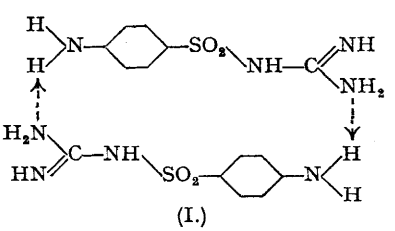
160. *Derivatives of Sulphanilylguanidine : Preparation for Pharmacological Study.*

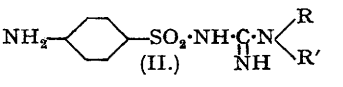
By E. Haworth, F. L. Rose and F. H. Slinger.

Mono- and di-alkyl derivatives of sulphanilylguanidine, prepared by a modification of the method of Birtwell *et al.* (*J.*, 1946, 491), together with *m*-aminobenzenesulphonylguanidine and β-sulphanilyl-α-acetylguanidine, are described. These substances were required in connection with a hypothesis relating to the pharmacological properties of the sulphanilylguanidine class of drug.

p-Aminobenzenesulphonylguanidine (sulphanilylguanidine, sulphaguanidine) is of value for the treatment of certain pathogenic intestinal infections. It was introduced for this purpose following the observation that, when given by mouth to animals, only a small percentage (20—40) was absorbed from the gut (Roblin *et al.*, *J. Amer. Chem. Soc.*, 1940, **62**, 2002; Marshall *et al.*, *Bull. Johns Hopkins Hosp.*, 1940, **67**, 163; 1944, **68**, 94). Sulphanilylguanidine is rather less soluble in water than sulphanilamide, but many times more soluble than drugs such as " sulphadiazine " and " sulphapyridine " which are well absorbed, so that this factor seems unimportant in determining pharmacological behaviour. Hitherto, no explanation of the peculiar influence of the guanidine group has been attempted, but recently it has been tentatively suggested by one of us (F. L. R.) that a physical association of sulphaguanidine through hydrogen-bonding either with some component of the gut wall or content or with itself to give a dimeric molecule of type (I) might be an important factor. The work of Hunter (*J.*, 1941, 777) has drawn attention to an intermolecular association through hydrogen bonds of amidino- and guanidino-groups, although in a different manner from the special case proposed in (I). Without discussing the theoretical merits of such an arrangement or the precise manner in which it might operate to inhibit passage through the gut wall, it was apparent that such changes in the molecule as the transfer of the primary amino-group to the meta position, or its replacement by nitro-, or the attachment of alkyl groups to the several nitrogen atoms, would depress or enhance the stability of any such association, and this should be reflected in greater or lesser absorption from the gastro-intestinal tract. The experimental determination of these effects and a discussion of the results obtained will be reported elsewhere (Rose and Spinks, *Brit. J. Pharm. Chemotherapy*, in the press); we record here the preparation of the new substances used in this



(I.)



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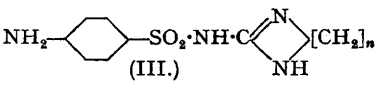

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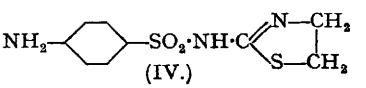
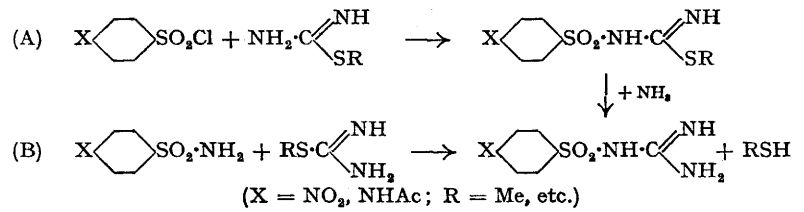


(IV.)

investigation together with several related compounds, which are novel either in themselves or in their preparative route. They are the monosubstituted derivatives (II; R = H, R′ = Me,

C_2H_4·OMe, C_2H_4·NEt_2, Ac), the disubstituted derivatives (II; R = R′ = Me, Et), the cyclic compounds (III, n = 2, 3) and (IV), and the meta-isomer of sulphaguanidine.

Winnek *et al.* (*J. Amer. Chem. Soc.*, 1942, **64**, 1682) have described the preparation of compounds of type (II) (R = H; R′ = Et, Pr, Bu) by the interaction of an *N*-sulphonylcyanamide with the appropriate alkylamine. Birtwell *et al.* (*J.*, 1946, 491) recorded the formation of sulphanilylguanidine by a number of routes including the following:



(X = NO_2, NHAc; R = Me, etc.)

