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Synthesis and Antibacterial Activities of Halogenated Hydroxy Diphenyl Ether Derivatives

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Seven halogenated hydroxy diphenyl ether derivatives have been synthesized, 6 of them are new compounds and their structures were identified by ^{1}H NMR, HR-MS and IR spectra. The antibacterial activities of all the present compounds were tested *via* the agar-well diffusion method *in vitro* in the concentration of 50 μg/mL. The results showed that most of the new compounds exhibited antibacterial activities against the tested bacterium.

Key Words: Hydroxy diphenyl ethers, Derivatives, Antibacterial activity.

INTRODUCTION

Chlorinated hydroxy diphenyl ethers are antibacterial agent against both gram positive and gram negative bacteria[1]. 2,4,4'-Trichloro-2'-hydroxyl diphenyl ether was used as a bacteriostat, fungistat, mildewstat and deodorizer in a broad variety of consumer products[2-4]. From then on, many of chlorinated hydroxy diphenyl ethers derivatives were designed, synthesized[5] and applied as an antimicrobial agent in environment and a biocide in the wood products industry[6-8]. Brominated 2-hydroxy diphenyl ethers, which could inhibit gram positive bacteria and gram negative bacteria, were isolated from sponge *Dysidea herbacea* in 1969[9]. Later, a great deal of brominated hydroxy diphenyl ethers with antibacterial activity was isolated[10] and synthesized[11,12].

In our previous endeavors, series of chlorinated and/or brominated hydroxy/dihydroxy diphenyl ethers were designed and synthesized[13-16]. All the synthesized hydroxy diphenyl ethers showed antibacterial activities. In order to understand more about the relationship between antibacterial activity and chemical structures of the halogenated hydroxy diphenyl ether derivatives, seven new compounds were designed and synthesized. The new compounds with amino group could be converted to the form of hydrochloride or quaternary ammonium salts, which make them to be water-soluble and more facile to be applied in the industry. Some complex groups were introduced in order to study whether complex compounds containing hydro diphenyl ethers have antibacterial activities.

The structures of the new compounds were identified by ^{1}H NMR, HR-MS and IR spectra. The antibacterial activities of these compounds were tested *via* the agar-well diffusion method *in vitro*. The results showed that all compounds exhibited antibacterial activity toward *S. albus, S. aureus ATCC26112, S. aureus SC, P. vulgaris* and *T. bacillus*.

