CHEMOTHERAPY OF BACTERIAL INFECTIONS

IX. Synthesis of Some Sulphathiazole Derivatives

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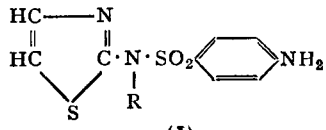
CONSIDERABLE attention is being given in recent times to the discovery of sulphanilamide derivatives for the treatment of infections of the typhoid-cholera-dysentery group. A drug to be ideal for these intestinal infections should, besides possessing very strong bacteriostatic and bactericidal action against the organism concerned, remain localised in the intestine with little of it being absorbed from there into the blood stream. Such a drug should be harmless even with very high concentrations in the intestine because the toxic effects produced by the drugs are mainly the results of their high concentrations in the blood. Basing on this principle, Marshall *et al.*[1] brought forward sulphanilylguanidine as a drug suitable for the treatment of the intestinal infections. Though there are fairly good reports on the treatment of bacilliary dysentery with this drug, it does not impress on us to be as excellent as sulphanilamide or sulphathiazole in their respective spheres of action (compare for example[2]). We attempted therefore to prepare other compounds which may fulfil the criteria mentioned above.

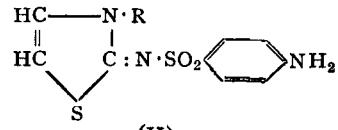
It has previously been reported[3] from this laboratory that sulphathiazole protects mice against septicæmia due to *B. typhosum* and that it shows distinct bacteriostasis against *V. cholerœ in vitro* in as low a concentration as 3 mg. per cent., while sulphanilamide even in 10 mg. per cent. shows no bacteriostasis. The disadvantage of this drug for our present purpose is that it is very rapidly absorbed from the intestine so that it is difficult to attain very high concentrations of this in the intestine without increasing correspondingly the concentration in the blood to dangerous limits. So we sought to prepare derivatives of sulphathiazole of such a type that the original therapeutic activity may not be much impaired and at the same time its absorption from the intestine will considerably be reduced. The poor absorption of sulphaguanidine from the intestine which is alkaline in pH, appeared to us to be due to its insolubility in alkali and so we attempted to prepare derivatives of sulphathiazole of formula (I) or (II).

The other object in synthesising compounds of this type is to aid us in correlating chemotherapeutic activity with chemical constitution. Derivatives of sulphathiazole with alkyl substituents at positions 4 and/or 5 of the thiazole ring were previously reported.[4] The compounds described here represent the third possibility of introducing further substituents in the molecule of sulphathiazole.

Sulphathiazole readily condensed with alkyl bromide or iodide (R. Hal) or sulphate in alkaline solution to yield a substitution product wherein the (N^4–) amino group was found to be unsubstituted. The yields were better and the products much purer if the sodium salt of sulphathiazole was treated with the halide in alcohol. While methyl, ethyl, butyl, *iso*amyl and hexyl bromides or iodides readily condensed, *iso*propylbromide was very reluctant to undergo the condensation under these conditions. β-Chloroethylamine and β-bromoethyldiethylamine did condense with sodium sulphathiazole



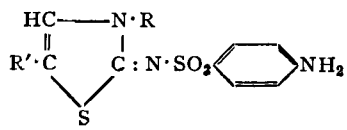
(I)



(II)

but the products obtained could not be crystallised. Ethylchloroacetate as well as ethyl α-chloroacetoacetate on condensation with sodium sulphathiazole yielded the same compound (No. 93); thus the acetyl group in the latter reagent appears to get eliminated in the process. The compounds prepared are listed in the table.

TABLE



Serial No.	R =	R′=	M.P. °C.	Molecular Formula	% Nitrogen	
					Found	Required
83	Methyl-	H	244–46	$C_{10}H_{11}N_3O_2S_2$	15·3	15·6
84	Ethyl-	H	183–85	$C_{11}H_{13}N_3O_2S_2$	15·2	14·8
85	*n*-Butyl-	H	186–88	$C_{13}H_{17}N_3O_2S_2$	13·2	13·5
86	*iso*-Amyl-	H	201– 3	$C_{14}H_{19}N_3O_2S_2$	12·2	12·9
82	*n*-Hexyl-	H	156	$C_{15}H_{21}N_3O_2S_2$	12·4	12·4
106	β-Hydroxyethyl- ..	H	154–56	$C_{11}H_{13}N_3O_5S_2$	13·8	14·0
94	β-Ethoxyethyl-	H	150–52	$C_{13}H_{17}N_3O_1S_2$	1·0	12·0
95	Acetonyl-	H	202	$C_{12}H_{13}N_3O_5S_2$	12·9	13·0
93	Carbethoxymethyl- ..	H	184–85	$C_{13}H_{15}N_3O_1S_2$	12·6	12·3
92	Methyl-	*iso*-Pr	157–60	$C_{13}H_{11}N_3O_2S_2$	13·3	13·0

