642. *Aminoalkanesulphonamides and Alkanedisulphonamides.*

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A general method has been developed for the preparation of ω-aminoalkane-α-sulphonamides $NH_2{\cdot}[CH_2]_x{\cdot}SO_2{\cdot}NH_2$ and of alkane-αω-disulphonamides $NH_2{\cdot}SO_2{\cdot}[CH_2]_y{\cdot}SO_2{\cdot}NH_2$, which is illustrated by the examples in which x is 2, 3, 4, and 5, and y is 3, 4, 5, and 10. A number of the corresponding sulphonylacetamides and sulphonamidopyridines is also described.

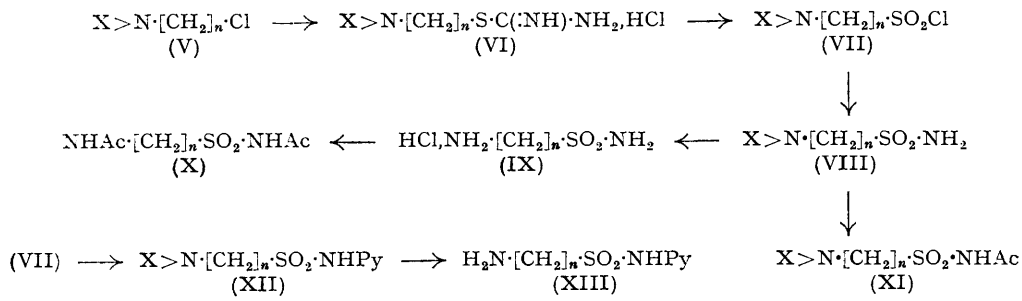
The concept that compounds chemically related to a metabolite may interfere with its normal function in the living cell instigated the present investigation, begun in 1946, into the methods of preparation and properties of some sulphonamides of the aliphatic series. The special pharmacological properties associated with marfanil (*p*-aminomethylbenzenesulphonamide) and in particular its non-inhibition by *p*-aminobenzoic acid (Klarer, *Klin. Wschr.*, 1941, **20**, 1250; Domagk, *ibid.*, 1942, **21**, 448; Evans, Fuller, and Walker, *Lancet*, 1944, II, 523; Mitchell, Rees, and Robinson, *Lancet*, 1944, I, 627) suggested that certain advantages might be associated with the presence of the more basic aliphatic amino-group (cf. Havinga and Veldstra, *Rec. Trav. chim.*, 1947, **66**, 257). Further, the recognition of the importance of amino-acids in metabolic processes suggested that the properties of the structurally related amino-sulphonic acids (or their amides) deserved attention. Work on similar lines has already been reported by McIlwain (*J.*, 1941, 75), Mead, Rapport, Senear, Maynard, and Koepfli (*J. Biol. Chem.*, 1946, **163**, 467), Ravel and Shive (*ibid.*, 1946, **166**, 407), and others. The present investigation is restricted to the ω-aminoalkane-α-sulphonamides, which may be regarded as being related to β-alanine, γ-aminobutyric acid, δ-aminovaleric acid, and 6-aminohexanoic acid and their derivatives, and to some alkane-αω-disulphonamides. In the latter connection reference may be made to the relation between pimelic acid and biotin (cf. also Iványovics and Vargha, *Z. physiol. Chem.*, 1944, **281**, 156) and to the isolation, by Work, of αε-diaminopimelic acid as a new naturally occurring amino-acid (*Proc. Biochem. Soc.*, 1950, v).

Some aminoalkanesulphonamides have been reported by Christiansen (U.S.P. 2,184,279/1940), who claimed that they possessed antibacterial properties. Miller, Sprague, Kissinger, and McBurney (*J. Amer. Chem. Soc.*, 1940, **62**, 2099) have also prepared 2-aminoethane-, 3-aminopropane-, and 4-aminobutane-1-sulphonamide, but declared them to be inactive. Their biological tests were confined, however, to streptococcal infections in mice and because of this the specific activity of marfanil, the preparation of which was included in the same communication, was overlooked by these workers. The method used by Miller, Sprague, Kissinger, and McBurney (*loc. cit.*) for the preparation of the amino-sulphonamides $NH_2{\cdot}[CH_2]_n{\cdot}SO_2{\cdot}NH_2$, in which $n = 3$ and 4, consisted of the conversion of the appropriate chloro-nitrile (I) into the *S*-cyanoalkylthiuronium chloride (II), which was then converted by the action of chlorine in cold aqueous solution into the sulphonyl chloride (III) (cf. Johnson and Sprague, *J. Amer. Chem. Soc.*, 1936, **58**, 1348; 1937, **59**, 1837). The last

