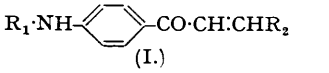
128. *Studies on Antibiotics. Part IV.*† *Substitued ω-Phenylsulphonyl-acetophenones, Bisphenylthio- and Bisphenylsulphonyl-alkane Derivatives.*

By F. Bergel, A. L. Morrison, and H. Rinderknecht.

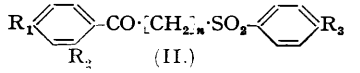
In continuation of previous work (Rinderknecht, Ward, Bergel, and Morrison, *Biochem. J.*, 1947, **41**, 463), the preparation of substances containing a combination of substituted benzoyl and phenylsulphonyl groups was undertaken with the aim (unfulfilled) of finding effective antibacterial agents. Thus various aromatic β-keto-sulphones (II; $n = 1$), β-bisthio-compounds (III), and β-disulphones (IV) were synthesised.

In Part II of our series " Studies on Antibiotics " (*Biochem. J.*, 1947, **41**, 463) we showed that benzoylacrylic acid and its 4-chloro- and 2 : 4-dichloro-derivatives possessed marked activities *in vitro* against Gram-positive and Gram-negative organisms. We deduced in agreement with Geiger and Conn (*J. Amer. Chem. Soc.*, 1945, **67**, 112) that the presence of the grouping $-CO-C{=}C-$ might be a pre-requisite for such antibacterial properties (cf. also Geiger, *Arch. Biochem.*, 1948, **16**, 423). In continuation of this work we prepared some time ago *p*-acetamidobenzoylacrylic acid (I; $R_1 = Ac$, $R_2 = CO_2H$) (cf. B.P. 588,108/1944) which we failed to hydrolyse to the 4-amino-compound. Since then, two groups of American workers, Papa, Schwenk, Villani, and Klingsberg (*J. Amer. Chem. Soc.*, 1948, **70**, 3356) and Cramer, Schroeder, Moran, Nield, Edwards, Sarowsky, and Puetzer (*J. Amer. Pharm. Assoc., Sci. Edn.*, 1948, **37**, 439), announced the preparation of this acetamido-compound among other derivatives of benzoylacrylic acid. We wished to replace the carboxyl group of benzoylacrylic acid by another structure and synthesised, independently of Marrian, Russell, and Todd (*J.*, 1947, 1419) 4 : 4′-diaminochalkone (I; $R_1 = H$, $R_2 = p\text{-}NH_2\cdot C_6H_4$); but unlike these authors we prepared the starting material, 4-nitro-4′-aminochalkone, directly from *p*-aminoacetophenone and *p*-nitrobenzaldehyde under acidic conditions and then reduced it with stannous chloride.

As the next step, we attempted the synthesis of substances containing both substituted benzoyl and phenylsulphonyl groups, being prompted by the results of Kuhn *et al.* (*Ber.*, 1942, **75**, 711; 1943, **76**, 405).



(I.)



(II.)

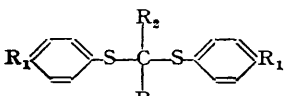
Whilst we failed to synthesise amino-substituted α-keto-sulphones (II; $n = 0$) in spite of the claims by Kohler and Macdonald (*Amer. Chem. J.*, 1899, **22**, 225) for unsubstituted ones, we succeeded in making a number of representatives of β-keto-sulphones (II; $n = 1$) by treating sodium acetamido- or acetamidomethyl-benzenesulphinate with ω-chloroacetophenone substituted by acetamido-, hydroxy-, or chloro-groups. In this we followed Troeger and Beck (*J. pr. Chem.*, 1913, [ii], **87**, 289) who prepared several arylsulphonylacetophenones, but none with amino- or aminomethyl substituents. After hydrolysis of the acetamido-

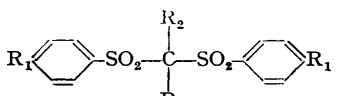
* The benzoyl–X dissociation energies in this figure are based on $x = -5$ kcals., in order to separate the two curves sufficiently to show their form more clearly.

