueous ethanolic potassium hydroxide to yield the 5-ethoxy substitution product (II; R = OEt, R′ = R″ = Me). It was apparent from this behaviour that the chlorine atom of disulphamide was markedly deactivated under strongly alkaline conditions, presumably through ionisation of the sulphamyl groups with formation of sulphamyl anions SO_2NH^-. If this were indeed the case, it followed that replacement of the halogen atom by a nucleophilic group would be facilitated under experimental conditions unfavourable to ionisation of the sulphamyl residues. The reaction of 5-chloro-2,4-disulphamyltoluene with ethanolic methylamine was consequently examined and, as anticipated, smooth reaction was effected (at 100° under pressure) with formation of 5-methylamino-2,4-disulphamyltoluene (I; R = NHMe, R′ = Me) in excellent yield. Extension of this reaction to ethanolamine gave the 5-(2-hydroxylethylamino)-derivative (I; R = $NH.CH_2CH_2OH$, R′ = Me), which approached the parent compound in diuretic potency, in tests made by Dr. A. David and his colleagues. This observation led to the preparation of the basic derivatives listed in Table I. These compounds, however, proved to be inferior to disulphamide in animal assays.

Reaction of 5-(2-hydroxyethylamino)-2,4-disulphamyltoluene with formamide and with formic acid (cf.[4]) yielded 4-(2-hydroxyethyl)-6-methyl-7-sulphamyl-1,2,4-benzothiadiazine-1,1-dioxide (III; R = OH) and the corresponding formate (III; R = O.CHO), respectively. These cyclic derivatives were degraded to the parent base by short heating with

