18. *Amino-sulphonic Acid Analogues of Natural Amino-carboxylic Acids.*

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Many substances which inhibit the growth of micro-organisms appear to do so by interfering with substances essential in reactions involved in growth. In some cases there is evidence that this occurs because similarity in structure between the essential substance and the inhibitor causes the latter to block enzymes whose normal substrate is the essential metabolite in question. Sulphanilamide interferes with *p*-aminobenzoic acid in this manner, and pyridine-3-sulphonic acid and its amide with nicotinic acid and its derivatives (Woods, *Brit. J. Exp. Path.*, 1940, **21**, 74; McIlwain, *ibid.*, p. 136). With the intention of making further inhibitory compounds, the amino-sulphonic acids described below have been prepared; they are related in the above manner to α-amino-acids and to β-alanine, which are known to be essential to many pathogenic micro-organisms.

It can now be accepted that the products of the action of aqueous ammonia on aldehyde bisulphite compounds are α-amino-sulphonic acids (Raschig and Prahl, *Annalen*, 1926, **448**, 265; Backer and Mulder, *Rec. Trav. chim.*, 1933, **52**, 454). The objections raised by Schroeter (*Ber.*, 1933, **66**, 1038) have been answered by Backer and Mulder (*Rec. Trav. chim.*, 1934, **53**, 1120) and by Rumpf (*Compt. rend.*, 1937, **204**, 592). The amino-sulphonic acid analogues of many of the naturally occurring α-amino-carboxylic acids are thus easily accessible, and α-amino-methane-, -ethane-, -*iso*butane-, *iso*pentane-, -phenyl-methane-sulphonic acids, and an amino-sulphonic acid derivative of citronellal, have been prepared as bacterial inhibitors for the reason outlined above. The first four members correspond to glycine, alanine, valine, and leucine, several of which are known to be limiting factors in the growth of some pathogenic organisms.

α-Amino-sulphonic acids are reported as unstable in aqueous solution, but experiments with typical members have shown that no appreciable decomposition occurred under the conditions of biological testing (p_H 7·6 at 37°) with the exception of the citronellal derivative, though extensive decomposition occurred at 100°.

Of the aliphatic amino-acids other than α-amino-acids, β-alanine is that known to be

of greatest importance in bacterial nutrition. The corresponding amino-sulphonic acid, taurine, is already well known, and it was decided to prepare also the corresponding *sulphonamide*. This was unsuccessfully attempted by the action of ammonia on β-chloroethanesulphonyl chloride, but conveniently achieved through the *carbobenzyloxy*-derivative, a method not previously used in connection with amino-sulphonic acids. The sulphonamide was stable to the reducing conditions necessary for removal of the carbobenzyloxy-group.

Results of bacteriological work with the amino-sulphonic acids have in some cases shown specific inhibitory relations with amino-carboxylic acids, and will be reported in full elsewhere.

Experimental.

Aminomethanesulphonic acid was prepared according to Raschig and Prahl (*loc. cit.*) in 25% yield and recrystallised from hot water; m. p. 210° (decomp.) (Found : N, 12·6; S, 28·9; alkali equiv., 111·5. Calc. for CH_5O_3NS : N, 12·6; S, 28·8%; equiv., 111).

α-Aminoethanesulphonic acid was prepared according to Backer and Mulder (*loc. cit.*, 1934) in 33% yield and recrystallised from water as detailed for the butane compound [Found : N (Kjeldahl), 11·05; N (nitrite), 11·1; S, 25·6. Calc. for $C_2H_7O_3NS$: N, 11·2; S, 25·6%].

α-*Amino*iso*butanesulphonic Acid.*—The corresponding hydroxy-compound (10 g.; prepared from freshly distilled *iso*butaldehyde and 5N-sodium bisulphite) was shaken at room temperature with aqueous ammonia (20 ml., *d* 0·88) for 1 hour, the mixture cooled, and cold 10N-sulphuric acid added so that the temperature remained below 20°, and until the p_H reached 3·5—4. The *amino-sulphonic acid* (4·5—5·5 g.), which separated in colourless crystals, was filtered off after ¼ hour (on longer standing it decomposed), washed with 50% alcohol, alcohol, and ether, and recrystallised by dissolving it in water (15 ml.) at 70° by vigorous shaking (at higher temperatures it decomposed; solution should be effected in 5 minutes) and allowing the filtered solution to stand in a vacuum over calcium chloride (Found : N, 9·2; S, 20·6. $C_4H_{11}O_3NS$ requires N, 9·2; S, 20·9%).

α-*Amino*iso*pentanesulphonic acid*, prepared from the hydroxy-compound (10 g.) and isolated as described for the *iso*butane compound, was obtained as a finely crystalline sludge (4·5—6 g.). Recrystallised from water (20 ml.) at 80°, it formed plates resembling leucine (Found : N, 8·3; S, 19·2. $C_5H_{13}O_3NS$ requires N, 8·3; S, 19·2%).

