PART-C

Syntheses of Drug Intermediates
With the growth and advancement of modern chemistry the chemical study of plant constituents in its various aspects has been a fascinating study in the world over both for chemists and medical men. It is only the 20th century and specially the recent thirtyfive years, which paved the way to the isolation of chemically pure constituents which are physiologically active. In many cases, these physiologically active constituents of the plants have provided the chemists with a clue to the preparation of synthetic drugs even of greater potency.

During recent years chemistry has made rapid strides and remarkable progress has been recorded particularly in the field of synthetic chemistry. Chemists have synthesised very potent and effective remedies such as arsenicals and antimalarials for the treatment of protozoal diseases and sulphonamides for the treatment of bacterial diseases. The group of antibiotic drugs have revolutionized the treatment of many bacterial and ricketsial diseases. Even some of the virus diseases are being effectively treated by these drugs.

Tuberculosis was so far one of the fatal diseases which took a huge toll of life. It is only through the efforts of the chemist that effective cures have been evolved for the disease. Out of these hydrazides are well known for their toxicological and
antitubercular activities, e.g., p-aminosalicylic acid hydrazide, commonly known as "PSa," is mostly used for the treatment of tuberculosis. Not only hydrazides but hydrazones have also been reported to have antitubercular activity. An interesting attempt has been made in this connection by Yale and al. to activate streptomycin by preparing its hydrazones with furfuryl, nicotinyl and benzylhydrazides. Further Yale and Bernstein have shown the importance of heterocyclic acyl hydrazones of carbohydrates as antimycobacterial and antitubercula agents. Another group of compounds, are amides, for example, p-aminosalicylic acid amide which are reported to be equally important medicinally being effective against mycobacterium tuberculosis.

2 Orestano & Ghione, ibid, 1953, 3, 337-43.
Pharmacologically, it is the hydroxy group which is essential for the antitubercular activity of the compounds. The activity is regarded as due to the ability of these compounds to form stable poorly soluble copper complexes, thereby disrupting essential enzyme system of tubercle bacillus.⁹

In view of the great importance of the hydrazides and amides, as given above, the following compounds were synthesised through new routes.

1. Salicylhydrazides ..... Paper I
2. Salicylamides ..... Paper II
3. Salicylhydrazide alcohohulates ..... Paper III
4. In addition a drug intermediate Quinhydrone has also been synthesised by anodic oxidation. Paper IV

The first three papers give the preparation of the derivatives of nitro hydroxy salicylic acids, which could be utilized after reduction to the corresponding amino derivatives for the treatment of tuberculosis. The fourth paper deals with the preparation of quinhydrone, which again is an important drug intermediate.

A NEW METHOD OF SYNTHESIS OF SALICYLHYDRAZIDE
AND ITS NITRO DERIVATIVES

BY
G. L. GUPTA

Reprinted from "Curr. Sci." October 20, 1964, 33, No. 20, 616-617
A NEW METHOD OF SYNTHESIS OF SALICYLHYDRAZIDE AND ITS NITRO DERIVATIVES

Syntheses of salicylic acid hydrazide and its substituted derivatives have been carried out by several workers, by refluxing the corresponding ester with hydrazine hydrate, \( \text{N}_2\text{H}_4\cdot\text{H}_2\text{O} \) in methanol or ethanol. Very low yields have been reported in some cases and the refluxing time varied from 15 minutes to 18 hours. Watt and McBride have shown that ammonolysis of hydrazine sulphate, \( \text{N}_2\text{H}_4\cdot\text{HSO}_4 \) provides the hydrazine, \( \text{N}_2\text{H}_4 \) of high purity. The present investigation aims at the hydrazinolysis of methyl salicylate and its nitro derivatives with hydrazine so obtained in situ. The author, however, made a variation in the above method by using liquor ammonia instead of liquid ammonia.

Methyl salicylate was nitrated according to the method of Barany and Planka as modified by Agarwal and Haksar. The mixture of methyl 3- and 5-nitosalicylates was divided into two parts. The first part was separated by petroleum ether (B.P. 40–60°C) when methyl 5-nitosalicylate dissolved leaving behind methyl 3-nitosalicylate. The second part was further nitrated by the method described by Hirsch as modified by Haksar and Wankhade. Methyl salicylate and methyl mono- and di-nitosalicylates so prepared were hydrazinolised by a new method described below.

Hydrazinolysis of methyl salicylates (0·1 Mole) was carried out with hydrazine sulphate (0·2 Mole), suspended in 50 ml liquor ammonia (d. 0·888). The contents were thoroughly shaken and kept aside for a week at room temperature. The ammonia was removed and the residues were washed with a little of ethanol and a good amount of ice-cold water and dried giving the corresponding salicylhydrazides.

The hydrazides prepared by this method are given in Table I.

