CHEMOTHERAPY OF BACTERIAL INFECTIONS

X. 2-Acetsulphanilimido-3-acetsulphanilylthiazolone and 2-Diacetsulphanilylamidothiazole. A New Route to Sulphathiazole

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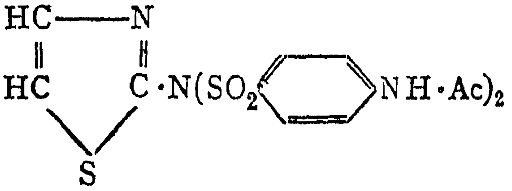
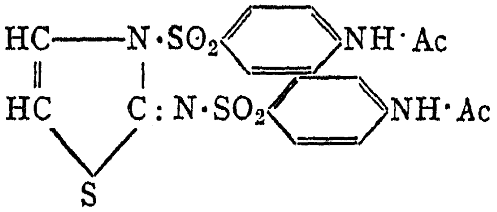
Received April 1, 1943
(Communicated by Lt.-Col. S. S. Sokhey, M.A., M.D., I.M.S., F.A.SC.)

When the condensation of 2-aminothiazole and acetsulphanilyl-chloride in molecular proportions is effected in the presence of pyridine, 2-acetsulphanilamidothiazole is produced in good yields. On the other hand, the use of inorganic basic condensing agents in the place of pyridine has now been found to yield different results. Tuda, Iticawa and So[2] have reported that the condensation of acetsulphanilylchloride with 2-aminopyridine in acetone in the presence of sodium bicarbonate yields 2-acetsulphanilamidopyridine; Bobranski and Eker[2] have obtained the same results by using sodium oxide in the place of sodium bicarbonate. But when the condensation of acetsulphanilylchloride with 2-aminothiazole was effected in the presence of sodium bicarbonate in acetone or aqueous solution, the product obtained was different from the expected 2-acetsulphanilamidothiazole. On crystallisation from alcohol it melted at 128–29°; it was insoluble in alkali but was hydrolysed to sulphathiazole by means of alkali or acid. The same product was obtained by condensing two molecules of acetsulphanilylchloride with one of 2-aminothiazole in pyridine or by the action of acetsulphanilylchloride on an alkaline solution of 2-acetsulphanilamidothiazole. On boiling this product, m.p. 128–29°, with alcohol for some time, it was quantitatively transformed into another, which turned yellow at 190° and charred at 225°. It was also insoluble in alkali and hydrolysed to sulphathiazole. These two compounds can be either dimorphic or isomeric. Though definite evidence against the first possibility has not yet been procured, we are inclined to believe that they are isomers to be represented by the two structures (I) and (II). Since a compound of structure (I) can be


(I)


(II)

expected to isomerise to one of structure (II) and not so easily *vice versa* for the obvious steric reasons, we suggest the structure (I) for the lower melting compound and (II) for the other. Jensen and Thorsteinsson,[3] in a paper which is not accessible and the abstract of which contains no details, have described a compound of structure (II), m.p. 200–220° (turning yellow at 190°); this may quite possibly be identical with the higher melting isomer described here.

It is thus of interest to note that whereas in the presence of pyridine, the condensation of 2-aminothiazole with a molecular equivalent of acetsulphanilylchloride yields 2-acetsulphanilamidothiazole, the use of sodium bicarbonate in the place of pyridine results in the bicondensation product (I) which is easily hydrolysed to sulphathiazole. We have investigated the latter reaction from the practical point of view of the manufacture of sulphathiazole since such a process has not so far been described. We are now satisfied that this is a very feasible method with many practical advantages. The condensation of 2-aminothiazole with two molecular equivalents of acetsulphanilylchloride can be effected in fairly good yields in aqueous suspension in the presence of sodium bicarbonate, calcium or barium carbonate. Calcium carbonate is preferred because of its cheapness and also giving better yields. Another observation made of practical importance is that the yields are better if the solution of aminothiazole is added to the slurry of the sulphochloride. The hydrolysis of the bicondensation product to sulphathiazole proceeds smoothly in good yields. The advantages of this method of preparation of sulphathiazole are: (1) the sulphochloride can be used in the wet state after washing with water by decantation, (2) the use of the costly and now practically unobtainable good grade of pyridine is dispensed with, (3) the products obtained are cleaner and much less coloured and (4) the whole working time is very much shortened. We are engaged in effecting further improvements in this method and studying the reaction with other alky aminothiazoles.

