CHEMOTHERAPY OF BACTERIAL INFECTIONS

Part IV. Synthesis of (N^1)-sulphonamide substituted heterocyclic derivatives of Sulphanilamide

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Received March 3, 1941

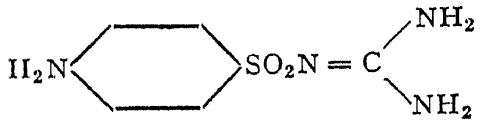
(Communicated by Lieut.-Col. S. S. Sokhey, M.A., M.D., I.M.S.)

The results of our testing many typical sulphanilamide derivatives for anti-bacterial activity having convinced us that the compounds more active and more polyvalent in therapeutic action than sulphanilamide should be searched for amongst its (N^1)-sulphonamide substituted derivatives,[1] the synthesis of such a class of compounds was undertaken. As suitable substituents for this purpose, we chose the significant radicals or ring systems present in the reputed antiseptics, chemotherapeuticals of undoubted value in the treatment of the protozoal infections and also the compounds with vital biochemical functions such as the vitamins, coenzymes, nucleic acids, etc. After a trial of the various radicals and ring systems (the results obtained are being published), success was met with in the thiazole derivatives and the very impressive results obtained by us with one of them, 2–N^1-sulphanilamidothiazole (sulphathiazole) in some experimental infections[2] and clinical trials in plague[3] have already been published. This paper presents the list of compounds further synthesised in accordance with our scheme (a preliminary report of which has already been published[4]). Since the immediate programme at hand is a preliminary survey of the various ring systems for anti-bacterial activity and we had to reap the maximum benefit of the very limited stock of chemicals available, only typical representatives of each group were prepared and tested to trace the direction in which further elaboration would be expected to be profitable. As is inevitable and is also becoming a rather common experience in this field wherein a large number of investigators are rushing for new and more potent compounds, there is much overlapping of work. Thus, some of the compounds prepared and tested here have been reported by other researchers also.[5,6,7] Though in our synthesis of sulphanilamidothiazole with substituents at the positions 4 or 5 or both in the thiazole ring, we were anticipated by a patent of Messrs. May and Baker,[8] we are still continuing our studies because the therapeutic properties of most of them have not yet been reported.

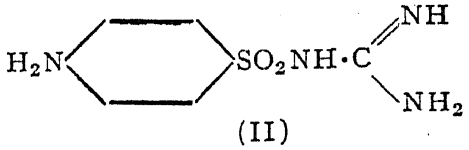
The compounds synthesised are given in the table that follows :—

Compound	Melting point (degrees)	Molecular formula	Percentage of nitrogen	
			Found	Required
Sulphanilylguanidine	188–89	$C_7H_{10}N_4O_2S$	25·8	26·2
Acetsulphanilylguanidine	266	$C_9H_{12}N_4O_3S$	21·8	21·9
N^4-Sulphanilylsulphanilylguanidine ..	155–60	$C_{13}H_{15}N_5O_4S_2$	19·2	19·0
N^4-Acetsulphanilylsulphanilylguanidine ..	143–45 (Dec.)	$C_{15}H_{17}N_5O_5S_2$	17·0	17·0
4-N^1-Sulphanilamidouracil	..	$C_{10}H_{10}N_4O_4S$	20·6	19·9
5-N^1-Sulphanilamidobarbituric acid ..	..	$C_{10}H_{10}N_4O_5S$	19·4	18·8
2-N^1-Sulphanilamido (1 : 3 : 4) thiodiazole	216–18	$C_8H_8N_4O_2S_2$	21·7	21·9
2-N^1-Sulphanilamido-5-methyl (1 : 3 : 4) thiodiazole	190–92	$C_9H_{10}N_4O_2S_2$	20·9	20·7
2-N^1-Sulphanilamidopyrimidine	240–42	$C_{10}H_{10}N_4O_2S$	22·0	22·4
2-N^1-Sulphanilamido-4-methyl pyrimidine..	236–38	$C_{11}H_{12}N_4O_2S$	21·0	21·2
2-N^1-Sulphanilamido-4 : 6-dimethyl-pyrimidine	235–40	$C_{12}H_{14}N_4O_2S$	19·6	20·1
2 :N^1-Sulphanilamido-4-methyl-6 : 6-dimethyl dihydropyrimidine ..	230–32	$C_{13}H_{18}N_4O_2S$	18·9	19·0
7-N^1-Sulphanilamidoalloxazine	..	$C_{16}H_{12}N_6O_4S$	22·5	21·9