† Part III, *Chem. and Ind.*, 1949, 640.

derivatives, p-*amino*- (II; $n = 1$, $R_1 = NH_2$, $R_2 = H$, $R_3 = NH_2$), and p-*hydroxy*-ω-p′-*amino*-*phenylsulphonylacetophenone* (II; $n = 1$, $R_1 = OH$, $R_2 = H$, $R_3 = NH_2$) and the corresponding p′-*aminomethyl* compounds ($R_3 = CH_2{\cdot}NH_2$) were obtained. Encouraged by the report on the antitubercular activity of 2 : 4 : 2′ : 4′-tetrachlorobenzophenone (Freedlander, *Proc. Soc. Exp. Biol. Med.*, 1942, **51**, 153; *Amer. Rev. Tubercul.*, 1944, **49**, 543) and the high effect of our 2 : 4-dichlorobenzoylacrylic acid *in vitro*, we added to our list of compounds 2 : 4-*dichloro*-ω-p′-*aminophenylsulphonylacetophenone* (II; $n = 1$, $R_1 = R_2 = Cl$, $R_3 = NH_2$) and the corresponding p′-*aminomethyl* analogue ($R_3 = CH_2{\cdot}NH_2$).

When, in the general structure (II; $n = 1$), the carbonyl group is exchanged for another sulphonyl group, substances (IV) emerge which can be prepared from β-bisthio-compounds (III) by oxidation. Methods for the synthesis of aliphatic and unsubstituted aromatic representatives of this series were described by Escales and Baumann (*Ber.*, 1886, **19**, 2814), Fromm (*Annalen*, 1889, **253**, 135), and Otto and Muehle (*Ber.*, 1895, **28**, 1121) who either condensed thiols with aldehydes or ketones or treated the sodium salt of thiols with dihalogeno-compounds. Concerning acylamino- or amino-derivatives of aromatic analogues, there are two American papers available: in the earlier, Waldron and Reid (*J. Amer. Chem. Soc.*, 1923, **45**, 2399) claimed the preparation of (III; $R_1 = NH_2$, $R_2 = R_3 = H$) by reduction of the corresponding dinitro-derivative; in the more recent, Cutter, Danielson, and Golden (*ibid.*, 1945, **67**, 1051, published while our investigation was in progress) described the synthesis of bis-*p*-acetamidophenylthiomethane (III; $R_1 = NHAc$, $R_2 = R_3 = H$) from *p*-acetamido-thiophenol or its sodium salt with formaldehyde or methylene iodide, respectively. This they also oxidised to (IV; $R_1 = NHAc$, $R_2 = R_3 = H$) which was hydrolysed to the diamino-disulphone (IV; $R_1 = NH_2$, $R_2 = R_3 = H$). In addition to preparing the same compounds, we succeeded in hydrolysing the bis-*p*-acetamidophenylthiomethane to Waldron and Reid's diamino-derivative which formed light ochre-coloured, and not, as they say, red, crystals; we also synthesised certain analogues. For instance, paraldehyde and *p*-acetamidothiophenol gave 1 : 1-*bis*-p-*acetamidophenylthioethane* (III; $R_1 = NHAc$, $R_2 = Me$, $R_3 = H$) which by alkaline hydrolysis, but not by acid (which caused decomposition), yielded the corresponding *diamino*-compound and by oxidation gave (IV; $R_1 = NHAc$, $R_2 = Me$, $R_3 = H$). This sulphone on treatment with alcoholic potassium hydroxide gave 1 : 1-*bis*-p-*aminophenylsulphonylethane* (IV; $R_1 = NH_2$, $R_2 = Me$, $R_3 = H$). By use of acetone or


(III.)


(IV.)

p-nitrobenzaldehyde in the first step of the synthesis 2 : 2-*bis*-p-*acetamidophenylthiopropane* (III; $R_1 = NHAc$, $R_2 = R_3 = Me$) and p-*nitro*-ωω-*bis*-p′-*acetamidophenylthiotoluene* (III; $R_1 = NHAc$, $R_2 = p\text{-}NO_2{\cdot}C_6H_4$, $R_3 = H$), respectively, were obtained. Finally in this group of compounds the use of dichloroacetic acid led to the formation of di-(*p*-acetamidophenylthio)acetic acid (III; $R_1 = NHAc$, $R_2 = CO_2H$, $R_3 = H$) and the corresponding *diamino*-derivative.

