46. *Anti-bacterial Substances allied to Sulphanilamide.*

By T. Dewing, W. H. Gray, B. C. Platt, and D. Stephenson.

A series of substances has been prepared to test the effects on anti-bacterial activity, when various substituents, mostly of a non-basic character, are introduced into the molecule of sulphanilamide. It is shown that such modifications, in contrast with those induced by the use of certain basic substituents, usually result at best in the retention of the original activity.

It is now well established that compounds represented by the general formula $NH_2 \cdot C_6H_4 \cdot SO_2X$, where NH_2 and SO_2X are in the *para*-position relative to each other, are potent anti-bacterial agents. Such activity is exhibited *in vitro* when X = OH, as in sulphanilic acid, and is greatly enhanced when X = NH_2, as in sulphanilamide, and is then shown *in vivo*.

This activity is greatly enhanced when X is a 2-aminopyridine (sulphapyridine), 2-aminothiazole (sulphathiazole), 2-aminopyrimidine (sulphadiazine) or a guanidine (sulphaguanidine) residue and is to some extent specialised. The four substances resulting from these substitutions have all been used clinically with success. In general, such secondary toxic effects as they exhibit are of a mild order and respond readily to treatment. Bieter *et al.* (*J. Amer. Med. Assoc.*, 1941, **116**, 2231) found that, in chickens, sulphanilamide and the sulphanilyl derivatives of 2-aminopyridine and 2-aminothiazole, as well as other compounds of this group, produced nervous effects due to a chronic cumulative concentration of the drug in the peripheral nerves.

When X = $C_6H_4 \cdot NH_2$, joined through carbon, the resulting product is 4 : 4′-diaminodiphenylsulphone, $NH_2 \cdot C_6H_4 \cdot SO_2 \cdot C_6H_4 \cdot NH_2$, which is probably the most potent anti-bacterial agent of this group, but, as its acute toxicity is high, it has not been used clinically. Also, when it is fed to rats for long periods, peripheral neuritis is observed. In Schiff's bases prepared from this sulphone (Wellcome Foundation Ltd., Henry and Gray, Brit. Pat. 491,265; Buttle, Dewing, Foster, Gray, Smith, and Stephenson, *Biochem. J.*, 1938, **32**, 1101) both kinds of toxic effects are reduced, and in at least two of its derivatives, sodium 4 : 4′-di-γ-phenylpropylaminodiphenylsulphonetetrasulphonate, $C_{30}H_{28}O_{14}N_2S_5Na_4,10H_2O$ (*loc. cit.*), and sodium 4 : 4′-bisvaleramidodiphenylsulphonedi-δ-carboxylate, $NaO_2C \cdot [CH_2]_4 \cdot CO \cdot NH \cdot C_6H_4 \cdot SO_2 \cdot C_6H_4 \cdot NH \cdot CO \cdot [CH_2]_4 \cdot CO_2Na$ (Wellcome Foundation Ltd., Henry, Gray, and Platt, Brit. Pat. 531,571), the acute toxicity is negligible and with them it has not been possible to produce neuritis in rats. Both these drugs show promise as means of utilising the remarkable anti-bacterial activity of the sulphone.

Although the compounds of this group already evolved have provided the physician with effective means of dealing in dramatic fashion with a number of intractable diseases of bacterial origin, there is still room for improvement and for an extension of their range of therapeutic activity. This justifies further systematic, exploratory work by the chemist and the biologist, both on compounds closely related to the effective substances already known and on compounds allied to these in general structure but with other substituents. The present paper is an essay in this direction. As the compounds described are largely derivatives of sulphanilamide, it will be convenient in referring to them to adopt the nomenclature

suggested by Crossley, Northey, and Hultquist (*J. Amer. Chem. Soc.*, 1938, **60**, 2217) whereby substitution in the nuclear amino-group is indicated by N^4 and in the NH_2 of the sulphonamido-group by N^1.

In the four effective therapeutic agents referred to above it will be noticed that the substituents introduced are all basic in character and it is of interest to investigate the effects of introducing non-basic groups at N^1 or N^4 or in both positions simultaneously. A number of such derivatives have been made, and their anti-bacterial action determined by one of us (D. S.). The results are summarised in the table.

TABLE.