was treated with ammonia and then submitted to catalytic hydrogenation, to give the amino-sulphonamide (IV) :

$$\underset{(I)}{CN\cdot[CH_2]_n\cdot Cl} \longrightarrow \underset{(II)}{CN\cdot[CH_2]_n\cdot S\cdot C(:NH)\cdot NH_2,HCl} \longrightarrow \underset{(III)}{CN\cdot[CH_2]_n\cdot SO_2Cl} \longrightarrow CN\cdot[CH_2]_n\cdot SO_2\cdot NH_2 \longrightarrow \underset{(IV)}{NH_2\cdot[CH_2]_{n+1}\cdot SO_2\cdot NH_2}$$

This method failed when $n = 1$ and for this member 2-chloroethylphthalimide (V; $n = 2$) was used in a similar sequence of reactions which may be represented as follows ($X> = o\text{-}C_6H_4\langle^{CO}_{CO}\rangle$; Py = 2-pyridyl) :

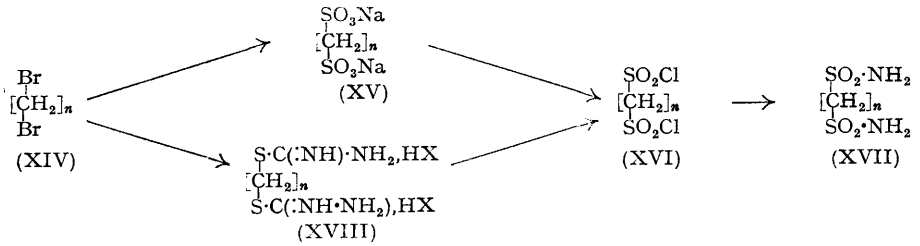


Repetition of the former method, based on the chloro-nitrile, having given unsatisfactory results, attention was directed to the second route based on the halogenoalkylphthalimide, but in place of the chloro-compound the bromo-compound was used following numerous reports that bromides react more readily with thiourea than do the corresponding chlorides (Johnson and Sprague, *loc. cit.*; Urquhart, Gates, and Connor, *Org. Synth.*, 1941, **21**, 37; Frank and Smith, *J. Amer. Chem. Soc.*, 1946, **68**, 2103). This modification necessitated the conversion of the thiuronium bromides (as VI) into the acetates and then into the chlorides (VI) before the treatment with chlorine, but these stages presented no difficulty and the sulphonyl chlorides (VII) were obtained in good yields. The latter were converted into the sulphonamides in benzene solution by means of dry ammonia, which gave improved yields (cf. Miller *et al.*, *loc. cit.*). By this sequence of reactions the ω-aminoalkanesulphonamide hydrochlorides (IX) in which $n = 2$, 3, 4, and 5 were prepared. The method failed with both *N*-chloro- and *N*-bromo-methylphthalimide (as V; $n = 1$) at the chlorination stages (VI ⟶ VII). Miller *et al.* (*loc. cit.*) have also reported a failure with *S*-cyanomethylthiuronium chloride (II; $n = 1$).

2-Phthalimidoethane-1-sulphonamide (VIII; $n = 2$) and 3-phthalimidopropane-1-sulphonamide (VIII; $n = 3$) were converted into their acetyl derivatives (XI). The phthalimidoalkane-1-sulphonyl chlorides (VII; $n = 3$, 4, and 5) were condensed with 2-aminopyridine and the resulting 2-(phthalimidoalkanesulphonamido)pyridines (XII) were converted into (XIII; $n = 3$, 4, and 5), the last two bases being isolated as hydrochlorides. The corresponding compound in the ethane series has been reported by Mead *et al.* (*loc. cit.*) and by Winterbottom, Clapp, Miller, English, and Roblin (*J. Amer. Chem. Soc.*, 1947, **69**, 1393). The amino-sulphonamides $NH_2\cdot[CH_2]_n\cdot SO_2\cdot NH_2$, in which $n = 2$, 3, 4, and 5, were also converted into the corresponding acetamidoalkanesulphonylacetamides (X; $n = 2$, 3, 4, and 5).