![Chemical Structure](image)

\[
\text{R}' = \text{H}, \text{R}'' = \text{H}; \quad \text{II R} = \text{NO}_2, \text{R}'' = \text{H}; \quad \text{III R} = \text{H}, \text{R}'' = \text{NO}_2; \quad \text{IV R} = \text{NO}_2, \text{R}'' = \text{NO}_2.
\]

**Table 1**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Hydrazides</th>
<th>Crystalline nature</th>
<th>Yield %</th>
<th>M.P. - °C.</th>
<th>Nitrogen Found %</th>
<th>Calculated %</th>
<th>Solvents for crystallisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Salicylhydrazide</td>
<td>White needles</td>
<td>73</td>
<td>146</td>
<td>18·29</td>
<td>18·42</td>
<td>Ethanol</td>
</tr>
<tr>
<td>II</td>
<td>3-Nitrosalicylhydrazide</td>
<td>Yellow needles</td>
<td>67</td>
<td>(decomp.)</td>
<td>21·84</td>
<td>21·32</td>
<td>Diuron/H_2O (9 : 1)</td>
</tr>
<tr>
<td>III</td>
<td>5-Nitrosalicylhydrazide</td>
<td>Yellow rhombic crystals</td>
<td>74</td>
<td>178 (decomp.)</td>
<td>21·71</td>
<td>21·32</td>
<td>Hot H_2O</td>
</tr>
<tr>
<td>IV</td>
<td>3: 5-Dinitrosalicylhydrazide</td>
<td>Yellow needles</td>
<td>65</td>
<td>235 (decomp.)</td>
<td>23·03</td>
<td>23·14</td>
<td>Hot H_2O</td>
</tr>
</tbody>
</table>

The author is grateful to Dr. C. N. Haksar, Director, Jiwaji Industrial Research Laboratory, Gwalior, for his valuable suggestions.

Department of Chemistry, G. L. GUPTA.
Motilal Vigyan Mahavidyalaya,

5. Ibid., 1960, 4(3), 137.
8. Yale, H. L. et al., Ibid., 1953, 75, 1933.
SYNTHESIS OF SALICYLAMIDE AND ITS NITRO DERIVATIVES

By

G. L. GUPTA

Dept. of Chemistry, University of Sagar, Sagar

(Received for publication on 10-7-65)

The author has recently communicated a new method for the synthesis of salicylhydrazide and its nitro derivatives by the action of a mixture of hydrazine sulphate and liquor ammonia on methyl salicylate and its nitro derivatives respectively. The formation of certain by-products which were comparatively less soluble in water than the corresponding hydrazides was observed in the reaction. These comparatively insoluble compounds were identified as the amides of the esters used. These amides obviously were formed by the direct ammonolysis of methyl salicylate and its nitro derivatives by liquor ammonia.

Ammonolysis by this method has the advantage over the methods described in the literature in the fact that no aluminium, ammonium sulphite, \((\text{NH}_4)_2\text{SO}_4\cdot\text{H}_2\text{O}\), alcohol or hydrochloric acid is required and at the same time good yields of amides are obtained.

Methyl salicylate and methyl mono and di-nitrosalicylates have been obtained by the method as described by the author and ammonolised as given below:

Ammonolysis of methyl salicylates (0.1 mole) was carried out with 55 ml. liquor ammonia (d. 0.888) in a glass stoppered conical flask. The contents were thoroughly shaken, stoppered tightly and kept aside for a week at room temperature.

\[
\begin{align*}
\text{\text{(Ammonolysis)}} \\
\text{I R=H, R'=H; II R=NO}_2, \text{R'=H; III R=H, R'=NO}_2; \text{IV R=NO}_2, \text{R'=NO}_2. \\
\end{align*}
\]

The contents were shaken once a day to ensure thorough mixing. After removal of ammonia the residues were washed with a little water giving almost quantitative yields of the corresponding salicylamides.

The amides prepared by this method are listed in table I.
<table>
<thead>
<tr>
<th>S. No.</th>
<th>Amides</th>
<th>Crystalline nature</th>
<th>Yield %</th>
<th>M.P. –°C</th>
<th>Nitrogen Found %</th>
<th>Nitrogen Calc. %</th>
<th>Solvent for crystallisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Salicylamide</td>
<td>White needles</td>
<td>96</td>
<td>140</td>
<td>10.15</td>
<td>10.22</td>
<td>H₂O</td>
</tr>
<tr>
<td>II</td>
<td>3-Nitrosalicylamide</td>
<td>Yellow needles</td>
<td>91</td>
<td>154</td>
<td>15.17</td>
<td>15.38</td>
<td>H₂O</td>
</tr>
<tr>
<td>III</td>
<td>5-Nitrosalicylamide</td>
<td>Yellow needles</td>
<td>89</td>
<td>223</td>
<td>15.61</td>
<td>15.88</td>
<td>H₂O</td>
</tr>
<tr>
<td>IV</td>
<td>3, 5-Dinitrosalicylamide</td>
<td>Yellow plates</td>
<td>93</td>
<td>181</td>
<td>18.28</td>
<td>18.50</td>
<td>Hot H₂O</td>
</tr>
</tbody>
</table>

**References**

PAPER III

ALCOHOLYSIS OF 5-NITROSALICYLHYDRAZIDE

(Received for publication on 28-5-64.)