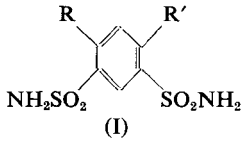
TABLE I

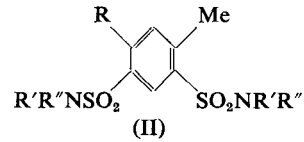


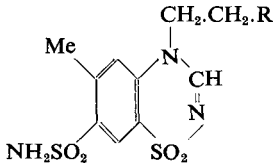
	R	R′	Formula	m.p. °C.	Found				Required			
	Substituent at position 4	6			C	H	N	S	C	H	N	S
1	$NH.CH_2.CH_2.OH$	—	$C_8H_{12}O_5N_2S_2$	190–191	32·4	4·6	13·9	—	32·5	4·4	14·2	—
2	$NH.CH_2.CHOH.Me$	—	$C_9H_{14}O_5N_2S_2$	206–208	35·4	5·0	13·3	20·5	34·9	4·9	13·6	20·7
3	$NH.(CH_2)_3.OH$	—	$C_9H_{14}O_5N_2S_2$	177–179	34·9	4·8	14·0	—	34·9	4·9	13·6	20·7
4	$N(CH_2.CH_2.OH)_2$	—	$C_{10}H_{17}O_6N_2S_2$	160–162	35·0	5·3	12·4	18·8	35·4	5·1	12·4	18·9
5	NH.Ph	—	$C_{12}H_{12}O_4N_2S_2$	226–227	44·0	3·9	13·1	19·4	44·0	4·0	12·8	19·6
6	$N<(CH_2)_4>NH$	—	$C_{10}H_{16}O_4N_2S_2$	217 (d.)†	37·7	4·9	17·1	20·1	37·5	5·0	17·5	20·0
7	$NH.NMe_2$	—	$C_8H_{14}O_4N_4S_2$	198–199	32·7	4·7	19·3	21·7	32·7	4·8	19·0	21·8
8	$NH.CH_2.CHOH.CH_2.OH$	—	$C_9H_{16}O_6N_2S_2$	190–192	32·9	4·4	12·3	—	33·2	4·6	12·9	—
9	Me	NH.Me	$C_8H_{12}O_4N_2S_2$	243	34·4	4·4	15·3	—	34·4	4·7	15·0	—
10	Me	$NH.CH_2.CH_2.OH$	$C_9H_{14}O_5N_2S_2$	216	35·0	4·6	13·3	—	35·0	4·9	13·6	—
11	Me	$NH.CH_2.CHOH.Me$	$C_{10}H_{17}O_5N_3S_2$	187–189	37·5	5·2	13·2	—	37·1	5·3	13·0	19·8
12	Me	$NMe.CH_2.CH_2.OH$	$C_{10}H_{17}O_5N_3S_2$	224–225 (d.)	37·5	5·1	12·8	19·7	37·1	5·3	13·0	19·8
13	Me	$NH.(CH_2)_3.OH$	$C_{10}H_{17}O_5N_3S_2$	171–173	37·6	5·5	12·8	19·3	37·1	5·3	13·0	19·8
14	Me	$NH.CH_2.C(Me)OH.C_2H_7$	$C_{12}H_{23}O_5N_3S_2$	174–176	42·9	6·1	—	—	42·7	6·4	—	—
15	Me	$NH.CH_2.CHOH.CH_2OH$	$C_{10}H_{17}O_6N_3S_2$	164–168	35·7	5·2	12·5	19·0	35·4	5·1	12·4	18·9
16	Me	$NH.NH_2$	$C_7H_{12}O_4N_4S_2$	227 (d.)	30·2	4·4	19·9	22·8	30·0	4·3	20·0	22·8
17	Me	$NH.NH.CO.NH_2$	$C_8H_{13}O_5N_5S_2$	237 (d.)	30·0	4·1	21·6	19·7	29·7	4·1	21·7	19·8
18	Me	$NH.CH_2.CH_2.NH_2.HCl$	$C_9H_{17}O_4N_4S_2Cl$	267 (d.)	31·7	5·0	16·3	10·4*	31·3	5·0	16·3	10·3*
19	Me	$NH.CH_2.CH_2.NH.CO.NH_2$	$C_{10}H_{17}O_6N_5S_2$	214 (d.)	34·1	5·0	19·8	—	34·2	4·9	19·9	—
20	Me	$N<(CH_2)_5$	$C_{12}H_{18}O_4N_2S_2$	211–212	43·4	5·9	12·6	—	43·2	5·8	12·6	—
21	Me	$N<(CH_2)_4>NH$	$C_{11}H_{18}O_4N_4S_2$	246 (d.)	40·0	5·4	17·0	19·1	39·5	5·4	16·8	19·2
22	Et	$NH.CH_2.CH_2.OH$	$C_{10}H_{17}O_5N_3S_2$	202–203	37·0	5·2	13·2	20·0	37·1	5·3	13·0	19·8
23	*Pr*^{n}	$NH.CH_2.CH_2.OH$	$C_{11}H_{19}O_5N_3S_2$	179–180	39·1	5·6	12·2	—	39·2	5·7	12·5	—
24	Cl	$NH.NH_2$	$C_6H_9O_4N_4S_2Cl$	243 (d.)	24·2	3·1	18·9	12·1*	24·0	3·0	18·6	11·8*
25	Cl	$NH.CH_2.CH_2.OH$	$C_8H_{12}O_5N_3S_2Cl$	200–202	29·6	4·0	12·9	10·8*	29·1	3·7	12·8	10·8*
26	$NH.NH_2$	$NH.NH_2$	$C_6H_{13}O_4N_6S_2$	228 (d.)	24·2	4·0	29·0	—	24·3	4·1	28·4	—
27	$NH.CH_2.CH_2.OH$	$NH.CH_2.CH_2.OH$	$C_{10}H_{18}O_6N_4S_2$	200–202	34·0	5·4	15·5	—	33·9	5·1	15·8	—

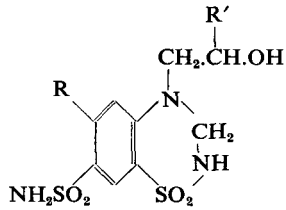
* = Cl. † d. = decomposition.

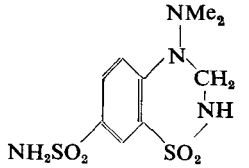
ethanolic hydrochloric acid. When the hydroxyethylamino-derivative (I; R = $NH.CH_2CH_2OH$, R′ = Me) was condensed with one equivalent of formaldehyde in 2-ethoxyethanol containing a trace of hydrogen chloride as catalyst, 4-(2-hydroxyethyl)-6-methyl-7-sulphamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (IV; R = Me, R′ = H) was obtained. This

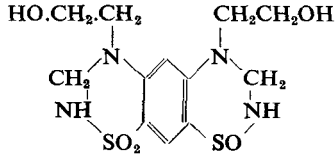

(I)

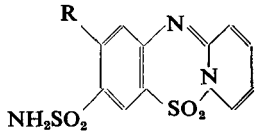

(II)


(III)


(IV)


(V)


(VI)


(VII)

analogue of hydrochlorothiazide[5] proved stable to short heating with ethanolic hydrochloric acid. The 4-(2-hydroxypropyl)-derivative (IV; R = R′ = Me) was prepared in a similar way.

