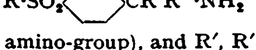
170. *Chemotherapeutic Agents of the Sulphone Type. Part II. Sulphones Related to Benzamidine and Benzylamine.*

By A. T. Fuller, (Miss) I. M. Tonkin, and James Walker.

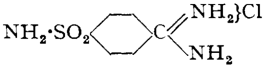
Marked antibacterial activity was observed in *p*-methylsulphonylbenzamidine (II) and further examination showed this property to be shared by the lower *p*-alkylsulphonyl-benzamidines and -benzylamines. When the functional groups occupied the *m*-positions, activity was greatly reduced, and the structural requirements for high activity are that the compounds should conform to the type

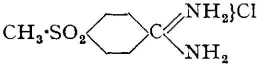


where R may be a small alkyl group (or an amino-group), and R′, R″ may be an imino-group, or two hydrogen atoms, or one hydrogen atom and one methyl group, such that basic powers are not impaired. Seventeen amidine and six amine types have been investigated.

p-Sulphonamidobenzamidine hydrochloride (I) was claimed (Boots Pure Drug Co., Levene and Pyman, B.P. 544,836/1942) to be an antibacterial agent of the " sulphonamide " type, and it has been shown to possess chemotherapeutic activity in experimental typhus infections (Andrewes, King, van den Ende, and Walker, *Lancet*, **1944**, i, 777; Andrewes, King, and Walker, *Proc. Roy. Soc.*, *B*, in the press). In the course of studying the relationship between antirickettsial activity and chemical constitution, and as an extension of the work described in the preceding paper, p-*methylsulphonylbenzamidine hydrochloride* (II) was synthesised, but the replacement of the $-SO_2{\cdot}NH_2$ group of (I) by the $-SO_2{\cdot}CH_3$ group in (II) abolished antirickettsial action; at the same time, however, antibacterial activity was markedly enhanced (Evans, Fuller, and Walker, *Lancet*, **1944**, ii, 523) and the present paper describes the further investigation of the latter feature.

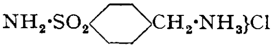
(I.)



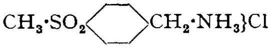


(II.)

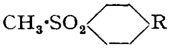
The first four members (II), (III), (IV) and (V) of the homologous series of *p*-alkylsulphonylbenzamidines and the requisite *nitriles* were synthesised by orthodox reactions. Condensation of benzyl chloride, chloroacetone, and chloroacetamide with sodium *p*-cyanobenzenesulphinate afforded *nitriles* from which the respective *amidines* (VI), (VII), and (VIII) were subsequently obtained, and chloroacetonitrile afforded a *dinitrile* leading to the *diamidine* (IX). *p*-Phenylsulphonylbenzamide afforded the *nitrile* from which the *amidine* (X) was obtained. The use of p-*methylsulphonylbenzmethylamide* (XXIV; R = CO·NHMe) for the preparation of *N*-methylated derivatives of (II) was not satisfactory, since a side reaction took place during iminochloride formation which consumed phosphorus pentachloride, although the N-*methyl* derivative (XI) of (II) was obtained by this route; the use of thionyl chloride (v. Braun and Pinkernelle, *Ber.*, 1934, **67**, 1218) was also unsatisfactory. Reaction of *p*-methylsulphonylbenzimino-ether hydrochloride [XXIV; R = $C(OEt){:}NH_2\}Cl$], however, with dimethylamine and γ-diethylaminopropylamine readily afforded the as.-*dimethyl* (XII) and the γ-*diethylaminopropyl* (XIII) derivative of (II) respectively. No satisfactory crystalline salt was obtained from the corresponding δ-diethylamino-α-methylbutyl derivative of (II). Reaction of the imino-ether hydrochloride with an excess of methylamine gave a product consisting largely of the s.-*dimethyl* derivative (XIV) of (II), indicating a facile interchange of radicals in the amidine group, but the *monomethyl* derivative (XI) resulted in good yield when little more than one molecular proportion of methylamine was used. A further *N*-substituted derivative of (II) studied was p-*methylsulphonylbenzamidoxime hydrochloride* (XV). p-*Methylthiobenzamidine hydrochloride* (XVI) was also prepared and the m-*isomerides* (XVII) and (XVIII) of (II) and (III) were obtained from the appropriate *nitriles*. In certain cases where crystallisation of hydrochlorides proved difficult through excessive solubility, it was found that, with amidines *unsubstituted* in the amidine group, double decomposition with sodium benzoate afforded much less soluble benzoates, *e.g.*, (V); it is noteworthy that Pinner obtained the sparingly soluble benzoate of benzamidine in 1884 (*Ber.*, **17**, 2005) but failed to identify it until some years later (*Ber.*, 1890, **23**, 2936), and it seems probable that the low solubility of the salt may have been responsible for the delayed recognition of its constitution.



(XIX.)



(XX.)

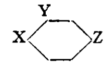


(XXIV.)

Since the biological results obtained with (II) recalled features shown by *p*-sulphonamidobenzylamine hydrochloride (XIX), the German drug "Marfanil," the appropriate nitriles were hydrogenated in the presence of Raney nickel to give the two isomeric pairs of benzylamines which were isolated as *hydrochlorides*: (XX), (XXI), (XXII) and (XXIII). After this work had been completed, a paper by Jensen and Schmith (*Z. physiol. Chem.*, 1944, **280**, 35) came to hand in which (XX) is mentioned as having been prepared by a different route but the m. p. recorded (265°) is not in good agreement with that observed in the present work (280°). Homologation of *p*-methylsulphonylbenzylamine hydrochloride (XX) was undertaken in two further ways. Reduction of *p*-methylsulphonylbenzonitrile (XXIV; R = CN) by Stephen's method (J., 1925, **127**, 1874) gave the *aldehyde* (XXIV; R = CHO) which was converted through the cinnamic *acid* (XXIV; R = $CH{:}CH{\cdot}CO_2H$) and β-phenylpropionic *acid* (XXIV; R = $CH_2{\cdot}CH_2{\cdot}CO_2H$) into β-p-*methylsulphonylphenylethylamine hydrochloride* (XXV), using Naegeli's technique (*Helv. Chim. Acta*, 1929, **12**, 227) at the last stage. The isomeric α-p-*methylsulphonylphenylethylamine hydrochloride* (XXVI) was prepared by applying Leuckart's reaction as modified by Ingersoll *et al.* (*J. Amer. Chem. Soc.*, 1936, **58**, 1808) to p-*methylsulphonylacetophenone* (XXIV; R = COMe), which was obtained in very high yield by introducing the chloride of p-*methylsulphonylbenzoic acid* (XXIV; R = CO_2H) into ethyl malonate by Lund's method (*Ber.*, 1934, **67**, 935) and submitting the resulting acylmalonic ester to acid hydrolysis. An attempt to prepare the ketone (XXIV; R = COMe) directly from the nitrile (XXIV; R = CN) and methylmagnesium iodide failed, since it was necessary to use hot benzene to dissolve the nitrile in a volume of convenient bulk and, at the temperature employed, the anticipated side reaction of the Grignard reagent (cf. Kohler and Potter, *J. Amer. Chem. Soc.*, 1935, **57**, 1316) at the methylsulphonyl group preponderated and the nitrile was largely recovered unchanged.