No.	Name.	Formula.	Anti-bacterial action *in vivo*.
1	N^4-Benzoylsulphanilamide	$C_6H_5\cdot CO\cdot NH\cdot C_6H_4\cdot SO_2\cdot NH_2$	Inactive
2	N^1N^4-Dibenzoylsulphanilamide	$C_6H_5\cdot CO\cdot NH\cdot C_6H_4\cdot SO_2\cdot NH\cdot CO\cdot C_6H_5$	Slightly less active than sulphanilamide (strep.); inactive (pneumo.)
3	Sulphanilylmyristamide	$NH_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot CO\cdot C_{13}H_{27}$	As active as sulphanilamide (strep.); inactive (pneumo.)
4	Sulphanilyladipamide	$NH_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot CO\cdot [CH_2]_4\cdot CO_2H$	One-tenth as active as sulphanilamide
5	Sulphanilylchaulmoogramide	$NH_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot CO\cdot [CH_2]_{12}\cdot C_5H_7$	As active as sulphanilamide (strep.); very slightly active (pneumo.)
6	Disulphanilylethyleneguanidine	$C_3H_5N_3(SO_2\cdot C_6H_4\cdot NH_2)_2$	One-tenth as active as sulphanilamide (strep.); one-sixth and one-tenth as active as sulphapyridine (pneumo. and staph. respectively)
7	Sulphanilylglutamic acid	$NH_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot CH(CO_2H)\cdot CH_2\cdot CH_2\cdot CO_2H$	Inactive (strep., pneumo.)
8	Sulphanilylaminoethylpyridinium bromide	$NH_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot C_2H_4(C_5H_5N)Br$	Inactive
9	4-Benzylideneaminobenzenesulphonylglycine	$C_6H_5\cdot CH{:}N\cdot C_6H_4\cdot SO_2\cdot NH\cdot CH_2\cdot CO_2H$	Inactive
10	2′-Acetoxymercuri-3′-hydroxybenzylidenesulphanilamide	$C_6H_3(OH)(HgO_2C\cdot CH_3)\cdot CH{:}N\cdot C_6H_4\cdot SO_2\cdot NH_2$	Slightly less active than sulphanilamide (strep.); inactive (pneumo., staph.)
11	8-Quinolyl *p*-nitrophenyl ether	$C_9H_6N\cdot O\cdot C_6H_4\cdot NO_2$	Inactive (strep., pneumo.)
12	4-*p*-Nitrophenoxybenzenesulphonamide	$NO_2\cdot C_6H_4\cdot O\cdot C_6H_4\cdot SO_2\cdot NH_2$	Inactive (strep., pneumo., staph.)
13	4 : 4′-Bis-(*p*-nitrobenzamido)diphenylsulphone	$SO_2(C_6H_4\cdot NH\cdot CO\cdot C_6H_4\cdot NO_2)_2$	One-hundredth as active as sulphanilamide (strep.); inactive (pneumo., staph.)
14	2-Pyrrolidone-5-carboxyamino-3′-methylbenzene-*x*-sulphonamide	$C_4H_6ON\cdot CO\cdot NH\cdot C_6H_3\cdot (CH_3)\cdot SO_2\cdot NH_2$	One-tenth as active as sulphanilamide (strep.); one-tenth as active as sulphapyridine (pneumo.); inactive (staph.)
15	2-(2′-Pyrrolidone-5′-carboxy-4″-aminobenzenesulphonamido)-pyridine	$C_4H_6ON\cdot CO\cdot NH\cdot C_6H_4\cdot SO_2\cdot NH\cdot C_5H_4N$	Inactive (pneumo., staph.)
16	Diphenylsulphone-4 : 4′-bisazo-β-naphthol	$SO_2(C_6H_4\cdot N_2\cdot C_{10}H_6\cdot OH)_2$	Inactive (strep., pneumo.)
17	2 : 2′-Dipyridylsulphone	$C_5H_4N\cdot SO_2\cdot C_5H_4N$	Stimulated pneumococci *in vitro*; inactive (strep.)
18	N^4-Quininoylsulphanilamide	$CH_3\cdot O\cdot C_9H_5N\cdot CO\cdot NH\cdot C_6H_4\cdot SO_2\cdot NH_2$	Inactive (strep., pneumo., staph.)
19	1-Phenyl-2 : 3-dimethyl-5-pyrazolone-*x*-sulphonamide	$C_5H_7ON_2\cdot C_6H_4\cdot SO_2\cdot NH_2$	Less than one-tenth as active as sulphanilamide (strep.); inactive (pneumo., staph.)
20	N^4-Dihydrochaulmoogrylsulphanilamide	$C_5H_9\cdot [CH_2]_{12}\cdot CO\cdot NH\cdot C_6H_4\cdot SO_2\cdot NH_2$	One-hundredth as active as sulphanilamide (strep.); inactive (pneumo., staph.)
21	Diphenylsulphone-4 : 4′-bisazosalicylic acid	$SO_2[C_6H_4\cdot N_2\cdot C_6H_3(OH)\cdot CO_2H]_2$	As active as sulphanilamide (strep.), as active as sulphapyridine (pneumo.), inactive (staph.)
22	Sodium 2-aminopyridine-*N*-methylenebisulphite	$C_5H_4N\cdot NH\cdot CH_2\cdot SO_3Na$	Inactive (strep., pneumo.)
23	Ethyl *p*-nitrobenzenesulphinate	$NO_2\cdot C_6H_4\cdot SO\cdot O\cdot C_2H_5$	One-tenth as active as sulphanilamide (strep.); inactive (pneumo.); trace of activity (staph.)
24	*p*-Nitrobenzenesulphenamide	$NO_2\cdot C_6H_4\cdot S\cdot NH_2$	Less active than sulphanilamide (strep.); trace of activity (pneumo.), less active than sulphapyridine (staph.)
25	4-Nitrobenzenesulphon-4′-nitroanilide	$NO_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot C_6H_4\cdot NO_2$	Trace of activity (strep.); inactive (pneumo., staph.)
26	4-(*p*-Nitrobenzenesulphonamido)-4′-nitrodiphenyl sulphide	$NO_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot C_6H_4\cdot S\cdot C_6H_4\cdot NO_2$	Trace of activity (strep.); inactive (pneumo., staph.)