A few alkane-αω-disulphonamides have been prepared by means of the reactions (XIV ⟶ XV ⟶ XVI ⟶ XVII) (Clutterbuck and Cohen, *J.*, 1922, **121**, 120; Autenrieth and Bölli, *Ber.*, 1925, **58**, 2149; Helferich and Grünert, *Ber.*, 1941, **74**, 1531). Johnson and Sprague (*loc. cit.*) have also prepared ethane-1 : 2-disulphonyl chloride (XVI; $n = 2$) by the action of chlorine on a cold aqueous solution of *SS*-ethylenebisthiuronium chloride (XVIII; $n = 2$, X = Cl). This method has now been applied to the alkylene-αω-bisthiuronium chlorides (XVIII; X = Cl) for the examples in which $n = 3$, 4, 5, and 10,

the chlorides being prepared from the bisthiuronium bromides through the acetates. In this manner the four αω-disulphonamides were conveniently obtained. Three of them were converted into their diacetyl derivatives and in addition pentane-1 : 5-disulphonamide was converted by the method of Birtwell, Haworth, Rose, Swain, and Vasey (*J.*, 1946, 491) into pentane-1 : 5-bis-sulphonylguanidine.



Experimental

2-*Aminoethane*-1-*sulphonamide Hydrochloride*.—2-Phthalimidoethanesulphonyl chloride was prepared from *N*-2-chloroethylphthalimide (Wenker, *J. Amer. Chem. Soc.*, 1937, **59**, 422) by the method of Miller *et al.* (*loc. cit.*) and converted into 2-phthalimidoethanesulphonamide, m. p. 209—210°. Removal of the phthaloyl group by means of hydrazine hydrate, as described by Miller *et al.*, gave 2-aminoethane-1-sulphonamide hydrochloride in needles, m. p. 131—133·5°, from 95% aqueous ethanol (Found: C, 15·0; H, 5·8. Calc. for $C_2H_8O_2N_2S,HCl$: C, 15·0; H, 5·6%). A solution of 2-aminoethane-1-sulphonamide hydrochloride (1·2 g.) in acetic anhydride (10 c.c.) was heated under reflux at 150—160° for 15 minutes. The excess of acetic anhydride was removed by boiling the mixture with alcohol in an open vessel. The solid residue was crystallised from alcohol. 2-*Acetamidoethane*-1-*sulphonylacetamide* (0·52 g.) separated in colourless plates, m. p. 153·5—154·5° (Found: C, 34·0; H, 5·8; N, 13·8. $C_6H_{12}O_4N_2S$ requires C, 34·6; H, 5·8; N, 13·5%).

S-3-*Phthalimidopropylthiuronium Bromide*.—1 : 3-Dibromopropane, b. p. 166° (Kamm and Marvel, *Org. Synth.*, Coll. Vol. I., edn. 2, p. 30) was converted into *N*-3-bromopropylphthalimide, m. p. 72°, by the method of Ing and Manske (*J.*, 1926, 2348). A mixture of the latter (414·5 g.), thiourea (117 g.), and 95% aqueous alcohol (830 c.c.) was boiled under reflux for 8 hours. When cold the precipitated salt was collected, washed with cold alcohol, and dried (434 g.; m. p. 218°). Crystallisation from water gave S-3-*phthalimidopropylthiuronium bromide* in colourless hexagonal plates, m. p. 226—228° (decomp.) (Found: C, 42·3; H, 4·3; N, 11·2. $C_{12}H_{14}O_2N_3BrS$ requires C, 41·9; H, 4·1; N, 12·2%).

3-*Phthalimidopropane*-1-*sulphonyl Chloride*.—A hot saturated aqueous solution of potassium acetate (117 g. in 102 c.c.) was added with stirring to a hot aqueous solution of *S*-3-phthalimidopropylthiuronium bromide (105 g. in 800 c.c.). The temperature was kept at 80° and the crystalline *S*-3-phthalimidopropylthiuronium acetate began to separate almost at once. The mixture was cooled and the thiuronium acetate was collected and dried [86 g.; m. p. 152·5—153·5° (decomp.)]. Chlorine was passed at 0—5° into a suspension of the thiuronium acetate (86 g.) in water (680 c.c.) to which concentrated hydrochloric acid (9 g.) had been added. After 3 hours the 3-phthalimidopropane-1-sulphonyl chloride was filtered from the green solution and washed with cold water. The crude sulphonyl chloride was dried (69 g.) and extracted with the minimum quantity of hot dry benzene. Addition of light petroleum (b. p. 40—60°) to the cooled benzene solution precipitated 3-*phthalimidopropane*-1-*sulphonyl chloride* (64 g.; m. p. 84—87°) (Found: C, 45·9; H, 3·7; Cl, 12·2. $C_{11}H_{10}O_4NClS$ requires C, 45·9; H, 3·5; Cl, 12·3%). The m. p., on recrystallisation from benzene–light petroleum (b. p. 40—60°), dropped to 76—78°, whereas crystallisation from hot benzene gave material of m. p. 82—85°, which when the substance was kept *in vacuo* over concentrated sulphuric acid again dropped to 76—78°.

