CHEMOTHERAPY OF BACTERIAL INFECTIONS

Part V. Synthesis of 2-N1-Sulphanilamido-5-alkyl- and 2-N1-Sulphanilamido-4-methyl-5-alkyl-thiazoles

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Received November 15, 1941

(Communicated by Lt.-Col. S. S. Sokhey, M.A., M.D., F.A.sc., I.M.S.)

The studies carried out in this Institute on the therapeutic properties of a pilot series of N1-sulphanilamido derivatives of various ring compounds in experimental β-hemolytic streptococcal, (type I) pneumococcal and P. pestis infections in mice, have led to the discovery of the outstanding therapeutic properties of 2-N1-sulphanilamido derivatives of thiazole and pyrimidine. The clinical studies carried out hitherto, extensively with the former and to a limited extent with the latter drug, have fully confirmed the results of the animal experiments. As a sequel to this, we undertook to investigate whether, by the proper manipulation of the molecular structure of these drugs, other derivatives could not be discovered which may be more effective or therapeutically active in the treatment of those infections in which they are of little value. The synthesis of many possible types of such compounds was therefore undertaken to study systematically the effects (pharmacological and physico-chemical) of different types of additional substituents in the sulphanilamido derivatives of thiazole and pyrimidine. This paper is concerned with the synthesis of a particular series of 2-N1-sulphanilamidothiazole derivatives with alkyl substituents in the positions 4 and/or 5 of thiazole; the other types of thiazole and pyrimidine compounds are being reported in the succeeding parts.

2-N1-sulphanilamido-5-alkylthiazoles were synthesised according to the following scheme:

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{SO}_{2}\text{Cl}_{2}} \text{CHO} \xrightarrow{\text{CS(NH}_{2})_{2}} \text{CH} \xrightarrow{\phi \text{Ac} \cdot \text{NH} \cdot \text{C}_{6}\text{H}_{4} \cdot \text{SO}_{2}\text{Cl}} \text{C} \xrightarrow{\text{NH}_{2}} \\
\text{R} \cdot \text{CH}_{2} & \xrightarrow{\text{R} \cdot \text{CH} \cdot \text{Cl}} \text{R} \cdot \text{CH} \cdot \text{C} \xrightarrow{\phi \text{Ac} \cdot \text{NH} \cdot \text{C}_{6}\text{H}_{4} \cdot \text{SO}_{2}\text{Cl} \text{NH}_{2}} \\
\text{CH} & \xrightarrow{\text{N}} \text{C} \xrightarrow{\phi \text{Ac} \cdot \text{NH} \cdot \text{C}_{6}\text{H}_{4} \cdot \text{SO}_{2}\text{Cl} \text{NH}_{2}}
\end{align*}
\]

R = C_{6}H_{5}; \text{Me} \cdot \text{CH} = \text{CH}_{3} \cdot \text{(CH}_{2})_{3} \cdot \text{&} \text{CH}_{3} \cdot \text{(CH}_{2})_{4}$. 

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The literature regarding the halogenation of the aliphatic aldehydes (I) is very scanty. Of the 2-amino-5-alkylthiazoles (III), only the 5-methyl derivative has previously been described. It has now been found that the 2-amino-5-alkylthiazoles (III) can smoothly be prepared by chlorinating the alkyl aldehydes (I) with sulphurylchloride and condensing the resulting chloroaldehydes (II) with thiourea. The bromination of the aldehydes was also tried but it appeared to be less advantageous for our purpose since tarry products were formed on condensing the bromoaldehydes with thiourea. The conversion of the aminothiazoles (III) into 2-N\(^1\)-sulphanilamido-5-alkylthiazoles (V) by the usual method was effected in good yields.