The *in vitro* antibacterial titres of the compounds, recorded in the table, show that, with the exception of (XX) against *Ps. pyocyanea*, activity against the Gram-negative test organisms was generally low or absent, a property shared by other antibacterial chemotherapeutic drugs. Marked activity, however, was found against the Gram-positive organisms of the hæmolytic streptococcal and clostridial types although, again with the exception of (XX), pronounced activity was not shown against *Staph. aureus*. High antibacterial activity

Antibacterial activity in vitro.
Minimal inhibiting concentrations in mg. of drug per 100 c.c. of culture medium.



	Compound,			Gram-positive.				Gram-negative.		
Organism.	X.	Y.	Z.	*Strep. hæmolyt.*		*Staph. aureus.*	*Cl. welchii.*	*Bact. proteus.*	*Ps. pyocyanea.*	*Bact. coli.*
Medium.				a.	b.	a.	a.	a.	a.	a.
*(II)	$CH_3{\cdot}SO_2$	H	$C(NH_2){:}NH_2\}Cl$	0·15	1	250	2	400	150	250
*(III)	$C_2H_5{\cdot}SO_2$	H	$C(NH_2){:}NH_2\}Cl$	3	5	200	10	>1000	1000	500
*(IV)	$C_3H_7{\cdot}SO_2$	H	$C(NH_2){:}NH_2\}Cl$	20	50	400	100	1000	500	800
(V)	$C_4H_9{\cdot}SO_2$	H	$C(NH_2){:}NH_2\}Ph{\cdot}CO_2$	50	100	500	150	500	500	500
*(VI)	$CH_2Ph{\cdot}SO_2$	H	$C(NH_2){:}NH_2\}Cl$	10	50	100	30	750	200	200
(VII)	$CH_3{\cdot}CO{\cdot}CH_2{\cdot}SO_2$	H	$C(NH_2){:}NH_2\}Cl$	100	200	1000	60	>2000	2000	1000
(VIII)	$NH_2{\cdot}CO{\cdot}CH_2{\cdot}SO_2$	H	$C(NH_2){:}NH_2\}Cl$	5	20	2000	25	>2000	>2000	2000
*(IX)	$Cl\{NH_2{:}C(NH_2){\cdot}CH_2{\cdot}SO_2$	H	$C(NH_2){:}NH_2\}Cl$	15	30	100	100	>2000	>2000	>2000
*(X)	$Ph{\cdot}SO_2$	H	$C(NH_2){:}NH_2\}Cl$	100	100	100	200	200	200	100
(XI)	$CH_3{\cdot}SO_2$	H	$C(NH_2){:}NHMe\}Cl$	60	500	1500	70	>2000	>2000	2000
(XII)	$CH_3{\cdot}SO_2$	H	$C(NH_2){:}NMe_2\}Cl$	500	500	>2000	1500	>2000	>2000	>2000
(XIV)	$CH_3{\cdot}SO_2$	H	$C(NHMe){:}NHMe\}Cl$	150	500	>2000	300	>2000	>2000	>2000
(XIII)	$CH_3{\cdot}SO_2$	H	$C(NH_2){:}NH{\cdot}[CH_2]_3{\cdot}NHEt_2\}Cl_2$	200	500	>2000	700	>2000	>2000	>2000
*(XV)	$CH_3{\cdot}SO_2$	H	$C({:}NOH){\cdot}NH_3\}Cl$	100	200	>200	200	>200	>200	>200
(XVI)	$CH_3{\cdot}S$	H	$C(NH_2){:}NH_2\}Cl$	2	10	50	1·5	200	150	100
(XVII)	H	$CH_3{\cdot}SO_2$	$C(NH_2){:}NH_2\}Cl$	500	500	1000	2000	>2000	>2000	800
(XVIII)	H	$C_2H_5{\cdot}SO_2$	$C(NH_2){:}NH_2\}Cl$	500	500	1000	1000	>2000	>2000	2000
*(XX)	$CH_3{\cdot}SO_2$	H	$CH_2{\cdot}NH_3\}Cl$	1	75	5	0·3	50	8	100
(XXI)	$C_2H_5{\cdot}SO_2$	H	$CH_2{\cdot}NH_3\}Cl$	10	80	50	0·7	750	200	1000
(XXII)	H	$CH_3{\cdot}SO_2$	$CH_2{\cdot}NH_3\}Cl$	1000	500	>2000	200	>2000	>2000	>2000
(XXIII)	H	$C_2H_5{\cdot}SO_2$	$CH_2{\cdot}NH_3\}Cl$	500	500	2000	1000	>2000	2000	2000
(XXV)	$CH_3{\cdot}SO_2$	H	$CH_2{\cdot}CH_2{\cdot}NH_3\}Cl$	300	500	1000	150	2000	1000	2000
(XXVI)	$CH_3{\cdot}SO_2$	H	$CHMe{\cdot}NH_3\}Cl$	10	20	50	1·5	2000	500	>2000

* Tested and found inactive in experimental typhus in mice.
Media. a, Nutrient broth. b, Blood.

was found to be a markedly specific property of the lower homologues of the *p*-series of alkylsulphonylbenzamidines and the corresponding benzylamines. In the amidine series activity against streptococci and *Cl. welchii* fell progressively as the homologous series was ascended from methyl to butyl, (II) $\longrightarrow$ (V), and a similar trend was discernible in the benzylamines, (XX) and (XXI). In contrast, it should be noted that antibacterial chemotherapeutic activity in *p*-alkylsulphonylanilines, $p\text{-}R{\cdot}SO_2{\cdot}C_6H_4{\cdot}NH_2$, has been shown to rise to a maximum at R = *n*-propyl (Fourneau, Tréfouël, Tréfouël, Nitti, and Bovet, *Compt. rend. Soc. Biol.*, 1938, **127**, 393) and a similar feature (maximum at *n*-hexyl) has been demonstrated in the antiseptic powers of the homologous 4-alkylresorcinols (Leonard, *J. Amer. Med. Assoc.*, 1924, **83**, 2005). The only sulphide (XVI) examined showed marked activity against the Gram-positive test organisms and was the most active of the amidines against *Staph. aureus*. When the *p*-orientation of (II) was altered to the *m*-orientation in (XVII) activity against hæmolytic streptococci and *Cl. welchii* was reduced about 1000-fold, and a similar ratio was found between the activities of the *p*- (XX) and *m*- (XXII) isomeric benzylamines. The reduction in the antibacterial activity of the *p*-substituted benzylamines in blood has been discussed previously (Evans, Fuller, and Walker, *loc. cit.*), and these compounds have recently been the subject of enzyme experiments [(XX) and marfanil, Dr. H. Blaschko and Mrs. R. Duthie, private communication; marfanil, Beyer and Govier, *Science*, 1945, **101**, 150], although it is not permissible to invoke amine oxidase as being responsible for the effect in blood since its presence therein has not been recognised; it should be noted, however, that the activity of (XXVI), which could not function as a substrate for amine oxidase, is only diminished to one-half in blood. The antibacterial activity of the compounds described in this paper is not inhibited by *p*-aminobenzoic acid and therefore their mode of action, like their spectrum of activity, is distinct from that of the group of drugs popularly, though irrationally, known as the "sulphonamides." It is apparent from the constitutions of the active compounds that the structural requirements for high activity are that the functional substituents should be in the *p*-position and that the formulæ should conform to the type $p\text{-}R{\cdot}SO_2{\cdot}C_6H_4{\cdot}CR'R''{\cdot}NH_2$, where R should not be too large, *e.g.*, Me or Et in the present work, although there may be some specificity with larger groups, as shown by comparing the antistreptococcal activities of (VII) and (VIII) with $R = CH_2{\cdot}CO{\cdot}CH_3$ and $R = CH_2{\cdot}CO{\cdot}NH_2$ respectively, and R′, R″ may be the imino-group as in (II), or two hydrogen atoms as in (XX), or a hydrogen atom and a methyl group as in (XXVI), which is still moderately active. In these cases the pronounced basic properties of the amidines and non-aromatic primary amines are not impaired, but the reduction in basicity occasioned when R′, R″ = :NOH in the amidoxime (XV) is accompanied by a marked diminution in antibacterial activity. In marfanil (XIX), where $R = NH_2$, the substitution of R = NHMe also affords an active substance, but the incorporation of heterocyclic radicals which gave such a fillip to drugs of the "sulphonamide" type increases toxicity in marfanil (Bergeim and Braker, *J. Amer. Chem. Soc.*, 1944, **66**, 1459; Hamre *et al.*, *Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 170). Goldacre (*Nature*, 1944, **154**, 796) has measured the p*K* values of marfanil but the evidence he adduces is insufficient to support the title of his communication as the "mode of action" of the drug. Lawrence (*J. Bact.*, 1945, **49**, 149) has compared the antibacterial activities of marfanil (XIX), and its α- and β-*p*-sulphonamidophenylethylamine homologues, and his observations parallel the results obtained with the analogous compounds (XX), (XXVI), and (XXV) in the present work.

