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Synthesis and Antibacterial Activities of 4-Hydroxy-*o*-phenylphenol and 3,6-Diallyl-4-hydroxy-*o*-phenylphenol against a Cariogenic Bacterium *Streptococcus mutans* OMZ 176.

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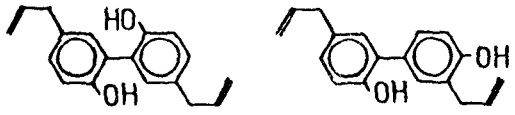
Abstract □ For the purpose of survey of the antibacterial activity against a cariogenic bacterium *Streptococcus mutans* OMZ 176 with the introduction of hydroxyl and allyl groups to *o*-phenylphenol (Fig. 2, **1**), 4-hydroxy-*o*-phenylphenol (**2**), and 3,6-diallyl-4-hydroxy-*o*-phenylphenol (**4**) were synthesized, sucessively. The synthesized compounds, **2** and **4** showed more potent antibacterial activity than the starting material, **1**. The hydroxyl group was supposed to the essential element for the antibacterial activity and the introduction of allyl group to phenolic ring to be another element to increase the activity.

Keywords □ Streptococcus mutans OMZ 176, Elb's oxidation, Claisen's rearrangement, *o*-phenylphenol, 4-hydroxy-*o*-phenylphenol, 3,6-diallyl-4-hydroxy-*o*-phenylphenol.



Magnolol Honokiol

Fig. 1. The structures of Magnolol and Honokiol.

It has been clarified that magnolol and honokiol (Fig. 1) isolated from the stem bark. of *Magnolia obovata* showed potent antibacterial activity against a cariogenic bacterium *Streptococcus mutans*.[2] They also showed antibacterial activity against the other microorganisms, *Staphylococcus aureus, Streptococcus faecium, Bacillus anthracis, Escherichia coli* and *Pseudomonas aeruginosa*.[3] Magnolol has biphenol moiety attached hydroxyl and allyl groups, and these functional groups were considered to be associated with the antibacterial activity.

In order to obtain some information about the structure-activity relationships in the magnolol (or honokiol) and structure requirement for more potent antibacterial agents, 4-hydroxyl-*o*-phenylphenol **2**, and 3,6-diallyl-4-hydroxy-*o*-phenylphenol **4** were synthesized successively from starting compound, o-phenylphenol **1** (Fig. 2).

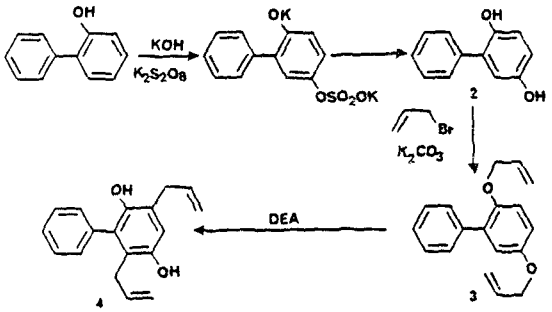


Fig. 2. Synthetic procedures of 4-hydroxyl-*o*-phenylphenol (2) and 3,6-diallyl-4-hydroxyl-o-phenylphenol (4).
DEA: N,N-diethylaniline

EXPERIMENTAL METHODS

Melting point (mp) was determined on a Electrothermal mp apparatus and uncorrected. IR spectrum was recorded on a Perkin-Elmer 783 spectrophotometer. NMR spectrum was recorded on a Varian EM 360 and given in ppm (δ), downfield from an internal TMS standard. The reagents, *o*-phenylphenol, allylbromide, N,N′-diethylaniline were purchased from Aldrich.

Synthesis of 4-hydroxy-o-phenylphenol (Fig. 2, 2)

The modified Elb's persulfate oxidation[4] was applied for the preparation to **2**. To a stirred solution **1** (1.7g, 10 mM) in pyridine 10 m*l* and 2 N-potassium hydroxide 5 m*l*, a saturated aqueous solution of 1 M potassium persulfate was added gradually with stirring during 3 hours. The temperature was controlled below 20° for the period of the addition, and then the mixture was left to stand overnight. After the reaction, pyridine was removed in vacuum and the aqueous solution was washed with chloroform 20 m*l* to remove the unreacted **1**. The aqueous layer was acidified with 2 N hydrochloric acid and heated for 30 minutes at 100°. After cooling, the solution was extracted with ether and dried over anhydrous sodium sulfate. The ether was evaporated and the residue was chromatographed on silica gel with chloroform-ethyl acetate (9:1), followed recrystalization in methanol, 588 mg (yield 28%).

