Asian Journal of Chemistry; Vol. 26, No. 16 (2014), 5165-5167

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16585

Synthesis and Antimicrobial Activities of 2,5-Substituent Hydroquinone Derivatives

HUI-LIAN LIU* and QING-ZHONG WANG

College of Biological and Agricultural Engineering, Weifang University, Key Laboratory of Biochemistry and Molecular Biology in Universities of Shandong, Weifang 261061, Shandong Province, P.R. China

*Corresponding author: Tel/Fax: +86 536 8785288; E-mail: huilian.liu@163.com

Received: 26 October 2013; *Accepted*: 18 March 2014; *Published online*: 28 July 2014; AJC-15653

A series of 2,5-substituent hydroquinone derivatives were designed and synthesized. Their structures were identified by elemental analysis, ^{1}H NMR, IR spectra. Their assayed antibacterial (*Escherichia coli*, *Bacillus subtilis*) and antifungal (*Candida albicans*) activities were also evaluated by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) method. The results of biological test showed compounds **1** and **10** have favorable antimicrobial activity with MICs of 20.5, 24.6, 18.9 and 28.6 μg/mL against *Escherichia coli* and *Bacillus subtilis,* respectively.

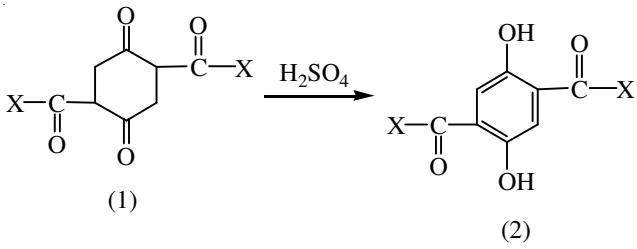
Keywords: Hydroquinone derivatives, Antimicrobial activities, Structure-activity relationships.

INTRODUCTION

As an important industrial organic compound, 2,5-substituted hydroquinone was used in rubber manufacture[1], plastic additives, dyes and specialty thermosetting resins[2-4]. They occurred in key biological processes as diverse as the oxidative maintenance of biological amine levels[5], tissue (collagen and elastin) formation[6] photosynthesis[7] and aerobic (mitochondrial) respiration[8]. 2,5-Substituted hydroquinone are vital for all life, occurring in key biological processes as diverse as the oxidative maintenance of biological amine levels. Their derivatives are the basic structure of the quinones, which is not only found in bacteria, plants and arthropods but are also the base for a large number of chemical derivatives with pharmacological applications[9-11]. However, the antibacterial activity of 2,5-substituted hydroquinone was less reported. In this paper, the compounds were prepared to study their antibacterial activity against *Bacillus subtilis*, *Escherichia coli* and *Candida albicans*. The results of this study may be useful to researchers attempting to gain more understanding of the antimicrobial activity of 2,5-substituted hydroquinone compounds. The synthesis route is described in **Scheme-I**.

EXPERIMENTAL

All chemicals and reagents were obtained from commercial sources and used without further purification. Melting points were measured on a Boetius micro melting point apparatus. The IR spectra were recorded in the 4000-400 cm^{-1} region using KBr pellets on a Nicolet 170SX spectrophotometer.



(1) (2)

Scheme-I

All the NMR spectra were recorded on a Bruker DRX500 model spectrometer in $CDCl_3$. Chemical shifts for ^{1}H NMR spectra were reported in parts per million to residual solvent protons.

General synthetic procedure: To a 100 mL flask 20 mL concentrated sulfuric acid, 0.05 mol 2,5-substituent 1,4-cyclohexanedione was added dropwise with stirring. The solid of 2,5-substituent 1,4-cyclohexanedione suspend on the concentrated sulfuric acid at first, gradually dissolved later. The reaction was maintained until the mixture was turned to clear solution for 4-5 h. Then add above clear solution into ice-water with rapidly stirring. The precipitation was formed and filtered. The light yellow or white solid produces have been obtained by recrystallized from EtOH. The yields of ten synthesized compounds are listed in Table-1.