Substitution in the N^4-position of an acyl group (Nos. 1, 14, 18, 20) or an arylidene group (Nos. 9, 10) for hydrogen led to a decrease in, or disappearance of, activity even when the substituent was a mercurated organic radical (No. 10) known to show marked bactericidal action.

Substitution in position N^1 on the contrary causes no diminution in activity (Nos. 3, 5) so long as a simple, monocarboxylic acid residue is the substituent and such substitution is even sufficient to neutralise the disadvantageous effect of acyl substitution in position N^4 (cf. Nos. 1 and 2). With a dicarboxylic acid, one carboxyl group being left free (No. 4), activity is much reduced and when both are left free (No. 7) the product is inactive.

The remaining items in the table illustrate several points of general interest.

It is a common experience that the accumulation of two or more potentially active substituents in one molecule generally produces an inactive substance, or at least leads to a reduction in activity (see Nos. 6, 15).

The two *p*-nitrophenyl ethers (Nos. 11, 12) were made in consequence of the observation by Buttle *et al.* (*Biochem. J.*, 1938, **32**, 1101) that 4 : 4′-dinitrodiphenyl ether has a slight protective activity, but it was not found in these. The nitro-group appears, from the relative inactivity of 4 : 4′-dinitrodiphenylsulphone (Buttle *et al.*, *Lancet*, 1937, i, 1331), to have little useful therapeutic effect in comparison with the amino-group, and the low activity of Nos. 23, 24, and 26 may be due in part to this fact.

No chemotherapeutical investigation seems to be complete without an inexplicable contrast, which in this case is provided by Nos. 16 and 21, the former being inactive, whereas the latter retains the action of sulphanilamide on the streptococcus and is also as active as sulphapyridine against the pneumococcus. Excluding No. 21, none of the 26 substances dealt with in this paper was sufficiently promising in these bacteriological tests to be worth detailed pharmacological investigation, but a careful biochemical comparison of Nos. 16 and 21 might yield results of scientific interest, which are much needed if the present haphazard methods of chemotherapeutical investigation are to be replaced by a more rational procedure.

Experimental.

N^4-Benzoyl- and N^1N^4-Dibenzoyl-sulphanilamide.—Sulphanilamide (30 g.) was dissolved in 2·5N-sodium hydroxide (150 c.c.) and shaken with benzoyl chloride (25 c.c.). A cream-coloured precipitate of *N^4-benzoylsulphanilamide* separated which, after being washed, dried, and crystallised from 16 parts of pyridine, had m. p. 284° (Found : N, 10·3; S, 11·6. $C_{13}H_{12}O_3N_2S$ requires N, 10·1; S, 11·6%).

The alkaline liquor on acidification gave an orange-coloured precipitate. This was crystallised by solution in 30 parts of alcohol and dilution with an equal volume of water. The crystals were recrystallised from alcohol, *N^1N^4-dibenzoylsulphanilamide* being obtained in white crystals, m. p. 268—270° (Found : N, 7·3; S, 8·3. $C_{20}H_{16}O_4N_2S$ requires N, 7·4; S, 8·4%).

The mono- and the di-benzoyl derivative do not dissolve readily in sodium hydroxide solution except on warming; sparingly soluble sodium salts are then formed. The dibenzoyl derivative is readily soluble in dilute aqueous ammonia.

N^1N^4-Dibenzoylsulphanilamide was more conveniently prepared in good yield by adding benzoyl chloride (3 c.c.) to a solution of *N^1*-benzoylsulphanilamide (5 g.) in pryidine (50 c.c.). After ½ hour the mixture was diluted with water and acidified; the required material was then precipitated in an almost pure condition.

Sulphanilylacylamides (*N^1-Acylsulphanilamides*).—Solutions of *N^4*-acetylsulphanilamide and of the appropriate acid chloride in pyridine (5 parts) were mixed, heated on the water-bath for 1 hour, poured into water, and acidified with hydrochloric acid if necessary to complete precipitation. The precipitate was collected and refluxed in N-sodium hydroxide for 1 hour. On acidification with acetic acid the crude product was obtained.