An account has already been given of the action of (II), (XX), and marfanil in experimental gas gangrene in guinea pigs (Evans, Fuller, and Walker, *loc. cit.*), and a further communication will describe a similar study of tetanus in mice and in guinea pigs. Routine antimalarial tests were carried out as described below, but the activity encountered was not of a high order and the most active compound (II) possessed a considerably lower degree of activity than sulphadiazine which was used as the standard prophylactic drug. The authors are indebted to Dr. C. H. Andrewes, F.R.S., for testing representative compounds (marked * in the table) in experimental typhus infections but no activity was found. Dr. J. D. Fulton kindly tested (I), (II), (IX), (XIX), and (XX) in hamsters heavily infected with an Indian strain of leishmaniasis but no activity was detected. The writers are indebted to Dr. Ann Bishop who found (II) to be inactive against *P. relictum* in the canary, and to Prof. W. H. Tytler who found (II) to be only slightly active against tubercle bacilli *in vitro*.

EXPERIMENTAL.

p-*Methylsulphonylaniline* (XXIV; R = NH_2).—(i) Acetanilide (200 g.) was treated with chlorosulphonic acid (*Org. Synth.*, Coll. Vol. I, 8), and the resulting sulphonyl chloride reduced with sodium sulphite (*ibid.*, p. 7). At the end of the reduction the turbid reaction mixture was left overnight in the refrigerator, and the inorganic salts which separated were removed by filtration before precipitation of the acetamidobenzenesulphinic acid with cold 60% sulphuric acid. (The precipitation should be accelerated by scratching; otherwise some deacetylation takes place in the supersaturated solution, giving a higher-melting product in poorer yield.) The product was collected, washed well with ice-water, and dried in a vacuum over concentrated sulphuric acid; m. p. sharp and in the range 151—155° (yield, 210 g.). The damp acid may be used at once for the next stage.

(ii) The crude acid was suspended in water and neutralised to pH 7 with sodium hydroxide (in a total volume of 750 c.c. at the end of the neutralisation). Alcohol (500 c.c.) and methyl iodide (120 c.c.) were added, and the mixture refluxed for 5—10 hours (5 hours minimal). The excess of methyl iodide and the alcohol were then distilled off. Any iodine colour was discharged by addition of small crystals of sodium thiosulphate. When the solution had been concentrated to about one-third of its bulk it was cooled, and the product separated, washed with water, and dried. The *p*-methylsulphonylacetanilide need not be purified at this stage; however, it separates from water in colourless prisms, m. p. 185—186° (Child and Smiles, J., 1926, 2699, record m. p. 183°).

(iii) The crude acetyl derivative from (ii) was refluxed with 1 l. of 5N-hydrochloric acid for ½—1 hour, and the product, liberated by rendering the mixture alkaline, was collected, and crystallised from water, the pure amine (120—125 g.) separating in fine colourless prisms, m. p. 133—134° (lit. 133°).

p-*Methylsulphonylbenzonitrile* (XXIV; R = CN).—The preceding amine (200 g.) was warmed with concentrated hydrochloric acid (245 c.c.) and water (530 c.c.) until it dissolved. The mixture was then cooled in ice, and the hydrochloride separated as a thick slush. A solution of sodium nitrite (81 g.) in water (200 c.c.) was added slowly with stirring and cooling in a freezing mixture until an immediate reaction to starch–iodide paper was shown. The cold orange suspension was then poured in a thin stream into a solution of sodium cyanide (280 g.) and hydrated nickel chloride (270 g.) in water (1800 c.c.), which was stirred and heated in a basin of boiling water. When all the diazo-solution had been added, heating was continued for 10—15 minutes, and the mixture was then cooled to room temperature, and the dark brown solid collected and drained thoroughly on the filter. The solid was extracted with acetone, the extract filtered from insoluble inorganic material, and the solid recovered by evaporation. Recrystallisation from water (norit) afforded a buff-coloured crystalline solid (140—150 g.), m. p. 140°, of adequate purity for subsequent amidine formation. The pure *compound* crystallised in colourless needles, m. p. 141° (Found: C, 52·9; H, 4·0; N, 7·7. $C_8H_7O_2NS$ requires C, 53·0; H, 3·9; N, 7·7%).

p-*Methylsulphonylbenzamidine Hydrochloride* (II).—A number of batches (*e.g.*, 5 × 50 g.) were run simultaneously and bulked after digestion with ammonia. The preceding nitrile (50 g.) was suspended in absolute alcohol (50 c.c.) and chloroform (300 c.c.) and the mixture, cooled in melting ice, was saturated with dry hydrogen chloride. On keeping in the refrigerator for 4—7 days, with daily gentle agitation, a homogeneous light brown solution resulted which frequently deposited copious amounts of the crystalline imino-ether hydrochloride but occasionally remained supersaturated. Solvent and excess of hydrogen chloride were exhaustively removed in a vacuum at room temperature, and when the imino-ether hydrochloride had been obtained as a dry granular powder it was transferred to a pressure bottle and set aside with 10% alcoholic ammonia solution (400 c.c.) at 37° for 4—6 days. At the end of the digestion the heavy crystalline solid, consisting of free amidine base, its hydrochloride, and some ammonium chloride, was bulked (from 5 batches) on the filter, ground, and air dried. The mother-liquors were evaporated to dryness, and the total solids suspended in water (4—5 l.); hydrochloric acid was cautiously added to neutralise all the free amidine and to produce a permanent incipient acid reaction to Congo-red. The solution, separated from a small amount of insoluble, flocculent material (mainly crude nitrile), was decolorised in the cold with norit and concentrated on the water-bath in a vacuum to small bulk (*ca.* 400 c.c.) and cooled, the heavy colourless crop of amidine hydrochloride then being collected and drained thoroughly. Further quantities were obtained by further concentration of the mother-liquors and the final mother-liquors contained ammonium chloride and practically no amidine hydrochloride. The *hydrochloride* separated from 1½ times its own weight of water in heavy, well-developed colourless prisms, m. p. 294°, with slight softening about 250—260° (change in crystal form?) (Found: C, 40·6; H, 4·9; N, 11·9; Cl, 15·1. $C_8H_{10}O_2N_2S,HCl$ requires C, 40·9; H, 4·7; N, 11·9; Cl, 15·1%). The yield of pure product was approximately 78%, *i.e.*, weight for weight the same as the nitrile used. The solubility of the hydrochloride in water at room temperature was about 10%, and the pH of a 1% solution was 6.