Condensation of 5-chloro-2,4-disulphamyltoluene with hydrazine hydrate on the steam bath gave a high yield of 5-methyl-2,4-disulphamylphenylhydrazine (I; R = $NHNH_2$, R′ = Me), which formed normal condensation products with acetone and with benzaldehyde. Attempts to obtain cyclic structures from these condensation products, or from the original phenylhydrazine, by reaction with formaldehyde under a variety of experimental conditions proved unsuccessful. *Inter alia*, the phenylhydrazine was converted into the semicarbazide (I; R = $NHNHCONH_2$, R′ = Me) and into the azide (I; R =  , R′ = Me) by reaction with potassium cyanate and nitrous acid, respectively. In addition, disulphamide was condensed with ethylenediamine to give 5(2-aminoethylamino)-2,4-disulphamyltoluene (I; R = $NH_2CH_2CH_2NH$, R′ = Me), which was

characterised as the urea (I; R = $NH_2CONHCH_2CH_2NH$, R′ = Me) and with piperazine to give 5-piperazino-2,4-disulphamyltoluene. Reaction with 1,1-dimethylhydrazine under reflux, or with aniline at 160°, could not be achieved.

2,4-Disulphamylfluorobenzene (I; R = F, R′ = H) proved to be more reactive than the chlorotoluene (I; R = Cl, R′ = Me) in reactions with bases. Thus it condensed readily with 1,1-dimethylhydrazine to give the dimethylphenylhydrazine (I; R = $NHNMe_2$, R′ = H), smoothly converted into 4-dimethylamino-7-sulphamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (V) by reaction with formaldehyde. Aniline similarly gave the anilino-derivative (I; R = NHPh, R′ = H). The behaviour of 2,4-disulphamylchlorobenzene (I; R = Cl, R′ = H), however, resembled that of the 5-chlorotoluene derivative.

1,5-Dichloro-2,4-disulphamylbenzene (I; R = R′ = Cl) was converted by ethanolic ammonia in an autoclave at 150° into 5-chloro-2,4-disulphamylaniline, the immediate precursor of the chlorothiazide and hydrochlorothiazide group of diuretic agents. With 2-hydroxyethylamine, it was possible to obtain mono- (I; R = $NHCH_2CH_2OH$, R′ = H) and bis- (I; R = R′ = $NHCH_2CH_2OH$) condensation products, converted by formaldehyde into 6-chloro-4-(2-hydroxyethyl)-7-sulphamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (IV; R = Cl, R′ = H) and the novel tricyclic structure (VI), respectively. Mono- and bis- condensation products were also obtained from hydrazine.

Both 5-chloro-2,4-disulphamyltoluene and 1,5-dichloro-2,4-disulphamylbenzene failed to react with 2-aminopyridine at temperatures up to 180°. 2,4-Disulphamylfluorobenzene and 5-chloro-2,4-disulphamylfluorobenzene, in contrast, reacted to give condensation products formulated as 8-sulphamyl-11-azaphenthiazine derivatives (VII). These novel structures, however, were without diuretic activity in the saline-loaded rat.

Experimental

Attempted alkaline hydrolysis of 5-chloro-2,4-disulphamyltoluene. A solution of the disulphamide (4·0 g.) in water (40 ml.) containing potassium hydroxide (10 g. = 12·5 equiv.) was heated under reflux for 4 hours. It was then cooled and acidified with dilute nitric acid. Unchanged material (3·5 g.) was collected which had m.p. 260–261° after crystallisation from aqueous ethanol. The acid-aqueous liquid gave no precipitate with silver nitrate solution.

Reaction of 5-chloro-2,4-dimethylsulphamyltoluene with sodium ethoxide. A solution of the compound (8·5 g.) in ethanol (90 ml.) containing sodium ethoxide [prepared from sodium (1·2 g.)] was heated under reflux for 6 hours. The solution was concentrated to half-bulk, diluted with a small amount of water and neutralised with hydrochloric acid. *5-Ethoxy-2,4-dimethylsulphamyltoluene* (8 g.) separated on cooling and had m.p. 126–128° after crystallisation from aqueous methanol. Found: C, 44·5; H, 6·2; N, 8·1; S, 18·5. $C_{13}H_{22}O_5N_2S_2$ requires C, 44·6; H, 6·3; N, 8·0; S, 18·3 per cent.

