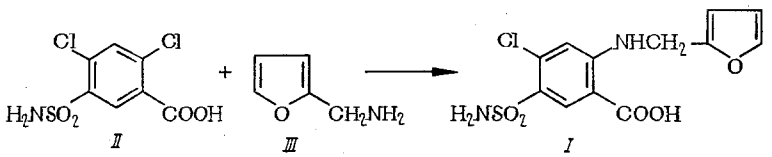
BRIEF COMMUNICATIONS

SYNTHESIS OF 2-FURFURYLAMINO-4-CHLORO-5-SULFAMOYLBENZOIC ACID

V. V. Avidon and M. G. Pleshakov

The compound 2-furfurylamino-4-chloro-5-sulfamoylbenzoic acid (I) (lazics, furocemide) is used as an effective saluretic. This compound was first synthesized by condensing [1] 2,4-dichloro- or 2-fluoro-4-chloro-5-sulfamoylbenzoic acid (II and IIa) with furfurylamine (III):



The present authors have developed an improved method of preparing lazics from the acid (II). The reaction was carried out in a nitrogen atmosphere in order to reduce oxidation of the furfurylamine and the lazics was isolated from the basic solution by means of 10% sulfuric acid. The unreacted furfurylamine was removed from the mother liquor after separating from the lazics by salting out with sodium hydroxide and sodium chloride.

EXPERIMENTAL

2,4-Dichloro-5-Sulfamoylbenzoic Acid (II). This was obtained in accordance with [1] from 120 ml of chlorosulfonic acid and 40 g of 2,4-dichlorobenzoic acid, the compound 2,4-dichloro-5-chlorosulfonylbenzoic acid being isolated as an intermediate; and the mixture was then treated with 400 ml of aqueous ammonia, to give 34.5-35.5 g (64-65%) of I, mp 231-233°.

2-Furfurylamino-4-chloro-5-sulfamoyl-benzoic Acid. (Lazics) (I). To 100 g of furfurylamine through which was passing a current of dry nitrogen was added in portions 50 g of 2,4-dichloro-5-sulfamoylbenzoic acid (II); the mixture was then heated using nitrogen stirring for 4 h at 130°, and was then cooled to 60° and decanted into 1 liter of 10% acetic acid. The mixture was allowed to stand for 15-16 h at 20° with occasional stirring and was then heated at 50-60° for 20 min and slowly cooled to 5° and held at 3-5° for 4 h. The residue was filtered off, washed, and dissolved in 500 ml of 1 N NaOH, heated to 75-80°, and decolorized with activated carbon; the mixture was then acidified to pH 2.0 by adding 10% sulfuric acid. The lazics was filtered off and crystallized twice from a mixture of alcohol and 10% acetic acid (1:1 by volume), using decolorizing carbon in each case, but with the addition of zinc dust in the case of the first recrystallization. This yielded 25.6 g (42%) of lazics, of mp 205-207°, and gave a single spot when subjected to thin layer chromatography on Al_2O_3 (grade II activity) in the solvent system alcohol-water-NH_4OH (100:12:16). The R_f value was 0.44-0.46 (spot brought out in ultraviolet light or with iodine vapor). The ultraviolet data were in agreement with the literature [2].

LITERATURE CITED

1. K. Sturm, W. Sciedal, R. Weyer, et al., Chem. Ber., 99, 328 (1966).
2. P. Hajdu and A. Häusbler, Arzneimittel Forsch., 14, 709 (1964).

S. Ordzhonikidze Pharmaceutical Chemistry Research Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 3, p. 25, March, 1969. Original article submitted October 7, 1968.