Synthesis of Compounds Related to Metabolites of Trimetazidine in Rabbits

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Abstract

Synthetic methods of trimetazidine metabolites in rabbits are described. One of the metabolites, 3-hydroxy-2,4-dimethoxybenzylpiperazine, is a new compound and its chemical structure is established.

Keyphrases

- Trimetazidine metabolites, in rabbits—synthesis of related compounds
- 3-Hydroxy-2,4-dimethoxybenzylpiperazine—synthesis, structure determination
- NMR spectroscopy—structure determination
- IR spectrophotometry—structure determination

In a previous paper (1), absorption, excretion, and distribution of trimetazidine [1-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride] in animals were investigated. The present work was performed to synthesize several compounds related to trimetazidine metabolites in rabbits. The compounds synthesized are shown here. 3-Hydroxy-2,4-dimethoxybenzylpiperazine is a new compound, and the chemical structure was established in the present work.

EXPERIMENTAL

2,3,4-Trimethoxybenzoic acid, 2,3,4-trihydroxybenzoic acid, 2,3,4-trimethoxytoluene, 2,3,4-trihydroxytoluene, 1,3-dimethylpyrogallol, 2-ethyl-1,3-dimethylpyrogallol, 3-ethoxy-2,4-dimethoxybenzaldehyde, and 3-ethoxy-2,4-dimethoxybenzoic acid were synthesized by methods described in the literature (cited in Table I).

1-(2,3,4-Trimethoxybenzyl)-N4-acetylpiperazine-To 10 g. of trimetazidine, a mixture of 20 ml. of acetic anhydride and 50 ml. of acetic acid was added and the reaction mixture was refluxed on a steam bath for 15 min. After cooling, 10% sodium carbonate solution was added to make the reaction mixture alkaline. The alkaline solution was extracted with ether, and the ethereal solution was evaporated on a steam bath. The residue was distilled in vacuo. Three grams of a colorless oily fraction, boiling at 175-185°/5 mm. Hg, was obtained. Anal.—Calc. for C24H22N2O4: C, 62.34; H, 7.79; N, 9.09. Found: C, 62.40; H, 7.81; N, 8.87.

Table I—Syntheses of Several Compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield, %</th>
<th>Melting Point</th>
<th>Formula</th>
<th>Calc., %</th>
<th>Found</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3,4-Trimethoxybenzoic acid</td>
<td>22</td>
<td>98-100°</td>
<td>C10H12O3</td>
<td>C, 49.41</td>
<td>C, 49.60</td>
<td>(2, 6)</td>
</tr>
<tr>
<td>2,3,4-Trihydroxybenzoic acid</td>
<td>52</td>
<td>B.p. 97-98°</td>
<td>C10H12O3</td>
<td>H, 3.53</td>
<td>H, 3.44</td>
<td>(7, 8)</td>
</tr>
<tr>
<td>2,3,4-Trimethoxytoluene</td>
<td>14</td>
<td>94-97°</td>
<td>C10H12O3</td>
<td>C, 65.93</td>
<td>C, 65.82</td>
<td>(9)</td>
</tr>
<tr>
<td>2,3,4-Trihydroxytoluene</td>
<td>13</td>
<td>B.p. 97-98°</td>
<td>C10H12O3</td>
<td>H, 7.69</td>
<td>H, 7.91</td>
<td>(7, 8)</td>
</tr>
<tr>
<td>1,3-Dimethylpyrogallol</td>
<td>23</td>
<td>B.p. 133-134°/17 mm. Hg</td>
<td>C20H18O3</td>
<td>C, 60.00</td>
<td>C, 60.18</td>
<td>(10)</td>
</tr>
<tr>
<td>2-Ethyl-1,3-dimethylpyrogallol</td>
<td>88</td>
<td>B.p. 98-99°</td>
<td>C20H18O3</td>
<td>H, 5.71</td>
<td>H, 5.85</td>
<td>(8)</td>
</tr>
<tr>
<td>3-Ethoxy-2,4-dimethoxybenzaldehyde</td>
<td>61</td>
<td>Not purified</td>
<td>C15H18O3</td>
<td>C, 52.30</td>
<td>C, 52.36</td>
<td>(8)</td>
</tr>
<tr>
<td>2,4-Dinitrophenylhydrazone of 3-Ethoxy-2,4-dimethoxybenzaldehyde</td>
<td>170°</td>
<td>C15H18O3</td>
<td>H, 4.65</td>
<td>H, 4.60</td>
<td>(8)</td>
<td></td>
</tr>
<tr>
<td>3-Ethoxy-2,4-dimethoxybenzoic acid</td>
<td>14</td>
<td>91-92°</td>
<td>C15H18O3</td>
<td>N, 14.36</td>
<td>N, 14.46</td>
<td>(8)</td>
</tr>
</tbody>
</table>

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14.6% in theoretical amount), melting at 240-245° dec., were ob-
tained.