Mp. 87-8°, IR ν_{max}^{KBr} cm^{-1}: 760 (1,2 and 4 substituted phenyl), ^{1}H-NMR ($CDCl_3$) δ: 5.3 (2H, s, −OH), 6.7-7.5 (8H, aromatic-H).

Synthesis of 3,6-diallyl-4-hydroxy-o-phenylphenol (Fig. 2, 4)

The Claisen's rearrangement[5] was applied to synthesize **4**. By direct reaction between **2** (86 mg, 2 mM) and allylbromide (363 mg, 3 mM) in the presence of potassium carbonate and acetone 10 m*l* for 4 hours, 1,4-diallyletherbiphenyl (**3**) was prepared. After filtrating and removing the solvent, **3** was refluxed above 190° in N,N′-diethylaniline 10 m*l* for 1 hour. The rearranged product was extracted by aqueous hydrochloric acid. The crude product **4** was purified by silica gel column chromatography, 157.5 mg (1.7 mM, yield 85%).

Mp. 182°, IR ν_{max}^{KBr} cm^{-1}: 710 (1,2,3,5 and 6 substituted phenyl), ^{1}H-NMR ($CDCl_3$) δ: 3.3 (4H, d, J=7.5 Hz, $-CH_2-$), 4.9 (4H, d, $=CH_2$, 5.3 (2H, bs, -OH), 5.9 (2H, m, -CH-), 6.8-7.6 (6H, aromatic-H).

Antibacterial activity

A cariogenic bacterium *Streptococcus mutans* was given from Prof. T. Choi, School of Medicine, Chungnam National University. The antibacterial activity was carried out as reported previously by Namba *et al.*[2] and Bauer *et al.*[6]

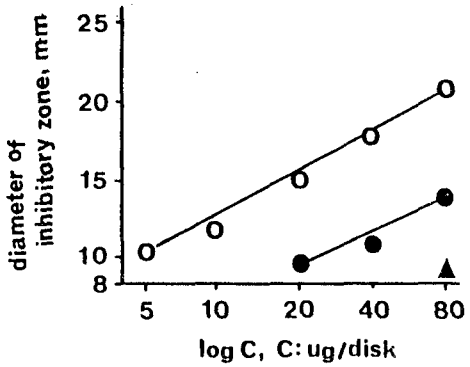


Fig. 3. The antibacterial activities of *o*-phenylphenol, 4-hydroxy-*o*-phenylphenol and 3,6-diallyl-4-hydroxy-*o*-phenylphenol.

According to the paper disk method, the disks (8 mm in diameter) containing various amounts of the chemicals were placed on Petri dishes which had been seeded with *Streptococcus mutans* OMZ 176. The incubation was then carried out at 37° for 16 hours.

▲ : *o*-phenylphenol
●-● : 4-hydroxy-*o*-phenylphenol
○-○ : 3,6-diallyl-4-hydroxy-*o*-phenylphenol

RESULTS AND DISCUSSION

The effect of the introduction of an another hydroxyl group to hydroxybiphenyl ring

The antibacterial activity of **2**, which was introduced another hydroxyl group from **1**, increased in comparison with that of **1** (Fig. 3). Furthermore **3**, which was the intermediate for **4** and had allylether group instead of hydroxyl one, showed no antibacterial activity. From the results, the introduction of another hydroxyl group to hydroxybiphenyl ring was clarified to enhance the activity. This result was also agreed with no activity of acetylated and benzoylated magnolol,[7] and suggested that the basic chemical moiety of magnolol or honokiol for antibacterial activity to be hydroxybiphenyl.

Introduction of allyl group to hydroxybiphenyl

The antibacterial activity of **4**, which was introduced two allyl groups from **2**, showed more potent antibacterial activity than that of **2** (Fig. 3). Therefore, the result allowed to conclude that the intro-

duction of allyl group to hydroxybiphenyl ring to increase the activity. Hamilton[8] proposed that a common feature of the mode of action of membrane-active antibacterial compounds, such as the phenols and biphenols, detergents, salicylanilides, carbanilides, polypeptide and macrotetralide, is their initial adsorption on the sensitive membrane. These compounds are active at the plasma membrane and known to affect its permeability and transport functions. Clearly, any compound affecting this structure is a potential antibacterial agent and its biochemical mechanism of action may be expressed in the inhibition or destruction of any one of several of the cell's vital functions. The introduction of allyl group into hydroxybiphenyl to increase the lipophilicity which could serve to adsorb easily on membrane and to destroy to vital function of bacteria.

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