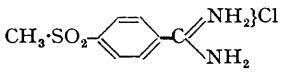
301. *Chemotherapeutic Agents of the Sulphone Type. Part III. Effect of Homologation on the Antibacterial Activity of* p-*Methylsulphonylbenzamidine and* p-*Methylsulphonylbenzylamine Hydrochlorides.*

By H. S. Forrest, A. T. Fuller, and James Walker.

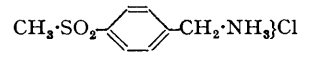
Separating the functional groups from the benzene ring in *p*-methylsulphonyl-benzamidine and -benzylamine hydrochlorides by one or more methylene groups is accompanied by a diminution in antibacterial activity *in vitro*.

Following the discovery of pronounced antibacterial activity in *p*-methylsulphonyl-benzamidine and -benzylamine hydrochlorides [(I) and (II)] (Evans, Fuller, and Walker, *Lancet*, 1944, *ii*, 523; 1945, *ii*, 336), the effects of altering the orientation of the functional groups and of varying the size of the alkyl radical attached to the sulphonyl group were studied (Fuller, Tonkin, and Walker, *J.*, 1945, 633). The conclusion was reached that, for high antibacterial activity, compounds should conform to type (III), where R may be a small alkyl group, as in (I) and in (II), or the $-NH_2$ group, as in marfanil (III; R = NH_2, R′R″ = H_2) which has a similar antibacterial " spectrum " (Evans, Fuller, and Walker, *locc. cit.*), and R′R″ may be an imino-group, as in (I), or two hydrogen atoms, as in (II) and in marfanil, or even one hydrogen atom and one methyl group. The work described in the present paper was designed to test the validity of the above generalisation by the study of further homologues (IV) of the original parent compounds (I) and (II), the aim being to observe the effect of increasing the separation of the functional groups from the benzene ring. In the previous study this had been limited to the α- and β-phenylethylamine

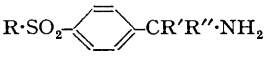
homologues of (II), where diminished antibacterial activity paralleled experience in the marfanil series (Lawrence, *J. Bact.*, 1945, **49**, 149).



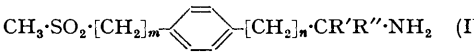
(I.)



(II.)



(III.)

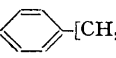


(IV.)