When we approached the synthesis of aminomethyl derivatives of (III) and (IV), we found that the preparation of *p*-acetamidomethylthiophenol, wanted as starting material, offered difficulties in view of its great solubility in water. However, three methods were tried which led eventually to success. First, the sodium salt from crude, oily *p*-acetamidomethylthiophenol was condensed with methylene dichloride to give *bis*-p-*acetamidomethylphenylthiomethane* (III; $R_1 = CH_2{\cdot}NHAc$, $R_2 = R_3 = H$). This was oxidised in the usual way to (IV; $R_1 = CH_2{\cdot}NHAc$, $R_2 = R_3 = H$) which hydrolysed with acid to the *bis*-p-*aminomethylphenylsulphonylmethane dihydrochloride* (IV; $R_1 = CH_2{\cdot}NH_2{,}HCl$, $R_2 = R_3 = H$). Although in our second approach p-*benzamidomethylthiophenol*, unlike the acetyl compound, formed sparingly soluble crystals and could be condensed to give *bis*-p-*benzamidomethylphenylthiomethane* (III; $R_1 = CH_2{\cdot}NHBz$, $R_2 = R_3 = H$), the oxidation of this compound to (IV; $R_1 = CH_2{\cdot}NHBz$, $R_2 = R_3 = H$) was difficult, and further neither the bisthio-compound nor the disulphone could be hydrolysed under alkaline or acidic conditions to the free aminomethyl derivatives. The third and best method used succinimido-derivatives. Succinbenzylamide reacted with chlorosulphonic acid to give p-*succinimidomethylbenzenesulphonyl chloride*, which was reduced in the usual way. p-*Succinimidomethylthiophenol*, thus formed, condensed with formaldehyde,

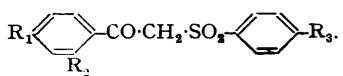
and the product, *bis*-p-*succinimidomethylphenylthiomethane* (III; R_1 = succinimidomethyl, $R_2 = R_3 = H$), was oxidised with hydrogen peroxide to the *disulphone* (IV; R_1 = succinimidomethyl, $R_2 = R_3 = H$). When this bisthio-compound was heated with dilute aqueous sodium hydroxide, and the solution was treated with potassium permanganate, a compound was isolated, very likely the succinamic acid derivative, which, on the one hand, with warm dilute hydrochloric acid gave the succinimido-disulphone described above, and, on the other hand, after prolonged heating with aqueous potassium hydroxide produced *bis*-p-*aminomethylphenylsulphonylmethane*, giving a dihydrochloride and a diacetyl derivative identical with those derived from the disulphone (IV; $R_1 = CH_2{\cdot}NH_2$, $R_2 = R_3 = H$) prepared from crude acetamidomethylthiophenol.

Preliminary bacteriological examination *in vitro* of some of the compounds just mentioned did not disclose any outstanding antibacterial activity.

Experimental.

4 : 4′-*Diaminochalkone* (I; $R_1 = H$, $R_2 = p$-$NH_2{\cdot}C_6H_4$).—*p*-Nitrobenzaldehyde (4·5 g.) and *p*-aminoacetophenone (4·05 g.) were dissolved in ethanol (100 ml.). After saturation of the solution with gaseous hydrogen chloride under ice-cooling, crystalline material separated overnight and was filtered off and dissolved in 2N-hydrochloric acid (*ca.* 700 ml.). On cooling, the hydrochloride of 4-nitro-4′-aminochalkone crystallised. It was suspended in methanol (100 ml.) and aqueous ammonia was added, whereupon orange-coloured 4-nitro-4′-aminochalkone was obtained; recrystallised from pyridine or chloroform, it had m. p. 221—223° (Found: C, 66·7; H, 4·5; N, 10·1. Calc. for $C_{15}H_{20}O_3N_2$: C, 67·2; H, 4·5; N, 10·4%). This compound (4·0 g.) in saturated alcoholic hydrochloric acid (40 ml.) was reduced with stannous chloride (11·0 g.). When warmed, a yellow solution was obtained which, after storage overnight, deposited a red tin salt. This was dissolved in water and decomposed with a solution of sodium acetate. The diaminochalkone was extracted with butanol and, obtained pure by recrystallising from aqueous acetone, melted at 181—183° (Found: C, 70·4; H, 6·3; N, 11·2. Calc. for $C_{15}H_{14}ON_2,H_2O$: C, 70·4; H, 6·3; N, 10·9%).