2,5-Dimethylformate hydroquinone (1): Yield: 98 %. m.p. 155-157 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 11.98 (s, 2H), 7.26 (s, 2H), 3.13 (s, 6H); IR (KBr, ν_{max}, cm^{-1}): 3168, 2961, 2910, 1669, 1347, 1224, 1073, 812, 796. Elemental analysis

TABLE-1
PRODUCTS AND YIELDS FROM THE DIFFERENT STARTING MATERIALS IN K_2CO_3/EtOH SYSTEM

Entry	X Groups	Melt point (°C)	Yield (%)
1	CH_3O	155-157	98.0
2	CH_3CH_2O	136.4	98.2
3	$CH_3CH_2CH_2O$	100.4	98.3
4	$(CH_3)_2CHO$	136.2-137.1	97.0
5	$CH_3(CH_2)_2CH_2O$	101.8	87.9
6	$CH_3CH_2(CH_3)CHO$	> 200	85.8
7	$(CH_3)_2CHCH_2O$	111	86.7
8	$CH_3(CH_2)_3CH_2O$	104.7-105	83.6
9	$(CH_3)_2CHCH_2CH_2O$	48-49	80.1
10		207-208.2	79.2

[Anal. calcd. (%) for $C_{10}H_{10}O_6$]: C 53.10, H 4.46; Found (%): C 53.02, H 4.22.

2,5-Diethylformate hydroquinone (2): Yield: 98.2 %. m.p. 136.4 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 9.87 (s, 2H), 7.27 (s, 2H), 4.39-4.31 (m, 4H), 1.34-1.31 (t, 6H); IR (KBr, ν_{max}, cm^{-1}): 3296, 2990, 2907, 1685, 1402, 1197, 1099, 802, 792. Elemental analysis [Anal. calcd. (%) for $C_{12}H_{14}O_6$]: C 56.68, H 5.55; Found (%): C 56.30, H 5.41.

2,5-Dipropylformate hydroquinone (3): Yield: 98.3 %. m.p. 100.4 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 10.11 (s, 2H), 7.25 (s, 2H), 3.41-3.36 (t, 4H), 1.46-1.30 (m, 4H), 0.94-0.86 (t, 6H); IR (KBr, ν_{max}, cm^{-1}): 3117, 2963, 2897, 1665, 1402, 1208, 1067, 815, 780. Elemental analysis [Anal. calcd. (%) for $C_{14}H_{18}O_6$]: C 59.57, H 6.43; Found (%): C 59.13, H 6.41.

2,5-Diisopropylformate hydroquinone (4): Yield: 97 %. m.p. 136.2-137.1 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 12.14 (s, 2H), 7.27 (s, 2H), 3.09-2.50 (m, 2H), 1.34-1.24 (d, 12H); IR (KBr, ν_{max}, cm^{-1}): 3125, 2973, 1663, 1377, 1219, 1061, 713, 753. Elemental analysis [Anal. calcd. (%) for $C_{14}H_{18}O_6$]: C 59.57, H 6.43; Found (%): C 59.04, H 6.13.

2,5-Dibutylformate hydroquinone (5): Yield: 87.9 %. m.p. 101.8 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 12.07 (s, 2H), 7.21 (s, 2H), 4.184.15 (t, 4H), 1.71-1.58 (m, 4H), 1.45-1.31 (m, 4H), 0.93-0.88 (t, 6H); IR (KBr, ν_{max}, cm^{-1}): 3126, 2962, 2898, 1663, 1402, 1212, 1066, 814, 799. Elemental analysis [Anal. calcd. (%) for $C_{16}H_{22}O_6$]: C 61.92, H 7.15; Found (%): C 61.84, H 6.89.

2,5-Di-α-methylpropylformate hydroquinone (6): Yield: 85.8 %. m.p. > 200 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 12.23 (s, 2H), 7.28 (s, 2H), 2.99-2.74 (m, 2H), 1.94-1.80 (m, 4H), 1.46-1.43 (d, 6H), 1.27-1.24 (t, 6H); IR (KBr, ν_{max}, cm^{-1}): 3125, 2935, 2565, 1669, 1440, 1217, 1058, 849, 753. Elemental analysis [Anal. calcd. (%) for $C_{16}H_{22}O_6$]: C 61.92, H 7.15; Found (%): C 61.90, H 7.07.

2,5-Diisobutylformate hydroquinone (7): Yield: 86.7 %. m.p. 111 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 12.07 (s, 2H), 7.29 (s, 2H), 3.97-3.95 (d, 4H), 1.98-1.91 (m, 2H), 0.99-0.88 (d, 12H); IR (KBr, ν_{max}, cm^{-1}): 3126, 2968, 2910, 1663, 1407, 1237, 1073, 826, 775. Elemental analysis [Anal. calcd. (%) for $C_{16}H_{22}O_6$]: C 61.92, H 7.15; Found (%): C 61.57, H 6.94.