With two exceptions, the substances described herein were made by a modification of (A) or (B), ammonia being replaced by a primary or secondary amine, and *iso*thiourea by an *N*-substituted *iso*thiourea. The para-substituent X was — NHAc in every instance save one, and the final reaction involving the synthesis of the guanidine residue was carried out mainly in phenol as solvent; in reaction (B) the appropriate *iso*thiourea was used in the form of its sulphate, and the sulphonamide as its sodio-derivative. The meta-isomer of sulphanilylguanidine was made by a route analogous to that employed by Roblin *et al.* (*loc. cit.*), namely the reduction of the condensation product of *m*-nitrobenzenesulphonyl chloride and guanidine. Compound (II, R = H, R′ = Ac) was obtained by reducing the reaction product of *p*-nitrobenzenesulphonylguanidine and acetic anhydride. The attachment of the acetyl residue to the terminal nitrogen atom was assumed.

The antibacterial activity of these substances against *Streptococcus pyogenes in vitro* has been examined by our colleague Dr. A. R. Martin. All were less effective than sulphanilylguanidine. The meta-isomer of sulphanilylguanidine, as anticipated, and the compound (II, R = H, R′ = C_2H_4·NEt_2), were devoid of antibacterial activity. Relatively high blood concentrations were achieved in mice following oral administration of *p*-nitrobenzenesulphonylguanidine, the meta-isomer of sulphanilylguanidine, and compound (II) in which R and R′ were both alkyl groups.

Experimental.

(Melting points are uncorrected.)

β-Sulphanilyl-α-methylguanidine (II, R = H, R′ = Me).—*p*-Acetamidobenzenesulphonyl-*S*-methyl-*iso*thiourea (27 g., Birtwell *et al.*, *loc. cit.*) was added to a stirred melt of phenol (48 g.) heated in an oil-bath maintained at 110°. Dry methylamine was passed into the mixture until the effluent gases gave no marked stain on lead acetate paper. The melt was added to sodium hydroxide (20 g.) in ice–water (250 c.c.), and the crystals which separated were filtered off, washed alkali-free with water, and dried at 100°. The crude product (12 g.) gave *β*-p-*acetamidobenzenesulphonyl-α-methylguanidine* (6 g.) in colourless rhombic prisms from water, m. p. 248—249° (Found: C, 44·65; H, 5·0; N, 20·0. $C_{10}H_{14}O_3N_4S$ requires C, 44·4; H, 5·2; N, 20·8%). The acetyl derivative (12·6 g.) was refluxed with N-hydrochloric acid (110 c.c.) for ½ hour. The resultant solution was made just alkaline with sodium hydroxide solution while still hot. On cooling, *β-sulphanilyl-α-methylguanidine* (7·4 g.) crystallised; after recrystallisation from water it had m. p. 163—165° (Found: C, 42·0; H, 5·25; N, 24·2. $C_8H_{12}O_2N_4S$ requires C, 42·2; H, 5·3; N, 24·6%).

β-Sulphanilyl-αα-dimethylguanidine (II, R = R′ = Me).—This *compound*, similarly prepared using dimethylamine, formed colourless rhombic plates, m. p. 164—165° (Found: C, 44·8; H, 5·7; N, 22·8. $C_9H_{14}O_2N_4S$ requires C, 44·6; H, 5·8; N, 23·2%). The intermediate *acetamido*-derivative had m. p. 263—265° (Found: C, 46·25; H, 6·1; N, 19·4. $C_{11}H_{16}O_3N_4S$ requires C, 46·1; H, 5·7; N, 19·8%).

β-Sulphanilyl-αα-diethylguanidine (II, R = R′ = Et).—This *compound*, similarly prepared using diethylamine, formed slender colourless prisms, m. p. 141—142° (Found: C, 44·75; H, 6·5; N, 20·05. $C_{11}H_{18}O_2N_4S$ requires C, 44·8; H, 6·7; N, 20·8%). The intermediate *acetamido*-derivative formed colourless plates from water, m. p. 177—178° (Found: N, 18·05. $C_{13}H_{20}O_3N_4S$ requires N, 18·0%).

β-Sulphanilyl-α-2-methoxyethylguanidine (II, R = H, R′ = C_2H_4·OMe).—The use of phenol as a solvent was dispensed with. *p*-Acetamidobenzenesulphonyl-*S*-methyl*iso*thiourea (5 g.) and 2-methoxyethylamine (10 g.) were stirred under reflux for 3 hours. The melt added to water gave crude *β*-p-*acetamidobenzenesulphonyl-α-2-methoxyethylguanidine* (3 g.) which when recrystallised from water had m. p. 178—180° (Found: C, 46·3; H, 5·9; N, 17·8. $C_{12}H_{18}O_4N_4S$ requires C, 45·8; H, 5·7; N, 17·8%). Hydrolysis at the acetamido-group effected as above gave *β-sulphanilyl-α-2-methoxyethylguanidine* as colourless prisms from water, m. p. 161—162° (Found: C, 44·25; H, 5·45; N, 19·95. $C_{10}H_{16}O_3N_4S$ requires C, 43·8; H, 5·1; N, 20·5%).

β-Sulphanilyl-α-2-diethylaminoethylguanidine (II, R = H, R′ = C_2H_4·NEt_2).—Prepared as for the methoxyethyl derivative using 2-diethylaminoethylamine in the same proportion, the *compound* formed colourless prisms from water, m. p. 154—156° (Found: C, 50·55; H, 7·65; N, 22·05.