Sulphanilylmyristamide was recrystallised from alcohol and obtained as a white crystalline product, m. p. 126° (Found : N, 7·6; S, 8·8. $C_{20}H_{34}O_3N_2S$ requires N, 7·3; S, 8·4%).

Sulphanilyladipamide, recrystallised from water, had m. p. 178° (Found : N, 9·8; S, 11·0. $C_{12}H_{16}O_5N_2S$ requires N, 9·3; S, 10·6%). Ethyl adipyl chloride was used in the preparation, the alkaline hydrolysis removing both the acetyl and the ethyl group.

Sulphanilylchaulmoogramide was prepared from chaulmoogric acid obtained by recrystallisation of high-melting fatty acids from oil of *Hydnocarpus Wightiana*. It had been hoped that some hydnocarpic acid would have been obtained, but the acylsulphanilamide obtained from these acids gave analytical results more nearly agreeing with those required for the chaulmoogryl compound. After several recrystallisations from alcohol it melted at 80—90° (Found : N, 6·45; S, 7·0. $C_{24}H_{38}O_3N_2S$ requires N, 6·45; S, 7·4%).

Dihydrosulphanilylchaulmoogramide.—Sulphanilylchaulmoogramide (10 g.) was dissolved in acetone (50 c.c.) and hydrogenated at 2 atms. by means of a charcoal–palladium catalyst. Absorption of hydrogen was rapid and ceased sharply when the theoretical quantity had been taken up. The *product*, precipitated by water, was crystallised three times from 2 parts of alcohol and then had m. p. 78—80° (Found : N, 6·3; S, 7·2. $C_{24}H_{40}O_3N_2S$ requires N, 6·4; S, 7·3%).

Disulphanilylethyleneguanidine.—Ethyleneguanidine hydrobromide (34 g.) was dissolved in 10% sodium carbonate solution (240 c.c.). To this was added slowly with shaking a solution of *p*-acetamidobenzenesul-

phonyl chloride (49 g.) in acetone (400 c.c.); the temperature rose to 30°. The precipitated solid was collected after 12 hours, and a second crop obtained from the mother-liquor by concentration. Total yield, 27 g.; m. p. 245°. The acetyl compound so obtained (32 g.) was refluxed for 1 hour with approximately 6N-hydrochloric acid (200 c.c.), and the liquid made alkaline with ammonia; the *base* (4 g.) precipitated had m. p. 178—180° (decomp.), not appreciably altered by crystallisation from 50% alcohol. The base is insoluble in alkali and therefore probably has the structure $NH_2 \cdot C_6H_4 \cdot SO_2 \cdot \overline{N \cdot [CH_2]_2 \cdot N(SO_2 \cdot C_6H_4 \cdot NH_2)} C{:}NH$ (Found: N, 16·8; S, 15·9. $C_{15}H_{17}O_4N_5S_2$ requires N, 17·7; S, 16·2%).

Sulphanilylglutamic Acid.—Glutamic acid (10 g.) was dissolved in 10% sodium hydroxide solution (100 c.c.), and *p*-acetamidobenzenesulphonyl chloride (16 g.) added slowly with shaking. After some hours the solution was acidified with hydrochloric acid and extracted with ether. The extract on evaporation left a brown residue, which was crystallised from ethyl acetate, yielding 8 g. of material, m. p. 142° (decomp.). This was hydrolysed by refluxing with 4 parts of 6N-hydrochloric acid for ½ hour. The solution was then evaporated to dryness, and the residue dissolved in a little water and neutralised with sodium acetate. Crystallisation took place; the *product* after recrystallisation from water had m. p. 192—194° (Found: N, 9·4; S, 10·8. $C_{11}H_{14}O_6N_2S$ requires N, 9·3; S, 10·6%). The *disodium* salt was obtained by adding dilute sodium hydroxide solution to an aqueous solution of the acid until it was just alkaline to phenolphthalein. The solution was concentrated and poured into alcohol, whereby the disodium salt was obtained as an amorphous precipitate, very soluble in water (Found: N, 7·9; S, 9·1; Na, 13·4. $C_{11}H_{12}O_6N_2SNa_2$ requires N, 8·1; S, 9·25; Na, 13·3%).

Sulphanilylaminoethylpyridinium Bromide.—β-Bromoethylamine hydrobromide (10 g.) was dissolved in water (90 c.c.) containing sodium carbonate (6 g.), and *p*-acetamidobenzenesulphonyl chloride (11 g.) added with stirring. After some hours the precipitate was collected, m. p. 161—164°, and refluxed for ½ hour with 6N-hydrochloric acid (100 c.c.). When the cold solution was made alkaline with ammonia, sulphanilylaminoethyl bromide was precipitated. Its solution in alcohol (7 c.c.) was diluted with an equal volume of water. The crystalline material (4·5 g.), m. p. 69—70°, thus obtained was refluxed in alcohol (15 c.c.) and pyridine (7 c.c.) for a short time. The *pyridinium bromide* crystallised on standing and after recrystallisation from alcohol (50 c.c.) and water (2 c.c.) was obtained in white crystals, very soluble in water, m. p. 218° (Found: N, 11·8; S, 8·8; Br, 22·1. $C_{13}H_{16}O_2N_3BrS$ requires N, 11·7; S, 8·9; Br, 22·3%).