The general method adopted to synthesise 2-N\(^1\)-sulphanilamido-4-methyl-5-alkylthiazoles was as follows:

\[
\begin{align*}
\text{CH}_3\cdot\text{CO}\cdot\text{CH} \cdot \text{Na} & \xrightarrow{\text{R} \cdot \text{Br}} \text{CH}_3\cdot\text{CO}\cdot\text{CH} \cdot \text{R} \xrightarrow{\text{hydrolysis}} \text{CH}_3\cdot\text{CO}\cdot\text{CH}_2 \cdot \text{R} \\
\text{Cl}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH} \cdot \text{R} & \xrightarrow{\text{SO}_2\text{Cl}_2} \text{Cl}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH} \cdot \text{R} \xrightarrow{\text{hydrolysis}} \text{Cl}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2 \cdot \text{R} \\
\text{CS} \cdot (\text{NH}_2)_2 & \xrightarrow{\text{R} \cdot \text{C} \cdot \text{S} \cdot \text{NH} \cdot \text{SO}_2\text{Cl} \cdot \& \text{CH}_3\cdot\text{C} \cdot \text{N}} \text{NH}_2 \xrightarrow{\text{hydrolysis}} \text{R} \cdot \text{C} \cdot \text{S} \cdot \text{NH} \cdot \text{NH}_2 \\
\end{align*}
\]

In the above scheme, excepting the ketonic esters (VI), ketones (VII) and 3-chloro-2-pentanone, all other compounds are not described in the literature. The preparation of the chloroketones (IX) via the chloroesters (VIII) furnished purer products (though in poorer yields) evidently because, the chlorination of the ketonic esters (VI) with sulphurylchloride, as is described, leads exclusively to the chloroketonic esters of formula (VIII), uncontaminated with the isomeric esters of formula (VIII \(a\)). In the chlorination of the ketones (VII) also with sulphurylchloride, it has been suggested that the chlorine atom enters the methylene carbon atom adjacent to the keto-group with the formation of the chloroketones of formula (IX). We have actually found that the final sulphanilamidothiazoles (XI) obtained
by both the methods are identical. The compounds obtained by the former procedure immediately yielded crystalline products; but those got by the latter did not crystallise readily which is probably due to the contamination of the chloroketone with isomeric products formed during the chlorination of the ketone. The aminothiazoles (X) in a few cases were also prepared via the bromoketones; the final sulphanilamidothiazoles obtained from these were also identical with those obtained by the other methods. Since it is known that in the bromination of the ketones (VII) and ketonic esters (VI) the orientation of the bromine atom depends upon the conditions of the reaction, other conditions are being studied to prepare the bromo-compounds corresponding to the chloro analogues (VIII \(a\) and IX \(a\)), with a view to preparing from them 2-amino-4-alkylthiazoles.

Since our immediate interest is only the preparation of the sulphanilamidothiazoles (V and XI) and our stock of chemicals is also very limited, the intermediate new products could not be studied in detail at present but will be done at a later date.

The compounds obtained by the above methods are listed in the table. It may be mentioned that 2-sulphanilamido-5-methylthiazole and 2-sulphanilamido-4: 5-dimethylthiazole have been described in a patent of Messrs. May and Baker.\(^4\) The sulphanilamido-alkyl-thiazoles are being tested in many bacterial infections and the results obtained will be reported in due course. If the results are encouraging, further synthesis of more compounds of these groups with higher alkyl groups will be undertaken.

**Experimental**

2-\(N^{1}\)-Sulphanilamido-5-alkylthiazoles (V):—Since all the compounds were prepared by essentially the same method with but slight alterations in conditions to suit the individual cases, only the general methods are here described.

The aliphatic aldehyde (I) (obtained from the Eastman Kodak Co., Rochester), under external cooling with ice cold water, was gradually treated with 1.1 molecular equivalent of sulphurylchloride. The reaction took place just at about the room temperature (25°-28° C.) and when it tended to become vigorous, the mixture was cooled in ice-cold water. After allowing it to stand with frequent shaking for 2-3 hours, it was poured into cold water, the heavy oil separated, washed free from acid with water and boiled with one molecular equivalent of an aqueous solution of thiourea. The boiling was continued till no more of the oil went into solution (usually 2-5 hours). The solution was then thoroughly extracted with ether to remove
any unchanged material and the aqueous clear solution basified with sodium hydroxide when the aminothiazole separated as an oil. This was taken up in ether, the extract dried and the solvent removed; 2-amino-5-alkylthiazole (III) was thus obtained as a mass of crystals in the case of the butyl and amyl derivatives and as a thick syrup in the rest. Without any further purifications, they were condensed with \( p \)-acetaminobenzensulphochloride in pyridine medium to yield the acetyl derivatives of formula (IV) which were then hydrolysed smoothly to the final 2-sulphanilamido-5-alkylthiazoles (V) with about 4-5 N hydrochloric acid. All the compounds were readily obtained in fine crystalline forms and the overall yields were good in all cases.