3-*Phthalimidopropane*-1-*sulphonamide*.—Dry ammonia was passed into a solution of 3-phthalimidopropane-1-sulphonyl chloride (53 g.) in dry benzene kept at 40° by means of external cooling. After 1½ hours precipitation was complete and the solvent was evaporated. The residue was treated with a small quantity of cold water to remove ammonium chloride, and the residual 3-*phthalimidopropane*-1-*sulphonamide* was collected. It separated from boiling water or aqueous alcohol in plates, m. p. 170·5—173° (Found: C, 49·3; H, 4·6; N, 11·0. $C_{11}H_{12}O_4N_2S$ requires C, 49·3; H, 4·5; N, 10·5%).

3-*Aminopropane*-1-*sulphonamide Hydrochloride.*—Aqueous hydrazine hydrate (5·9 g. of 30% solution) was added dropwise with stirring to a suspension of 3-phthalimidopropane-1-sulphonamide (14·6 g.) in boiling alcohol (250 c.c.) under reflux. After 3 hours the mixture was cooled and filtered and the filtrate was evaporated to dryness under reduced pressure. A solution of the residue in water (600 c.c.) at 70° was acidified to Congo-red with hydrochloric acid. When cold the precipitated phthalhydrazide was removed and the filtrate evaporated to dryness. Water (10 c.c.) was added to the residue, and the solution was filtered. Evaporation gave the crude 3-aminopropanesulphonamide hydrochloride (8 g.), which after purification by crystallisation from 80% aqueous alcohol was obtained in colourless prisms, m. p. 161—163° (Found : C, 21·5; H, 6·2; N, 16·1. Calc. for $C_3H_{10}O_2N_2S$,HCl : C, 20·6; H, 6·3; N, 16·0%). Miller *et al.* (*loc. cit.*) recorded m. p. 159—160° for this hydrochloride prepared by the catalytic reduction of 2-cyanoethane-1-sulphonamide. Acetic anhydride (0·3 g.) was added to a solution of 3-aminopropane-1-sulphonamide hydrochloride (0·5 g.) in aqueous sodium hydroxide (0·23 g. in 25 c.c.). After five minutes' shaking alcohol was added and the solution evaporated to dryness. From the residue hot acetone extracted 3-*acetamidopropane*-1-*sulphonamide* (0·3 g.), which separated from alcohol in colourless plates, m. p. 121·5—123° (Found : C, 34·0; H, 6·7; N, 15·3. $C_5H_{12}O_3N_2S$ requires C, 33·6; H, 6·7; N, 15·6%).

3-*Acetamidopropane*-1-*sulphonylacetamide*, prepared as described above for the corresponding derivative of ethane, separated from alcohol in plates, m. p. 162·5—163·5° (Found : C, 38·1; H, 6·5; N, 12·2. $C_7H_{14}O_4N_2S$ requires C, 37·8; H, 6·3; N, 12·6%).

S-4-*Phthalimidobutylthiuronium Bromide.*—A mixture of 1 : 4-dibromobutane (860 g.; Fried and Kleene, *J. Amer. Chem. Soc.*, 1940, **62**, 3258), finely powdered anhydrous potassium carbonate (121 g.), and phthalimide (245 g.) was heated under reflux at 180—190° for 2 hours. The product was separated into 1 : 4-diphthalimidobutane (28 g.; m. p. 224—226°, from acetic acid) and *N*-4-bromobutylphthalimide (280 g.; m. p. 79—80·5°) as in the preparation of the corresponding derivatives of propane. 1 : 4-Dibromobutane (507 g.) was recovered. From *N*-4-bromobutylphthalimide (280 g.) and thiourea (78·8 g.) in 95% aqueous alcohol (650 c.c.), after 22 hours' boiling, S-4-*phthalimidobutylthiuronium bromide* (329·5 g.) was obtained in plates, m. p. 174·5—177° (from boiling water) (Found : C, 11·4. $C_{13}H_{16}O_2N_3BrS$ requires N, 11·7%).