4-*Benzylideneaminobenzenesulphonylglycine.*—Sulphanilylglycine was readily prepared by the Schotten–Baumann method from *p*-acetamidobenzenesulphonyl chloride and glycine. The acetyl compound which was precipitated on acidification was hydrolysed by boiling for ½ hour with 6N-hydrochloric acid. The mixture was neutralised with ammonia and made just acid to methyl-orange with dilute hydrochloric acid. The material which crystallised was recrystallised several times from water and then had m. p. 154°. A solution of it (5 g.) in hot alcohol (50 c.c.) was refluxed with benzaldehyde (2·5 c.c.) for 1 hour and then concentrated to half its bulk. After standing for several hours in the ice-box, the crystalline material was collected, m. p. 185—186° (Found: N, 9·1; S, 10·3. $C_{15}H_{14}O_4N_2S$ requires N, 8·8; S, 10·1%).

2′-*Acetoxymercuri*-3′-*hydroxybenzylidenesulphanilamide.*—Solutions of 2-acetoxymercuri-3-hydroxybenzaldehyde (5 g.) in hot acetic acid (30 c.c.) and of sulphanilamide (2·5 g.) in alcohol (50 c.c.) were mixed and refluxed, yielding yellow crystals, m. p. 282° (Found: N, 5·3; S, 6·3. $C_{15}H_{14}O_5N_2SHg$ requires N, 5·25; S, 6·0%).

8-*Quinolyl* p-*Nitrophenyl Ether.*—8-Hydroxyquinoline (44 g.) and potassium hydroxide (13·3 g.) were melted together in a three-necked flask, fitted with a stirrer and a short air-condenser, which was then placed in an oil-bath at 180°. *p*-Chloronitrobenzene (26·2 g.; 1 mol.) was added in two portions, and heating continued, with stirring, for 1½ hours. The melt was poured into 5% sodium hydroxide solution (250 c.c.) containing ice. The granular precipitate obtained was washed (55 g.), crystallised from alcohol, and distilled under 3 mm. The fraction, b. p. 285—295°, after being recrystallised from carbon disulphide, had m. p. 170°; yield, 8·4 g. It was insoluble in water and sparingly soluble in alcohol and carbon disulphide (Found: C, 68·4; H, 3·7; N, 10·5. $C_{15}H_{10}O_3N_2$ requires C, 67·7; H, 3·8; N, 10·5%).

4-p-*Nitrophenoxybenzenesulphonamide.*—*p*-Nitrodiphenyl ether (7·2 g.) was added in small portions to chlorosulphonic acid (11 c.c.; 5 mols.) at 10° with stirring. The syrup was added to ice (120 g.), and the mixture extracted with ether. The extract was shaken with 15% aqueous ammonia (14 c.c.), and the whole evaporated until a solid separated from the aqueous layer. This crystallised from alcohol in rosettes (5·4 g.), m. p. 129°, sparingly soluble in water, more freely in alcohol, readily in acetone (Found: C, 49·7; H, 3·4; N, 9·5; S, 10·7. $C_{12}H_{10}O_5N_2S$ requires C, 49·0; H, 3·4; N, 9·5; S, 10·9%).

p-*Nitrophenoxybenzenedisulphonamide* was obtained when the chlorosulphonic acid solution (previous paragraph) was heated at 95° for 2 hours and then worked up in the same way, the yield, in this case, being small. The disulphonamide crystallised from methyl alcohol in stout prisms, m. p. 270°, insoluble in water, sparingly soluble in ethyl alcohol, more soluble in methyl alcohol (Found: C, 39·1; H, 3·2; N, 11·2; S, 17·1. $C_{12}H_{11}O_7N_3S_2$ requires C, 38·6; H, 3·0; N, 11·3; S, 17·1%).

4 : 4′-*Bis*-(p-*nitrobenzamido*)*diphenylsulphone.*—4 : 4′-Diaminodiphenylsulphone (2·5 g.), dissolved in dry pyridine (4 c.c.), was treated with *p*-nitrobenzoyl chloride (3·7 g.). The *product* was recrystallised from pyridine, forming minute needles (3 g.), m. p. 346°, insoluble in water, alcohol, acetic acid or dioxan (Found: C, 57·0; H, 3·4; N, 10·3; S, 5·8. $C_{26}H_{18}O_8N_4S$ requires C, 57·2; H, 3·3; N, 10·3; S, 5·9%).

