COMPOUNDS WITH POTENTIAL ANTITUBERCULAR ACTIVITY
XI. Synthesis of Some Derivatives of 2-Aminobenzoxazole

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2-Aminobenzoxazole and a series of its N-substituted derivatives were prepared by the reaction of potassium benzoxazole-2-sulfonate with ammonia and various amines; some 6-nitro- and 6-acetamido-2-aminobenzoxazoles were also obtained. The reaction of 6-nitro-2-mercaptobenzoxazole with heterocyclic amines involves the initial formation of salt-like compounds with the mercapto-group, with subsequent elimination of hydrogen sulfide. Nitration of 2-aminobenzoxazole yields a mixture of 6-nitro-2-aminobenzoxazole and 6-nitro-2-nitraminobenzoxazole.

The object of this work was the synthesis of some 2-amino- and N-substituted 2-aminobenzoxazoles (unsubstituted in the benzene ring, and also with nitro- and acetamido groups in the 6-position) with a view to investigating their antibacterial and, in particular, tuberculostatic activity.

The methods most generally used for the preparation of 2-aminobenzoxazoles and their N-substituted derivatives are: reaction of 2-chlorobenzoxazole with various amines [1], condensation of the corresponding o-aminophenols with cyanogen bromide [2], and cyclization of substituted 2-hydroxyphenylthioureas by means of lead oxide [2, 3]. Some N-alkyl-substituted 2-aminobenzoxazoles have been prepared by reaction of the corresponding amines with 2-methylsulfonylbenzoxazole [4], but the authors give no yields for this reaction. Bearing in mind the fact that the sulfo group in the 2-position of the benzoxazole ring is very labile and can be replaced by various nucleophilic groups [5], we decided to try potassium 2-benzoxazolesulfonate as starting material. (A convenient method for the synthesis of this compound is given in [6]). This salt reacts with a variety of aliphatic, alicyclic, and heterocyclic amines; the reaction is usually carried out in aqueous solution, using a two- to threefold excess of the amine. By heating potassium 2-benzoxazole sulfonate briefly with aqueous ammonia, 2-aminobenzoxazole was obtained in 90% yield. Similarly, the reaction with piperidine and cyclohexylamine gave 2-(N-piperidino)- and 2-cyclohexylaminobenzoxazole, but in poorer yield. With diethanolamine, dimethylaminopropylamine, and 6-morpholinoethylamine, syrupy products were obtained which were difficult to crystallize, and some of these were therefore isolated as dihydrochlorides. In obtaining 2-(2-pyridylamino)- and 2-(2-thiazolylamino) benzoxazoles, the low basicity of the corresponding amines made it necessary to heat the reaction mixture for 16-21 hr at 110-120° (bath temp.); under these conditions the potassium 2-benzoxazolesulfonate was partially converted to 2-benzoxazolone, which was isolated as a by-product. It is interesting to note that the hydrogen atom of the secondary amino group in 2-(2-thiazolylamino)benzoxazole is acidic in character; this compound is insoluble in mineral acids but readily soluble in aqueous alkalies, ammonia, and triethylamine. In an attempt to react potassium 2-benzoxazolesulfonate with 2-amino-4, 6-dimethylpyrimidine, only 2-benzoxazolone was isolated.

Attempts to obtain the monosubstituted compound from ethylenediamine using a large excess of the amine were unsuccessful, both amino groups reacting.

The synthesis of 6-nitro-2-aminobenzoxazole by the reaction of 4-nitro-2-hydroxybenzonitrile with sodium azide has been described in the literature [7]; we have synthesized this compound from potassium 6-nitro-2-aminobenzoxazole sulfonate and ammonia. The influence of the nitro group causes this reaction to proceed instantaneously, with cooling, to give 6-nitro-2-aminobenzoxazole in 93% yield. Potassium 6-nitro-2-benzoxazole sulfonate is, however, obtained in rather low yields, and the nitration of 2-aminobenzoxazole was therefore investigated. By carrying out this reaction with a mixture of nitric acid (d 1.5) and concentrated sulfuric acid, a mixture of two compounds was obtained. One of these, insoluble in mineral acids, was 6-nitro-2-nitraminobenzoxazole, and the other 6-nitro-2-aminobenzoxazole, identical with that obtained from potassium 6-nitro-2-benzoxazole sulfonate. The amount of 2-nitramino-6-nitrobenzoxazole obtained increases with increasing reaction time. Thus, on keeping the reaction mixture at room temperature for two weeks, only 2-nitramino-6-nitrobenzoxazole was obtained, in about 82% yield.