For sulphanilylguanidine two structures (I) and (II) are possible; Marshall *et al.*,[5] who also prepared this compound, do not choose one in preference to the other. But this compound being insoluble in alkali indicating the absence of a hydrogen atom attached to the nitrogen of the sulphonamide group, we prefer to represent it as (I). Our interest in this compound



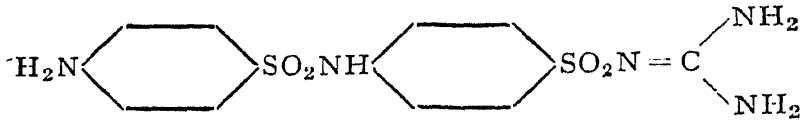
(I)



(II)

as well as its acetyl derivative is also as an intermediate for the construction of the pyrimidine derivatives with the guanidine residue. In sharp contrast to the free guanidine or amidine derivatives, these compounds are very reluctant to condense with β-diketones, β-ketonic esters and $\alpha : \beta$-unsaturated ketones under the usual conditions. Other conditions are being tried and the results will be reported in a subsequent communication.

When sulphanilylguanidine (I) is condensed with *para*acetaminobenzene sulphochloride, a compound insoluble in dilute hydrochloric acid is formed ; hence for the product obtained by hydrolysis, the structure of N^4-sulphanilyl-sulphanilylguanidine (III) has been assigned. Acetsulphanilylguanidine,



(III)

however, under the above conditions did not condense with *para*acetamino-benzenesulphochloride, indicating the comparative inertness of the two amino groups in the former. Since 2-N^1-sulphanilamido-4-methylpyrimidine, tested by us as a representative of the pyrimidines, shows interesting therapeutic properties,[6] a series of 4 : 5- and 4 : 6-dialkyl derivatives of this group are being synthesised by obvious methods. The synthesis of the 4 : 6-derivatives are of special interest to us because the condensation of β-diketones with guanidine in one step yields the starting 2-aminopyrimidine derivative. In the place of the aminopyrimidine in the above condensations, the corresponding pyrimidones and chloropyrimidines have also been tried, but herein the condensations so far tried have not been so smooth. These are being further studied.

Most of the compounds reported here have been tested in experimental *β-hæmolytic streptococcal* and *pneumococcal* (type I) infections in mice and those worthwhile among them in plague infection also. The results obtained will be reported elsewhere in detail. The uracil, barbituric acid and alloxazine derivatives were inactive, while none of the rest surpassed sulphathiazole in therapeutic activity.

The knowledge so far obtained by testing hundreds of sulphanilamide derivatives of diverse structures by us and other workers can be summed up as follows : The grouping  is essential for the therapeutic activity, the *degree* and *range* of which being governed by the nature of the substitutent (R) present at the sulphonamide radical. Of the various types of substituents (R) tried, only the heterocyclic compounds, the ring structure of which are present in products of vital biochemical functions (as vitamins, coenzymes), yield sulphanilamide derivatives of outstanding value. Among these heterocycles themselves, the groups or atoms present therein and also the position of their attachment to the sulphonamide radical do govern the activity. It looks as though some specific spatial configuration of the whole molecule is essential for intense therapeutic activity.

Experimental

The methods of synthesis of these compounds being so much standardised, the details of their preparation are omitted to save space. The starting amines were all prepared by methods described in literature. In the condensations of the sulphochlorides with the amines, pyridine or alkali (sodium bicarbonate) was used as the condensing agent and acetone as the diluent. Hydrolysis of the acetylderivatives was always carried out with (4-6 N) hydrochloric acid since this was much quicker and the end point could be seen. Since our interest in these compounds is frankly only for testing their antibacterial properties, the intermediate acetyl derivatives (known to be very little active) were not isolated. The meltings of many of the compounds were not at all sharp even though they gave correct analytical figures and possessed the unmistakable properties of the sulphanilamides.

My grateful thanks are due to Lieut.-Col. S. S. Sokhey, Director, Haffkine Institute, Bombay, for his keen interest in this investigation and also to the Lady Tata Memorial Trust for the extension of the Scholarship for the fourth year to continue these researches.

Summary

In an attempt to assess the antibacterial effect of sulphanilamides with various heterocyclic rings introduced into the (N^1)-sulphonamide radical, typical derivatives, of guanidine, thiodiazole, uracil, barbituric and pyrimidine have been synthesised and are reported here.

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