4-*Aminobutane*-1-*sulphonamide Hydrochloride.*—By the methods described above for the corresponding derivatives of propane, *S*-4-phthalimidobutylthiuronium bromide (104 g.) gave 4-*phthalimidobutane*-1-*sulphonyl chloride* (60 g.) in plates, m. p. 126·5—128° (from acetone) (Found : Cl, 12·0; N, 4·4. $C_{12}H_{12}O_4NClS$ requires Cl, 11·8; N, 4·6%). This sulphonyl chloride (40 g.) gave a mixture of ammonium chloride and the amide, which was extracted with hot acetone. Evaporation of the solvent gave 4-*phthalimidobutane*-1-*sulphonamide* (21·8 g.), which separated from alcohol in plates, m. p. 148·5—149·5° (Found : C, 51·0; H, 4·8; N, 9·6. $C_{12}H_{14}O_4N_2S$ requires C, 51·1; H, 5·0; N, 9·9%). The amide (21·8 g.) was converted into 4-aminobutane-1-sulphonamide hydrochloride (5·7 g.), m. p. 129—129·5° (after crystallisation from 90% alcohol) (Found : C, 26·0; H, 6·8; N, 14·6. Calc. for $C_4H_{12}O_2N_2S$,HCl : C, 25·5; H, 6·9; N, 14·9%). Miller *et al.* (*loc. cit.*) have recorded m. p. 127—129° for this hydrochloride prepared by the catalytic reduction of 3-cyanopropane-1-sulphonamide. 4-*Acetamidobutane*-1-*sulphonylacetamide*, prepared as described for the corresponding derivative of ethane, separated from alcohol in plates, m. p. 143—144·5° (Found : C, 41·1; H, 6·6; N, 11·8. $C_8H_{16}O_4N_2S$ requires C, 40·7; H, 6·8; N, 11·9%).

S-5-*Phthalimidoamylthiuronium Bromide.*—A mixture of 1 : 5-dibromopentane (470 g.; prepared in 80% yield from pentane-1 : 5-diol by the general procedure of Kamm and Marvel, *loc. cit.*), anhydrous potassium carbonate (62 g.), and phthalimide (130 g.) was heated under reflux at 190—200° for 4 hours. The excess of 1 : 5-dibromopentane (270 g.) was removed by distillation with steam. When cold the reaction flask contained two layers. The lower layer was separated by addition of chloroform, washed with water, and dried ($CaCl_2$). The syrup obtained on removal of the chloroform was triturated with light petroleum (b. p. 40—60°) and a little absolute alcohol. Extraction with light petroleum (b. p. 80—100°) of the solid thus obtained (171 g.) left a residue of 1 : 5-phthalimidopentane (11·2 g.), m. p. 182—183°, while removal of the solvent under reduced pressure gave *N*-5-bromoamylphthalimide (145 g.), m. p. 59—62°. The latter, with thiourea (39 g.) in 95% aqueous alcohol, was heated under reflux for 17 hours and gave S-5-*phthalimidoamylthiuronium bromide* (151 g.), isolated as in the previous examples, in needles, m. p. 188·5—189·5°, from ethyl alcohol (Found : C, 45·4; H, 5·0; N, 11·1. $C_{14}H_{18}O_2N_3BrS$ requires C, 45·2; H, 4·8; N, 11·3%).

5-*Aminopentane*-1-*sulphonamide Hydrochloride.*—By the methods described above, *S*-5-phthalimidoamylthiuronium bromide (42 g.) gave 5-*phthalimidopentane*-1-*sulphonyl chloride*

(34 g.) in needles, m. p. 77—79°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 49·2; H, 4·4; N, 4·2; Cl, 11·7. $C_{13}H_{14}O_4NClS$ requires C, 49·4; H, 4·4; N, 4·4; Cl, 11·3%). This (5·5 g.) gave 5-*phthalimidopentane*-1-*sulphonamide* (3·5 g.) in needles, m. p. 163·5—164·5°, from boiling water (Found: C, 52·8; H, 5·4; N, 8·9. $C_{13}H_{16}O_4N_2S$ requires C, 52·7; H, 5·4; N, 9·5%). The amide (4·5 g.) gave 5-*aminopentane*-1-*sulphonamide hydrochloride* (2 g.), which separated from alcohol in fine hygroscopic needles, m. p. 126·5—129° (Found: C, 29·9; H, 7·9; N, 14·0. $C_5H_{14}O_2N_2S,HCl$ requires C, 29·6; H, 7·4; N, 13·8%). 5-*Acetamidopentane*-1-*sulphonylacetamide*, prepared as described for the corresponding derivative of ethane, separated from alcohol in rhombohedra, m. p. 114—115° (Found: C, 43·5; H, 7·3; N, 11·2. $C_9H_{18}O_4N_2S$ requires C, 43·2; H, 7·2; N, 11·2%).