By

G. L. GUPTA

Government Degree College, Datia, M.P.

Baker et al. obtained a solvate of 5-nitrosalicylhydrazide, m.p. 153-54°C, with one molecule of methanol on crystallisation. Agarwal and Haksar in quest of the anhydrous form of 5-nitrosalicylhydrazide, synthesised a compound, m.p. 178°C, in 48% yield by changing the refluxing medium from methanol to ethanol and increasing the refluxing time from 15 minutes to 18 hours.

It has been observed experimentally that (a) 5-nitrosalicylhydrazide could be obtained without solvolysis within 20 minutes by hydrazinolysis of methyl salicylate in methanol and then crystallising the product from hot water, (b) the hydrazide so called anhydrate (I) on refluxing with methanol and ethanol forms 5-nitrosalicylhydrazide methanolate (II) and 5-nitrosalicylhydrazide ethanolate (III) respectively, (c) methanolate and ethanolate on boiling with water dealcoholate and (d) methanolate converts into ethanolate and vice versa on refluxing with corresponding solvents. The whole of the phenomenon could be summarised as shown below:—

\[
\text{Methanolate (II)} \\
\text{Anhydrate (I)} \xrightarrow{\text{H}_2\text{O}} \text{MeOH} \quad \xrightarrow{\text{EtOH}} \text{EtOH} \\
\text{Ethanolate (III)}
\]
The phenomenon shows that hydrazide reacts with alcohols similar to aliphatic esters, except for the fact that transalcohohates, II and III, are stable, similar to the more stable nature of benzodiazonium compounds to that of aliphatic diazonium compounds.

**Experimental**

5-Nitrosalicylhydrazide Anhydrate (I):

Methyl 5-nitrosalicylate (20 gm.) in methanol (80 ml.) was refluxed with 60% hydrazine hydrate (50 ml.) on a steam bath for 20 minutes with occasional shaking. A crystalline product separated on cooling, was crystallised from hot water giving anhydrate (I) as reddish yellow rhombic crystals, m.p. 178° (decomp.). The yield was 1.8 gm. (Calcd. for (I), C₇H₅O₂N₃, C=42.64%, H=3.35%, N=21.32%; found C=42.52%, H=3.54%, N=21.25%).

5-Nitrosalicylhydrazide Methanolate (II) and Ethanolate (III):

The anhydrate (0.5 gm.) was refluxed with methanol (100 ml.) on a water bath for 20 minutes. The solution so obtained was filtered hot and concentrated in volume to 25 ml. The solid which separated on cooling was crystallised from methanol giving methanolate (II) as yellow needles, m.p. 154° (decomp.). The yield was 0.48 gm. (Calcd. for (II), C₇H₅O₂N₃CH₃OH, C=41.92%, H=4.80%, N=18.34%; found C=42.31%, H=4.85%, N=18.22%).

Similarly, ethanolate (III) was obtained by refluxing anhydrate (I) with absolute ethanol for 30 minutes as yellow needles, m.p. 163° (decomp.). The yield was 0.42 gm. (Calcd. for (III), C₇H₅O₂N₃C₂H₅OH, C=44.44%, H=5.35%, N=17.28%; found C=44.56%, H=5.37%, N=17.35%).

**Dealcoholysis of Methanolate and Ethanolate:**

Methanolate (0.5 gm.) was dissolved in hot water (50 ml.) and then kept on a steam bath with stirring for 10 minutes. The solution so obtained was allowed to cool and the solid which separated was crystallised from hot water giving anhydrate (I), m.p. 178° (decomp.). The yield was 0.28 gm.

Similarly, ethanolate was converted into anhydrate. The yield was 0.45 gm.

**Conversion of Methanolate to Ethanolate and vice versa:**

Methanolate (0.5 gm.) was refluxed with ethanol (30 ml.) for 15 minutes with occasional shaking. The solution so obtained was poured while hot in a beaker for crystallisation. The residue was then crystallised from ethanol giving ethanolate, m.p. 163° (decomp.). The yield was 0.46 gm.

Similarly, ethanolate was converted into methanolate by refluxing with methanol. The yield was 0.33 gm.

The rate of conversion of ethanolate to methanolate is slower than vice versa.
The author acknowledge his indebtedness to Dr. C. N. Haksar, Director for permission to work at Jiwaji Research Laboratory, Gwalior.

REFERENCES