172. *Studies in the Indole Series. Part IV. Sulphonamides derived from Indole.*

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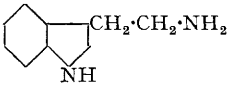
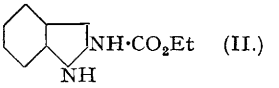
Three new sulphonamides containing the indole nucleus have been prepared, namely, 3-sulphanilamidoethylindole, 3-sulphanilamidoindole, and 5-sulphanilamido-2 : 3-dimethylindole. These showed moderate antibacterial activity, but were very sparingly soluble in water.

In continuation of the work on indole compounds, it appeared to be of interest to prepare and study the properties of sulphonamides containing the indole nucleus. Up to the present, efforts have been restricted to the condensation of *p*-acetamidobenzenesulphonyl chloride with the most readily accessible indole amines. These are β-3-indolylethylamine (I) (tryptamine) (Majima and Hoshino, *Ber.*, 1925, **58**, 2045), 2-aminoindole (Pschorr and Hoppe, *Ber.*, 1910, **43**, 2550), 3-aminoindole (Madelung, *Annalen*, 1914, **405**, 92), and 5-amino-2 : 3-dimethylindole (Bauer and Strauss, *Ber.*, 1932, **65**, 308).

(I.)  (II.) 

These amino-compounds, especially 2- and 3-aminoindole, are rapidly oxidised by air and they are best prepared in an atmosphere of nitrogen. Condensation of the latter or of tryptamine or 5-amino-2 : 3-dimethylindole with *p*-acetamidobenzenesulphonyl chloride is readily accomplished in pyridine solution, and the products can be hydrolysed by the usual methods to the corresponding sulphonamides, 3-*sulphanilamidoethyl-*, 3-*sulphanilamido-*, and 5-*sulphanilamido*-2 : 3-*dimethyl-indole*.

Several unsuccessful attempts were made to condense 2-aminoindole with *p*-acetamidobenzenesulphonyl chloride in presence of pyridine or aqueous sodium hydroxide solution. Reaction of indole-2-urethane (II) (Piccinini and Salmoni, *Gazzetta*, 1902, **32**, I, 252) with *p*-acetamidobenzenesulphonyl chloride also failed to yield a product that could be characterised. In both these reactions highly coloured tars of unknown composition were produced.

The new sulphonamides proved to be very sparingly soluble in water, and this made it difficult to test them for antibacterial activity. For the *in vitro* tests it was necessary to use strongly alkaline solutions (pH 10—12) with the risk of precipitation when these were added to the medium. Even under these conditions, using a synthetic medium, 3-sulphanilamidoethyl- and 3-sulphanilamido-indole inhibited the growth of *Streptococcus hæmolyticus* at a dilution of 1 in 50,000, and 5-sulphanilamido-2 : 3-dimethylindole at a dilution of 1 in 500,000. Suspensions of these compounds were administered orally to mice infected with *Pneumococcus* and *Streptococcus hæmolyticus*; 3-sulphanilamido- and 5-sulphanilamido-2 : 3-dimethyl-indole appeared to prolong the life of the animals for a few days, but the effect was not sufficiently marked to warrant further investigation.

Experimental.

The indole amines (1 g.) were condensed with the theoretical quantity of *p*-acetamidobenzenesulphonyl chloride in cold pyridine solution (dried over barium oxide; 10 c.c.) in an atmosphere of nitrogen, and after standing overnight, the reaction mixtures were poured on ice and 2N-hydrochloric acid. The following data were obtained for the acetyl sulphonamides: 3-*Acetylsulphanilamidoethylindole*, dense crystals from ethyl acetate, m. p. 134° (yield 66%) (Found: C, 60·4; H, 5·2; N, 11·75; S, 8·4. $C_{18}H_{19}O_3N_3S$ requires C, 60·5; H, 5·4; N, 11·8; S, 9·0%). 3-*Acetylsulphanilamidoindole*, dense yellow prisms from acetone, m. p. 248—250° (decomp.) (yield 92%) (Found: C, 58·5; H, 4·8; S, 9·8. $C_{16}H_{15}O_3N_3S$ requires C, 58·4; H, 4·6; S, 9·7%). 5-*Acetylsulphanilamido*-2 : 3-*dimethylindole*, dense prisms from acetone, m. p. 266—267° (decomp.) (yield 96%) (Found: C, 60·7; H, 5·35; N, 11·6; S, 9·1. $C_{18}H_{19}O_3N_3S$ requires C, 60·5; H, 5·4; N, 11·8; S, 9·0%).

The sulphonamides were prepared from their acetyl derivatives as follows: 3-*Sulphanilamidoethylindole*. The acetyl compound (1 g.) was refluxed for 15 minutes with a mixture of concentrated hydrochloric acid (3 c.c.) and water (6 c.c.). A mass of the sparingly soluble hydrochloride of the free base was produced, and was decomposed by addition of excess of aqueous ammonia to the warm solution. The free *base* was filtered off, and crystallised from ethyl acetate and then from aqueous alcohol after treatment with charcoal, to give sheaves of needles, m. p. 143—144° (Found: C, 61·1; H, 5·5; N, 13·0; S, 10·2. $C_{16}H_{17}O_2N_3S$ requires C, 60·9; H, 5·4; N, 13·3; S, 10·2%). 3-*Sulphanilamidoindole*. The acetyl compound (0·3 g.) was refluxed with 2N-sodium hydroxide (2 c.c.) for 15 minutes. The cooled solution was diluted with water (2 c.c.) and made faintly acid with dilute acetic acid. The precipitate was filtered off and crystallised several times from alcohol after treatment with charcoal. The *sulphonamide* formed plates with a pink tinge, m. p.

219—220° (decomp.) (Found : C, 58·6; H, 4·8; N, 14·3; S, 10·9. $C_{14}H_{13}O_2N_3S$ requires C, 58·5; H, 4·6; N, 14·6; S, 11·2%). *5-Sulphanilamido-2 : 3-dimethylindole.* The acetyl compound (1 g.) was refluxed for 30 minutes with 2N-sodium hydroxide (7 c.c.), cooled, and the solution acidified with dilute acetic acid. The crude product was dissolved in excess of hot 2N-hydrochloric acid, filtered, and the filtrate neutralised with sodium carbonate. The free *base*, crystallised from alcohol, formed needles, m. p. 243—244° (Found : C, 60·8; H, 5·5; N, 13·05; S, 10·05. $C_{16}H_{17}O_2N_3S$ requires C, 60·9; H, 5·4; N, 13·3; S, 10·2%).

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