EXPERIMENTAL

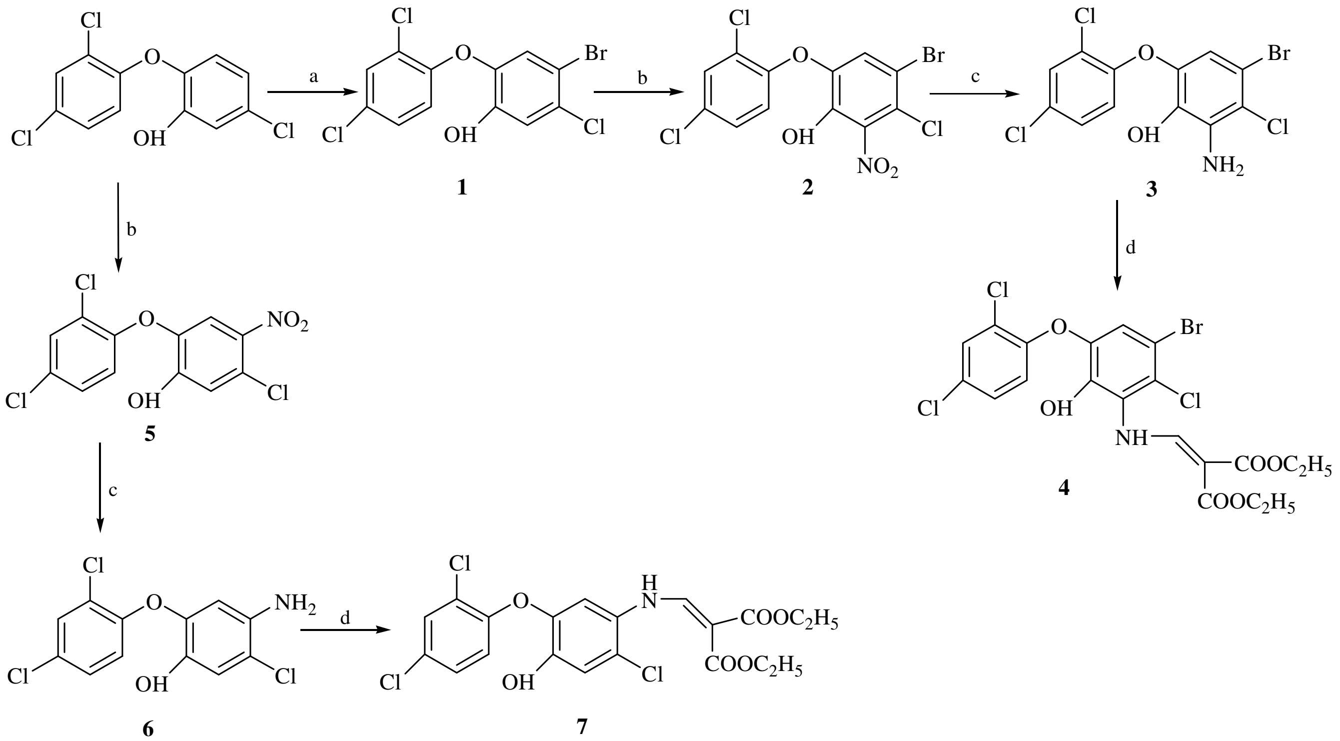
Compounds were prepared as shown in **Scheme-I**. Compound **1** was prepared according to the literature[14].

Synthesis of compound 2: Water (3 mL) was added to the mixture of **1** (3.68 g, 0.01 mol) and AcOH (10 mL), then the mixture was cold below 10 ºC and 65 % nitric acid (0.97 g, 0.01 mol) was added drop-wise to the mixture. The reaction mixture was stirred below 10 ºC for 6 h, poured into 10 mL of water. The resulted precipitate was filtered and dried to give **2** in 95 % yield.

Synthesis of compound 3: A sample of **2** (2.05 g, 5 mmol) was reduced by 5 % Pd/C (0.10 g) catalyzed hydrogenation in ethyl acetate (25 mL) at the experimental value of pressure. The reaction finished after 8 h. After filteration, the filtrate was evaporated to dryness under reduced pressure to give the compound **3** in 98 % yield.

Synthesis of compound 4: Diethyl ethoxymethylenemalonate (1.08 g, 5 mmol) was added drop-wise to the above solution and the mixture was heated under reflux for 4 h. After the mixture was cooled down and filtered off, the filtrate was concentrated under reduced pressure to afford a solid. Then the crude product was recrystallized in ethanol and vacuum-dried to yield **4** in 90 %.

Compound 1: White solid; yield: 90 %; m.p.: 96-98 ºC; ^{1}H NMR spectrum (400 MHz; $CDCl_3$; TMS): δ (ppm) = 7.50



Scheme-I: Synthetic route of compounds **1-7**; General synthesis route for compounds. Reaction reagents and conditions: (a) Br_2, CH_2Cl_2, refluxed; (b) HNO_3, $AcOH/H_2O$; (c) Pd/C, H_2, $CH_3COOC_2H_5$; (d) Diethyl ethoxymethylenemalonate, EtOH, refluxed

(1H, d, J = 2.4 Hz), 7.27 (1H, dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 7.17 (1H, s), 7.00 (1H, d, J = 8.8 Hz), 6.88 (1H, s), 5.77 (1H, s); IR (KBr, ν_{max}, cm^{-1}) 3430, 3089, 1578, 1470, 1092, 1057, 871, 836, 754, 665, 567; HR-MS (-ESI): Calcd. for $C_{12}H_6O_2BrCl_3$ $[M-H]^-$: 365.8617; Found: 365.8638.

