BACTERIAL CHEMOTHERAPY, II : SYNTHESIS OF POSSIBLE INTESTINAL ANTISEPTICS OF THE SULPHANILAMIDE GROUP

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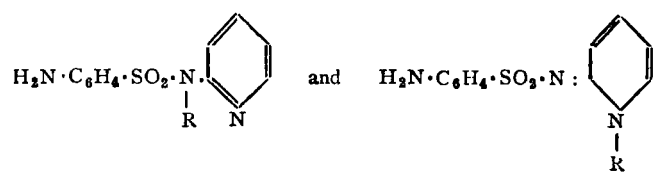
THE successful application of the sulphonamides to the chemotherapy of many types of bacterial infections led to their trial in infections of the Cholera-dysentery-typhoid group, which are characterised by their main or entire localisation in the intestinal tract. The prerequisites of a compound to be an ideal intestinal antiseptic are that it should be poorly absorbed and also possess a strong bacteriostatic and bactericidal local action. The properties of such a compound would permit the attainment of a high concentration in the intestine without being too toxic, due to a low concentration in the blood and tissues. Sulphaguanidine, a drug fulfilling these specifications, has been introduced by Marshall *et al.*[1] and heralds an advance in intestinal antisepsis. Although sulphapyridine and sulphathiazole were found on clinical trial to have some curative value in bacillary dysentery, these drugs have the disadvantage, as far as intestinal infections are concerned, of being readily absorbed from the bowels and perhaps of being renal irritants in dehydrated patients. However, the evolution of succinyl sulphathiazole[2]—a drug which is believed to owe its activity to its slow cleavage into sulphathiazole in the intestine—should be considered a right step in this direction.

Three compounds of the sulphonamide group—sulphathiazoline, sulphapyridine and sulphathiazole—were therefore chosen for further synthetic elaboration and study of the resulting products as to their usefulness in intestinal as well as a few other bacterial infections. It appeared that by introducing substituents at the sulphonamide part of the molecules of the sulphonamido heterocycles, compounds insoluble in alkali and therefore unlikely to be absorbed from the intestine, which is alkaline in pH, could be obtained. A list of some of the compounds prepared with this object are listed.

Serial No.	Name	M.P./°C.	Nitrogen percentage	
			Found	Required
27	3-Methyl, 2-sulphanilimido, 2 : 3-dihydro-thiazoline	196–98	15·4	15·5
28	3-Ethyl, 2-sulphanilimido, 2 : 3-dihydro-thiazoline	181–82 dec.	14·6	14·7
29	N^1-Phenyl sulphathiazoline	glassy liquid at 156, which clears at ca. 185	12·6	12·6
	N^4-Acetyl, N^1-phenyl sulphathiazoline ..	230 —	..	..
30	N^1-Allyl sulphathiazoline	186–89, softg. 187	13·8	14·1
	N^4-Acetyl, N^1-allyl sulphathiazoline ..	179–81, sintg. 176	..	..
32	1-*p*, Nitrobenzyl, 2-sulphanilimido, 1 : 2-dihydro pyridine	234 dec.	14·4	14·6
	1-*p*, Nitrobenzyl-2-acetyl sulphanilimido, 1 : 2-dihydropyridine	215–18	..	..
33	1-*p*, Nitrobenzyl-2-(*p*, nitrobenzylamino)-benzene sulphonilimido, 1 : 2-dihydro-pyridine	208–10	13·3	13·3
34	3-*p*, Nitrobenzyl-2-sulphanilimido, 2 : 3-dihydrothiazole	199–200 dec.	13·8	14·4
35	3-*m*, Nitrophenacyl-2-sulphanilimido, 2 : 3-dihydrothiazole	238–39	13·4	13·4
	3-*m*, Nitrophenacyl-2-acetyl-sulphanilimido, 2 : 3-dihydrothiazole	216–18	..	..

The nitro aralkyl derivatives (Nos. 32–35) were selected because of the high activities reported for a somewhat similar compound, N,[4] 4′-nitrobenzyl sulphanilamide.[3]

There are two alternative structures possible for the compounds obtained by the above kind of operation on the sulphonamides. Taking the example of one of the sulphonamido heterocycles, namely, sulphapyridine, the introduction of an alkyl radical (R) can furnish the following isomeric products.



The production of one or other of the isomeric forms are conditioned by the experimental technique adopted and have recently been well investigated. The nomenclature adopted for the compounds reported herein are, therefore, in accordance with these studies.[4,5]

Experimental

3-Methyl- and 3-ethyl, 2-sulphanilimido, 2 : 3-dihydrothiazolines (Nos. 27 and 28) were obtained by the action of a slight excess of the appropriate alkyl

sulphate or iodide on an aqueous alkaline solution of sulphathiazoline. They consisted of colourless needles or plates after crystallisation from alcohol.

N^1-Phenyl sulphathiazoline (No. 29): *2-Anilino thiazoline.*—The method available in literature[6] gave only a poor yield of this compound. A modified procedure afforded the desired amine in a very much better yield; a mixture of β-bromoethylamine hydrobromide (10 gm.) in water and phenyl *iso*thiocyanate (6·7 gm., 1 mol.) was cooled and treated with excess of 20 per cent. sodium hydroxide. The separated crystals were purified through a dilute hydrochloric acid solution and separated from alcohol in colourless needles, m.p. 158–60°.

N^1-Phenyl sulphathiazoline was prepared by the acid hydrolysis of its N^4-acetyl derivative, in turn obtained by condensation of acetyl sulphanilyl chloride with anilino thiazoline in pyridine according to general procedure.

N^1-Allyl sulphathiazoline (No. 30): *2-Allylamino thiazoline,* prepared by the same procedure as adopted for 2-anilino thiazoline, was obtained as an oil which was used as such without further purification.

The sulphonamide (No. 30) was prepared as usual from the above amine.

1-p, Nitrobenzyl-2-(p, nitrobenzylamino-) benzene sulphonimido, 1 : 2-dihydro pyridine.—A mixture of equimolecular amounts of sodium sulphapyridine and *p*-nitrobenzyl bromide in alcohol was refluxed until a neutral reaction resulted. The desired compound, which is insoluble in both dilute hydrochloric acid and sodium hydroxide, was separated from the accompanying basic monosubstitution product (No. 32) and from unreacted sulphapyridine.

The compounds (Nos. 32, 34, 35) were obtained by the acid hydrolysis of the corresponding N^4-acetyl derivatives, which in their turn were prepared by the interaction of the respective N^1-sodio sulphonamides and the appropriate alkyl bromides in alcoholic solution.

The nitro compounds (Nos. 32–35) were obtained as yellow crystals from pyridine.

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Summary

Chiefly by the action of alkyl or aralkyl halides or the alkyl sulphates on the sulphanilamido heterocycles, a series of compounds, insoluble in alkali, has been obtained. Because of the likelihood of these not being absorbed from the intestine, which is alkaline in pH, the type of compounds synthesised are expected to prove particularly useful in infections of the intestinal tract.

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