S-*Phthalimidomethylthiuronium Bromide*.—Thiourea (1·8 g.) and *N*-bromomethylphthalimide (5 g.; Pucher and Johnson, *J. Amer. Chem. Soc.*, 1922, **44**, 820) in dry benzene (25 c.c.) were boiled under reflux for 24 hours. When cold the mixture was filtered and the residue was washed with hot benzene to remove unchanged *N*-bromomethylphthalimide (1·4 g.). Crystallisation from aqueous alcohol gave S-*phthalimidomethylthiuronium bromide* (3·15 g.) in prisms, m. p. 219—220° (decomp.) (Found: C, 39·1; H, 3·3; N, 13·1. $C_{10}H_{10}O_2N_3BrS$ requires C, 40·0; H, 3·2; N, 13·3%).

S-*Phthalimidomethylthiuronium Chloride*.—In similar manner, thiourea (5·4 g.) and *N*-chloromethylphthalimide (13·7 g.; Sachs, *Ber.*, 1898, **31**, 1232), after being boiled in alcohol (50 c.c.) for 60 hours, gave S-*phthalimidomethylthiuronium chloride* (17 g.), which separated from alcohol in needles, m. p. 216° (Found: C, 43·8; H, 3·9; N, 15·4. $C_{10}H_{10}O_2N_3ClS$ requires C, 44·2; H, 3·7; N, 15·5%.

Action of Chlorine on S-*Phthalimidomethylthiuronium Salts in Aqueous Solution*.—The action of chlorine at 0—5° on an aqueous suspension of the acetate, prepared in the usual manner from the bromide, gave only a small quantity of a greyish gum. Similar treatment of the thiuronium bromide (9 g.) gave only *N*-chloromethylphthalimide (1·7 g.), m. p. 133·5—135°; in an experiment with the thiuronium chloride (2 g.) only *N*-hydroxymethylphthalimide (0·6), m. p. 145—148°, was isolated (Found: C, 60·5; H, 3·9. Calc. for $C_9H_7O_3N$: C, 61·0; H, 4·0%).

2-*Phthalimidoethane*-1-*sulphonylacetamide*.—A solution of 2-phthalimidoethanesulphonamide (1 g.) in acetic anhydride (10 c.c.) containing one drop of concentrated sulphuric acid was boiled under reflux for 15 minutes. The *acetyl* derivative (0·8 g.), which separated when the solution was poured into water, crystallised from 50% ethyl alcohol in needles, m. p. 194—195° (Found: C, 48·3; H, 4·2; N, 8·9. $C_{12}H_{12}O_5N_2S$ requires C, 48·7; H, 4·1; N, 9·5%). In similar manner there was prepared 3-*phthalimidopropane*-1-*sulphonylacetamide* in prisms (from alcohol), m. p. 175—176° (Found: C, 50·5; H, 4·4; N, 9·0. $C_{13}H_{14}O_5N_2S$ requires C, 50·3; H, 4·5; N, 9·0%).

2-3′-*Phthalimidopropanesulphonamidopyridine*.—Finely powdered 3-phthalimidopropane-1-sulphonyl chloride (33 g.) was added during 15 minutes to a solution of 2-aminopyridine (22 g.) in dry benzene (340 c.c.). The solution was stirred and kept at room temperature (cooling) for 2 hours. The precipitate was collected, washed successively with a little benzene, cold alcohol, 1% aqueous sodium hydrogen carbonate, and water, and then dried *in vacuo*. The crude product (24·5 g.) separated from glacial acetic acid in prisms and from benzene in needles, m. p. 169·5—170·5° (Found: C, 55·7; H, 4·4; N, 12·2. $C_{16}H_{15}O_4N_3S$ requires C, 54·7; H, 4·5; N, 11·8%).

2-3′-*Aminopropanesulphonamidopyridine*.—By the procedure for the removal of the phthalimido-group outlined above 2-3′-phthalimidopropanesulphonamidopyridine (20·7 g.) gave the hydrochloride (18·5 g.), which was dissolved in a little water to which sodium hydrogen carbonate was then added. Evaporation left a syrupy residue which was extracted with 50% alcohol and boiled with charcoal. On concentration and cooling, 2-3′-*aminopropanesulphonamidopyridine* (1·4 g.) separated in yellowish plates, m. p. 182·5—183·5° (Found: C, 44·6; H, 5·8; N, 18·9. $C_8H_{13}O_2N_3S$ requires C, 44·7; H, 6·1; N, 19·5%). It was almost insoluble in hot alcohol, but very soluble in cold water.