The introduction of a methylene group between the benzene ring and the methylsulphonyl group of (I) and (II) was first undertaken, the essential intermediate, p-*cyanobenzyl methyl sulphone* (V), being obtained in quantitative yield by oxidation of p-*cyanobenzyl methyl sulphide* (VI). p-*Amidinobenzyl methyl sulphone hydrochloride* (VII) was obtained from (V) by the orthodox Pinner technique, while p-(*aminomethyl*)*benzyl methyl sulphone hydrochloride* (VIII) resulted from catalytic hydrogenation of (V) in presence of Raney nickel. Since the original survey had shown *p*-methylthiobenzamidine hydrochloride to have marked antibacterial activity, the homologous p-*amidinobenzyl methyl sulphide hydrochloride* (IX) was prepared from the appropriate nitrile (VI) in the usual way. Access to the corresponding primary amine was obtained only with difficulty. As was expected from the presence of unshared electrons on the sulphur atom, the nitrile (VI) poisoned the catalyst when catalytic hydrogenation was attempted (cf. Maxted, *J.*, 1945, 204; Deem and Kaveckis, *Ind. Eng. Chem.*, 1941, **33**, 1373), and the product consisted of a mixture of the unchanged starting material and *p*-tolunitrile, as (VI), being a benzyl thioether, was particularly readily susceptible to hydrogenolysis in the presence of Raney nickel (Bougault, Cattelain, and Chabrier, *Bull. Soc. chim.*, 1940, **7**, 781; Mozingo, Wolf, Harris, and Folkers, *J. Amer. Chem. Soc.*, 1943, **65**, 1013). Hydrogenolysis also took place when sodium and alcohol reduction was attempted, the only basic product isolated being *p*-tolubenzylamine. A small yield of p-(*aminomethyl*)*benzyl methyl sulphide hydrochloride* (X) was, however, obtained by reducing (VI) with chromous acetate and alcoholic alkali (cf. Graf, *J. pr. Chem.*, 1934, **140**, 39; 1936, **146**, 88). Further homologation at this position in the molecule was not undertaken, attention being directed to compounds homologated in the alternative position (IV; $m = 0$, $n = 1$—3). When the Willgerodt reaction (Willgerodt and Merk, *J. pr. Chem.*, 1902, **80**, 192; Fieser and Kilmer, *J. Amer. Chem. Soc.*, 1940, **62**, 1354) was applied to *p*-methylsulphonylacetophenone, only a poor yield of p-*methylsulphonylphenylacetamide* (XI) resulted, and a much better yield of p-*methylsulphonylphenylthioacetmorpholide* (XII) resulted by using morpholine in Kindler and Li's process (*Ber.*, 1941, **74**, 321), which was recognised by Schwenk and Bloch (*J. Amer. Chem. Soc.*, 1942, **64**, 3051) as fundamentally a variant of the Willgerodt reaction. Hydrolysis of (XII) to p-*methylsulphonylphenylacetic acid* then gave access to (XI) in convenient amounts, and dehydration of (XI) afforded p-*methylsulphonylphenylacetonitrile*, from which p-*methylsulphonylphenylacetamidine hydrochloride* (XIII) was obtained. The corresponding amine (XIV) was included in the earlier survey (Fuller, Tonkin, and Walker, *loc. cit.*), being obtained by the Curtius–Naegeli degradation of β-*p*-methylsulphonylphenylpropionic acid. An attempt to apply the reaction between diazonium salts and acrylonitrile (Koelsch, *J. Amer. Chem. Soc.*, 1943, **65**, 57; Koelsch and Boekelheide, *ibid.*, 1944, **66**, 412), using diazotised *p*-methylsulphonylaniline, was unsuccessful in providing access to β-p-*methylsulphonylphenylpropionitrile* (XV), which was obtained instead by dehydration of β-p-*methylsulphonylphenylpropionamide*. On amidine formation and catalytic hydrogenation respectively, (XV) afforded β-p-*methylsulphonylphenylpropionamidine hydrochloride* (XVI) and γ-p-*methylsulphonylphenyl*-n-*propylamine hydrochloride* (XVII). Further homologation was accomplished by converting β-*p*-methylsulphonylphenylpropionic acid through the acid chloride into the *diazomethyl ketone* and submitting the latter to the Arndt–Eistert reaction. Dehydration of the resulting γ-p-*methylsulphonylphenyl*-n-*butyramide* afforded the *nitrile* required for the preparation of γ-p-*methylsulphonylphenyl*-n-*butyramidine hydrochloride* (XVIII) and δ-p-*methylsulphonylphenyl*-n-*butylamine hydrochloride* (XIX), by amidine formation and catalytic hydrogenation respectively. As an alternative route to the compounds described above and one which would have been applicable to the further extension of the series if such had been warranted by the biological results, the preparation of *ethyl* p-*methylsulphonylbenzoylacetate* (XX) was undertaken, since this ester could be alkylated with ω-halogenated fatty acid esters, or with ω-phthalimidoalkyl halides, to give essential intermediates after ketonic hydrolysis and Clemmensen reduction. The yields of (XX), however, were not promising, and this route was not further examined.

As all the aromatic α-amino-acids of biological importance—phenylalanine, tyrosine, histidine, and tryptophan—are β-substituted derivatives of α-alanine, it appeared desirable to include β-p-*methylsulphonylphenylalanine* (XXI) in this survey, particularly since Schaffer (*Proc. Soc. Exp. Biol. Med.*, 1937, **37**, 648) has claimed that *p*-sulphonamidophenylalanine is superior to sulphanilamide in hæmolytic streptococcal infections in mice. *p*-Methylsulphonylbenzaldehyde was therefore condensed with hippuric acid, and the resulting 2-*phenyl*-4-p-*methylsulphonylbenzylidene*-5-*oxazolone* afforded (XXI) on reductive hydrolysis with red phosphorus and hydriodic acid.

The results of antibacterial tests *in vitro*, which support the conclusions reached in the previous paper, are recorded in the Table, the cultures and technique employed being those previously described (Fuller, *Biochem. J.*, 1942, **36**, 548; Evans, Fuller, and Walker, *locc. cit.*). For comparative purposes the values found for a few substances described in earlier papers are included.