5-*Methylamino*-2,4-*disulphamyltoluene*. (*a*) A solution of 5-chloro-2,4-disulphamyltoluene (20 g.) in 30 per cent ethanolic methylamine (200 ml.) was heated on the steam bath for 14 hours. *Unchanged* material (19·5 g.), m.p. 256–258°, was recovered.

(*b*) The disulphonamide (47·1 g.) was dissolved in 30 per cent ethanolic methylamine (300 ml.) and the solution heated in the autoclave at 100° for 5 hours. After removal of excess amine the residual solid was crystallised from aqueous methanol to yield the *product* (40 g.), m.p. 243°.

5-*Methylaminotoluene*-2,4-*disulphonmethylamide*. 5-Chlorotoluene-2,4-disulphonchloride (12·94 g.) was added in portions with cooling to 33 per cent ethanolic methylamine (100 ml.) and the solution heated at 60° for 16 hours. After evaporation to dryness the residual solid was crystallised from aqueous ethanol to yield the product (12 g.), m.p. 206–207°. Found: C, 39·0; H, 5·7; N, 13·9; S, 21·0. $C_{10}H_{17}O_4N_3S_2$ requires C, 39·1; H, 5·5; N, 13·7; S, 20·8 per cent.

N-(*β-Hydroxyethyl*)-5-*methyl*-2,4-*disulphamylaniline*. A solution of 5-chloro-2,4-disulphamyltoluene (50 g.) in 2-hydroxyethylamine (50 ml.) was heated on the steam bath for 10 hours, when the hot mixture was poured into water (200 ml.) with stirring. The *product* (53 g.) which separated, had m.p. 216° after crystallisation from water.

Reaction of the foregoing compound (6·2 g.) with 98 per cent formic acid (30 ml.) under reflux for 3 hours, followed by removal of the excess formic acid at reduced pressure and crystallisation from aqueous ethanol yielded 4-(*β-formyloxyethyl*)-6-*methyl*-7-*sulphamyl*-1,2,4-*benzothiadiazine*-1,1-*dioxide*, m.p. 280° (decomp.). Found: C, 38·4; H, 3·6; N, 12·1. $C_{11}H_{13}O_6N_3S_2$ requires C, 38·0; H, 3·7; N, 12·1 per cent.

With formamide (30 ml.) at 130° for 3 hours, the compound (6·2 g.) yielded 4-(*β-hydroxyethyl*)-6-*methyl*-7-*sulphamyl*-1,2,4-*benzothiadiazine*-1,1-*dioxide*, m.p. 275–277° after crystallisation from aqueous ethanol. Found: C, 37·3; H, 4·2; N, 13·3. $C_{10}H_{13}O_5N_3S_2$ requires C, 37·6; H, 4·1; N, 13·2 per cent. The m.p. of this compound was strongly depressed on admixture with the foregoing formyl derivative.

4-(*β-Acetoxyethyl*)-3,6-*dimethyl*-7-*acetylsulphamyl*-1,2,4-*benzothiadiazine*-1,1-*dioxide*. A solution of *N*-(β-hydroxyethyl)-5-methyl-2,4-disulphamylaniline (6·2 g.) in acetic anhydride (30 ml.) was heated under reflux for 3·5 hours. The *product* (7·0 g.) separated (from 50 per cent ethanol) in minute shining plates, m.p. 237° (decomp.). Found: C, 43·4; H, 4·7; N, 9·8; S, 14·9. $C_{15}H_{19}O_7N_3S_2$ requires C, 43·2; H, 4·6; N, 10·1; S, 15·3 per cent.