Experimental

2-*Diacetsulphanilylamidothiazole* (I).—(1) To 2-aminothiazole (10 g.) dissolved in dry pyridine (50 c.c.) was added with good shaking crystallised acetsulphanilylchloride (46 g.). After all of it was added, the mixture was warmed on the water-bath for about half an hour, cooled and then poured into cold water. The solid that separated was filtered off, triturated with dilute sodium hydroxide solution, filtered, washed and crystallised from alcohol; yield, 35·0 g. The condensation product obtained in colourless needles melted at 128–29° (Found: N, 11·4; $C_{19}H_{18}N_4O_6S_3$ requires

N, 11·3%). When this product was hydrolysed by boiling for one half hour with about 4 N hydrochloric acid and further worked up as usual, sulphathiazole was obtained in very good yields.

(2) To a solution of 2-acetsulphanilamidothiazole (7·2 g.) in sodium hydroxide (60 c.c. of 2·5 N) was added with cooling and good shaking finely powdered acetsulphanilylchloride (6·0 g.). The whole was kept well ground in a mortar and the solution maintained slightly alkaline if necessary by addition of alkali. After allowing to stand for some hours, the product was filtered off, washed with water and crystallised from alcohol; m.p. 127–29° (mixed m.p. with the foregoing sample being the same). Yield, about 10 g.

(3) The same product was obtained on condensing 2-aminothiazole with one or two molecular equivalents of acetsulphanilchloride in aqueous solution in cold in the presence of 2·5 molecular equivalents of sodium bicarbonate.

2-Acetsulphanilimido-3-acetsulphanilylthiazolone (II).—When the product, m.p. 127°–29°, was boiled in alcohol for one to two hours, it was transformed into one of higher melting point; this product which is sparingly soluble in alcohol, after repeated crystallisations from alcohol, was obtained in colourless needles which turns yellow at 190° and charrs at 225° (Found: N, 11·3; $C_{19}H_{19}N_4O_6S_3$ requires N, 11·3%).

Preparation of Sulphathiazole.—The acetsulphanilylchloride prepared from acetanilide (1·0 kg.) and commercial chlorosulphonic acid (2·4 l.), was washed free from acid with water and suspended in water (8 to 10 l.). In case the solution was acidic, it was neutralised with calcium carbonate and then a further quantity of calcium carbonate (500 g.) was added and stirred well. A solution of crude 2-aminothiazole (250 g.) in water (4 l.) was slowly run in with good stirring. There was a vigorous evolution of carbon dioxide and the stirring was continued till it practically subsided. After allowing it to stand overnight, the solid was filtered off, triturated with dilute hydrochloric acid to decompose the excess of calcium carbonate and then washed with water (a sample of the condensation product on crystallisation from ethyl alcohol had m.p. 128–29°). The solid obtained was hydrolysed as usual by boiling with about 5 N hydrochloric acid or about ten per cent. sodium hydroxide. On neutralising the filtrate, sulphathiazole was thrown out. This was collected and recrystallised from boiling water (charcoal). The yield of the product obtained in colourless needles was about 250 g. and this can doubtless be improved.

We thank Lt.-Col. S. S. Sokhey, Director, for his keen interest in these investigations.

Summary

2-Aminothiazole condensed with acetsulphanilylchloride in aqueous solution or suspension in the presence of sodium bicarbonate, calcium carbonate or barium carbonate to yield 2-diacetsulphanilylamidothiazole, m.p. 128–29°; the same product is also obtained by condensing 2-aminothiazole with two molecular equivalents of acetsulphanilylchloride in pyridine or by condensing 2-acetsulphanilamidothiazole with acetsulphanilylchloride in alkaline solution. This compound on boiling with alcohol isomerises into 2-acetsulphanilimido-3-sulphanilylthiazolone. These two products are hydrolysed by acid or alkali to sulphathiazole in good yield. A process of preparation of sulphathiazole is described.

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