	Compound, X  [CH$_2$]$_n$·Y.			Antibacterial activity *in vitro*. Minimal inhibiting concentrations in mg. of drug per 100 c.c. of nutrient broth.		
	X.	*n*.	Y.	*Strep. hæmolyt.*	*Staph. aureus.*	*Bact. coli.*
(IX)	$CH_3·S·CH_2$	0	$C(NH_2):NH_2\}Cl$	10	100	500
(VII)	$CH_3·SO_2·CH_2$	0	$C(NH_2):NH_2\}Cl$	100	1000	>1000
* (I)	$CH_3·SO_2$	0	$C(NH_2):NH_2\}Cl$	0·15	250	250
(XIII)	$CH_3·SO_2$	1	$C(NH_2):NH_2\}Cl$	0·5	100	750
(XVI)	$CH_3·SO_2$	2	$C(NH_2):NH_2\}Cl$	50	200	750
(XVIII)	$CH_3·SO_2$	3	$C(NH_2):NH_2\}Cl$	150	200	500
(VIII)	$CH_3·SO_2·CH_2$	1	$NH_3\}Cl$	>1000	>1000	>1000
†	$CH_3·SO_2$	0	NH_2	25	750	75
* (II)	$CH_3·SO_2$	1	$NH_3\}Cl$	1	5	100
* (XIV)	$CH_3·SO_2$	2	$NH_3\}Cl$	300	1000	2000
(XVII)	$CH_3·SO_2$	3	$NH_3\}Cl$	30	300	1000
(XIX)	$CH_3·SO_2$	4	$NH_3\}Cl$	200	1000	1000
(XXI)	$CH_3·SO_2$	1	$CH(NH_2)·CO_2H$	500	>500	500

* *J.*, 1945, 633. † *J.*, 1945, 630.

The inhibition of growth of hæmolytic streptococci provides the best basis of comparison, being most sensitive to structural variations in the compounds tested. Comparing (VII) with (I), and (VIII) with (II), it is obvious that the insertion of a methylene group between the methylsulphonyl radical and the benzene ring has the most marked effect of all, causing about a thousand-fold reduction in activity against hæmolytic streptococci. Homologation in the alternative position had a less marked effect on activity, there being a gradual decline in activity with the amidines (I), (XIII), (XVI), and (XVIII), the amidine (XIII) being comparable in activity with the original amidine (I). Analogously, *p*-sulphonamidobenzamidine hydrochloride and the homologous *p*-sulphonamidophenylacetamidine hydrochloride are also comparable in antibacterial activity (Fuller, *Biochem. J.*, 1947, **41**, 403), although, of the two, only the former was found to be active in experimental typhus (Andrewes, King, van den Ende, and Walker, *Lancet*, 1944, *i*, 777; Andrewes, King, and Walker, *Proc. Roy. Soc.*, 1946, *B*, **133**, 20), recalling the fact that the antirickettsial activity of *p*-aminobenzoic acid is lost on similar homologation to *p*-aminophenylacetic acid and related compounds (Hamilton, *Proc. Soc. Exp. Biol. Med.*, 1945, **59**, 220). Among the amines (II), (XIV), (XVII), and (XIX) a clearly marked alternation in antibacterial activity was observable. The activity of (XXI) was lower than expected in view of Schaffer's claim (*loc. cit.*), and also in view of the fact that the biosynthesis, or utilisation, of phenylalanine by some micro-organisms is antagonised by certain structural analogues (Beerstecher and Shive, *J. Biol. Chem.*, 1946, **164**, 53; 1947, **167**, 527; *J. Amer. Chem. Soc.*, 1947, **69**, 461; du Vigneaud *et al.*, *J. Biol. Chem.*, 1945, **159**, 385; Dittmer *et al.*, *ibid.*, 1946, **164**, 761), although the levels at which these structural analogues inhibit the relevant micro-organisms are not of the low order encountered in antibacterial compounds.

Experimental.

p-*Cyanobenzyl Methyl Sulphide* (VI).—To a solution of sodium methyl sulphide, obtained by adding 5N-sodium hydroxide solution (16 c.c.) to *S*-methylthiouronium sulphate (11 g.) and collecting the evolved methanethiol in absolute alcohol (30 c.c.) containing sodium ethoxide (from 1·6 g. of sodium), there was added, in the course of about 5 minutes, a hot saturated solution of *p*-cyanobenzyl bromide (14·8 g.) (Case, *J. Amer. Chem. Soc.*, 1925, **47**, 1144); the reaction was exothermic. Precipitated sodium bromide was removed and the alcoholic solution fractionated. After being washed in ethereal solution with water, the *product* (10·4 g.; 85%) distilled at 178°/25 mm. as a colourless evil-smelling liquid (Found: C, 66·3; H, 5·5. C_9H_9NS requires C, 66·3; H, 5·5%).