The *benzoate*, precipitated by mixing aqueous solutions of the above hydrochloride and sodium benzoate, separated from water in colourless rectangular plates, m. p. 240—241° (efferv.) (Found: C, 56·1; H, 5·0; N, 8·6. $C_8H_{10}O_2N_2S,C_7H_6O_2$ requires C, 56·2; H, 5·0; N, 8·7%); its solubility in water was only 1·3% at room temperature and 10·6% at the b. p.

p-*Cyanobenzenesulphinic Acid*.—The following modification of the method described by Andrewes, King, and Walker (*loc. cit.*) afforded improved yields. *p*-Cyanobenzenesulphonyl chloride (122·3 g.) (Remsen, Hartman, and Muckenfuss, *Amer. Chem. J.*, 1896, **18**, 156) was reduced at room temperature with sodium sulphite heptahydrate (375 g.) in water (775 c.c.), the pH being maintained at approximately 8 throughout. The solution, filtered from a small quantity of solid, was chilled in the refrigerator for 18 hours, and ice-water added in sufficient amount to dissolve salts which had separated. Acidification with 60% sulphuric acid afforded a copious precipitate of needles of the sulphinic acid, which was collected, resuspended in ice-water (120 c.c.), again collected, and dried (yield 88·7 g.; 87·4%), m. p. 128—129°. The acid required the calculated volume of standard sodium hydroxide solution for neutralisation to pH 7·0, and the sodium salt (98 g.) was recovered by evaporating the aqueous solution to dryness in a vacuum on the water-bath.

p-*Ethylsulphonylbenzonitrile*.—Sodium *p*-cyanobenzenesulphinate (13·6 g.) and excess of ethyl iodide (15 c.c.) were refluxed in 60% alcohol (30 c.c.) for 16 hours. The alcohol was removed by distillation, and water was added along with a crystal of sodium thiosulphate to remove traces of free iodine. The resulting oil rapidly crystallised, and the *nitrile* (13·3 g.) was collected and dried. Recrystallisation from spirit afforded colourless, diamond-shaped plates, m. p. 94—95° (Found : C, 55·1; H, 4·6. $C_9H_9O_2NS$ requires C, 55·4; H, 4·6%).

p-*Ethylsulphonylbenzamidine Hydrochloride* (III).—A solution of the preceding nitrile (11 g.) in absolute alcohol (10 c.c.) and chloroform (25 c.c.) was saturated at 0° with hydrogen chloride and kept in the refrigerator for 14 days. Solvent and excess of hydrogen chloride were exhaustively removed as described above, and the resulting solid imino-ether hydrochloride was digested at 37° for 7 days with 10% alcoholic ammonia solution (120 c.c.). The clear solution was filtered from traces of ammonium chloride and evaporated to dryness. The residue was taken up in water, decolorised (norit), and recovered (13·5 g.) by evaporation to dryness. The *hydrochloride* crystallised from its own weight of water in colourless prisms, m. p. 246—247° (Found : C, 43·6; H, 5·4; N, 11·3. $C_9H_{12}O_2N_2S,HCl$ requires C, 43·5; H, 5·2; N, 11·3%).

p-*Allylsulphonylbenzonitrile*.—Sodium *p*-cyanobenzenesulphinate (6·3 g.) and excess of allyl bromide (8 c.c.) were refluxed in 70% alcohol (20 c.c.) for 4 hours. The *nitrile* (6·9 g.) separated from spirit in large colourless columns, m. p. 92—93° (Found : C, 57·7; H, 4·4. $C_{10}H_9O_2NS$ requires C, 58·0; H, 4·3%).

p-n-*Propylsulphonylbenzonitrile*.—The above allyl derivative (11·95 g.) was hydrogenated in ethyl acetate under slight pressure (12″ of water) in presence of 2% palladised strontium carbonate (5 g.). The theoretical volume of hydrogen was absorbed in about ½ hour. The catalyst was collected, and the *nitrile* separated from spirit in large colourless prisms (10·2 g.), m. p. 84—85° (Found : C, 57·5; H, 5·4. $C_{10}H_{11}O_2NS$ requires C, 57·4; H, 5·3%).

p-n-*Propylsulphonylbenzamidine Hydrochloride* (IV).—The preceding nitrile (9·94 g.) was treated in precisely the same manner as the ethyl homologue, 6 days being given for imino-ether formation and 5 days for the amidine stage. The *hydrochloride* (11·5 g.) separated from its own weight of water, or from rather more absolute alcohol, in colourless prisms, m. p. 215—216° (Found : C, 45·8; H, 5·7; N, 10·6. $C_{10}H_{14}O_2N_2S,HCl$ requires C, 45·7; H, 5·7; N, 10·7%).

p-n-*Butylsulphonylbenzonitrile*.—Sodium *p*-cyanobenzenesulphinate (9·7 g.) and excess of *n*-butyl bromide (10 c.c.) were refluxed in a mixture of *n*-propyl alcohol (40 c.c.) and water (10 c.c.) for 14 hours. The *nitrile* (8·3 g.), isolated in the usual way, separated from 75% aqueous methyl alcohol in large, thin, colourless plates, m. p. 75—76° (Found : C, 59·2; H, 5·5. $C_{11}H_{13}O_2NS$ requires C, 59·2; H, 5·8%).

p-n-*Butylsulphonylbenzamidine Benzoate* (V).—The preceding nitrile (8·25 g.) was submitted to amidine formation precisely as described above, and the resulting amidine hydrochloride was obtained as a syrup which crystallised spontaneously but could not be satisfactorily recrystallised from a solvent. An aqueous solution, treated with an aqueous solution of sodium benzoate (5·5 g.), afforded the sparingly soluble *benzoate* (9 g.). This salt had the peculiar property of separating from a colourless solution in 20 times its weight of water either in pale yellow plates, m. p. 224—225° (efferv.), or in fine colourless needles, m. p. 227° (efferv.) (Found : C, 59·3; H, 5·9; N, 7·6. $C_{11}H_{16}O_2N_2S,C_7H_6O_2$ requires C, 59·7; H, 6·1; N, 7·7%).

p-*Benzylsulphonylbenzonitrile*.—Sodium *p*-cyanobenzenesulphinate (6·3 g.) and excess of benzyl chloride (5·5 c.c.) were refluxed in 90% alcohol (32 c.c.) for 9 hours. The *nitrile* (7·3 g.) separated from glacial acetic acid in colourless, nacreous plates, m. p. 194—195° (Found : C, 65·3; H, 4·4; N, 5·5. $C_{14}H_{11}O_2NS$ requires C, 65·4; H, 4·3; N, 5·4%).