4-(*β-Hydroxyethyl*)-6-*methyl*-7-*sulphamyl*-3,4-*dihydro*-1,2,4-*benzothiadiazine*-1,1-*dioxide*. A suspension of *N*-(β-hydroxyethyl)-5-methyl-2,4-disulphamylaniline (6·2 g.) in ethoxyethanol (50 ml.) was treated with 40 per cent formaldehyde solution (2 ml.) and ethoxyethanol (1 ml.) saturated with hydrogen chloride added. The suspended solid dissolved rapidly on warming and the solution was heated at 140° for 2 hours. Excess of solvent was removed under reduced pressure and the residue crystallised from water. The *product* (5·4 g.) had m.p. 214°. Found: C, 37·8; H, 5·0; N, 13·1; S, 19·8. $C_{10}H_{15}O_5N_3S_2$ requires C, 37·4; H, 4·7;

N, 13·1; S, 19·9 per cent. Infra-red spectra in Nujol confirmed that the compound had a free hydroxyl group. The compound (0·7 g.) was recovered unchanged after heating under reflux with 3N hydrochloric acid (20 ml.) for 3 hours.

4-(*β*-*Hydroxypropyl*)-6-*methyl*-7-*sulphamyl*-3,4-*dihydro*-1,2,4-*benzothiadiazine*-1,1-*dioxide*, was obtained by condensation of *N*-(*β*-hydroxypropyl) 5-methyl-2,4-disulphamylaniline (12·9 g.) in ethoxyethanol (100 ml.) with 40 per cent formaldehyde solution (4 ml.) using a trace of hydrogen chloride as catalyst as described in the preceding preparation. The *product* had m.p. 221–222° after crystallisation from water. Found: C, 39·5; H, 5·2; N, 12·3; S, 19·1. $C_{11}H_{17}O_5N_3S_2$ requires C, 39·4; H, 5·1; N, 12·5; S, 19·1 per cent.

5-*Methyl*-2,4-*disulphamylphenylhydrazine*. A solution of 5-chloro-2,4-disulphamyltoluene (56·8 g.) in 100 per cent hydrazine hydrate (100 ml.) was heated on the steam bath for 5 hours. Excess of hydrazine was removed under reduced pressure and the residue crystallised from water to yield the *product* (52·3 g.), m.p. 227° (decomp.). Found: C, 30·3; H, 4·4; N, 19·9; S, 22·8. $C_7H_{12}O_4N_4S_2$ requires C, 30·0; H, 4·3; N, 20·0; S, 22·8 per cent. The *hydrochloride* had m.p. 206° (decomp.) after crystallisation from methanol-ether. Found: C, 26·7; H, 4·3; N, 17·3; Cl, 11·1; S, 19·9. $C_7H_{13}O_4N_4S_2Cl$ requires C, 26·5; H, 4·1; N, 17·7; Cl, 11·2; S, 20·2 per cent. The phenylhydrazine formed an iso*propylidene* derivative with acetone, which had m.p. 247–248° after crystallisation from ethanol. Found: C, 37·3; H, 5·1; N, 17·5; S, 19·9. $C_{10}H_{16}O_4N_4S_2$ requires C, 37·5; H, 5·0; N, 17·5; S, 20·0 per cent. The *benzylidene* derivative had m.p. 279–281° (decomp.) after crystallisation from aqueous methanol. Found: C, 45·9; H, 4·6; N, 14·8. $C_{14}H_{16}O_4N_4S_2$ requires C, 45·6; H, 4·4; N, 15·2 per cent.

5-*Methyl*-2,4-*disulphamylphenyl azide*. A solution of the phenylhydrazine (5·6 g.) in 2N hydrochloric acid (35 ml.) was treated at 0–5° with sodium nitrite (1·4 g.). The *product* (4·4 g.), separated in pale-yellow prisms of m.p. 194° (decomp.) after crystallisation from 50 per cent ethanol. Found: C, 29·2; H, 3·3; N, 23·8; S, 21·7. $C_7H_9O_4N_5S_2$ requires C, 28·9; H, 3·1; N, 24·1; S, 22·0 per cent. The *azide* was recovered unchanged after heating with 6N hydrochloric acid or 10 per cent potassium hydroxide at 100° for 2 hours.

NN-*Dimethyl*-2,4-*disulphamylphenylhydrazine*. A mixture of 2,4-disulphamylfluorobenzene (5·1 g.) and 1,1-dimethylhydrazine (4·8 g.) was heated under reflux for 4 hours when excess of the hydrazine was boiled off. The residual solid was crystallised from 20 per cent ethanol to yield the *product* (4·55 g.), m.p. 198–199°.