p-*Amidinobenzyl Methyl Sulphide Hydrochloride* (IX).—A solution of the above nitrile (10 g.) in chloroform (30 c.c.) and absolute alcohol (13 c.c.) was saturated with dry hydrogen chloride at 0° and kept in the ice-chest for 7 days. Solvent and excess of hydrogen chloride were removed in a vacuum at room temperature and the resulting imino-ether hydrochloride was set aside at 37° with 10% alcoholic ammonia solution (100 c.c.) for several days. The gum, obtained on removal of the solvent by distillation, was dissolved in water, and the solution, brought to about pH 6 with hydrochloric acid, was treated with " norite " and evaporated to dryness. The *product* (10·8 g.) separated from a small volume of water in colourless prisms, m. p. 80°, and, after being dried at 100°/vac., 139—140° (Found: C, 46·1; H, 6·4; loss at 100°/vac., 7·7. $C_9H_{12}N_2S,HCl,H_2O$ requires C, 46·1; H, 6·4; H_2O, 7·8%).

The *acetate*, obtained by double decomposition in concentrated aqueous solution, crystallised from water in radiating clusters of flattened needles, m. p. 243—244° (Found: C, 55·0; H, 6·9. $C_9H_{12}N_2S,C_2H_4O_2$ requires C, 55·0; H, 6·7%).

p-(*Aminomethyl*)*benzyl Methyl Sulphide Hydrochloride* (X).—Aqueous potassium hydroxide (25 g. in 50 c.c.) was dropped into a boiling stirred suspension of chromous acetate (from 50 g. of potassium dichromate) in an alcoholic solution (150 c.c.) of *p*-cyanobenzyl methyl sulphide (7 g.), through which hydrogen was bubbled continuously. Heating and stirring were maintained for 30 minutes after the addition of the alkali, and the mixture was thereafter acidified and steam-distilled. An ethereal extract of this distillate afforded an oil (4·7 g.), yielding unchanged starting material (3·6 g.), b. p. 170°/20 mm., on fractionation. The residual mixture from the steam-distillation was made strongly alkaline and again steam-distilled, the volatile base being neutralised with N-hydrochloric acid. The *product*, freed from some ammonium chloride (0·45 g.) by filtration of a solution in absolute alcohol, separated from *iso*propyl alcohol in colourless, irregular plates (0·4 g.), m. p. 250—254° (Found: C, 53·2; H, 6·7. $C_9H_{13}NS,HCl$ requires C, 53·1; H, 6·9%).

p-*Cyanobenzyl Methyl Sulphone* (V).—A solution of *p*-cyanobenzyl methyl sulphide (5 g.) in glacial acetic acid (10 c.c.) was cautiously treated with 30% hydrogen peroxide (8 c.c.). In the course of a week at room temperature a crystalline solid separated; water was then added and the substance collected. The *product* separated from alcohol in colourless needles (6 g.), m. p. 166° (Found: C, 55·7; H, 4·6; N, 7·5. $C_9H_9O_2NS$ requires C, 55·4; H, 4·6; N, 7·2%).

p-*Amidinobenzyl Methyl Sulphone Hydrochloride* (VII).—The preceding cyano-sulphone (13 g.) was converted into the imino-ether hydrochloride in the usual way. The latter, freed from solvents and excess of hydrogen chloride in a vacuum at room temperature, was incubated with 10% alcoholic ammonia (120 c.c.) at 37° for 4 days, during which time a heavy crystalline solid separated. The substance was separated and combined with the residue left on evaporation of the solvent. A solution of the combined solids in water was brought to pH 6 with hydrochloric acid, freed from a small amount (0·8 g.) of unchanged nitrile, decolourised with " norite ", and evaporated to dryness. The *product* crystallised from a small volume of water in colourless prisms (13 g.), m. p. 284° (Found: C, 43·6; H, 5·5; N, 11·4. $C_9H_{12}O_2N_2S,HCl$ requires C, 43·5; H, 5·2; N, 11·2%).