Since the presence of a nitro group in the 6-position of the benzoxazole nucleus increases the lability of the 2-mercapto group [8], to prepare 2-(2-pyridylamino) and 2-(2-thiazolylamino)-6-nitrobenzoxazole we reacted 6-nitro-2-mercaptobenzoxazole with 2-aminopyridine and 2-aminothiazole. On carrying out this reaction in aqueous solution at 100°, stable salt-like compounds of the amines with the mercapto group were obtained. On heating above their melting points either in the absence of a solvent or in diphenyl ether, these compounds lose hydrogen sulfide to give the corresponding 2-(2-pyridylamino) and 2-(2-thiazolylamino)-6-nitrobenzoxazoles.

* For Part X see [6].
<table>
<thead>
<tr>
<th>N-Substituted 2-Aminobenzoxazoles</th>
<th>Reaction Time (hr)</th>
<th>Reaction Temperature (°C)</th>
<th>Molecular Formula</th>
<th>Found</th>
<th>Calc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{16}H_{14}N_{2}O_{2}</td>
<td>1.5: 60-70</td>
<td>73-74 (petroleum ether)</td>
<td>C_{16}H_{14}N_{2}O_{2}</td>
<td>71.17%</td>
<td>71.20%</td>
</tr>
<tr>
<td>C_{18}H_{16}N_{2}O_{3}</td>
<td>5: 60</td>
<td>100-110 (50% ethanol+water)</td>
<td>C_{18}H_{16}N_{2}O_{3}</td>
<td>72.39%</td>
<td>72.19%</td>
</tr>
<tr>
<td>C_{12}H_{14}N_{2}O_{2}</td>
<td>21: 100-110</td>
<td>240-262 (isobutyralcohol)</td>
<td>C_{12}H_{14}N_{2}O_{2}</td>
<td>55.14%</td>
<td>55.29%</td>
</tr>
<tr>
<td>C_{16}H_{12}N_{2}O_{3}</td>
<td>16: 100</td>
<td>223.5-224 (ethanol)</td>
<td>C_{16}H_{12}N_{2}O_{3} .2HCl</td>
<td>68.23%</td>
<td>68.33%</td>
</tr>
<tr>
<td>C_{16}H_{14}N_{2}O_{2} .2HCl</td>
<td>3: 60</td>
<td>255 (decomp) (abs. ethanol)</td>
<td>C_{16}H_{14}N_{2}O_{2} .2HCl</td>
<td>49.30%</td>
<td>49.32%</td>
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<tr>
<td>C_{16}H_{12}N_{2}O_{3} .2HCl</td>
<td>4: 90</td>
<td>112-114 (ethyl acetate)</td>
<td>C_{16}H_{12}N_{2}O_{3} .2HCl</td>
<td>59.25%</td>
<td>59.36%</td>
</tr>
<tr>
<td>C_{18}H_{14}N_{2}O_{2} .2HCl</td>
<td>7: 60-70</td>
<td>242 (decomp) (abs. ethanol)</td>
<td>C_{18}H_{14}N_{2}O_{2} .2HCl</td>
<td>59.25%</td>
<td>59.36%</td>
</tr>
</tbody>
</table>

Molecular Formula:
- C_{16}H_{14}N_{2}O_{2}
- C_{18}H_{16}N_{2}O_{3}
- C_{12}H_{14}N_{2}O_{2}
- C_{16}H_{12}N_{2}O_{3}
- C_{16}H_{14}N_{2}O_{2} .2HCl
- C_{16}H_{12}N_{2}O_{3} .2HCl
- C_{18}H_{14}N_{2}O_{2} .2HCl

Yield, %
- 69
- 77
- 50
- 50
- 37
- 36
- 30

Found: C1.24-26%, Calculated: C1.24-25%.
- Found: C1.22-25%, Calculated: C1.22-25%. 

N.R.H

\[ R \]

H

\[ N \]