2-*Pyrrolidone-5-carboxy*-m-*toluidide*.—*d*-Glutamic acid (19·6 g.) and *m*-toluidine (69·8 c.c.) were heated for 24 hours at 160—170°, approximately the calculated quantity of water distilling. The excess of *m*-toluidine was removed by steam-distillation, and the solid residue crystallised from alcohol, forming thin colourless plates (17 g.), m. p. 147° (Found: C, 66·0; H, 6·3; N, 12·8. $C_{12}H_{14}O_2N_2$ requires C, 66·0; H, 6·5; N, 12·8%).

2-*Pyrrolidone-5-carboxyamino-3′-methylbenzene*-x-*sulphonamide*.—2-Pyrrolidone-5-carboxy-*m*-toluidide (10·9 g.) was added in portions to chlorosulphonic acid (19·4 c.c.; 5 mols.), cooled by water, and the syrup heated at 50—60° for 3 hours. On pouring on ice, a solid was obtained which quickly became friable; it was washed with ice-water, treated with concentrated aqueous ammonia (7 c.c.), and kept for 1 hour. The *product*, thrice crystallised from water, formed aggregates of small plates (4 g.), m. p. 222° (Found: C, 48·9; H, 5·0; N, 14·1. S, 10·8. $C_{12}H_{15}O_4N_3S$ requires C, 48·5; H, 5·1; N, 14·1; S, 10·8%).

2-*Pyrrolidone-5-carboxy-α-naphthalide*.—An intimate mixture of *d*-glutamic acid (25·2 g.) and α-naphthylamine (115·2 g.) was heated at 185—190° for 3 hours, cooled, and triturated with ether. The insoluble residue, crystallised from alcohol, had m. p. 207°; yield, 19·2 g. (Found: C, 70·9; H, 5·5; N, 11·0. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·6; N, 11·0%).

In another experiment, after additional heating for 8 hours at 210°, an *isomer* was obtained, less soluble in alcohol, and crystallising in silky needles, m. p. 224° (Found: C, 71·0; H, 5·4; N, 11·4%).

Attempts to convert these two substances into the sulphonyl chlorides were unsuccessful.

2-*Pyrrolidone-5-carboxy*-p-*nitroanilide*.—*d*-Glutamic acid (25 g.) and *p*-nitroaniline (111 g.) were heated together at 160° for 5 hours. The cooled melt was ground with water, dried, and extracted with ether to remove the excess of base. The residue crystallised from alcohol in clusters of yellow plates (15·6 g.), m. p. 225°, sparingly soluble in boiling water, more readily in alcohol and easily in acetic acid (Found: C, 53·3; H 4·5; N, 16·7. $C_{11}H_{11}O_4N_3$ requires C, 53·0; H, 4·5; N, 16·9%).

2-(2′-*Pyrrolidone-5′-carboxy-4″-aminobenzenesulphonamido*)*pyridine*.—Chlorosulphonic acid (5·2 c.c.), cooled in running water, was treated gradually with *l*-2-pyrrolidone-5-carboxyanilide (3 g.), and the mixture heated at 60—70° for 3 hours, cooled, and poured on ice. The solid was twice drained on tile for ½ hour and ground with ice-water and then dried in a vacuum at room temperature [m. p. 173° (decomp.)] and added to a solution of 2-aminopyridine (1·6 g.; 2 mols.) in dry dioxan (6·4 c.c.). This mixture was heated at 95° for 15 minutes, and the upper layer poured off, leaving a viscous syrup, which was obtained crystalline by treatment with boiling alcohol. After recrystallisation from 50% alcohol the *substance* had m. p. 273°; it was very sparingly soluble in water or alcohol. Yield, 0·9 g. (Found: C, 53·2; H, 4·5; N, 15·1; S, 8·8. $C_{16}H_{16}O_4N_4S$ requires C, 53·3; H, 4·5; N, 15·6; S, 8·9%).

Diphenylsulphone-4 : 4′-*bisazo*-β-*naphthol*.—A solution of 4 · 4′-diaminodiphenylsulphone (4·61 g.) in warm 17% hydrochloric acid (92 c.c.) was rapidly cooled to — 7°, diazotised, and coupled with a solution of β-naphthol (5·75 g.) in 12·5% aqueous sodium hydroxide (154 c.c.). The scarlet *dye* was washed with hot water and alcohol; it had m. p. 304° and was very sparingly soluble in the ordinary organic solvents. Yield, 7·6 g. (Found: C, 68·5; H, 4·1; N, 9·6; S, 5·7. $C_{32}H_{22}O_4N_4S$ requires C, 68·8; H, 4·0; N, 10·0; S, 5·7%).