The *benzoate*, prepared by double decomposition in aqueous solution, crystallised from water in elongated rectangular plates, m. p. 244° (Found: C, 57·3; H, 5·4; N, 8·1. $C_9H_{12}O_2N_2S,C_7H_6O_2$ requires C, 57·5; H, 5·4; N, 8·4%).

p-(*Aminomethyl*)*benzyl Methyl Sulphone Hydrochloride* (VIII).—*p*-Cyanobenzyl methyl sulphone (12 g.) was hydrogenated in 10% alcoholic ammonia (130 c.c.) in the presence of Raney nickel (4 g.) at an initial pressure of 26 atm., the temperature being allowed to rise to 60° during the reaction by the application of external heat. Catalyst was removed by filtration and solvent by distillation. The resulting solid was neutralised with N-hydrochloric acid (required, 58 c.c.; calc., 60 c.c.), and the solution, decolourised with " norite," was evaporated to dryness. The *product* separated from 90% alcohol in tiny, irregular, colourless plates (11·5 g.), m. p. 272—274° (Found: C, 45·9; H, 6·2; N, 5·8. $C_9H_{13}O_2NS,HCl$ requires C, 46·0; H, 6·0; N, 6·0%).

p-*Methylsulphonylphenylacetamide* (XI).—*p*-Methylsulphonylacetophenone (3 g.) (Fuller, Tonkin, and Walker, *loc. cit.*) in dioxan (9 c.c.) was heated for 8 hours at 160° in a sealed tube with sulphur (1 g.) in ammonium sulphide solution (10 g.), obtained by saturating aqueous ammonia (*d* 0·88) with hydrogen sulphide. On cooling, a thick oily layer separated and partly solidified on treatment with water. The crude solid (2·2 g.) was digested with ammonium sulphide solution (100 c.c.) on the water-bath for ½ hour, cooled, and collected. On crystallisation from water (" norite "), the *product* separated in colourless needles (1 g.), m. p. 200° (Found: C, 50·6; H, 5·1; N, 6·6. $C_9H_{11}O_3NS$ requires C, 50·7; H, 5·1; N, 6·6%).

A number of modifications of the foregoing experiment were examined, but no significant improvement in yield resulted.

p-*Methylsulphonylphenylthioacetmorpholide* (XII).—*p*-Methylsulphonylacetophenone (5 g.) was heated in an oil-bath at 130—150° for 8 hours with morpholine (2·3 g.) and sulphur (0·8 g.). The thick oil so obtained rapidly crystallised on treatment with ethyl acetate, affording material (4 g.), m. p. 142—143°, sufficiently pure for subsequent use directly. Evaporation of the ethyl acetate and crystallisation of the residue from methyl alcohol (" norite ") gave a further quantity (1 g.) of the same material. The pure *compound* separated from methyl alcohol in yellow rectangular prisms, m. p. 143·5° (Found: C, 52·3; H, 6·0; N, 4·8. $C_{13}H_{17}O_3NS_2$ requires C, 52·1; H, 5·7; N, 4·7%).

p-*Methylsulphonylphenylacetic Acid*.—The preceding compound (16 g.) was refluxed for 13 hours with 2N-potassium hydroxide (190 c.c.), and the solution was then cooled, filtered from a small amount of sulphur, and acidified. The *product* (9·2 g.) separated from water in clusters of colourless needles, m. p. 137° (Found: C, 50·7; H, 5·0. $C_9H_{10}O_4S$ requires C, 50·5; H, 4·7%).

The *ethyl* ester (9·5 g.), obtained by refluxing the acid (9·1 g.) with absolute alcohol (25 c.c.) and concentrated sulphuric acid (1·8 c.c.) for 3 hours, separated from benzene–ligroin in colourless felted needles, m. p. 79° (Found: C, 54·7; H, 5·8. $C_{11}H_{14}O_4S$ requires C, 54·5; H, 5·8%). The amide (XI), m. p. 200°, was obtained in good yield by treating this ester with concentrated aqueous ammonia.

p-*Methylsulphonylphenylacetonitrile*.—*p*-Methylsulphonylphenylacetamide (6·4 g.) was refluxed with phosphoryl chloride (6·3 c.c.) in chloroform (20 c.c.) for 20 minutes. Excess of oxychloride and solvent

were then removed and the residue was treated with ice and water. The *product* separated from water in colourless, rectangular plates (5 g.), m. p. 124° (Found : C, 55·7; H, 4·6; N, 7·0. $C_9H_9O_2NS$ requires C, 55·4; H, 4·6; N, 7·2%). The mother-liquors on concentration afforded a mixture of nitrile and amide.