Compound 2: Yellow solid; yield: 95 %; m.p.: 66-68 °C; ^{1}H NMR spectrum (400 MHz; $CDCl_3$; TMS): δ (ppm) = 7.55 (1H, d, J = 2.4 Hz), 7.35 (1H, dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 7.21 (1H, s); 7.12 (1H, d, J = 9.2 Hz); 6.46 (1H, s); IR (KBr, ν_{max}, cm^{-1}) 3456, 3090, 1575, 1532, 1473, 1325, 1099, 1058, 867, 839, 659, HR-MS (-ESI): Calcd. for $C_{12}H_5NO_4BrCl_3$ $[M-H]^-$: 410.8468; Found: 410.8460.

Compound 3: White solid; yield: 98 %; m.p.: 101-103 °C; ^{1}H NMR spectrum (400 MHz; $CDCl_3$; TMS): δ (ppm) = 7.49 (1H, d, J = 2.8 Hz); 7.25 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz); 6.99 (1H, d, J = 8.4 Hz); 5.56 (1H, s); 4.39 (2H, s); IR (KBr, ν_{max}, cm^{-1}) 3430, 3402, 3325, 3090, 1612, 1577, 1476, 1435, 1095, 1059, 865, 564, HR-MS (-ESI): Calcd. for $C_{12}H_7NO_2BrCl_3$ $[M-H]^-$: 380.8726; Found: 380.8752.

Compound 4: White solid; yield: 90 %; m.p.: 158-160 °C; ^{1}H NMR spectrum (400 MHz; $CDCl_3$; TMS): δ (ppm) = 11.20 (1H, d, J = 12.8 Hz); 9.04 (1H, d, J = 13.2 Hz); 7.52 (1H, d, J = 2.8 Hz); 7.31 (1H, dd, J_1 = 2.4 Hz, J_2 = 6.4 Hz); 7.07 (1H, d, J = 8.8 Hz); 6.69 (1H, s); 6.44 (1H, s); 4.34 (2H, q); 4.22 (2H, q); 1.36 (3H, t); 1.28 (3H, t); IR (KBr, ν_{max}, cm^{-1}) 3386, 3207, 2981, 1687, 1657, 1614, 1585, 1475, 1090, 1030, 870, 576, HR-MS (-ESI): Calcd. for $C_{20}H_{17}BrCl_3NO_6$ $[M-H]^-$: 550.9305; Found: 550.9325.

Compound 5: Yellow solid; yield: 93 %; m.p.: 112-114 °C; ^{1}H NMR spectrum (400 MHz; $CDCl_3$; TMS): δ (ppm) = 7.55 (1H, d, J = 2.4 Hz); 7.35 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz); 7.32 (1H, s) 7.21 (1H, s); 7.13 (1H, d, J = 8.8 Hz); 6.35 (1H, s); IR (KBr, ν_{max}, cm^{-1}) 3435, 3091, 1585, 1528, 1495, 1328, 1100, 1058, 870, 805, 565, HR-MS (-ESI): Calcd. for $C_{12}H_6NO_4Cl_3$ $[M-H]^-$: 332.9362; Found: 332.9352.

Compound 6: White solid; yield: 98 %; mp: 148-150 °C; ^{1}H NMR spectrum (400 MHz; $CDCl_3$; TMS): δ (ppm) = 7.48 (1H, d, J = 2.4 Hz); 7.21 (1H, dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz); 7.00 (1H, s); 6.78 (1H,d, J = 9.2 Hz); 6.21 (1H, s); 5.57 (1H, s); 5.09 (2H, s); IR (KBr, ν_{max}, cm^{-1}) 3485, 3408, 3323, 3082, 1619, 1586, 1475, 1201, 1100, 865, 810, HR-MS (-ESI): Calcd. for $C_{12}H_8NO_2Cl_3$ $[M-H]^-$: 302.9621; Found: 302.9628.