ω-p-*Substituted Phenylsulphonylacetophenones* (II; $n = 1$).—A number of compounds of this series was prepared by the general method of Troeger and Beck (*loc. cit.*) from *ω*-chloroacetophenones and sodium salts of *p*-acetamidophenylsulphinic (cf. *Org. Synth.*, Coll. Vol. I, p. 7) and *p*-acetamidomethylphenylsulphinic acid (cf. F.I.A.T. Final Report No. 915, 52; Miller, Sprague, Kissinger, and McBurney, *J. Amer. Chem. Soc.*, 1940, **62**, 2099). The acetyl derivatives were hydrolysed by heating them to the b. p. with 2N-hydrochloric acid until a clear solution was obtained. Addition of sodium carbonate solution precipitated the free amino-compounds which were recrystallised from the appropriate solvents. These compounds are listed in the table.

ω-Arylsulphonylacetophenones, 

R_1.	R_2.	R_3.	M. p.	Solvent for recrystn.	Formula.	Found, %. C.	Found, %. H.	Found, %. N.	Required, %. C.	Required, %. H.	Required, %. N.
NHAc	H	NHAc	271—274[c]	A	$C_{18}H_{18}O_5N_2S$	57·6	5·0	—	57·7	4·8	—
NH_2	H	NH_2	225—227	B	$C_{14}H_{14}O_3N_2S$	57·8	4·9	—	58·0	4·8	—
NHAc	H	$CH_2{\cdot}NHAc$	203—205	A	$C_{19}H_{20}O_5N_2S$	59·2	5·3	7·2	58·8	5·2	7·2
NH_2	H	$CH_2{\cdot}NH_2$	185—186	B	$C_{15}H_{16}O_3N_2S$	59·2	5·4	9·3	59·2	5·3	9·2
OH	H	NHAc	235—238	A	$C_{16}H_{15}O_5NS$	—	—	4·3	—	—	4·2
OH	H	NH_2	225—226	C	$C_{14}H_{13}O_4NS$	57·8	4·6	5·2	57·8	4·5	4·8
OH	H	$CH_2{\cdot}NHAc$	168—173	C	$C_{17}H_{17}O_5NS$	58·7	5·2	4·2	58·8	4·8	4·0
OH	H	$CH_2{\cdot}NH_2$	203 *	B	$C_{15}H_{15}O_4NS$	58·8	5·9	4·7	59·0	4·9	4·6
Cl	Cl	NHAc	164—167	C	$C_{16}H_{13}O_4NCl_2S$	49·8	3·2	—	49·8	3·4	—
Cl	Cl	NH_2	172—175	C	$C_{14}H_{11}O_3NCl_2S$	48·5	3·1	4·5	48·8	3·2	4·1
Cl	Cl	$CH_2{\cdot}NHAc$	125—127	C	$C_{17}H_{15}O_4NCl_2S$	51·3	3·3	—[b]	51·0	3·8	—[b]
Cl	Cl	$CH_2{\cdot}NH_2$	194—195	D	$C_{15}H_{13}O_3NCl_2S$	50·4	3·7	3·7	50·3	3·6	3·9

* With decomp.
Solvents: A, acetic acid; B, aqueous ethanol; C, ethanol; D, pyridine.
[c] Found: Cl, 18·3. Required: Cl, 18·4%. [b] Found: Cl, 17·9. Required: Cl, 17·8%.

Bis-p-*aminophenylthiomethane* (III; $R_1 = NH_2$, $R_2 = R_3 = H$).—Bis-*p*-acetamidophenylthiomethane (3·8 g.) was hydrolysed by hot 2N-sulphuric acid (100 ml.), the sulphate of the diamine crystallising on cooling. The base itself, obtained by neutralisation with sodium carbonate solution, formed light ochre-coloured crystals when recrystallised from ethanol. It melted at 98—100° (Found: N, 11·1. Calc. for $C_{13}H_{14}N_2S_2$: N, 10·7%).

1 : 1-*Bis*-p-*acetamido- and* -p-*amino-phenylthioethane* (III; R_1 = NHAc or NH_2, R_2 = Me, R_3 = H).—To *p*-acetamidothiophenol (6·68 g.) and chloroform (70 ml.), paraldehyde (0·88 g.) was added and the mixture was saturated with hydrogen chloride. The oily material which separated after 24 hours was treated with boiling water, a white solid being formed. Recrystallisation from ethyl acetate gave pure 1 : 1-*bis*-p-*acetamidophenylthioethane*, m. p. 191—193° (5·9 g.) (Found: N, 7·9. $C_{18}H_{20}O_2N_2S_2$ requires N, 7·8%).