$C_{13}H_{23}O_2N_3S$ requires C, 49·9; H, 7·4; N, 22·5%). The intermediate *acetamido*-derivative had m. p. 141—142° (Found: C, 50·7; H, 7·0; N, 19·95. $C_{15}H_{25}O_3N_5S$ requires C, 50·6; H, 7·0; N, 19·8%).

β-Sulphanilyl-α-acetylguanidine (II, R = H, R′ = Ac).—*p*-Nitrobenzenesulphonylguanidine (15 g., Roblin *et al.*, *loc. cit.*) and acetic anhydride (30 c.c.) were refluxed for ½ hour. The precipitate which formed after water had been added (40 c.c.) and the mixture allowed to stand was collected, warmed with ethanol, filtered off, and dried at 100°. The product (8·2 g.) without further purification was reduced in methanol (150 c.c.) with hydrogen at atmospheric pressure and temperature in the presence of Raney nickel (H_2 absorbed, 1970 c.c. Theory for $C_9H_{10}O_5N_4S$ at N.T.P., 2030 c.c.). Water (40 c.c.) was added to the methanol suspension which was then heated to the boil and filtered. On cooling, the *amine* crystallised out as colourless needles, m. p. 208—209° (Found: N, 21·4; S, 12·3. $C_9H_{12}O_3N_4S$ requires N, 21·9; S, 12·5%). It dissolved rapidly in cold dilute sodium hydroxide, but the solution on standing deposited colourless crystals of sulphanilylguanidine (no depression of m. p. when mixed with authentic specimen).

2-p-*Aminobenzenesulphonamidoiminazoline* (III, *n* = 2).—2-Methylthioiminazoline sulphate (4·1 g.) was added continuously during ½ hour to a mixture of N^1-acetylsulphanilamide (5·3 g.), sodium hydroxide (1 g.), and phenol (15 g.) stirred in an oil-bath maintained at 190—200°. The cooled melt was digested with excess of dilute sodium hydroxide solution, and the solid collected, washed thoroughly with water, and dried. Yield, 3·3 g.; m. p. 252—255°. Without further purification the solid was heated on the water-bath for 1½ hours in N-hydrochloric acid (16 c.c.). After being cooled, diluted with water, allowed to stand, and filtered from a little insoluble matter, the solution was made alkaline with ammonia. The precipitated *amine* gave colourless prisms from water (1·5 g.), m. p. 225·5—226·5° (Found: C, 45·45; H, 4·75; N, 23·2. $C_9H_{12}O_3N_4S$ requires C, 45·0; H, 5·0; N, 23·2%). The same compound was obtained in a similar manner starting directly from sulphanilamide, or from *p*-nitrobenzenesulphonamide followed by reduction of the nitro-group, but the yields were lower.

2-p-*Aminobenzenesulphonamidotetrahydropyrimidine* (III, *n* = 3).—Similarly prepared from N^1-acetylsulphanilamide (5·3 g.) and 2-methylthiotetrahydropyrimidine sulphate (5·4 g.) the *amine* formed colourless prisms (1·3 g.) from water, m. p. 239—240° (Found: C, 47·4; H, 5·35; N, 21·9. $C_{10}H_{14}O_3N_4S$ requires C, 47·3; H, 5·5; N, 22·1%).

2-p-*Aminobenzenesulphonamidothiazoline* (IV).—Similarly prepared from *N′*-acetylsulphanilamide (34·7 g.) and 2-methylthiothiazoline sulphate (29·5 g.), the *amine* formed colourless needles from aqueous ethanol (3·2 g.), m. p. 202—203·5° (Found: S, 25·1. Calc. for $C_9H_{11}O_3N_3S$: S, 24·9%). Sprague and Kissinger (*J. Amer. Chem. Soc.*, 1941, **63**, 578), who made the same compound by a route involving the use of a sulphonyl chloride, give m. p. 204—205°.

m-*Aminobenzenesulphonamidoguanidine* ("metanilylguanidine").—*m*-Nitrobenzenesulphonyl chloride (22·2 g.) in acetone (40 c.c.) was added during ¾ hour to a solution of guanidine nitrate (12·2 g.) in 5N-sodium hydroxide (50 c.c.) stirred at 10—15°. After a further 1 hour the suspension was diluted with water (250 c.c.) and filtered, and the solid washed with ethanol and then recrystallised from water. The nitro-compound so obtained (11·2 g.) was stirred under reflux for 1 hour with a mixture of N-hydrochloric acid (110 c.c.) and iron filings (40 g.), and the suspension then made alkaline with sodium carbonate and filtered hot. On cooling, the *amine* crystallised in colourless needles. Further recrystallisation from water gave 1·8 g., m. p. 182—184° (Found: C, 39·25; H, 4·45; N, 25·65. $C_7H_{10}O_2N_4S$ requires C, 39·2; H, 4·7; N, 26·2%).

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