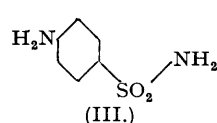
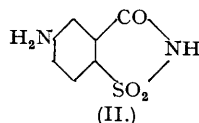
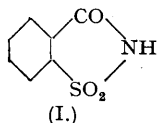


28. 5-Acetamididosaccharin, a Derivative of Sulphanilamide.

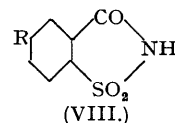
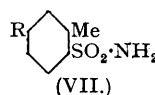
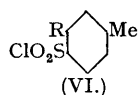
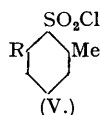
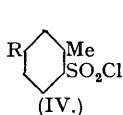
By O. G. BACKEBERG and J. L. C. MARAIS.

Aceto-*m*-toluidide is converted by the action of chlorosulphonic acid into aceto-*m*-toluidide-6-sulphonyl chloride (IV), which forms the corresponding *sulphonamide* (VII) with ammonia. This compound is oxidised by potassium permanganate to 5-acetamididosaccharin (VIII), which may be regarded as a derivative of sulphanilamide. Attempts to deacetylate this compound formed a syrup from which a crystalline product could not be obtained.

OWING to the non-toxic nature of saccharin (I) (Meyer and Jacobson, "Lehrbuch der Organischen Chemie," Vol. II, Part 1, p. 572), and to the presence in it of the group $\text{SO}_2\cdot\text{NH}$, it appeared of interest to attempt the preparation of 5-aminosaccharin (II), in which the amino-group is *para* to the sulphonamido-group, and which may therefore be regarded as a derivative of sulphanilamide (III); the compound (II) may also be regarded as an N^1 -aroyl derivative of sulphanilamide, and as such might be expected to exhibit activity, according to the results of Dewing, Gray, Platt, and Stephenson (J., 1942, 239).



By the action of chlorosulphonic acid, aceto-*m*-toluidide was converted into aceto-*m*-toluidide-6-sulphonyl chloride (IV). It was important to establish the constitution of this compound unambiguously, other possibilities being that it might be the 2- or the 4-isomer (V or VI).



R = NHAc

The constitution of the sulphonyl chloride was established as follows: Treatment with ammonia yielded the *sulphonamide* (VII), which was deacetylated, diazotised, and converted into the corresponding *cresol*, and this on methylation formed 3-methoxy-6-sulphonamidotoluene (VII, R = OMe), m. p. 128°, identical with the compound prepared according to Haworth and Lapworth (J., 1923, 123, 2988).

That chlorosulphonic acid would react in the position indicated appeared probable from the fact that concentrated sulphuric acid forms *m*-toluidine-6-sulphonic acid with *m*-toluidine (Shah, Bhatt, and Kanga, J., 1934, 2010); these authors established the constitution of their product by converting it into a number of known compounds, including the above methoxy-derivative; they also stated that the acid formed a tribromo-derivative, m. p. 101°. Hydrolysis of the sulphonyl chloride (IV), followed by deacetylation, gave a *m*-toluidine-sulphonic acid which formed a tribromo-derivative, m. p. 101°, identical with the above compound, which, however, proved to be 2 : 4 : 6-tribromo-*m*-toluidine, and was therefore of no value in establishing the constitution of the sulphonic acid (compare Limpricht, *Ber.*, 1874, 7, 449).

Oxidation of aceto-*m*-toluidine-6-sulphonamide (VII) with potassium permanganate formed 5-acetamididosaccharin (VIII). Deacetylation of this compound formed a syrup from which a crystalline product could not be obtained. The investigation of related compounds is proceeding.

EXPERIMENTAL.

Aceto-m-toluidide-6-sulphonamide (VII).—74.5 G. of aceto-*m*-toluidide were melted and cooled in ice-water with shaking; 290 g. of chlorosulphonic acid, previously cooled in ice, were added in several portions. The flask was fitted with a calcium chloride tube and gradually warmed on a water-bath; the reaction was complete after about an hour. The syrupy product was poured on ice with vigorous stirring. The sulphonyl chloride (IV) separated as a gummy solid, which was washed by decantation, stirred with ice-water, and treated with an excess of concentrated aqueous ammonia. The *sulphonamide*, obtained as a granular solid (55 g.) after 12 hours, crystallised from hot water (charcoal) in colourless silky needles, m. p. 204° (Found : N, 12.3. $\text{C}_9\text{H}_{11}\text{O}_3\text{N}_2\text{S}$ requires N, 12.3%). On bromination in acetic acid solution, or on addition of alkaline hypobromite to its solution in sodium hydroxide and acidification, it formed 4(?)*-bromoaceto-m-toluidide-6-sulphonamide*, small colourless needles from dilute acetic acid, m. p. 262° (Found : C, 35.3; H, 3.45; N, 8.8. $\text{C}_9\text{H}_{10}\text{O}_3\text{N}_2\text{BrS}$ requires C, 35.2; H, 3.6; N, 9.1%). Deacetylation of this bromo-derivative by refluxing for 30 minutes with 10% sodium hydroxide solution gave 4(?)*-bromo-m-toluidine-6-sulphonamide*, colourless plates from dilute acetic acid, m. p. 185° (Found : C, 31.5; H, 3.5; N, 10.4. $\text{C}_8\text{H}_9\text{O}_3\text{N}_2\text{BrS}$ requires C, 31.7; H, 3.4; N, 10.6%).