2-4′-*Aminobutanesulphonamidopyridine Hydrochloride*.—In similar manner 4-phthalimidobutane-1-sulphonyl chloride (60 g.) and 2-aminopyridine (37·5 g.) after 4 hours gave 2-4′-*phthalimidobutanesulphonamidopyridine*, which separated as a viscous semi-solid which became granular after washing (28·3 g.). Crystallisation from glacial acetic acid gave needles (18·7 g.), m. p. 191·5—193·5° (Found: C, 56·0; H, 5·0; N, 11·6. $C_{17}H_{17}O_4N_3S$ requires C, 56·8; H, 4·7; N, 11·7%). The phthalimido-derivative (14·7 g.) on treatment with 30% hydrazine hydrate solution (4·4 g.) in hot alcohol (200 c.c.) gave the crude hydrochloride, which was extracted (Soxhlet) with hot alcohol. 2-4′-*Aminobutanesulphonamidopyridine hydrochloride* (5·5 g.)

separated from the extract in colourless plates, m. p. 136·5—137·5° (Found: N, 15·2. $C_9H_{15}O_2N_3S$,HCl requires N, 15·8%).

2-5′-*Phthalimidopentanesulphonamidopyridine.*—(*a*) By the procedure described above, 5-phthalimidopentane-1-sulphonyl chloride (34 g.) and 2-aminopyridine (21 g.) in dry benzene (340 c.c.) gave 2-5′-*phthalimidopentanesulphonamidopyridine* (16·6 g.), which separated from hot methyl alcohol in cream-coloured prisms, m. p. 144·5—145·5° (Found: C, 57·9; H, 5·2; N, 10·7. $C_{18}H_{19}O_4N_3S$ requires C, 57·9; H, 5·1; N, 11·3%). (*b*) (cf. Winterbottom *et al.*, *loc. cit.*). The phthalimido-sulphonyl chloride (2 g.) was added in portions to a stirred solution of 2-aminopyridine (1·2 g.) in dry pyridine (5 c.c.) at 0°. The red reaction mixture was allowed to warm to room temperature and poured into an excess of 1·5N-hydrochloric acid with stirring. The solid which separated was collected, washed with cold water, and recrystallised from methyl alcohol. 2-5′-Phthalimidopentanesulphonamidopyridine (0·32 g.) was obtained in prisms, m. p. 145—147° undepressed on admixture with a specimen prepared by method (*a*) above.

2-5′-*Aminopentanesulphonamidopyridine Hydrochloride.*—2-5′-Phthalimidopentanesulphonamidopyridine (15·8 g.), suspended in hot alcohol (150 c.c.), on treatment with 35% hydrazine hydrate (4·2 g.), as described in the previous examples, gave 2-5′-*aminopentanesulphonamidopyridine hydrochloride* (7 g.) which separated from alcohol in colourless plates, m. p. 127·5—129° (Found: C, 43·4; H, 6·3; N, 14·3; Cl, 13·2. $C_{10}H_{17}O_2N_3S$,HCl requires C, 42·9; H, 6·4; N, 15·0; Cl, 12·7%).

Propylene-1 : 3-*bisthiuronium Bromide.*—A mixture of 1 : 3-dibromopropane (101 g.) and thiourea (76 g.) in 95% alcohol (375 c.c.) was boiled under reflux for 18 hours. When cold a syrup separated which became crystalline on trituration. The *thiuronium bromide* (153 g.) separated from aqueous alcohol in needles, m. p. 196·5—199·5° (Found: C, 18·0; H, 4·0; N, 16·0. $C_5H_{14}N_4Br_2S_2$ requires C, 17·0; H, 4·0; N, 15·8%).

Propane-1 : 3-*disulphonamide.*—A cold solution of potassium acetate (11·1 g.) in water (4·6 c.c.) was added to a cold solution of propylene-1 : 3-bisthiuronium bromide (20 g.) in water (20 c.c.) at <20°. The precipitated dithiuronium acetate was collected (m. p. 125—127°) and to its solution in water (160 c.c.) was added concentrated hydrochloric acid (13 g.). Chlorine was passed into the solution at 0—10°. The solid which separated melted on warming to room temperature and was extracted with chloroform. The extract was washed with aqueous sodium hydrogen sulphite and with water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure left the propane-1 : 3-disulphonyl chloride as an oil (5·4 g.), which crystallised on the addition of light petroleum (b. p. 40—60°). Dry ammonia was passed into a solution of the crude disulphonyl chloride (m. p. 40—45°; 8·1 g.) in dry benzene (100 c.c.) with external cooling. When precipitation was complete excess of ammonia was removed with dry air, and the benzene was distilled off under reduced pressure. From the residue acetone extracted propane-1 : 3-disulphonamide (3·4 g.), which crystallised from aqueous acetone in needles, m. p. 172·5—174·5° (Found: N, 13·7. Calc. for $C_3H_{10}O_4N_2S_2$: N, 13·9%). Autenrieth and Bölli (*Ber.*, 1925, **58**, 2149) record m. p. 165° and Clutterbuck and Cohen (*loc. cit.*) m. p. 169° for this compound.