2-N°-Sulphanilamido-4-methyl-5-alkylthiazoles (XI).—The general methods of synthesis of these compounds are as follows:—

The alkylbromides (R.Br) used in these experiments were all prepared from the corresponding alcohols by the usual sodium bromide-sulphuric acid method. The condensation of the alkylhalides with sodium ethyl acetoacetate to yield the alkylketonic esters (VI) and the hydrolysis of these to the

### Table

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Name of Compound</th>
<th>Melting Point °C.</th>
<th>Molecular Formula</th>
<th>% Nitrogen Found</th>
<th>% Nitrogen Required</th>
</tr>
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<tbody>
<tr>
<td>2-Amino-5-ethylthiazole</td>
<td>170</td>
<td>C_{11}H_{14}N_{2}S_{2}</td>
<td>14.8</td>
<td>14.8</td>
<td></td>
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<td>2-Amino-5-methyl-5-i-soamylthiazole</td>
<td>217-18</td>
<td>C_{12}H_{15}N_{2}S_{2}</td>
<td>14.1</td>
<td>14.1</td>
<td></td>
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<tr>
<td>2-N°-Sulphanilamido-5-ethylthiazole</td>
<td>246</td>
<td>C_{13}H_{16}N_{2}S_{2}</td>
<td>14.0</td>
<td>13.5</td>
<td></td>
</tr>
<tr>
<td>73 Ac</td>
<td>4-methyl-5-ethylthiazole</td>
<td>192-93</td>
<td>C_{14}H_{17}N_{2}S_{2}</td>
<td>13.5</td>
<td>12.9</td>
</tr>
<tr>
<td>74</td>
<td>4-methyl-5-n-propylthiazole</td>
<td>187-88</td>
<td>C_{15}H_{18}N_{2}S_{2}</td>
<td>12.3</td>
<td>12.4</td>
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<tr>
<td>75</td>
<td>4-methyl-5-n-isopropylthiazole</td>
<td>202-04</td>
<td>C_{16}H_{19}N_{2}S_{2}</td>
<td>12.2</td>
<td>12.4</td>
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<tr>
<td>79</td>
<td>4-methyl-5-n-hexylthiazole</td>
<td>191-92</td>
<td>C_{17}H_{20}N_{2}S_{2}</td>
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<td>90 Ac</td>
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<td>C_{19}H_{22}N_{2}S_{2}</td>
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<td>88 Ac</td>
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<td>C_{20}H_{23}N_{2}S_{2}</td>
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<td>229</td>
<td>C_{21}H_{24}N_{2}S_{2}</td>
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<td>11.4</td>
</tr>
<tr>
<td>73 Ac</td>
<td>4-methyl-5-n-propylthiazole</td>
<td>236-36</td>
<td>C_{22}H_{25}N_{2}S_{2}</td>
<td>11.8</td>
<td>11.9</td>
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<tr>
<td>72 Ac</td>
<td>4-methyl-5-n-isopropylthiazole</td>
<td>216-17</td>
<td>C_{23}H_{26}N_{2}S_{2}</td>
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<td>11.4</td>
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<tr>
<td>75 Ac</td>
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<td>234-36</td>
<td>C_{24}H_{27}N_{2}S_{2}</td>
<td>11.3</td>
<td>11.0</td>
</tr>
<tr>
<td>79 Ac</td>
<td>4-methyl-5-n-hexylthiazole</td>
<td>216-18</td>
<td>C_{25}H_{28}N_{2}S_{2}</td>
<td>10.8</td>
<td>10.6</td>
</tr>
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</table>
ketones (VII) were carried out according to methods described in Literature. Methylhexylketone was prepared by the oxidation of capryl alcohol.