Hydrolysis of the above acetyl derivative (3·4 g.) by refluxing in 10% alcoholic potassium hydroxide

solution (34 ml.) for 3 hours yielded only a small amount of the desired material, most of the product being unchanged acetyl derivative. The *bisthio-ethane* was separated from the starting material by dissolution in 2N-hydrochloric acid and then basification, and was obtained pure by recrystallisation from alcohol, whereafter it melted at 81—83° (Found: C, 61·0; H, 5·8; N, 10·5. $C_{14}H_{16}N_2S_2$ requires C, 60·8; H, 5·8; N, 10·1%).

1 : 1-*Bis*-p-*acetamido- and* -p-*amino-phenylsulphonylethane* (IV; R_1 = NHAc or NH_2, R_2 = Me, R_3 = H).—The above bisthio-ethane (III; R_1 = NHAc, R_2 = CH_3, R_3 = H) (5·8 g.) was dissolved in glacial acetic acid (40 ml.), and 60% (w/v) hydrogen peroxide (12 ml.) was added at 40°. After 24 hours at room temperature, the precipitate which had formed was filtered off, washed with water, and recrystallised from 60% aqueous acetic acid (120 ml.), the *diacetyl* compound being obtained pure as a light ochre-coloured compound with m. p. 263—266° (3·7 g.) (Found: N, 6·5. $C_{18}H_{20}O_6N_2S_2$ requires N, 6·6%).

Heating this acetyl compound (2 g.) with a solution of potassium hydroxide (5 g.) in ethanol (14 ml.) and water (7 ml.) under reflux for 4 hours yielded a potassium salt, very sparingly soluble in water, which, on treatment with dilute hydrochloric acid, gave the *diamine*, m. p. 202—204° [recrystallised from ethanol (150 ml.)] (1 g.) (Found: C, 49·9; H, 4·9; N, 8·6. $C_{14}H_{16}O_4N_2S_2$ requires C, 49·4; H, 4·7; N, 8·2%).

2 : 2-*Bis*-p-*acetamidophenylthiopropane* (III; R_1 = NHAc, R_2 = R_3 = Me).—*p*-Acetamidothiophenol (3·4 g.) was condensed with acetone (0·58 g.) in chloroform (35 ml.) by passing in hydrogen chloride. The product which separated overnight was worked up in the usual manner to give the *bisthio-propane*, m. p. 224—225° (recrystallised from ethanol several times) (Found: N, 7·6. $C_{19}H_{22}O_2N_2S_2$ requires N, 7·5%).

p-*Nitro-ωω-bis*-p′-*acetamidophenylthiotoluene* (III; R_1 = NHAc, R_2 = *p*-NO_2·C_6H_4, R_3 = H).—*p*-Acetamidothiophenol (3·4 g.) was condensed with *p*-nitrobenzaldehyde (1·51 g.) in chloroform (150 ml.) in the usual manner by passing in hydrogen chloride. The *bisthio-toluene* was obtained pure by recrystallising it from glacial acetic acid and melted at 221—223° (Found: N, 9·15. $C_{23}H_{21}O_4N_3S_2$ requires N, 9·0%).

Di-(p-*acetamido- and* -p-*amino-phenylthio*)*acetic acid* (III; R_1 = NHAc or NH_2, R_2 = CO_2H, R_3 = H).—Sodium *p*-acetamidothiophenoxide, prepared from sodium (0·7 g.) in ethanol (20 ml.) and the thiol (3·34 g.), was refluxed together with dichloroacetic acid (1·5 g.) for 2 hours. The residue of *bis*-p-*acetamido-acid*, after removal of the solvent by distillation, was treated with dilute hydrochloric acid and water and then sodium hydrogen carbonate, liberated from the resulting sodium salt by dilute hydrochloric acid, and finally recrystallised from ethanol, showing m. p. 230—235° (decomp.) (Found: N, 7·1. $C_{18}H_{18}O_4N_2S_2$ requires N, 7·2%). This derivative (2·5 g.) was hydrolysed by heating it under reflux for 4 hours with 2N-hydrochloric acid (75 ml.). On concentration, a crystalline hydrochloride separated out. This was dissolved in water and the solution neutralised carefully with dilute aqueous ammonia to give the *diamine* which, recrystallised from aqueous alcohol, melted at 117—119° (Found: N, 9·1. $C_{14}H_{14}O_2N_2S_2$ requires N, 9·2%).