p-*Benzylsulphonylbenzamidine Hydrochloride* (VI).—The preceding nitrile (12·2 g.) was converted into the imino-ether hydrochloride in absolute alcohol (30 c.c.) and chloroform (150 c.c.). When the imino-ether hydrochloride, freed from solvent and excess of hydrogen chloride, was digested for 10 days at 37° with saturated alcoholic ammonia (120 c.c.), a heavy crystalline solid separated. This was collected, and the mother-liquors were evaporated to dryness. The combined product was dissolved in water with addition of a slight excess of hydrochloric acid, filtered from traces of amorphous flocculent material, decolorised with norit, and recovered by evaporation to dryness in a vacuum on the water-bath. The residue (13·6 g.) separated from 1½ times its weight of water in stout colourless prisms (9·8 g.), m. p. 215—216° with slight softening (loss of water?) at *ca.* 140° (Found : loss at 110°/vac., 5·0. Found, on dried material : C, 53·8; H, 5·2; N, 8·9. $C_{14}H_{14}O_2N_2S,HCl,H_2O$ requires H_2O, 5·4%. $C_{14}H_{14}O_2N_2S,HCl$ requires C, 54·2; H, 4·8; N, 9·0%).

p-*Cyanophenylsulphonylacetone*.—Sodium *p*-cyanobenzenesulphinate (12·6 g.) and freshly distilled chloroacetone (6·5 c.c.) were refluxed for 8½ hours in a mixture of spirit (70 c.c.) and water (10 c.c.). The *product* (12 g.) separated from methyl alcohol in colourless needles, m. p. 112—113° (Found : C, 53·4; H, 4·0; N, 6·3. $C_{10}H_9O_3NS$ requires C, 53·8; H, 4·0; N, 6·3%).

p-*Acetomethylsulphonylbenzamidine Hydrochloride* (VII).—The preceding nitrile was converted into the amidine in the usual way. The clear solution, obtained at the end of the treatment with alcoholic ammonia, was evaporated to dryness, and the *hydrochloride*, which was very soluble in water, methyl and ethyl alcohols, separated from *iso*propyl alcohol in fine colourless needles, m. p. 193—194° (Found : C, 43·5; H, 4·5; N, 10·3. $C_{10}H_{12}O_3N_2S,HCl$ requires C, 43·4; H, 4·7; N, 10·1%).

p-*Cyanophenylsulphonylacetamide*.—Sodium *p*-cyanobenzenesulphinate (10 g.) and chloroacetamide (5 g.) were refluxed for 10 hours in spirit (45 c.c.). The *product* (8·2 g.) separated from a large volume of 20% aqueous alcohol in fine, colourless needles, m. p. 204° (Found : C, 48·5; H, 3·6; N, 12·3. $C_9H_8O_3N_2S$ requires C, 48·2; H, 3·6; N, 12·5%).

p-*Carbamidomethylsulphonylbenzamidine Hydrochloride* (VIII).—The preceding nitrile (7·5 g.), suspended in chloroform (120 c.c.) and alcohol (10 c.c.), was treated with hydrogen chloride in the usual way. It slowly reacted during 29 days in the refrigerator and crystals of a different habit separated. The imino-ether hydrochloride, isolated in the usual way, dissolved readily in saturated alcoholic ammonia (100 c.c.) and heavy crystals separated during 10 days' keeping at 37°. The solid and residue from the ammoniacal mother-liquors were dissolved in water, treated with norit, and recovered (9·6 g.) by evaporation to dryness in a vacuum. The *hydrochloride* separated from its own weight of water in colourless prisms which effloresced on drying, m. p. 235—236° (decomp.) (Found : loss at 100°/vac., 3·4. Found, on dried material : C, 39·0; H, 4·7; N, 14·7. $C_9H_{12}O_3N_3S,HCl,\frac{1}{2}H_2O$ requires H_2O, 3·1%. $C_9H_{12}O_3N_3S,HCl$ requires C, 38·8; H, 4·7; N, 15·1%).

p-*Cyanophenylsulphonylacetonitrile*.—Sodium *p*-cyanobenzenesulphinate (12·6 g.) and chloroacetonitrile (6 g.) were refluxed for 12 hours in 90% alcohol (27 c.c.). The *dinitrile* (11·2 g.) separated from methyl alcohol in clusters of colourless prisms, m. p. 142—143° (Found : C, 52·5; H, 2·8; N, 13·6. $C_9H_6O_2N_2S$ requires C, 52·4; H, 2·9; N, 13·6%).

p-*Guanylmethylsulphonylbenzamidine Dihydrochloride* (IX).—A suspension of the preceding dinitrile (11·2 g.) in absolute alcohol (40 c.c.) and chloroform (150 c.c.) was saturated with hydrogen chloride and kept in the refrigerator for 13 days, a copious separation of the di-imino-ether hydrochloride taking place. Solvent and excess of hydrogen chloride were exhaustively removed, and the residue was digested with saturated alcoholic ammonia (230 c.c.) at 37° for 7 days. The resulting solution was evaporated to dryness, and the residue was dissolved in water, decolorised with norit, and recovered (18·9 g.) by evaporation to dryness in a vacuum. The *dihydrochloride* separated from water in minute colourless prisms, m. p. 283° (decomp.) (Found : C, 34·5; H, 4·6; N, 18·1. $C_9H_{12}O_2N_4S,2HCl$ requires C, 34·5; H, 4·5; N, 17·9%).

p-*Phenylsulphonylbenzonitrile*.—*p*-Phenylsulphonylbenzamide (22·9 g.) (Newell, *Amer. Chem. J.*, 1898, **20**, 302), phosphoryl chloride (23 c.c.), and chloroform (100 c.c.) were refluxed for 3 hours, the amide slowly dissolving. Solvent and unused phosphoryl chloride were removed in a vacuum, and water and ether added to the residue. A portion of the product, consisting of unchanged amide (2·2 g.), remained undissolved and was collected. The ethereal solution was separated, washed with aqueous sodium bicarbonate solution, dried, and evaporated. The resulting *nitrile* separated from spirit (norit) in colourless, etched plates, m. p. 126° (Found: C, 64·4; H, 3·8; N, 5·9. $C_{13}H_9O_2NS$ requires C, 64·2; H, 3·7; N, 5·8%).

p-*Phenylsulphonylbenzamidine Hydrochloride* (X).—The preceding nitrile (14 g.) was converted into the amidine in the usual way. Long, colourless needles (10·8 g.) separated during the digestion with alcoholic ammonia, and a further crop was obtained on evaporating the mother-liquor to dryness. A small amount (1 g.) of amide remained undissolved on treating the bulked solids with water, and the *amidine hydrochloride* (15·8 g.), recovered on evaporation to dryness, separated from a small volume of water in colourless prisms, m. p. 201—202° (Found: C, 52·0; H, 4·5; N, 9·1. $C_{13}H_{12}O_2N_2S,HCl,\frac{1}{2}H_2O$ requires C, 52·3; H, 4·6; N, 9·2%).

p-*Methylsulphonylbenz*-N-*methylamidine Hydrochloride* (XI).—(A) *p*-Methylsulphonylbenzmethylamide (10 g.) (below) was warmed on the water-bath for 3 hours with finely powdered phosphorus pentachloride (10 g.) in toluene (100 c.c.). When no further evolution of hydrogen chloride took place there was still much unchanged methylamide left in suspension, indicating the occurrence of a side reaction consuming phosphorus pentachloride. After thorough removal of the toluene and phosphoryl chloride, the dark brown residue was set aside with 10% alcoholic ammonia (120 c.c.) at 37° for several days. The dark brown solution was filtered from the crude unchanged methylamide (3·1 g., m. p. 187—189°), decolorised with norit, and evaporated to dryness. The product (5·0 g.) was extracted with a small volume of alcohol from the residue of ammonium chloride, and recrystallisation from methyl alcohol–ethyl acetate (2 : 3) afforded the *hydrochloride* as stellate clusters of colourless prisms, m. p. 243° (Found: C, 42·9; H, 5·3; N, 11·3. $C_9H_{12}O_2N_2S,HCl$ requires C, 43·5; H, 5·2; N, 11·3%).

