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 vulagers, 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).

Materials and Method

2-Synthesis of 2,6-Dialkoxy methylene-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-Dimethoxy methylene-4-bromophenol (2), m.p= 75-80 C°, yield 70%, . 2,6-Diethoxy methylene-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 Sciences Al-Qadissiya University. The bacteria cultured in nutrient moller- hanten agar at 37 C° (0.5 ml ) of each bacteria was
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-bromophenolformaldehyde resin. The FT-IR spectrum of compounds (1) showed absorption band in the region (3500-3200) cm⁻¹ which was as signal to methylol group and absorption band at 2900 cm⁻¹ due to C-H aliphatic group and two absorption band at 1470 cm⁻¹, 1350 cm⁻¹ due to CH₂ group. See fig.(1). Table (1). The methylol derivative (1) was transferred into ether derivatives (2,3) by its condensation with methanol and ethanol respectively in the presence of conc. H₂SO₄ as catalyst under strict experimental condition for example, temperature, conc. of acid, rate of addition of compound (1). The FT-IR spectra of ether derivatives showed the absence of phenolic OH absorption band at 3500 cm⁻¹ and appearance of –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). Table (1). The ¹H-NMR of 2,6-diethoxymethylene-4-bromophenol (3) using CDCl₃ as a solvent showed δ(ppm): 1-2(2t,6H, 2–CH₃), 3.6-4.7(q,4H, 2–OCH₂), 4.4(s,4H,2CH₂O), 6.7(s,1H,OH phenolic),7-8(m,2H,Aromatic ). See fig. (4). All compounds showed high activity against Staph. aureus and Proteus. vulgaras while the E.colli and Ps.aerugenosa showed resistance. The anti bacteria activity diameter of inhibition 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>$\nu$OH phenolic</th>
<th>$\nu$OH methylol</th>
<th>$\nu$CH$_3$</th>
<th>$\nu$CH$_2$</th>
<th>$\nu$C-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.vulagers 10/1/0.1/0.01 mg/ml</th>
<th>Ps. aerugenosa 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 dsic.

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

References

تحضير مشتقات ايثرية لـ ٦,٢-ثنائي مثيلول - ٤- برومو فينول ودراسة الفعالية البيولوجية لها

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الخلاصة

تم في هذه الدراسة تحضير بعض مشتقات الميثيلولات. إذ حضر المشتق ٦,٢-ثنائي مثيلول - ٤- برومو فينول (1) بتكثيف ٤- برومو فينول مع زيادة من الفورماليد ووجود NaOH. بعدها فوعل مشتق الميثيلول (1) مع كلا من الايثانول والميثانول بوجود H2SO4 المركز معطيا المشتقات الايثيرية (2), (3) والتي شخت باستخدام مطية NMR. H NMR, IR وكذلك بنقاط الانصهار. تم فحص فعالية هذه المركبات تجاه بعض أنواع البكتريا.