p-*Methylsulphonylphenylacetamidine Hydrochloride* (XIII).—The imino-ether hydrochloride prepared from the above nitrile (4·4 g.) was incubated with 10% alcoholic ammonia in the manner described above. The alcoholic ammonia solution was filtered from a small amount of ammonium chloride and evaporated to dryness, affording a sticky gum. The gum was dissolved in water and the solution was brought to pH 6 with hydrochloric acid, decolourised with " norite," and evaporated to dryness. The last traces of water were removed by repeated evaporation to dryness with absolute alcohol in a vacuum on the water-bath, affording a stiff glass (4·2 g.). The *product* eventually crystallised from methyl alcohol–ethyl acetate, or from *n*-propyl alcohol, in fine needles (2·4 g.), m. p. 175—177°, softening at 170° (Found : C, 43·9; H, 5·1. $C_9H_{12}O_2N_2S$,HCl requires C, 43·5; H, 5·2%). Unlike the amidines described above, this one did not yield a sparingly soluble benzoate, and attempts to prepare other salts less soluble than the hydrochloride, such as the acetate or the nitrate, were unsuccessful.

β-p-*Methylsulphonylphenylpropionamide*.—*β*-*p*-Methylsulphonylphenylpropionyl chloride (from 15 g. of the acid) (Fuller, Tonkin, and Walker, *loc. cit.*) was dissolved in acetone and slowly added to aqueous ammonia (100 c.c.; *d* 0·88). The *product* (13·2 g.) separated from water in rectangular plates, m. p. 182° (Found : C, 52·7; H, 5·5. $C_{10}H_{13}O_3NS$ requires C, 52·9; H, 5·7%).

β-p-*Methylsulphonylphenylpropionitrile* (XV).—The above amide (11·7 g.) was dehydrated with phosphoryl chloride in chloroform in the manner described for the lower homologue (above). The *nitrile* (9 g.) separated from aqueous alcohol in rectangular prisms, m. p. 96° (Found : C, 57·0; H, 5·0; N, 6·8. $C_{10}H_{11}O_2NS$ requires C, 57·4; H, 5·3; N, 6·7%).

β-p-*Methylsulphonylphenylpropionamidine Hydrochloride* (XVI).—The above nitrile (4·25 g.) was converted into the amidine by way of the imino-ether hydrochloride. The crude product separated during the digestion with ammonia as a heavy crystalline precipitate. The *compound* crystallised from spirit in irregular, colourless plates (4·4 g.), m. p. 213°, softening at 209° (Found : C, 45·8; H, 5·7. $C_{10}H_{14}O_2N_2S$,HCl requires C, 45·7; H, 5·7%).

The *benzoate*, obtained by double decomposition, separated from water in rectangular plates, m. p. 219°, softening at 213° (Found : C, 58·5; H, 5·5. $C_{10}H_{14}O_2N_2S,C_7H_6O_2$ requires C, 58·6; H, 5·7%).

γ-p-*Methylsulphonylphenyl*-n-*propylamine Hydrochloride* (XVII).—*β*-*p*-Methylsulphonylphenylpropionitrile (4·5 g.) was hydrogenated in saturated alcoholic ammonia (50 c.c.) at 50 atm. in the presence of Raney nickel (1 g.). The temperature was raised to about 70° in the course of 2 hours, and the autoclave was then allowed to cool. The catalyst was collected, and the solvent was evaporated under reduced pressure. The residue was taken up in water and neutralised with N-hydrochloric acid (required, approx. 12 c.c.; calc. 21·5 c.c.). A small volume of alcohol was added to give a homogeneous solution, which was then decolourised with " norite " and evaporated to small bulk. On cooling, unchanged nitrile (2·4 g.) separated and was collected. On further evaporation to dryness and crystallisation from absolute alcohol, the *product* separated in colourless square plates (1·3 g.), m. p. 214—215° (Found : C, 48·3; H, 6·2. $C_{10}H_{15}O_2NS$,HCl requires C, 48·1; H, 6·4%).

Diazomethyl β-p-*Methylsulphonylphenylethyl Ketone*.—*β*-*p*-Methylsulphonylphenylpropionyl chloride (from 10·5 g. of acid) was dissolved in a mixture of ether (50 c.c.) and chloroform (50 c.c.), and added to a dried ethereal solution of diazomethane (from 20·5 g. of nitrosomethylurea). After standing overnight, the product, which had separated, was collected (8·5 g.; m. p. 95—97°); it was sufficiently pure for further use directly. The pure *compound* separated from benzene–ligroin in pale yellow needles, m. p. 97° (Found : C, 52·8; H, 4·7. $C_{11}H_{12}O_3N_2S$ requires C, 52·4; H, 4·8%).