2 : 2′-*Dipyridyl Sulphide Dihydrobromide*.—This was prepared by the method given by Kolmer, Brown, and Raiziss (*J. Pharm. Exper. Ther.*, 1937, **61**, 256), and the m. p. and complete analysis are now recorded; m. p. 274° (Found: C, 34·4; H, 2·9; N, 8·0; S, 9·0; Br, 45·5. $C_{10}H_{10}N_2Br_2S$ requires C, 34·3; H, 2·9; N, 8·0; S, 9·2; Br, 45·6%).

2 : 2′-*Dipyridylsulphone*.—2 : 2′-Dipyridyl sulphide dihydrobromide (1 g.), dissolved in a warm mixture of acetic acid (15 c.c.) and water (3 c.c.), was treated at 50° with potassium dichromate (1·4 g.) dissolved in concentrated sulphuric acid (11 c.c.) and water (15·4 c.c.). After 1½ hours the mixture was cooled in ice and poured into water. After some hours the *sulphone* crystallised (0·42 g.), m. p. 216°. It was soluble in water and acetone, but sparingly in alcohol (Found: C, 54·7; H, 3·7; N, 13·0; S, 14·1. $C_{10}H_8O_2N_2S$ requires C, 54·5; H, 3·7; N, 12·7; S, 14·6%).

N^4-*Quininoylsulphanilamide*.—Quininic acid (4·3 g.) was heated at 100° for 1 hour with thionyl chloride (28 c.c.), the excess of the latter removed in a vacuum at 40°, and the residue heated with a solution of sulphanilamide (3·7 g.) in dry pyridine (11 c.c.) at 110° for 1 hour. The syrup was stirred with water, and the resulting solid crystallised from alcohol. It formed nodules (3·8 g.), m. p. 255°, sparingly soluble in water (Found: C, 54·3; H, 4·7; N, 11·2; S, 8·5. $C_{17}H_{15}O_4N_3S,H_2O$ requires C, 54·4; H, 4·6; N, 11·2; S, 8·5%). This *substance* was also obtained by treatment of quininanilide with chlorosulphonic acid, and of the resulting sulphonyl chloride with ammonia.

1-*Phenyl*-2 : 3-*dimethyl*-5-*pyrazolone*-x-*sulphonamide*.—Antipyrine (10 g.) was added to chlorosulphonic acid (19·4 c.c.), cooled to — 15°. When the vigorous reaction had moderated, the mixture was heated at 90° for 1½ hours, cooled, and poured on ice. The resulting solid was treated with concentrated aqueous ammonia (8 c.c.); the product crystallised from water in stout rectangular tablets (3·6 g.), m. p. 239° (Found: C, 49·5; H, 4·8; N, 15·7; S, 12·0. $C_{11}H_{13}O_3N_3S$ requires C, 49·4; H, 4·9; N, 15·7; S, 12·0%).

In an attempt to obtain the corresponding sulphinic acid, oxidation appeared to take place with the production of the sulphonic acid (Found for the *sodium* salt: Na, 7·9. $C_{11}H_{11}O_4N_2SNa$ requires Na, 7·7%).

N^4-*Dihydrochaulmoogrylsulphanilamide*.—Dihydrochaulmoogric acid (5 g.) was heated at 90° with purified thionyl chloride (30 c.c.) for 2½ hours and the product was freed from the excess of thionyl chloride in a vacuum at 35° and heated on the steam-bath with a solution of sulphanilamide (3 g.) in dry pyridine (9 c.c.) for 2 hours.

The resulting syrup was poured into water (250 c.c.), and the solid collected and washed (7·1 g., m. p. 178—193°). This was warmed with benzene (150 c.c.), the liquid extract centrifuged off and rejected, the paste shaken with acetone (120 c.c.) and again centrifuged. The supernatant solution was now treated with an equal volume of ether, shaken with charcoal (5 g.), and allowed to stand. The charcoal was filtered off, dried, and extracted with alcohol, which yielded the *amide* in clusters of colourless crystals, m. p. 208°, sparingly soluble in alcohol, benzene, and light petroleum, more soluble in acetone (Found : C, 66·1; H, 9·2; N, 6·4; S, 7·1. $C_{24}H_{40}O_3N_2S$ requires C, 66·0; H, 9·2; N, 6·4; S, 7·3%).

Diphenylsulpnone-4 : 4′-*bisazosalicylic Acid*.—4 : 4′-Diaminodiphenylsulphone (5 g.), suspended in concentrated hydrochloric acid (12 c.c.) and water (24 c.c.), was diazotised in an ice-bath, and the turbid solution added to sodium salicylate (6·4 g.), disssolved in 25% sodium hydroxide solution (20 c.c.). Treatment of the clear, dark red solution with carbon dioxide precipitated a sodium salt, which formed a clear gel when suspended in 20 parts of water. This was acidified with dilute hydrochloric acid, and the precipitated solid washed with water, before and after being dried, until the washings were free from acid; m. p. 316° (decomp.) (Found : C, 57·4; H, 3·5; N, 10·0; S, 5·8. $C_{26}H_{18}O_8N_4S$ requires C, 57·1; H, 3·3; N, 10·2; S, 5·7%).