α-*Aminophenylmethanesulphonic Acid.*—Ammonium sulphite (15 g.) was dissolved in water (15 ml.) by warming and shaken with freshly distilled benzaldehyde (10·5 ml.) at 40—50°; after ½ hour the solution was cooled in ice, and cold 10N-sulphuric acid added gradually until the p_H was 3. The granular *amino-acid* (4 g.) was filtered off after 2 hours, washed with 50% alcohol, and recrystallised from water (20 ml.) as above, forming colourless prisms, m. p., with loss of water, 123° (Found : N, 6·8; S, 15·5. $C_7H_9O_3NS,H_2O$ requires N, 6·8; S, 15·6%). The dried material melted at 185° (Found : N, 7·5. $C_7H_9O_3NS$ requires N, 7·5%).

Amino-sulphonic Acid from Citronellal.—The hydroxy-compound (10 g., prepared from redistilled citronellal and 5N-sodium bisulphite) was treated with aqueous ammonia, and the product (4—5 g.) separated, as described above. The *acid* crystallised from water in soft colourless plates, m. p. 142—143° (Found : N, 5·95; S, 13·9. $C_{10}H_{21}O_3NS$ requires N, 6·0; S, 13·6%).

Stability of Amino-sulphonic Acid Solutions.—This was determined by titration of the sulphur dioxide liberated from M/50-solutions of the amino-sulphonic acids in air-free buffer of p_H 7·6, heated under various conditions in oxygen-free nitrogen. No decomposition was found with aminoethane- and aminobutane-sulphonic acids at 37° or 50° in 1—4 days; aminopentanesulphonic acid decomposed to the extent of 2% after 3 days at 37° and 5% after 2 days at 50°. The citronellal derivative decomposed at room temperature in 1 day.

Sodium N-*Carbobenzyloxytaurine.*—Taurine (8 g.) was dissolved by warming in water (40 ml.), the solution stirred with ice cooling, and sodium bicarbonate (11·2 g.) added, followed by benzyl chloroformate [from benzyl alcohol (12 ml.) and carbonyl chloride (Bergmann and Zervas, *Ber.*, 1932, **65**, 1192)] during 10 minutes. Stirring was continued at room temperature for 4 hours, the solution extracted three times with its own bulk of ether, and the aqueous layer made acid with hydrochloric acid and evaporated under reduced pressure to about 60 ml.; it then began to crystallise. The solution was warmed and filtered from sodium chloride; the *product* (16 g.) separated on cooling. A little was recrystallised from aqueous alcohol (Found : N, 4·85. $C_{10}H_{12}O_5NSNa$ requires N, 4·8%).

N-*Carbobenzyloxytaurine Amide.*—The sodium salt (8 g.) and phosphorus pentachloride (8 g.), both finely ground, and benzene (80 ml.) were refluxed for 25 minutes, and the benzene and phosphorus oxychloride removed under reduced pressure. The sulphonyl chloride was extracted from sodium chloride with dry benzene (250 ml.), this solution cooled in ice, and an excess of dry ammonia passed in; it was then refluxed in a slow stream of the gas for 2 hours. The product was exhaustively extracted with hot benzene, from which the *amide* (4 g.) separated on concentrating and cooling. It was recrystallised from benzene or aqueous methanol, forming colourless prisms, m. p. 133° (Found: N, 10·6. $C_{10}H_{14}O_4N_2S$ requires N, 10·8%).

Taurine Amide Hydrochloride.—Finely ground carbobenzyloxytaurine amide (2 g.) and palladium-black (0·1 g.; Willstätter, *Ber.*, 1921, **54**, 123) were shaken with water (20 ml.), methanol (20 ml.), and glacial acetic acid (6 ml.) in a stream of hydrogen. Evolution of carbon dioxide and solution of the solid were complete in ½ hour; the palladium was then filtered off, and the solvents removed under reduced pressure and by standing in a vacuum over sodium hydroxide. The residue was dissolved in alcohol (10 ml.), and saturated alcoholic hydrogen chloride added gradually with scratching till no further material separated. The *hydrochloride* was collected; it crystallised from hot alcohol in colourless plates (1·2 g.), m. p. 133° (Found: C, 15·25; H, 5·6; S, 19·7. $C_2H_9O_2N_2ClS$ requires C, 15·0; H, 5·6; S, 19·9%).

This compound has been prepared by Miller, Sprague, Kissinger, and McBurney (*J. Amer. Chem. Soc.*, 1940, **62**, 2099) by a different method.

This work was carried out in the Department of Bacterial Chemistry (Medical Research Council), in the Bland Sutton Institute of Pathology and the Courtauld Institute of Biochemistry, during the tenure of a Leverhulme Research Fellowship. My thanks are due to Mr. D. E. Hughes for carrying out most of the analyses reported.

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