Bis-p-*acetamidomethylphenylthiomethane* (III; R_1 = CH_2·NHAc, R_2 = R_3 = H).—*p*-Acetamidomethylbenzenesulphonyl chloride, prepared from *N*-benzylacetamide (48 g.), was dissolved in a mixture of alcohol (30 ml.) and water (100 ml.), zinc dust (100 g.) and concentrated hydrochloric acid (150 ml.) were added in portions with stirring and cooling, and the reaction mixture was finally heated to 80° for 5 minutes. After being cooled the solution was saturated with ammonium sulphate, and the oil which separated was dissolved in amyl alcohol and washed with a small amount of cold water. After removal of the amyl alcohol under reduced pressure, the residue was added to a mixture of ethanol (30 ml.), sodium (1·2 g.), and methylene dichloride (5 g.) and the whole refluxed for 1½ hours. The hot reaction mixture was then centrifuged, and from the separated supernatant layer the *bisthio-methane* crystallised on cooling. It melted at 144—146° when recrystallised from ethanol (Found: C, 61·4; H, 5·7; N, 7·9; S, 17·4. $C_{19}H_{22}O_2N_2S_2$ requires C, 61·0; H, 5·9; N, 7·5; S, 17·1%).

Bis-p-*acetamidomethylphenylsulphonylmethane* (IV; R_1 = CH_2·NHAc, R_2 = R_3 = H).—Oxidation of the above bisthio-methane (0·75 g.) in acetic acid (5 ml.) with 60% hydrogen peroxide (1·5 ml.) in the usual way gave the *disulphone* which, recrystallised from 60% aqueous acetic acid, melted at 236—239° (Found: C, 52·0; H, 5·0; N, 5·9. $C_{19}H_{22}O_6N_2S_2$ requires C, 52·1; H, 5·0; N, 6·4%).

Bis-p-*aminomethylphenylsulphonylmethane Dihydrochloride* (IV; R_1 = CH_2·NH_2, R_2 = R_3 = H).—Hydrolysis of the above acetyl derivative (0·5 g.) with 2N-hydrochloric acid (15 ml.) for 4 hours gave the *dihydrochloride* which, recrystallised from dilute hydrochloric acid, gave white needles which did not melt at 400° but sublimed (Found: C, 42·6; H, 5·0; N, 6·4; Cl, 17·1. $C_{15}H_{18}O_4N_2S_2$,2HCl requires C, 42·2; H, 4·7; N, 6·6; Cl, 16·6%).

p-*Benzamidomethylbenzenesulphonyl Chloride*.—*N*-Benzylbenzamide (100 g.) was gradually added to chlorosulphonic acid (300 ml.) at 15° with stirring. The temperature was then raised to 45° and kept at this level for 1 hour. The reaction mixture was worked up as described for *p*-succinimidomethylbenzenesulphonyl chloride, to give the *sulphonyl chloride*, m. p. 183—184° (after recrystallisation from chloroform–light petroleum) (Found: N, 4·7; Cl, 11·8. $C_{14}H_{12}O_3NSCl$ requires N, 4·5; Cl, 11·3%).

p-*Benzamidomethylthiophenol*.—Reduction of the above sulphonyl chloride (17 g.) with zinc (25 g.) and concentrated hydrochloric acid (55 ml.) (cf. above) yielded the *thiol*, m. p. 134—138° (after recrystallisation from alcohol) (Found: N, 6·0. $C_{14}H_{13}ONS$ requires N, 5·8%).

Bis-p-*benzamidomethylphenylthiomethane* (III; R_1 = CH_2·NHBz, R_2 = R_3 = H).—The above thiol (12·15 g.) and methylene dichloride (4·2 g.) were condensed in methanol (70 ml.) in which sodium (1·08 g.) had been dissolved. The *bisthio-methane*, recrystallised from acetic acid, had m. p. 163—165° (Found: N, 5·6. $C_{29}H_{26}O_2N_2S_2$ requires N, 5·6%).