γ-p-*Methylsulphonylphenyl*-n-*butyramide*.—The preceding diazo-ketone (9·2 g.) in dioxan (46 c.c.) was treated with aqueous ammonia (60 c.c. of ammonia solution, *d* 0·88; 9 c.c. of water) and 10% aqueous silver nitrate (14 c.c.) at 60—70°. After a few minutes a brisk evolution of nitrogen took place, and after this slackened the reaction was completed at the boiling point for a short time. The solution was filtered hot, diluted with water, and decolourised with " norite." The *product*, which separated on concentration to small bulk, crystallised from water in colourless fern-like needles (6·7 g.), m. p. 134° (Found : C, 54·9; H, 6·0. $C_{11}H_{15}O_3NS$ requires C, 54·8; H, 6·2%).

As a by-product in one experiment *chloromethyl* β-p-*methylsulphonylphenylethyl ketone* was isolated. This separated from methyl alcohol in colourless prisms, m. p. 114° (Found : C, 51·1; H, 5·4. $C_{11}H_{13}O_3SCl$ requires C, 50·7; H, 5·0%). On condensation with thiourea (0·27 g.) in alcohol (7 c.c.) on the water-bath for 2 hours, this compound (0·9 g.) afforded 4-*β*-p-*methylsulphonylphenylethyl*-2-*aminothiazole hydrochloride* (1·1 g.), which crystallised on cooling. Recrystallisation from methyl alcohol afforded colourless plates, m. p. 219—220° (Found : N, 8·4. $C_{12}H_{14}O_2N_2S_2$,HCl requires N, 8·8%).

γ-p-*Methylsulphonylphenyl*-n-*butyronitrile*.—*γ*-*p*-Methylsulphonylphenyl-*n*-butyramide (8·2 g.) was dehydrated with phosphoryl chloride (8 g.) in chloroform (40 c.c.). On working up the reaction mixture a solid was obtained which was taken up in chloroform. The chloroform solution was dried and evaporated. The residue, on distillation in a high vacuum, crystallised in the receiver in the form of tiny rectangular plates (6·7 g.), m. p. 66°. The *product* had m. p. 70° after crystallisation from carbon tetrachloride, the only suitable solvent (Found : C, 58·8; H, 6·1; N, 6·5. $C_{11}H_{13}O_2NS$ requires C, 59·2; H, 5·8; N, 6·3%).

γ-p-*Methylsulphonylphenyl*-n-*butyramidine Hydrochloride* (XVIII).—The preceding nitrile (3 g.) was converted into the amidine by way of the imino-ether hydrochloride. A clear solution resulted at the end of the digestion with alcoholic ammonia. The residue obtained on evaporation to dryness was dissolved in water, brought to pH 6, decolourised with " norite," and recovered by evaporation to dryness. The last traces of water were removed by evaporation under reduced pressure with absolute alcohol. A concentrated solution in absolute alcohol was filtered from traces of ammonium chloride, and the alcohol was again removed. On crystallisation from methyl alcohol–ethyl acetate, the *product* separated in colourless rectangular prisms (3 g.), m. p. 141—142° (Found : C, 48·0; H, 6·3. $C_{11}H_{16}O_2N_2S$,HCl requires C, 47·7; H, 6·2%).

The *benzoate* crystallised from water in elongated, rectangular plates, m. p. 185° (Found: C, 59·7; H, 6·3. $C_{11}H_{16}O_2N_2S,C_7H_6O_2$ requires C, 59·7; H, 6·1%).

δ-p-*Methylsulphonylphenyl*-n-*butylamine Hydrochloride* (XIX).—γ-*p*-Methylsulphonylphenyl-*n*-butyronitrile (3 g.) was reduced in alcoholic ammonia solution (170 c.c., saturated) in the presence of Raney nickel (1 g.) in hydrogen at a pressure of 57 atm., the temperature being raised to 50° during the reaction. After 4 hours the reaction mixture was worked up. Unchanged nitrile (1·6 g.) was recovered, and the *product* crystallised from methyl alcohol–ether in colourless, irregular plates (1·2 g.), m. p. 158—159° (Found: C, 50·0; H, 6·8; N, 5·6. $C_{11}H_{17}O_2NS,HCl$ requires C, 50·1; H, 6·8; N, 5·3%).

Note on the Physical Properties of the Above Amidine Salts.—The amidine hydrochlorides (I), (XIII), (XVI), and (XVIII) presented the noteworthy feature of showing alternations in the melting points and solubilities as the homologous series was ascended. The melting points followed the sequence: 294°, 175—177°, 213°, and 141—142°. Similarly the solubilities in water were alternately moderate and excessively high.