When the sulphonyl chloride (IV) was refluxed with 10% sodium hydroxide solution for 2 hours, and the solution acidified, *m*-toluidine-6-sulphonic acid, which chars above 300° without melting, was obtained. Addition of bromine water to its aqueous solution formed 2 : 4 : 6-tribromo-*m*-toluidine, m. p. 101°, identical with the compound prepared according to Shah, Bhatt, and Kanga (*loc. cit.*) and with the product from the bromination of *m*-toluidine (Wroblewski, *Annalen*, 1873, 168, 195, who gave the m. p. as 97°) (Found : N, 4.15. Calc. for $\text{C}_7\text{H}_6\text{NBr}_3$: N, 4.1%).

Treatment of the sulphonyl chloride (IV) in ether with aniline (2 mols.) gave after 12 hours a gummy product after removal of the ether, which was dissolved in hot dilute acetic acid (charcoal). *Aceto-m-toluidide-6-sulphonamide* crystallised in colourless plates, m. p. 155° (Found : C, 58.95; H, 4.9. $\text{C}_{15}\text{H}_{16}\text{O}_3\text{N}_2\text{S}$ requires C, 59.2; H, 5.25%).

m-Toluidine-6-sulphonamide (VII, R = NH_2), obtained by refluxing the compound (VII) with 10% sodium hydroxide

solution for 30 minutes and acidifying the product, formed colourless plates from hot water, m. p. 172° (Found : N, 15.0. $C_7H_{10}O_2N_2S$ requires N, 15.05%). Bromination of its solution in hydrochloric acid formed 2:4(?)-dibromo-*m*-toluidine-6-sulphonamide, small colourless needles from dilute alcohol or dilute acetic acid, m. p. 198° (Found : C, 24.55; H, 2.25; N, 7.95. $C_7H_8O_2N_2Br_2S$ requires C, 24.4; H, 2.3; N, 8.1%). On benzylation, *m*-toluidine-6-sulphonamide formed benzo-*m*-toluidide-6-sulphonamide (VII, R = NHBr), small colourless needles from dilute pyridine, m. p. 265°. This was also obtained in good yield from the action of chlorosulphonic acid on benzo-*m*-toluidide (by the procedure described above), followed by the action of ammonia on the gummy sulphonyl chloride (Found : C, 58.1; H, 4.85. $C_{14}H_{14}O_2N_2S$ requires C, 57.9; H, 4.8%).

m-Cresol-6-sulphonamide (VII, R = OH).—5 G. of the 3-amino-compound were dissolved in methyl alcohol, 3 c.c. of concentrated sulphuric acid added, the solution cooled in ice, and methyl nitrite (Slater, J., 1920, 117, 588) passed into it. After a short time the diazonium sulphate suddenly crystallised; it was collected and dissolved in 100 c.c. of water, and the solution heated to boiling during an hour and then kept in the ice-chest overnight. The product (4.2 g.) crystallised well from hot water (charcoal) in stout colourless prisms, m. p. 207° (Found : N, 7.6. $C_7H_9O_3NS$ requires N, 7.5%). The *m*-cresol-6-sulphonamide was readily methylated by sodium hydroxide and methyl sulphate; the product (yield, almost quantitative) crystallised from hot water in stout colourless prisms, m. p. and mixed m. p. 128° (Found : N, 6.95. Calc. for $C_8H_{11}O_3NS$: N, 7.0%).

5-Acetamido-*o*-benzoic sulphimide (5-Acetamidossaccharin) (VIII).—10 G. of aceto-*m*-toluidide-6-sulphonamide were dissolved in 1600 c.c. of hot water, 14 g. of potassium permanganate added, the solution stirred mechanically, and the temperature kept at 85°, water being added from time to time to keep the volume constant. The oxidation was complete in about 3 hours, as indicated by the disappearance of the colour of the permanganate. The hot solution was filtered by suction and left in the ice-chest overnight. 4.5 G. of unchanged sulphonamide had crystallised; this was removed and the filtrate made faintly acid with acetic acid and evaporated on the water-bath to about 100 c.c.; on cooling, a small quantity of unchanged sulphonamide separated, which was filtered off. 2 c.c. of concentrated hydrochloric acid were added, and the solution left in the ice-chest overnight. 2 G. of a solid separated, which crystallised from dilute alcohol in pale yellow prisms, m. p. 299° (Found : C, 45.0; H, 3.5; N, 11.7. $C_8H_8O_4N_2S$ requires C, 45.0; H, 3.3; N, 11.7%).

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