Synthesis and biological study of new ether derivatives of 2,6-dimethylol-4-bromophenol

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Abstract
The methylol derivatives of 2,6-dimethylol-4-bromophenol was synthesized by the condensation of 4-bromophenol with formaldehyde in the presence of NaOH as a catalyst under very critical conditions. The derivative (1) was transferred to ether derivatives (2), (3) by its reaction with methanol and ethanol in presence of H2SO4 as a catalyst respectively under strict experimental condition. The ether derivatives were tested against Staphylococcus aureus, Proteus vulgaris, Escherichia coli and Pseudomonas aeruginosa. The structure of new synthesized compounds were confirmed by physical data and FT-IR, 1HNMR spectroscopy.

Introduction
Phenol react with formaldehyde in presence of alkali or acid as a catalyst to give condensation product when found Para or Ortho free position to the –OH group(1). Trimethylol derivatives were synthesized from phenol or substituted phenol by condensation with formaldehyde(2,3). Dimethylol derivatives were synthesized from Para or Ortho-substituted phenol(4,5). The methylol derivatives were transferred to ether derivatives by their reaction with alcohols(6,7). The phenol with ether linkage are found to possess good anti-bacterial, anti-inflammatory, anti-septic and CNS activity(8),(9),(10). Some of the studies indicate a wide interest in phenol and used it as a start material to prepared a huge number of hetero cyclic compounds(11),(12),(13). Due to these finding and as apart of our research program we are interested in preparing some new phenolic ethers derivatives and the biological activity was studied.

Materials and Method
The melting points were measured on a stuart melting point apparatus and uncorrected. IR spectra were recorded in Shimadzu FTIR-8400S Spectrophotometer in the 4000-400 cm−1 range using KBr disc. 1HNMR spectra were recorded on a Bruker 400 MHz in Al-Baath university collage of science in Syria, by using CDCl3 as solvent and TMS as internal reference.

1-Synthesis of 2,6-Dimethylol-4-bromophenol:-
A (8.65g, 0.05mole) of 4-bromophenol was mixed with (4.1ml , 0.2 mole) of formaldehyde (41-37 %), then sodium hydroxide (1.6g ,0.04 mole) was added. The mixture was heated by refluxed with stirring for 3 hr, at 60 C°, then cooled to the room temperature and neutralized with 5% phosphoric acid. The organic layer was separated and purified. m.p =130 C°, yield 90%.

2-Synthesis of 2,6-Dialkoxymethylene-4-bromophenol (2,3):-
A (18.64g, 0.08mole) of compound (1) was added slowly to mixture of 0.2 mole of alcohol and 1 ml of conc. H2SO4 at boiling point of alcohol. The mixture was heated by refluxed with stirring for 20hrs. at the same temperature. Then the excess of alcohol was evaporated and the mixture was neutralized. The precipitate was filtered. 2,6-Dimethoxymethylene-4-bromophenol (2), m.p= 75-80 C°, yield 70%, . 2,6-Diethoxymethylene-4-bromophenol (3), m.p= 93- 95 C°, yield 70%.

3-Biological Test:
1) Bacteria strain:
All of bacteria strain were obtained from biology department,Al-Mothna Collage of
The bacteria cultured in nutrient moller-hanten agar at 37 °C (0.5 ml) of each bacteria was spread over surface of moller-hanten agar\(^{(14)}\).

2) Antibacterial activity:

Disc of filter paper (6 mm diameter) were sterilized at 140 °C for 1 h. and impregnated with (1ml) of a concentration (10,1,0.1 ,0.01) mg/ml of solution of each compound and then dried, dry DMSO was used as a solvent for all compounds and blank disc of DMSO were used as a control. The inoculated plate were incubated at 37 °C for 24 hrs. and the inhibition zones were measured\(^{(15)}\) in all experiments, the mean of each triplicate was measured\(^{(16)}\) . All data are listed in table (1).

**Results and Discussion**

Scheme (1) summarizes all reactions in this work

The methylol derivative 2,6-methylol-4-bromophenol (1) was prepared by condensation reaction between 4-bromophenol and formaldehyde in the presence of NaOH as catalyst under very critical conditions, for example, temperature, pH, reactant ratio and reaction time. Thus, any failure in controlling condition lead to not form these compounds but formed high molecular weight compounds, for example, P-bromophenol formaldehyde resin. The FT-IR spectra of compounds (1) showed the absence of phenolic OH absorption band at 3500 cm\(^{-1}\) and appearance of \(-\text{OH}\) stretching of methylol group in 3300 cm\(^{-1}\) and asymmetrical stretching of C-O-C absorption bands near 1245 cm\(^{-1}\) and 1030 cm\(^{-1}\). See fig.(2,3).