Ethyl p-*Methylsulphonylbenzoylacetate* (XX).—*p*-Methylsulphonylbenzoyl chloride (from 20 g. of acid; 1 mol.) in benzene (120 c.c.) was added to ethyl sodioacetoacetate (from 4·6 g. of sodium and 26 g. of ethyl acetoacetate; 2 mols.) in benzene (300 c.c.). The mixture was refluxed for 4 hours and then allowed to stand overnight. After addition of excess of dilute sulphuric acid a small amount of *p*-methylsulphonylbenzoic acid (2·9 g.) was recovered by filtration. The benzene layer was evaporated and the residue treated with methyl alcohol (250 c.c.) containing sodium methoxide (from 5 g. of sodium). After 5½ hours at room temperature the solution was poured into a mixture of ice and dilute sulphuric acid, and the precipitated oil was extracted with ether. The residue, obtained on evaporation of the dried ether extract, was fractionally crystallised from methyl alcohol. The first fraction (2·8 g.), m. p. 118—119°, was shown to be methyl *p*-methylsulphonylbenzoate by comparison with an authentic specimen (below). The second fraction (5·8 g.), m. p. 80—90°, after crystallisation from benzene and again from methyl alcohol, afforded the pure *product* (XX), m. p. 86—88°, in the form of colourless rectangular plates (Found: C, 53·7; H, 5·1. $C_{12}H_{14}O_5S$ requires C, 53·3; H, 5·2%).

The substance gave a typical blood-red ferric reaction in alcoholic solution and it was further characterised as the *phenylpyrazolone*. The keto-ester (0·24 g.) and phenylhydrazine (0·1 c.c.) were heated on the water-bath for 3 hours. The thick gum solidified on trituration with ether and the solid (0·1 g.), after crystallisation from dilute acetic acid, had m. p. 215° (Found: N, 9·3. $C_{16}H_{14}O_3N_2S$ requires N, 9·0%).

Methyl p-*Methylsulphonylbenzoate.*—*p*-Methylsulphonylbenzoic acid (2 g.) was esterified with methyl alcohol (10 c.c.) in the presence of concentrated sulphuric acid (0·5 c.c.) on the water-bath for 2 hours. The *product*, obtained on diluting the reaction mixture with water, separated from methyl alcohol in elongated, rectangular colourless plates, m. p. 118—119° (Found: C, 50·1; H, 4·8. $C_9H_{10}O_4S$ requires C, 50·5; H, 4·7%).

2-*Phenyl*-4-p-*methylsulphonylbenzylidene*-5-*oxazolone.*—*p*-Methylsulphonylbenzaldehyde (9·2 g.) (Fuller, Tonkin, and Walker, *loc. cit.*), hippuric acid (9·6 g.), and sodium acetate (4 g.) were intimately mixed. Acetic anhydride (14 c.c.) was then added and the paste was heated until fusion occurred and then left on the water-bath for 2 hours. The mixture was then cooled, treated with absolute alcohol (20 c.c.), and left in the ice-chest overnight. The product (13 g.) was then collected, and washed with two successive portions of boiling water (5 c.c.) and with a little cold water. The m. p. was 182—184° and the material was sufficiently pure for further use directly. The pure *compound* separated from acetic acid in yellow needles, m. p. 184—186° (Found: C, 62·7; H, 3·8; N, 4·2. $C_{17}H_{13}O_4NS$ requires C, 62·4; H, 4·0; N, 4·3%).

β-p-*Methylsulphonylphenylalanine* (XXI).—To the crude azlactone (11·8 g.), mixed with red phosphorus (7 g.) and acetic anhydride (44 c.c.), hydriodic acid (41 c.c.; *d* 1·7) was added slowly, with constant shaking, during 30 minutes. The solution was then refluxed for 3 hours, cooled, freed from phosphorus by filtration, and evaporated to dryness. The residue was taken up in water (30 c.c.), again evaporated to dryness, and again redissolved in water (100 c.c.). The aqueous solution was thrice extracted with ether, treated with " norite " after removal of dissolved ether, and then heated to the boiling point. On bringing the pH to about 4 and cooling, the product (7·5 g.) separated. It was recrystallised with difficulty from water when the pure *compound* separated as a micro-crystalline powder, m. p. 250—256° (Found: C, 49·8; H, 5·5; N, 5·6. $C_{10}H_{13}O_4NS$ requires C, 49·4; H, 5·3; N, 5·8%).

NATIONAL INSTITUTE FOR MEDICAL RESEARCH,
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