Bis-p-*benzamidomethylphenylsulphonylmethane* (IV; R_1 = CH_2·NHBz, R_2 = R_3 = H).—The above bisthio-methane (1·25 g.) was oxidised with 60% hydrogen peroxide (2 ml.) in glacial acetic acid (15 ml.), a very large amount of acetic acid being necessary to keep the material in solution. The *product*, which is sparingly soluble in acetic acid, melted at 233—235° (Found: N, 5·0. $C_{29}H_{26}O_6N_2S_2$ requires N, 5·0%).

p-*Succinimidomethylbenzenesulphonyl Chloride.*—To chlorosulphonic acid (140 ml.), succinbenzylimide (14 g.) was added in portions, with stirring, at <10°. The reaction mixture was then heated to 60° for ½ hour and poured on ice. The gummy mass was stirred with two lots of ice-cold water, whereupon it crystallised. Recrystallised from chloroform–light petroleum, it melted at 153—157° (38%) (Found : Cl, 12·8. $C_{11}H_{10}O_4NCl$ requires Cl, 12·4%).

p-*Succinimidomethylthiophenol.*—To the above sulphonyl chloride (6·5 g.) in a mixture of alcohol (12 ml.) and water (7 ml.) were added zinc dust (11 g.) and concentrated hydrochloric acid (20 ml.) during 1 hour with continuous stirring. The reaction mixture was then heated for 2 minutes to 80°. It was then filtered and the filtrate poured into a mixture of ice-water (200 ml.) and concentrated hydrochloric acid (10 ml.). The precipitate was filtered off and dissolved in chloroform (50 ml.), and the chloroform solution washed with water, dried, and evaporated. The residue, recrystallised from alcohol, yielded the pure *thiol* as lemon-yellow crystals, m. p. 119° (68%) (Found : C, 60·0; H, 5·1. $C_{11}H_{11}NS$ requires C, 59·7; H, 5·0%).

Bis-p-*succinimidomethylphenylthiomethane* (III; R_1 = succinimidomethyl, $R_2 = R_3 = H$).—A mixture of the above thiol (1·1 g.), paraformaldehyde (0·15 g.), and chloroform (15 ml.) was saturated with hydrogen chloride. After 1 day, the reaction mixture was poured into water and the chloroform distilled off. The *bisthio-methane* which separated from the aqueous layer was recrystallised from acetic acid and had m. p. 212—216° (Found : C, 60·3; H, 4·9; N, 6·4. $C_{23}H_{22}O_6N_2S_2$ requires C, 60·8; H, 4·8; N, 6·2%).

Bis-p-*succinimidomethylphenylsulphonylmethane* (IV; R_1 = succinimidomethyl, $R_2 = R_3 = H$).—(*a*) The above bisthio-methane (0·6 g.) was oxidised in glacial acetic acid (40 ml.), in which it is sparingly soluble, with 60% hydrogen peroxide (16 ml.) as described in preceding experiments. The *disulphone* was recrystallised from a large volume of acetic acid and obtained as a white powder, m. p. 295—298° (Found : C, 53·6; H, 4·6; N, 5·3. $C_{23}H_{22}O_8N_2S_2$ requires C, 53·3; H, 4·2; N, 5·4%).

(*b*) When the bisthio-methane (7 g.) was heated with 2N-sodium hydroxide (50 ml.), it dissolved with formation of the succinyl derivative. A 3% aqueous potassium permanganate solution (9 g. of permanganate) was then added with vigorous stirring while carbon dioxide was passed through the mixture. The whole was filtered, and the filtrate decolorised with sulphur dioxide and acidified, a precipitate separating which, recrystallised from acetic acid, melted at 188—190°. On refluxing of this substance with 2N-hydrochloric acid, the succinimido-derivative, m. p. 295—298°, identical with that prepared by method (*a*), was formed.

Hydrolysis of bis-*p*-succinylaminomethylphenylsulphonylmethane (1·3 g.), m. p. 188—190°, as obtained above, by refluxing with a solution of potassium hydroxide (4 g.) in water (20 ml.) for 4 hours yielded bis-*p*-aminomethylphenylsulphonylmethane, the constitution of which was established by acetylating it to give the previously described diacetyl derivative (IV; $R_1 = CH_2{\cdot}NHAc$, $R_2 = R_3 = H$), m. p. 236—239°.

RESEARCH DEPARTMENT, ROCHE PRODUCTS LTD.,
WELWYN GARDEN CITY, HERTS.

[*Received, November 24th,* 1949.]