For the compounds obtained as above described, two structures (I) and (II) are possible. Because of the existence of the triad system, $-N=C-N\cdot R \rightleftharpoons R\cdot N-C=N-$, the compound (I) can easily isomerise to (II) and there are instances known in literature of such an isomerisation. On boiling the alkyl bromides with an alkaline solution of sulphathiazole, a low melting product is first obtained in many cases, which during the process of crystallisation is gradually transformed into one of higher melting point. We have not succeeded in isolating the lower melting ones in these cases (an instance wherein this has been done is reported in the next part) and it is difficult to assert that this is due to isomerisation since dimorphism is also well known among these compounds. After this work was completed, Hartmann and Druey[5] have found that acetsulphanilylchloride condensed with 3-methyl-2-thiazolonimin to yield the same product obtained by methylating acetylsulphathiazole with dimethyl sulphate; this on hydrolysis yielded the methyl derivative (II, R = Me), m.p. 245–6°. On the other hand, *p*-nitrobenzenesulphochloride condensed with 2-methylaminothiazole and the product obtained on reduction yielded a compound, m.p. 109–10°, to be represented as (I, R = Me). Jensen[6] has also reported the same. Druey[7] has recently reported the preparation of a series of compounds of formula (II) by condensing 3-substituted thiazolonimids with *p*-nitrobenzenesulphochloride and reducing the resulting compound and also by condensing (N^4) acetylsulphathiazole with the alkyl halides and hydrolysing the resulting products. The products thus prepared appear to be identical with those reported by us here, though there are slight differences in the melting points (these compounds as a class frequently do not give sharp melting points). Thus we assign the structure (II) to the compounds obtained by us.

The compounds described here, excepting that number 92, have been tested in experimental plague infections in mice during December 1941–January 1942, according to the technique of Sokhey and Dikshit.[8] The methyl derivative 83, showed therapeutic activity comparable to sulphathiazole. The ethyl compound, 84, gave only one survivor out of ten and the average survival time of the mice was slightly greater than that of the controls; so also was the case with the β-hydroxyethyl derivative, 106. All the others were inactive. The methyl derivative, 83, also showed good therapeutic effect in experimental streptococcal and pneumococcal infections in mice. Because of its sparing solubility in water (less than 0·5 mg. per cent.) its *in vitro* bacteriostatic effect could not be studied; however, it is interesting that this compound after oral administration to mice produces sufficient concentration in the blood to exert a pronounced therapeutic effect.

Experimental

Unless otherwise stated, the yields are all to be understood as good in the following experiments.

2-(p-*Aminobenzenesulphonimido*)-3-*methyl thiazolone* (*II*, $R = Me$).—To 2-sulphanilamidothiazole (50 g.) dissolved in sodium hydroxide (2·5 N, 160 c.c.) was added gradually under good shaking dimethyl sulphate (40 c.c.). A crystalline product began to separate. After good shaking it was allowed to stand for about one hour (the solution was distinctly alkaline), then filtered, the crystalline product triturated well with dil. sodium hydroxide, washed well and crystallised from alcohol. Yield, 46 g.

This compound could also be obtained by reacting sulphathiazole in alkaline solution or sodium sulphathiazole in alcohol with methyl iodide. In no case could the low melting isomer be obtained.

This compound was recovered unchanged after boiling with 4 N hydrochloric acid or 2·5 N sodium hydroxide for one hour.

2-(p-*Aminobenzenesulphonimido*)-3-*butylthiazolone* (*II*, $R = Bu$).—Sulphathiazole (12·4 g.) dissolved in sodium hydroxide (2·5 N, 40 c.c.) was boiled with butyl bromide (10 c.c.) or butyl iodide (8 c.c.) till there was no further increase in the quantity of the crystalline solid that separated (about 1 hour). It was cooled, the crystalline solid separated, washed well with alkali, then with water and crystallised from alcohol.

2-(p-*Aminobenzenesulphonimido*)-3-*isoamyl thiazolone* (*II*, $R =$ iso*amyl*).—To sodium salt of sulphathiazole (13·7 g.) was added methyl alcohol (50 c.c.) followed by *iso*amyl bromide (10 c.c.), and the whole heated under reflux for about one hour and then allowed to stand overnight. The crystalline product that separated as such and also from the mother-liquors on dilution, was washed well with dil. alkali, then with water and crystallised from alcohol.

Similarly, the ethyl and hexyl compounds were prepared by utilising ethyl iodide and hexyl bromide.

2-(p-*Aminobenzenesulphonimido*)-3-*carbethoxymethylthiazolone* (*II*, $R = CH_2COOEt$).—Sodium (1·2 g.) was dissolved in absolute alcohol (50 c.c.) and to this was added sulphathiazole (12·8 g.) and the mixture refluxed for 15 minutes. To the solution was added ethyl chloroacetate (8·0 g.) and the refluxing continued for about one hour more. After allowing it to stand overnight the product that had separated was filtered, rapidly washed with alkali, then with water and crystallised from alcohol.

The same compound was obtained when sodium sulphathiazole was condensed with ethyl α-chloroacetoacetate.

2-(p-*Aminobenzenesulphonimido*)-3-*acetonyl thiazolone* (*II*, $R = CH_2CO\ CH_3$).—The sodium salt of sulphathiazole (13·7 g.) was taken up in absolute ethyl alcohol (75 c.c.), chloroacetone (5 g.) was added and the mixture heated under reflux. A crystalline solid soon separated. The mixture was heated for about an hour more when the chloracetone had completely disappeared. It was then filtered, the product washed with alkali, then with water and crystallised from alcohol.

2-(p-*Aminobenzenesulphonimido*)-3-*β-hydroxyethyl thiazolone* (*II*, $R = HO \cdot CH_2CH_2-$).—To sodium salt of sulphathiazole (13·7 g.) in methyl alcohol (20 c.c.) was added ethylene chlorhydrin (10 g.) and the mixture refluxed for about one hour. Further working up of this was as described in the previous cases.

I am indebted to Mr. C. V. Deliwala for the nitrogen estimations recorded here. I also thank Lt.-Col. S. S. Sokhey for his kind interest in these investigations.

Summary

The synthesis of various derivatives of sulphathiazole with alkyl and substituted alkyl substituents at the ring nitrogen of the thiazole nucleus has been described. Of these compounds only the methyl derivative showed good therapeutic activity in experimental streptococcal, pneumococcal and plague infections in mice.

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