Anal.—Calc. for C38H36Cl8N4O6: C, 48.13; H, 7.00; Cl, 21.80; 
N, 8.61. Found: C, 48.13; H, 7.00; Cl, 21.94; N, 8.56.

NMR (D2O)1:
\[ ^1H, d, J = 9 Hz, \]
\[ ^1H, d, J = 9 Hz, \]
\[ ^1H, s, \]
\[ ^1H, s, \]
\[ ^1H, s, \]
\[ ^1H, s, \]
\[ ^1H, s, \]
\[ ^1H, s, \]
\[ ^1H, s, \]
\[ ^1H, s, \]

IR cm\(^{-1}\): δ\(\equiv\)C 830 (KBr); \(\pi\equiv\pi\) 1615 (KBr).

RESULTS AND DISCUSSION

The compounds, 2,3,4-trimethoxybenzoic acid, 2,3,4-trihydroxy- 
benzoic acid, 2,3,4-trimethoxytoluene, 2,3,4-trihydroxytoluene, 1-
(2,3,4-trimethoxybenzyl)-N-acetylpiperazine, and 3-hydroxy-2,4- 
dimethoxybenzylpiperazine, were used as the authentic samples for 
identification of trimetazidine metabolites in rabbit urine.

One of the trimetazidine monohydroxydimethoxybenzyl piper-
azine metabolites (3-hydroxy-2,4-dimethoxybenzylpiperazine) is 
a new compound and was obtained from demethylation of trimetazi-
dine with anhydrous aluminum chloride. The chemical structure of 
this new compound was established as shown in Scheme 1.

\[ OCH_3 \]
\[ OCH_3 \]
\[ OCH_3 \]
\[ OCH_3 \]

Scheme 1

The results of instrumental analysis of the new compound reveal 
the following facts:

1. \(AB\)-type couplings at \(\tau\) 2.89 and 3.07 were observed in the 
NMR spectrum of the new compound. \(J_{AB}=9\) Hz. In the NMR 
(D2O) existed in the range of 5–10 Hz. in \(J\)-value, corresponding to 
2H adjoined with each other. The signals of \(\tau\) 6.05 and 6.08 came 
from CH and showed the existence of two methoxy groups on a 
benzene skeleton

2. Absorptions corresponding to \(\pi\equiv\pi\) at 1620 cm\(^{-1}\) and \(\pi\equiv\pi\) 
at 820 cm\(^{-1}\) were recognized in the IR spectrum of the new 
compound.

3. In the NMR (dimethyl sulfoxide) spectrum of the new 
compound, the signal of \(\tau\) -0.04, which disappeared in the NMR 
(D2O), was detected.
Color Reaction of Thyroxine and Its Derivatives with Nitrous Acid

S. E. SAHEB and M. A. SANASSIAN

Abstract The 3',5-diiodo-4'-hydroxydiphenylether system in thyroxine was shown to be indispensable for the success of the color reaction with nitrous acid. This reaction was also successful with sodium hypochlorite and chlorine gas. The products were separated, and evidence is presented to show that this reaction involves an oxidation of the 3'- and/or 5'-position to iodoso or iodoxy derivatives while the amino acid side chain remains intact.

Keyphrases Thyroxine, derivatives—chemical nature of color reaction with nitrous acid—3',5'-Diiodo-4'-hydroxydiphenylether system—role in color formation of thyroxine and nitrous acid

Thyroxine (I), when treated with nitrous acid, is reported to give a characteristic red color, even in a concentration of 1 in 40,000 (1). This standard procedure is described in various pharmacopeias (2) for the identification of thyroxine. Roche and Michel (3) reported on the analytical aspect of this reaction and suggested its use as a quantitative method for the determination of thyroxine. The absorption of the color formed obeyed Beer-Lambert's law within a certain concentration range, 100-300 mcg. This paper reports on the chemical nature of this reaction, which has not been investigated previously.

EXPERIMENTAL

Thyroxine (I), tetraiodothyropionic acid (II), 3,5,3'-triiodo- and 3,5-diiodothyronine, 3,5-di- and 3-iodotyrosine, and tyrosine...