4-*Dimethylamino*-7-*sulphamyl*-3,4-*dihydro*-1,2,4-*benzothiadiazine*-1,1-*dioxide*. The foregoing dimethylphenylhydrazine (5·9 g.) was dissolved in ethoxyethanol (40 ml.) containing paraformaldehyde (0·6 g.) and a trace of hydrogen chloride as catalyst. The mixture was heated on the steam bath for 6 hours when excess of solvent was removed under reduced pressure. The viscous residue was stirred with aqueous sodium acetate to yield the *product* which formed pale-yellow crystals, m.p. 211–213°

after crystallisation from water. Found: C, 35·3; H, 4·3; N, 18·3; S, 20·8. $C_9H_{14}O_4N_4S_2$ requires C, 35·3; H, 4·6; N, 18·3; S, 20·9 per cent.

1-(5-*Methyl*-2,4-*disulphamylphenyl*)-1,2-*diaminoethane hydrochloride.* A solution of 5-chloro-2,4-disulphamyltoluene (28·4 g.) in 1,2-diaminoethane (30 g.) was heated at 140° for 3 hours when excess of amine was removed under reduced pressure. The residual gum was dissolved in water (2 volumes) and the solution brought to pH 6 by the addition of concentrated hydrochloric acid. The *product* (31 g.) had m.p. 267° (decomp.) after crystallisation from ethanol-ethyl acetate or from 95 per cent ethanol.

5-*Chloro*-2,4-*disulphamyl aniline.* A mixture of 2,4-disulphamyl-1,5-dichlorobenzene (30 g.), ethanol (700 ml.) and liquid ammonia (100 ml.) was heated in an autoclave at 150° for 7 hours. The solution was concentrated to about 300 ml., when the *product* (22 g.) crystallised on cooling. It had m.p. 256–258° after crystallisation from water. Found: C, 25·3; H, 3·1; N, 14·6. Calc. for $C_6H_8O_4N_3S_2Cl$: C, 25·2; H, 2·8; N, 14·7 per cent.

5-*Chloro*-2,4-*disulphamyl*-N-(*β-hydroxyethyl*)-*aniline.* 2-Hydroxyethylamine (6·5 ml., 2 mole equiv.) was added to a hot solution of 2,4-disulphamyl-1,5-dichlorobenzene (15·2 g.) in ethane diol (25 ml.) and the mixture heated at 130° for 1·5 hours. Excess of diol was removed at 100°/0·2 mm. and the viscous residue stirred with water (125 ml.). The solid (13·6 g.) which separated had m.p. 200–202° after crystallisation from water.

1,5-*Di*-(*β-hydroxyethyl*)-*amino*-2,4-*disulphamylbenzene.* A solution of 2,4-disulphamyl-1,5-dichlorobenzene (15·2 g.) in 2-hydroxyethylamine (24 ml., 8 mole. equiv.) was heated on the steam bath for 15 hours when excess of base was distilled off at 0·1 mm. Trituration of the residue with water (100 ml.) yielded solids (12 g.) which had m.p. 200–202° after crystallisation from water. The melting point was strongly depressed on admixture with the foregoing mono-substituted product.

6-*Chloro*-4-(*β-hydroxyethyl*)-7-*sulphamyl*-3,4-*dihydro*-1,2,4-*benzothiadiazine*-1,1-*dioxide.* A suspension of 5-chloro-2,4-disulphamyl-*N*-(*β*-hydroxyethyl)-aniline (16·5 g.) and paraformaldehyde (1·65 g.) in 2-ethoxyethanol (100 ml.) was warmed on the steam bath and treated with a saturated solution of hydrogen chloride in 2-ethoxyethanol (2 ml.), when all solids dissolved immediately. The solution was heated for 2 hours when the solvent was distilled off under reduced pressure. The solid residue (17 g.) crystallised from water to yield the *product* (11·2 g.), m.p. 204–206°. Found: C, 32·1; H, 3·4; N, 11·9; Cl, 10·4. $C_9H_{12}O_5N_3S_2Cl$ requires C, 31·6; H, 3·6; N, 12·3; Cl, 10·4 per cent. The melting point was strongly depressed on admixture with the starting material.

4,5-Di-(*β-Hydroxyethyl*)-1,8-*dithia*-2,4,5,7-*tetraza*-1,2,3,4,5,6,7,8-*octahydroanthracene*-1,1,8,8-*tetroxide.* A suspension of 1,5-di-(*β*-hydroxyethyl)-amino-2,4-disulphamylbenzene (14·2 g.) and paraformaldehyde (2·64 g.) in 2-ethoxyethanol (50 ml.) was heated on the steam bath and treated with a saturated solution of hydrogen chloride in 2-ethoxyethanol (2 ml.), when all solids dissolved. The solution was heated for 15

minutes when the *product* (10·5 g.) separated. It had m.p. 238°, not raised by a further crystallisation from water. Found: C, 38·1; H, 4·6; N, 15·2; S, 16·7. $C_{12}H_{18}O_6N_4S_2$ requires C, 38·1; H, 4·8; N, 14·8; S, 16·9 per cent.