The \(^1\)H-NMR of 2,6-dithoxymethylene-4-bromophenol (3) using CDCl\(_3\) as a solvent showed \(\delta\) (ppm): 1-2(t,6H, 2 –CH\(_3\)), 3.6-4.7(q,4H, 2–OCH\(_2\)), 4.4(s,4H,2CH\(_2\)O), 6.7(s,1H,OH phenolic),7-8(m,2H,Aromatic ). See fig. (4). All compounds showed high activity against *Staph. aureus* and *Proteus*. 

\[\text{OH} \hspace{1cm} \text{CH}_3\text{O} / \text{NaOH} \hspace{1cm} \text{OH} \]

\[\begin{align*}
\text{OH} & \hspace{1cm} \text{CH}_2\text{O} \hspace{1cm} \text{OH} \\
\text{Br} & \hspace{1cm} \text{MeOH} \hspace{1cm} \text{Br} \\
\text{OH} & \hspace{1cm} \text{EtOH} \hspace{1cm} \text{EtOH} \\
\text{H}_3\text{CO} & \hspace{1cm} \text{OCH}_3 \hspace{1cm} \text{OCH}_3 \\
\text{Br} & \hspace{1cm} \text{Br} \\
\end{align*}\]
vulagras while the E.colli and bacteria activity diameter of inhibition Ps.aerugonosa showed resistance. The anti zone is shown in table (2).

Table (1) Major FT-IR absorption of compounds 1-3 in KBr disc in cm⁻¹.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>υOH phenolic</th>
<th>υOH methylol</th>
<th>υCH₃</th>
<th>υCH₂</th>
<th>υC-O-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3500-3400</td>
<td>-</td>
<td>-</td>
<td>1470-1350</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>3500</td>
<td>3300</td>
<td>1520</td>
<td>1470-1400</td>
<td>1245-1030</td>
</tr>
<tr>
<td>3</td>
<td>3500</td>
<td>3300</td>
<td>1560-1410</td>
<td>1470-1390</td>
<td>1245-1030</td>
</tr>
</tbody>
</table>

Table (2) Antimicrobial activity and diameter of inhibition zone(mm) of compound (2,3).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>E.coli 10/1/0.1/0.01 mg/ml</th>
<th>Staph aureus 10/1/0.1/0.01 mg/ml</th>
<th>Proteus.vulageras 10/1/0.1/0.01 mg/ml</th>
<th>Ps. aerugonosa 10/1/0.1/0.01 mg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-/-/-/-</td>
<td>18/12/9/5</td>
<td>12/10/3/0.5</td>
<td>-/-/-/-</td>
</tr>
<tr>
<td>3</td>
<td>0.5/-/-/-</td>
<td>16/15/14/12</td>
<td>6/2/1/0.3</td>
<td>-/-/-/-</td>
</tr>
</tbody>
</table>

Fig No(1 ). FT-IR for 2,6-methylol-4-bromophenol (1) in KBr disc.

Fig No(2). FT-IR for 2,6-Dimethoxymethylene-4-bromophenol (2) in KBr disc.
Fig No(3). FT-IR for 2,6-Diethoxymethylene-4-bromophenol (3) in KBr disc.

Fig. No.(4). $^1$HNMR spectra of 2,6-Diethoxymethylene-4-bromophenol using CDCl$_3$.

References

تحضير مشتقات إيثرية لـ 6-ثنائي ميثيلول - 4- برومو فينول ودراسة الفعالية البيولوجية لها

رياض جليل ناهي
كليّة علوم حيوانات جامعة الموصل

الخلاصة

تم في هذه الدراسة تحضير بعض مشتقات الميثيلولات، إذ حضر المشتقات الـ 6-ثنائي ميثيلول - 4- برومو فينول (1) بتكتيف 4- برومو فينول مع زيادة من الفورمالدهيد بوجود NaOH. بعداً فعّل مشتقتين الميثيلول (1) مع كلاً من الإيثانول والميثانول بوجود H2SO4 المركز معطياً المشتقات الإثيرية (2).3 والتي شُخصت باستخدام مطيافية H1 NMR, IR. وكذلك ب نقاط الأنصهار. تم فحص فعالية هذه المركبات تجاه بعض أنواع البكتيريا.