(B) The following procedure gave a much purer product. *p*-Methylsulphonylbenzimino-ether hydrochloride, prepared in the usual way from the nitrile (12 g.), was set aside at 37° with a mixture of 22% w/v alcoholic methylamine (11 c.c.; 1·15 mols.) and absolute alcohol (40 c.c.) for 8 days. The homogeneous solution obtained by addition of water was neutralised with hydrochloric acid to Congo-red, decolorised with norit, and evaporated to dryness. On recrystallisation from spirit the residue afforded crystals as in (A) (11·85 g.), m. p. 246° (Found: C, 43·5; H, 5·3; N, 11·6%).

p-*Methylsulphonylbenz*-NN′-*dimethylamidine Hydrochloride* (XIV).—When the preceding experiment (B) was carried out with 2·75 molar proportions of methylamine and only 5 days at 37°, the main product of the reaction was the symmetrical and less soluble *dimethylamidine hydrochloride*, which separated from absolute alcohol in small, stout, colourless prisms (6·9 g.), m. p. 285—286° (Found: C, 45·7; H, 5·6; N, 10·3. $C_{10}H_{14}O_2N_2S,HCl$ requires C, 45·7; H, 5·7; N, 10·7%), and it was impossible to obtain a completely pure specimen of the monomethylamidine from the mother-liquors.

p-*Methylsulphonylbenz*-NN-*dimethylamidine Hydrochloride* (XII).—*p*-Methylsulphonylbenzimino-ether hydrochloride, prepared from the nitrile (12 g.) in the usual way, was kept at 37° for 2 weeks with an alcoholic solution (110 c.c.) of dimethylamine (9·6 g.). Part of the product crystallised, and the remainder was isolated by evaporating the mother-liquors to dryness. The entire product was dissolved in cold water with addition of 2N-hydrochloric acid until the solution was just acid to Congo-red, decolorised with norit, and recovered. The *compound* separated from absolute alcohol in minute colourless prisms (11·5 g.), m. p. 274—275°, varying somewhat with the rate of heating (Found: C, 46·0; H, 5·9; N, 10·5. $C_{10}H_{14}O_2N_2S,HCl$ requires C, 45·7; H, 5·7; N, 10·7%).

p-*Methylsulphonyl*-N-γ-*diethylaminopropylbenzamidine Dihydrochloride* (XIII).—*p*-Methylsulphonylbenzimino-ether hydrochloride (from 12 g. of nitrile) was kept at 37° for 2 weeks with γ-diethylaminopropylamine (9 g.) in alcoholic solution (100 c.c.). The brown syrupy residue, left on evaporation of the reaction mixture, dissolved in water to give an alkaline solution, which was neutralised to pH 7 with 2N-hydrochloric acid. Decolorisation with norit and evaporation to dryness afforded a stiff glass, which crystallised in contact with alcohol. Recrystallisation from spirit afforded tiny clusters of colourless needles (12·9 g.), m. p. 254° (softening 251°) (Found: C, 46·6; H, 7·2; N, 10·9. $C_{15}H_{25}O_2N_3S,2HCl$ requires C, 46·9; H, 7·0; N, 10·9%).

p-*Methylsulphonylbenzamidoxime Hydrochloride* (XV).—*p*-Methylsulphonylbenzamidoxime (Andrewes, King, and Walker, *loc. cit.*) was neutralised with the theoretical volume of N-hydrochloric acid, and the solution was evaporated to dryness. The *hydrochloride* separated from spirit in fine colourless prisms, m. p. 227° (efferv.) (Found: C, 38·6; H, 4·7; N, 11·4. $C_8H_{10}O_3N_2S,HCl$ requires C, 38·3; H, 4·4; N, 11·2%).

p-*Methylthioaniline Hydrochloride*.—*p*-Methylthionitrobenzene (28·6 g.) (Waldron and Reid, *J. Amer. Chem. Soc.*, 1923, **45**, 2402) was reduced by West's method (J., 1925, **127**, 494), and the product isolated as the hydrochloride (28·4 g.). Recrystallisation from alcoholic hydrochloric acid afforded fine, flattened, colourless needles, m. p. 260—261° (decomp.) (Found: C, 47·9; H, 5·7. Calc. for C_7H_9NS,HCl: C, 47·9; H, 5·7%). Brand and Wirsing (*Ber.*, 1912, **45**, 1765) record m. p. 215—220° (decomp.) for a substance, stated to be of this constitution, resulting from the action of hydrochloric acid on *pp*′-bismethylthiohydrazobenzene.

p-*Methylthiobenzamidine Hydrochloride* (XVI).—A solution of *p*-methylthiobenzonitrile (13·9 g.) (Zincke and Jörg, *Ber.*, 1910, **43**, 3447) in alcohol (15 c.c.) and chloroform (25 c.c.) was saturated with hydrogen chloride and kept at 0° for 5 days. The imino-ether hydrochloride, recovered in the usual way from the clear solution, was kept with 10% alcoholic ammonia (120 c.c.) at 37° for 5 days; much of the product separated as a heavy crop of large crystals and a further amount was obtained on evaporating the mother-liquor to dryness. The crude material was dissolved in water with addition of sufficient hydrochloric acid to give an acid reaction to Congo-red, and recovered (17·3 g.), after treatment with norit, by evaporation to dryness. The *hydrochloride* separated from water in stout, colourless prisms, m. p. 218—219° (Found: C, 47·8; H, 5·5; N, 14·0. $C_8H_{10}N_2S,HCl$ requires C, 47·4; H, 5·4; N, 13·8%). The *benzoate*, precipitated with sodium benzoate, separated from a large volume of water in small colourless prisms, m. p. 251—252° (Found: C, 62·8; H, 5·3; N, 9·4. $C_8H_{10}N_2S,C_7H_6O_2$ requires C, 62·5; H, 5·6; N, 9·7%).

m-*Methylsulphonylbenzonitrile*.—*m*-Nitrophenylmethylsulphone (100 g.) (Twist and Smiles, J., 1925, **127**, 1249) was hydrogenated in alcohol (600 c.c.) in the presence of 2% palladised strontium carbonate (12 g.) under pressure. As the nitro-compound was not very soluble in alcohol, the temperature was raised to about 100° during the reduction, which required about an hour for completion. The crude amine was submitted at once to the Sandmeyer reaction, using the conditions described for the *p*-isomer (p. 636). The *product*, isolated from the acetone extract, was collected at 210°/4 mm. (54·5 g.), and then separated from spirit in colourless rectangular prisms (49·4 g.), m. p. 103—104° (Found: C, 52·7; H, 3·9; N, 7·8. $C_8H_7O_2NS$ requires C, 53·0; H, 3·9; N, 7·7%).

m-*Methylsulphonylbenzamidine Hydrochloride* (XVII).—The preceding nitrile (12·75 g.) was converted into the imino-ether hydrochloride and amidine in the usual way. The *salt* separated from absolute alcohol in fine colourless needles (10·3 g.), m. p. 216° (Found: C, 41·0; H, 4·9; N, 11·8. $C_8H_{10}O_2N_2S,HCl$ requires C, 40·9; H, 4·7; N, 11·9%).

m-*Ethylsulphonylbenzonitrile*.—(i) Phenylethylsulphone (109 g.) was nitrated under the conditions used by Twist and Smiles (*loc. cit.*) for the lower homologue, and the nitro-compound separated from spirit in colourless bipyramids (115 g.), m. p. 103°. Baldwin and Robinson (J., 1932, 1448) record m. p. 101—102°

(ii) Pressure hydrogenation in the manner described above for the methyl derivative proceeded readily and the *amine* *hydrochloride* (106·2 g.) separated from spirit in thin, colourless hexagonal plates, m. p. 239—240° (Found : C, 42·9; H, 5·3; N, 6·5. $C_8H_{11}O_2NS,HCl$ requires C, 43·3; H, 5·4; N, 6·3%).