2,4-*Disulphamyl*-N-(*β,γ-dihydroxypropyl*)-*aniline*. A solution of 2,4-disulphamylchlorobenzene (27 g.) in 2,3-dihydroxypropylamine (50 ml.) was heated on the steam bath for 3 hours. Excess of amine was removed at 0·1 mm. when the residual gum solidified on trituration with water. The *product* had m.p. 190–192° after crystallisation from water.

2,4-*Disulphamyl*-N-*bis*-(*β-hydroxyethyl*)-*aniline*. A solution of 2,4-disulphamylfluorobenzene (15 g.), and di-β-hydroxyethylamine in 2-ethoxyethanol (50 ml.) was heated under reflux for 2 hours and excess of volatile material then removed at 100°/0·1 mm. The viscous residue was extracted with hot chloroform to remove excess of di-β-hydroxyethylamine and its hydrochloride. The viscous material solidified overnight and the *product*, obtained by recrystallisation from water, had m.p. 160–162°.

5-*Chloro*-2,4-*disulphamylphenylhydrazine*. A suspension of 2,4-disulphamyl-1,5-dichlorobenzene (31 g.), in 20 per cent aqueous hydrazine hydrate (100 ml.) was heated under reflux. All solid dissolved after about 10 minutes then the *product* (26 g.) crystallised rapidly. It had m.p. 243° (decomp.) after crystallisation from water.

2,4-*Disulphamyl*-1,5-*phenylenedihydrazine*. A mixture of 2,4-disulphamyl-1,5-dichlorobenzene (6·2 g.), and 90 per cent hydrazine hydrate (10 ml.) was heated under reflux when the solid dissolved rapidly and crystals began to separate after about 15 minutes. Heating was continued for 1 hour when the mixture was cooled and the *product* (4·9 g.) collected. It had m.p. 228° (decomp.) after crystallisation from water.

3-*Sulphamyl*-5a-aza-*isophenthiazine*-5,5-*dioxide*. A mixture of 2,4-disulphamylfluorobenzene (5·1 g.) and 2-aminopyridine (1·9 g.) was heated with occasional stirring at 150° for 12 hours. Trituration of the hot residue with methanol furnished solids (2·47 g.), m.p. 338° (decomp.). Crystallisation from ethane diol yielded the *product* in yellow leaflets, m.p. 343° (decomp.). Found: C, 42·2; H, 3·3; N, 13·4; S, 20·4. $C_{11}H_9O_4N_3S_2$ requires C, 42·4; H, 2·9; N, 13·5; S, 20·6 per cent.

2-*Chloro*-3-*sulphamyl*-5a-aza-*isophenthiazine*-5,5-*dioxide*. An intimate mixture of 5-chloro-2,4-disulphamylfluorobenzene (5·8 g.) and 2-aminopyridine (3·8 g.) was heated at 140–160° for 4 hours with occasional stirring. Trituration of the hot residue with methanol yielded the *product* (1·4 g.), m.p. 375° (decomp.). The m.p. was not raised by crystallisation from ethane diol. Found: C, 38·4; H, 2·1; N, 12·0; Cl, 10·4; S, 18·8. $C_{11}H_8O_4N_3S_2Cl$ requires C, 38·2; H, 2·3; N, 12·1; Cl, 10·3; S, 18·6 per cent.

REFERENCES

1. Boggiano, Condon, Davies, Jackman, Overell, Petrow, Stephenson and Wild, *J. Pharm. Pharmacol.*, 1960, **12**, 419.
2. Davies and Wood, *J. chem. Soc.*, 1928, 1122.
3. Bealey, Petrow, Stephenson and Wild, *J. Pharm. Pharmacol.*, 1959, **11**, 36.
4. Novello and Sprague, *J. Amer. chem. Soc.*, 1957, **79**, 2028.
5. Stevens, Werner, Halamandaris and Ricca, *Experientia*, 1958, **14**, 463.