In similar manner the following compounds were prepared: *butylene*-1 : 4-*bisthiuronium bromide* (98% yield) in prisms, m. p. 208—210°, from water (Found: C, 20·0; H, 4·6; N, 15·1. $C_6H_{16}N_4Br_2S_2$ requires C, 19·6; H, 4·4; N, 15·2%); butane-1 : 4-disulphonyl chloride (80% yield) in needles, m. p. 83—84·5°, from benzene–light petroleum (cf. Helferich and Grünert, *loc. cit.*); butane-1 : 4-disulphonamide (60% yield) in plates, m. p. 179·5—180·5°, from hot water (cf. Helferich and Grünert, *loc. cit.*); NN′-*diacetylbutane*-1 : 4-*disulphonamide* in plates, m. p. 195·5—197·5°, from 95% alcohol (Found: C, 32·3; H, 5·1; N, 9·0. $C_8H_{16}O_6N_2S_2$ requires C, 32·0; H, 5·3; N, 9·3%); *pentylene*-1 : 5-*bisthiuronium bromide* (88% yield) in prisms, m. p. 159·5—161·5°, from alcohol (Found: C, 22·4; H, 5·0; N, 14·5. $C_7H_{18}N_4Br_2S_2$ requires C, 22·0; H, 4·7; N, 14·7%); pentane-1 : 5-disulphonyl chloride (88% yield) in needles, m. p. 67—69°, from benzene–light petroleum (cf. Clutterbuck and Cohen, *loc. cit.*); pentane-1 : 5-disulphonamide (60% yield) in needles, m. p. 131—133°, from aqueous alcohol (cf. Clutterbuck and Cohen, *loc. cit.*); NN′-*diacetylpentane*-1 : 5-*disulphonamide* in needles, m. p. 149·5—150·5°, from alcohol (Found: C, 34·3; H, 5·6; N, 9·2. $C_9H_{18}O_6N_2S_2$ requires C, 34·4; H, 5·7; N, 8·9%); *decylene*-1 : 10-*bisthiuronium bromide* (89% yield) in needles, m. p. 158·5—160·5°, from acetic acid (Found: C, 31·6; H, 6·0. $C_{12}H_{28}N_4Br_2S_2$ requires C, 31·85; H, 6·2%); *decane*-1 : 10-*disulphonamide* (63% yield from dithiuronium bromide) in plates, m. p. 162·5—164·5°, from acetic acid (Found: C, 40·5; H, 8·4; N, 9·2. $C_{10}H_{24}O_4N_2S_2$ requires C, 40·0; H, 8·0; N, 9·3%); NN′-*diacetyldecane*-1 : 10-*disulphonamide* in plates, m. p. 157·5—158·5°, from alcohol (Found: C, 43·8; H, 7·4; N, 7·3. $C_{14}H_{28}O_6N_2S_2$ requires C, 43·8; H, 7·3; N, 7·3%).

Pentylene-1 : 5-*bis-sulphonylguanidine* (cf. Birtwell *et al.*, *loc. cit.*).—Guanidine nitrate (5·6 g.)

was added to a solution of sodium hydroxide (1·84 g.) in hot methyl alcohol (12 c.c.) and after 15 minutes the mixture was cooled to 20° and the sodium nitrate filtered off and washed with methyl alcohol. Pentane-1 : 5-disulphonamide (5 g.) was added to the filtrate kept at 50—55° and, after removal of the methyl alcohol, *cyclo*hexanol (30 c.c.) was added and the temperature raised to 180—190° and kept thereat for 3 hours. When cold, hot benzene (25 c.c.) was added and, after warming, the upper layer was removed by decantation. The residue was dissolved in a minimum of hot water and the solution was cooled, and made just acid with 1·5N-hydrochloric acid and then just alkaline with 1·5N-sodium hydroxide. On scratching and cooling *pentylene*-1 : 5-*bis*-*sulphonylguanidine* (1·6 g.) separated, which crystallised from aqueous alcohol in needles, m. p. 190·5—191·5° (Found : C, 27·4; H, 5·6; N, 27·2. $C_7H_{18}O_4N_6S_2$ requires C, 26·8; H, 5·7; N, 26·8%).

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