**Method 1.**—The methylalkylketone (VII), cooled in ice-cold water, was treated gradually with about one molecular equivalent of sulphurylchloride. The mixture was allowed to stand for about two hours or more with frequent shaking, treated with water, the heavy oil that separated was washed with water, dried and fractionated. The first fraction consisted of the unchanged ketone and the higher boiling one was the required chloroketone (IX) which usually collected within a range of 5–10°C. (this was not refractionated unless the range was much greater). The chloroketone, thus obtained in yields of 80–90%, was boiled with an aqueous solution of thiourea (one molecular equivalent) till no more of the oil could go into solution (2–4 hours). The cooled solution was thoroughly extracted with ether and the clear acid solution basified with sodium hydroxide. The precipitated thick oil was extracted with ether, the extract dried and the solvent removed whereby the aminothiazole (X) was obtained as a syrup (yield, 50–80%). Without any further purification, this was condensed with p-acetamino-benzenesulphochloride in pyridine medium. After allowing the mixture to stand overnight it was warmed on the water-bath for about an hour and on dilution with water, a gummy product was obtained which solidified on vigorous scratching (yield, 50–80%). Further purification of this was effected by dissolving it in ammonia or soda solution (charcoal) and precipitating with hydrochloric acid. The 2-acetsulphanilamido-4-methyl-5-alkylthiazole thus obtained was repeatedly crystallised from isopropyl alcohol. To prepare the 2-sulphanilamido-4-methyl-5-alkylthiazole (XI), the crude acetyl compound was boiled with about ten parts of 4–5 N hydrochloric acid till the solid went into solution (20–60 minutes). In case the hydrochloride separated on cooling, just enough water was added to get a clear solution. After treating it with charcoal, the partly decolourised solution was neutralised when the final product separated as a gum and solidified on scratching (yield, 60–80%). After a few crystallisations from isopropyl alcohol, the 2-sulphanilamidom-4-methyl-5-alkylthiazoles (XI) were obtained as colourless or almost colourless crystals. Only the isopropyl derivative, 78, could not so far be obtained as a sharp melting product though it gave the correct analytical figures. According to this procedure, all the compounds except 80 were prepared.

**Method 2.**—The ketoester (VI) was chlorinated as usual with sulphurylchloride and the resulting chloroester (VIII), obtained in 40–60% yield, was refluxed with a mixture of four parts of 35% sulphuric acid and four
parts of glacial acetic acid for 6-8 hours. The oil obtained on dilution was taken up in ether, the ether extract dried, the solvent removed and the resulting oil fractionated. The chloroketone (IX) thus furnished in yields of 10-40% corresponded in boiling point to that obtained by the previous method. The rest of the procedure in obtaining the final sulphanilamidothiazoles (XI) was as described under method 1. The products obtained by this method were much purer and crystallised very readily. The sulphanilamidothiazoles (XI) obtained by this and the previous method 1 were identical (there being no depression in melting point). According to this method all compounds excepting compounds 74 and 78 were prepared.

Method 3.—The ketone (VII) dissolved in five times the weight of glacial acetic acid and a few drops of hydrobromic acid (48%), under cooling in ice-water, was treated gradually with one molecular equivalent of bromine dissolved in three times the quantity of glacial acetic acid. The decolourisation was immediate and after allowing to stand for about 15 minutes, the solution was poured into cold water, the heavy oil separated, washed free from acid and boiled with one molecular equivalent of thiourea in aqueous solution. The rest of the procedure was as indicated in the previous method 1. According to this method, compounds 72, 73, 74 and 75 were prepared and were found to be identical with the corresponding ones prepared by the foregoing methods.

We express our grateful thanks to Lt.-Col. S. S. Sokhey, Director, Haffkine Institute, Bombay, for his keen interest in these investigations.

Summary

In the course of the attempts to study the effects of the different types of substituents in the molecule of 2-N'-sulphanilamidothiazole, the synthesis of a series of 2-N'-sulphanilamido-5-alkyl- and 2-N'-sulphanilamido-4-methyl-5-alkyl-thiazoles, wherein the alkyl group varies from ethyl to hexyl, have been effected and these compounds are described.

REFERENCES