Sodium 2-*Aminopyridine*-N-*methylenebisulphite*.—29 C.c. of an aqueous solution of sodium bisulphite containing 10·6 g. were treated at 80° with formalin (7 c.c.), and 2-aminopyridine (9·6 g.) in small portions with mechanical stirring. After being kept at this temperature for 1 hour, the solution was allowed to stand overnight; it then deposited 11·2 g. of well-formed compact plates, which were recrystallised from 2 parts of hot water. The *sodium* salt had m. p. 282° (decomp.). It was readily soluble in water and very sparingly soluble in alcohol (Found : loss at 105°, 11·6; Na, for the dried substance, 10·9. $C_6H_7O_3N_2SNa,1\frac{1}{2}H_2O$ requires H_2O, 11·4%. $C_6H_7O_3N_2SNa$ requires Na, 10·94%).

Ethyl p-*Nitrobenzenesulphinate*.—Absolute ethyl alcohol (15 c.c.) containing hydrazine hydrate (3·9 c.c.) was slowly run into an ice-cooled solution of crude *p*-nitrobenzenesulphinyl chloride (obtained from 6·3 g. of *p*-nitrobenzenesulphinic acid; B.P. 509,804) in dry ether (80 c.c.). The red-brown precipitate which remained after standing for ½ hour was removed, and the filtrate evaporated to small volume; on cooling, pale yellow crystals (3·4 g.) were deposited, m. p. 48—49°. Recrystallisation from ether–light petroleum yielded long, pale yellow rhombs, m. p. 49—51° (Found : C, 45·0; H, 4·3; N, 6·4; S, 15·0. $C_8H_9O_4NS$ requires C, 44·65; H, 4·2; N, 6·5; S, 14·9%). The *ester* was readily hydrolysed to *p*-nitrobenzenesulphinic acid by aqueous-alcoholic sodium hydroxide solution.

The corresponding *methyl* ester, obtained by interaction of the acid chloride in pyridine solution with methyl alcohol, and recrystallised from ether–light petroleum, had m. p. 47° (Found : C, 42·0; H, 3·4; N, 6·8; S, 16·0. $C_7H_7O_4NS$ requires C, 41·8; H, 3·5; N, 7·0; S, 15·9%).

p-*Nitrobenzenesulphenamide*.—A dry ethereal solution of crude *p*-nitrobenzenesulphenyl chloride (9 g.) (Zincke and Lenhardt, *Annalen*, 1913, **400**, 13) was slowly run into an ice-cooled dry ethereal solution of ammonia. After ¼ hour, water was added to dissolve the precipitated ammonium chloride, the ethereal solution dried over sodium sulphate, and the ether removed. The bright yellow solid residue was extracted with cold ethyl alcohol (200 c.c.), the insoluble 4 : 4′-dinitrodiphenyl disulphide filtered off, and water added to precipitate yellow crystals (4·2 g.), m. p. 101—103° (Found : C, 42·9; H, 3·6; N, 16·0; S, 18·6. $C_6H_6O_2N_2S$ requires C, 42·3; H, 3·6; N, 16·5; S, 18·8%).

4-*Nitrobenzenesulphon*-4′-*nitroanilide*.—*p*-Nitroaniline (0·7 g.) was added to a solution of *p*-nitrobenzenesulphonyl chloride (1·1 g.) in pyridine (1·5 g.) and heated for 2 hours on the water-bath. After cooling, the yellow mass was ground with dilute hydrochloric acid; the insoluble portion crystallised from alcohol in yellow needles or rhombs (1·2 g.), m. p. 171—173° (Found : C, 45·5; H, 2·95; N, 13·2; S, 9·5. $C_{12}H_9O_6N_3S$ requires C, 44·6; H, 2·8; N, 13·0; S, 9·9%).

4-(p-*Nitrobenzenesulphonamido*-)-4′-*nitrodiphenyl Sulphide*.—4-Nitro-4′-aminodiphenyl sulphide (1·2 g.) was added to a solution of *p*-nitrobenzenesulphonyl chloride (1·1 g.) in pyridine (1·2 g.) and heated for 1 hour on the water-bath. The resultant solid mass was cooled, ground with dilute hydrochloric acid, washed with water, and dried. Recrystallisation from alcohol or aqueous dioxan gave short, pale yellow needles (1·5 g.), m. p. 190° (Found : C, 50·0; H, 3·1; N, 10·2; S, 14·7. $C_{18}H_{13}O_6N_3S_2$ required C, 50·1; H, 3·0; N, 9·7; S, 14·9%).

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Wellcome Chemical Research Laboratories, London.
Wellcome Chemical Works, Dartford.
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