(iii) The cold diazo-solution from the amine hydrochloride (100 g.) was added to a hot solution of sodium nickel cyanide in the usual way, and the resulting nitrile was recovered by chloroform extraction. The crude product was distilled in a vacuum (b. p. *ca.* 230—240°/2·5 mm.) and then recrystallised from *n*-propyl alcohol, microscopic colourless prisms (50·2 g.) separating, m. p. 49—52°. The pure *nitrile* has m. p. 51—52° (Found : C, 55·6; H, 4·8; N, 7·0. $C_9H_9O_2NS$ requires C, 55·4; H, 4·6; N, 7·2%).

m-*Ethylsulphonylbenzamidine Hydrochloride* (XVIII).—The preceding nitrile (15 g.) was converted into the amidine in the usual way *via* the imino-ether hydrochloride. The *product* was extremely soluble in water and the lower alcohols and separated from absolute alcohol in small, stout, colourless prisms (10·1 g.), m. p. 196° (Found : C, 43·8; H, 5·3; N, 11·2. $C_9H_{12}O_2N_2S,HCl$ requires C, 43·5; H, 5·2; N, 11·3%).

Hydrochlorides of p-*Methylsulphonylbenzyl-* (XX) *and Di*-p-*methylsulphonylbenzyl-amine*.—*p*-Methylsulphonylbenzonitrile (100 g.) was reduced with Raney nickel (10 g.) in 10% alcoholic ammonia solution (600 c.c.) under an initial pressure of 95 atm. at 15°. Hydrogenation was complete in about 1½ hours, in the course of which the temperature had been raised to about 70°. The cooled solution was filtered from catalyst, and evaporated to dryness; the syrupy residue crystallised. A solution of the solid in warm water (*ca.* 500 c.c.), clarified by filtration with kieselguhr, was neutralised to Congo-red with 5N-hydrochloric acid, and the crop (3·2 g.) of secondary amine hydrochloride which separated was collected. The filtrate was evaporated to dryness, and the residue recrystallised from 90% alcohol; a small further crop (0·8 g.) of the secondary amine hydrochloride was removed by filtration of the hot solution, from which the *primary amine hydrochloride* (106 g.) then separated in colourless plates, m. p. 279—280° (Found : C, 43·4; H, 5·2; N, 6·2. $C_8H_{11}O_2NS,HCl$ requires C, 43·3; H, 5·4; N, 6·3%). It was extremely soluble in water. The less soluble *secondary amine hydrochloride* (4 g.) separated from a large volume of water in colourless rectangular plates, m. p. *ca.* 310° (decomp.) (Found : C, 49·4; H, 5·4; N, 3·6. $C_{16}H_{19}O_4NS_2,HCl$ requires C, 49·3; H, 5·1; N, 3·6%).

Hydrogenation of the nitrile was also effected at 3—4 atm. pressure of hydrogen but the time required was much longer.

p-*Ethylsulphonylbenzylamine Hydrochloride* (XXI).—*p*-Ethylsulphonylbenzonitrile (16 g.) was reduced in saturated alcoholic ammonia (250 c.c.) with Raney nickel (4·2 g.) under 70 lb./sq. in. pressure of hydrogen. The expected absorption took place in 2 hours, and there was no further fall during the subsequent 1½ hours. The solution was filtered from catalyst and evaporated to dryness. The syrupy residue was dissolved in warm water and neutralised to Congo-red with N-hydrochloric acid (75 c.c. Calc. for 100% conversion of nitrile and no mechanical loss : 81·8 c.c.). The solution was treated with norit and evaporated to dryness. Recrystallisation from absolute alcohol, whereby traces of a sparingly soluble impurity (secondary base hydrochloride ?) were removed, afforded colourless plates (14·1 g.), m. p. 222° (Found : C, 46·1; H, 6·2; N, 6·2. $C_9H_{13}O_2NS,HCl$ requires C, 45·9; H, 5·9; N, 5·9%).

m-*Methylsulphonylbenzylamine Hydrochloride* (XXII).—*m*-Methylsulphonylbenzonitrile (18·1 g.) was hydrogenated in 10% alcoholic ammonia (400 c.c.) in the presence of Raney nickel (3·6 g.) at 50 atm. pressure, the temperature being raised to about 90° during reduction. The product was worked up in the same manner as in the preceding analogous cases, and the *hydrochloride* separated from a small volume of water in fine, colourless prisms (17·5 g.), m. p. 250—251° (Found : C, 43·3; H, 5·6; N, 6·4. $C_8H_{11}O_2NS,HCl$ requires C, 43·3; H, 5·4; N, 6·3%).

m-*Ethylsulphonylbenzylamine Hydrochloride* (XXIII).—*m*-Ethylsulphonylbenzonitrile (15 g.) was hydrogenated in the manner described above for the analogous cases. The *hydrochloride* separated from a small volume of absolute alcohol in clusters of minute, colourless plates (10·3 g.), m. p. 155—156° (Found : C, 45·8; H, 6·2; N, 5·5. $C_9H_{13}O_2NS,HCl$ requires C, 45·9; H, 6·2; N, 5·9%).

p-*Methylsulphonylbenzaldehyde* (XXIV; R = CHO).—A solution of *p*-methylsulphonylbenzonitrile (36 g.) in chloroform (320 c.c.) was added to Stephen's reagent (from 72 g. of anhydrous stannous chloride) (J., 1925, **127**, 1874) in ether (240 c.c.). The mixture was shaken mechanically for 6 hours, and next day the solid stannichloride was collected and decomposed with water. The *aldehyde* separated from spirit in clusters of colourless tablets (24·9 g.), m. p. 157° (Found : C, 52·3; H, 4·6. $C_8H_8O_3S$ requires C, 52·2; H, 4·3%).

p-*Methylsulphonylcinnamic Acid* (XXIV; R = $CH{:}CH\cdot CO_2H$).—The preceding aldehyde (24·8 g.) and malonic acid (17 g.) were heated on the water-bath in pyridine (30 c.c.) containing 8 drops of piperidine until effervescence ceased and for one hour thereafter. The *acid*, isolated in the normal way, separated from 80% acetic acid in clusters of colourless plates with pointed ends (25·8 g.), m. p. 288° (Found : C, 53·0; H, 4·8. $C_{10}H_{10}O_4S$ requires C, 53·1; H, 4·4%).