Compound 7: White solid; yield: 94 %, m.p.: 178-180 °C; ^{1}H NMR spectrum (400 MHz; $CDCl_3$; TMS): δ (ppm) = 11.18 (1H, d, J = 13.6 Hz); 8.16 (1H, d, J = 5.2 Hz); 7.52 (1H, d, J = 2.0 Hz); 7.28 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz); 7.16 (1H, s); 6.99 (1H, d, J = 8.8 Hz); 6.64 (1H, s); 5.57 (1H, s); 4.31 (2H, q); 4.20 (2H, q), 1.36 (3H, t); 1.28 (3H, t); IR (KBr, ν_{max}, cm^{-1}) 3430, 3270, 2923, 2853, 1684, 1657, 1612, 1513, 1475, 1095, 1025, 868, 806, HR-MS (-ESI): Calcd. for $C_{20}H_{18}NO_6Cl_3$ $[M-H]^-$: 473.0220; Found: 473.0200.

Biological assay: The antibacterial activities of the target compounds *in vitro* were tested *via* agar-well diffusion method. The cryopreserved bacteria was suspended in LB (Luria Bertani) culture medium and then kept at 37 °C for 24 h. Later, the typical single colony bacteria solution was inoculated in flesh Luria Bertani culture medium and then kept at 37 °C for 24 h. The bacteria solution was corrected to 0.5 McF (amount of bacteria: about 10^8 colony-forming units (CFU)/mL) with physiological saline solution.0.5mL bacteria solution (0.5 McF) was added into the Luria Bertani culture medium (50 mL) [the amount of bacteria: about 10^6 colony-forming units (CFU/mL)] and the resulting mixture was shaken up until it was well-distributed, then the mixture was poured into plate. Five wells (6 mm) were made in each plate using a sterile cork borer when the mixture became curdled. A 50 μL solution of each target compound or contrast compound was injected into the corresponding well and the plates were incubated at 37 °C for 24 h. Then the diameters of bacteriostatic circle were recorded. Results of test are given in Table-1.

TABLE-1
ANTIBACTERIAL ACTIVITIES OF 50 μg/mL COMPOUNDS AGAINST BACTERIAL STRAINS

Compounds	Diameter of bacteriostatic circle (mm)				
	S. albus	*S. aureus ATCC*	*S. aureus SC*	*P. vulgaris*	*T. bacillus*
1	26.0	23.0	27.0	14.0	17.0
2	14.5	19.0	26.0	8.0	10.0
3	9.0	9.0	10.0	9.0	8.0
4	12.5	10.0	12.5	9.5	9.0
5	22.0	21.0	16.0	10.0	13.5
6	9.0	15.0	12.0	9.0	9.5
7	8.0	8.0	6.0	8.0	8.0
Ethanol	8.0	8.0	8.0	8.0	10.5

RESULTS AND DISCUSSION

Usually, nitrosation of phenols are high selective of *p*-position *vs. o*-position, so at the first compound **6** was synthesized *via* nitrosation-reduction of **1**, but the starting materials could not be converted completely. Later nitration was used to synthesis of **6**, water was added to the AcOH solution in order to prevent solidification below 15 ºC. Nitro group could be introduced to the *o*-position or *p*-position of hydroxy, the ^{1}H NMR date of the product **5** gave two single peaks at 7.32 and 7.21 which meant that nitro group was on the *p*-position of hydroxy. The Pd/C catalytic reduction is better than Fe/HCl reduction, because the latter formed iron mud which is very difficult to deal with.

Most of the compounds exhibited antibacterial activities in the concentration of 50 μg/mL. Compounds **1**, **2** and **5** which contain bromo and/or nitro group showed potent antibacterial activities, so they have possibility to be used just like other diphenyl ethers. Compounds **3** and **6** showed antibacterial activities in the concentration of 50 μg/mL, so they could be converted to the form of hydrochloride or quaternary ammonium salt and used as broad spectrum antibacterial agents in certain areas. Comparing compounds **4** with **7**, it's believed that bromo group is important to improve the antibacterial activities. More related researches are in progress.

Conclusion

In conclusion, a series of halogenated hydroxy diphenyl ethers derivatives have been designed and synthesized. The results showed that most of the object compounds displayed antibacterial activities. The preliminary relationship between antibacterial activity and chemical structures provided a foundation to design other practicable and securit biocides with diphenyl ether moiety.

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