β-p-*Methylsulphonylphenylpropionic Acid* (XXIV; R = $CH_2\cdot CH_2\cdot CO_2H$).—The preceding unsaturated acid (35·6 g.) was dissolved in a slight excess of 1·5N-sodium hydroxide, and the solution shaken in hydrogen in the presence of 2% palladised strontium carbonate (5 g.); the expected volume of hydrogen was absorbed in about 6½ hours. The catalyst was collected and the *product* (33·1 g.), precipitated on acidification to Congo-red, separated from water in colourless rectangular plates (31 g.), m. p. 171—172° (Found : C, 52·6; H, 5·3. $C_{10}H_{12}O_4S$ requires C, 52·6; H, 5·3%).

β-p-*Methylsulphonylphenylethylamine Hydrochloride* (XXV).—The foregoing acid (6·9 g.) was converted into the chloride by thionyl chloride (6 c.c.) in chloroform (35 c.c.) containing 1 drop of pyridine. Solvent and excess of thionyl chloride were removed, and the last traces of the latter were entrained in benzene. The chloride was dissolved in acetone (35 c.c.), and the solution was stirred vigorously during addition of an aqueous solution (6 c.c.) of sodium azide (1·95 g.). The mixture was stirred for 10 minutes in melting ice, and the azide was precipitated with water (150 c.c.), collected, and dried for 4½ hours in a vacuum desiccator. The azide was warmed cautiously with benzene (45 c.c.), and the solution then boiled for 5 minutes. 2N-Hydrochloric acid (50 c.c.) was added, and the benzene distilled away. The solution was decolorised with norit and evaporated to dryness, finally with alcohol, in a vacuum on the water-bath, affording a crystalline solid (4·7 g.). The *hydrochloride* separated from absolute alcohol in colourless, rectangular plates, m. p. 204—205° (Found : C, 45·6; H, 6·2; N, 6·2. $C_9H_{13}O_2NS,HCl$ requires C, 45·9; H, 5·9; N, 5·9%).

p-*Methylsulphonylbenzoic Acid* (XXIV; R = CO_2H).—*p*-Methylsulphonylbenzonitrile (94 g.) was added to 75% sulphuric acid (200 c.c.) at 150° during ½ hour, and the mixture heated at 190° for 3 further hours, crystals separating. The mixture was treated with water, and the product collected. The *acid* (99·1 g.) was recovered in a pure condition from a filtered solution of the product in 2N-sodium hydroxide by acidification with concentrated hydrochloric acid; it separated from glacial acetic acid in colourless plates, m. p. 267—268° (Found : C, 47·9; H, 4·1. $C_8H_8O_4S$ requires C, 48·0; H, 4·0%).

p-*Methylsulphonylbenzmethylamide* (XXIV; R = $CO\cdot NHMe$).—The acid (30 g.) was treated with thionyl chloride in the manner described below, and the acid chloride was shaken mechanically with 30% aqueous methylamine (50 c.c.) for an hour with intermittent cooling. The mixture was left for 36 hours at room temperature, and the product (29·2 g.) collected and dried. The *amide* separated from spirit in flattened, colourless needles, m. p. 192° (Found : C, 50·7; H, 4·9; N, 6·6. $C_9H_{11}O_3NS$ requires C, 50·7; H, 5·1; N, 6·6%).

p-*Methylsulphonylacetophenone* (XXIV; R = COMe).—*p*-Methylsulphonylbenzoic acid (40 g.) was converted into the chloride by treatment on the water-bath with thionyl chloride (30 c.c.) in benzene (300 c.c.) containing a few drops of pyridine, about 2 hours being required for solution of the acid. Solvent and excess of thionyl chloride were removed as above (p. 639). The chloride, dissolved in hot benzene (300 c.c.) was added to a solution of ethoxymagnesiomalonic ester (from 6 g. magnesium, 40 c.c. ethyl malonate, 32·5 c.c. absolute alcohol, 1 c.c. carbon tetrachloride) (Lund, *Ber.*, 1934, **67**, 937) in warm benzene (250 c.c.). A brown gelatinous mass separated, and the mixture was warmed on the water-bath for ½ hour, cooled, and treated with water and 2N-sulphuric acid. The benzene solution was separated, dried, and evaporated. The stiff brown syrupy residue was refluxed for 2—3 hours with a mixture of concentrated hydrochloric acid (200 c.c.), glacial acetic acid (200 c.c.), and water (100 c.c.). The mixture was cooled, treated with water (*ca.* 800 c.c.) and chloroform (*ca.* 350 c.c.), filtered from a small quantity of solid (A), shaken with norit, and filtered. The pale yellow chloroform layer was separated, washed with water and aqueous sodium bicarbonate solution, dried, and evaporated, affording the crude *ketone* (33·1 g.; 88%), which crystallised promptly. Recrystallisation from methyl alcohol afforded clusters of colourless prisms, m. p. 128—129° (Found: C, 54·4; H, 5·3. $C_9H_{10}O_3S$ requires C, 54·5; H, 5·0). Crude methylsulphonylbenzoic acid (3·17 g.; 8%) was recovered from (A) and the bicarbonate washings. The *oxime* separated from a small volume of spirit in small stout prisms, m. p. 155—156° (Found: C, 51·0; H, 5·1; N, 6·9. $C_9H_{11}O_3NS$ requires C, 50·7; H, 5·1; N, 6·6%).

α-p-*Methylsulphonylphenylethylamine Hydrochloride* (XXVI).—*p*-Methylsulphonylacetophenone (29·7 g.) was heated for 6 hours at 180° with formamide (from 32·3 g. of commercial ammonium carbonate and 30 c.c. of 90% formic acid) according to Ingersoll *et al.* (*loc. cit.*). The gum, obtained by adding 6 vols. of water to the cooled reaction mixture, was extracted with chloroform, and the extract washed with water, dried, and evaporated. The resulting brown syrup (25·4 g.) was at once hydrolysed by refluxing it with 12% aqueous hydrochloric acid (60 c.c.) for 40 minutes. The hydrolysis solution, diluted with water (100 c.c.) and decolorised with norit, was evaporated to dryness in a vacuum on the water-bath, affording a colourless crystalline *hydrochloride* (20·5 g.; 60%), which separated from glacial acetic acid in fine prisms (17·3 g.), m. p. 274° (Found: C, 46·2; H, 6·2; N, 5·9. $C_9H_{13}O_2NS,HCl$ requires C, 45·9; H, 5·9; N, 5·9%).

Biological Tests.

In vitro *Antibacterial Tests.*—The cultures and technique employed were those previously described (Fuller, *Biochem. J.*, 1942, **36**, 548; Evans, Fuller, and Walker, *loc. cit.*).

Antimalarial Tests on P. gallinaceum *Infections in Chicks.*—In the prophylactic tests the chicks were infected by intravenous inoculation of a suspension of sporozoites, medication being commenced 2 hours before infection. In the therapeutic tests infection was induced by the intravenous inoculation of blood from a highly parasitised donor, and drug treatment was initiated directly thereafter. In both cases drug treatment was continued twice daily for 4 days, and blood smears from treated and control birds were subsequently examined and compared in regard to degree of parasitemia. With (II) definite prophylactic activity was observed at a dosage level of 1000 mg. drug/kg. body-weight, and slight activity at 500 mg./kg; slight therapeutic action was observed at the higher dosage. Of the other compounds examined, (XV) and (XXVI) exhibited slight prophylactic activity, as did (XII) which was, however, toxic to chicks.

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