2,5-Diamylformate hydroquinone (8): Yield: 83.6 %. m.p. 104-105 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 12.10 (s, 2H), 7.26 (s, 2H), 4.30-4.27 (t, 4H), 4.18-4.13 (m, 4H), 3.19-2.96 (m, 4H), 1.73-1.56 (m, 4H), 1.36-1.27 (t, 6H); IR (KBr, ν_{max}, cm^{-1}): 3124, 2973, 2896, 1657, 1404, 1226, 1073, 823, 780. Elemental analysis [Anal. calcd. (%) for $C_{18}H_{26}O_6$]: C 63.89, H 7.74; Found (%): C 63.71, H 7.32.

2,5-Diisoamylformate hydroquinone (9): Yield: 80.1 %. m.p. 48-49 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 12.07 (s, 2H), 7.26 (s, 2H), 4.34-4.31 (t, 4H), 3-2.89 (m, 4H), 1.72-1.60 (m, 2H), 0.92-0.90 (d, 12 H); IR (KBr, ν_{max}, cm^{-1}): 3128, 2959, 2872, 1655, 1401, 1220, 1074, 822, 778. Elemental analysis [Anal. calcd. (%) for $C_{18}H_{26}O_6$]: C 63.89, H 7.74; Found (%): C 63.53, H 7.47.

2,5-Dicyclohexylformate hydroquinone (10): Yield: 79.2 %. m.p. 207-208 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 12.24 (s, 2H), 7.34 (t, 2H), 4-3.98 (m, 2H), 2.03-1.95 (m, 8H), 1.87-1.66 (m, 8H), 1.44-1.27 (m, 4H); IR (KBr, ν_{max}, cm^{-1}): 3048, 2627, 2561, 1646, 1424, 1228, 1058, 836, 749. Elemental analysis [Anal. calcd. (%) for $C_{20}H_{26}O_6$]: C 66.28, H 7.23; Found (%): C 66.04, H 7.15.

Antimicrobial activity: The antibacterial activity of the synthesized compounds was tested against *Escherichia coli* and *Bacillus subtilis* using MH medium (Mueller-Hinton medium), the antifungal activity of the compounds was tested against *Candida albicans* using RPMI-1640 mediun. The MICs (minimum inhibitory concentrations) of the test compounds were determined by a colorimetric method using the dye MTT[12,13]. Suspension of the microbes prepared to contain approximately 10^5 cfu/mL and applied to 96-well microplates with serially diluted compounds in DMSO to be tested and incubated at 37 °C for 24 h and 48 h for bacteria and fungi, respectively. After the MICs were visually determined on each of microtitration plates, 50 µL MTT solution was added to each well for 4-5 h. The supernatant of each well was removed and 100 µL of isopropanol containing 5 % 1 mol/L HCl was added to extract the dye. The optical density (OD value) was measured with a microplate reader at 550 nm.

RESULTS AND DISCUSSION

The MICs of the compounds against three bacterias are presented in Table-2. The compounds **2-9** showed to be inactive against *Escherichia coli* and *Bacillus subtilis*. To the contrary, compounds **1** and **10** exhibited antimicrobial activity against the two bacteria strain with an MIC value of 18.9-28.6 µg/mL, which was comparable to the positive control kanamycin and penicillin. Although all the inhibiting activities were lower than the positive control, the activities of compounds **1** and **10** exhibited similar antibacterial activities with commercial antibiotics. Compounds **1-10** were also tested against *Candida albicans* which they had no antifungal activity.

Compounds **1** and **10** showed strong antimicrobial activities. According to structure-activity relationships, it is assumed that the non-substitutional group phenyl ring may play a key role. Other compounds showed no significant inhibition. This may be due to the large substituents hindering the compounds to permeate the cell membrane. Nevertheless, the biological activities of their potential metabolites seems to be worth studying.

Conclusion

We have synthesized a series of 2,5-substituent hydroquinone derivatives derivatives using a successful method

TABLE-2
ANTIMICROBIAL ACTIVITY OF
THE SYNTHESIZED COMPOUNDS

Compound	Minimum inhibitory concentration [μg/mL]		
	Escherichia coli	*Bacillus subtilis*	*Candida albicans*
1	>20.5	>24.6	>50
2	>50	>50	>50
3	>50	>50	>50
4	>50	>50	>50
5	>50	>50	>50
6	>50	>50	>50
7	>50	>50	>50
8	>50	>50	>50
9	>50	>50	>50
10	>18.9	>28.6	>50
[a]Ketoconazole	>50	>50	3.9
[b]Kanamycin	3.6	3.1	>50
[c]Penicillin	>50	2.6	>50

[a,b,c]Used as positive control

under mild conditions in a high yield. All the compounds were tested for their antibacterial (*Escherichia coli* and *Bacillus subtilis*) and antifungal (*Candida albicans*) activities by MTT method. It may be concluded that compounds **1** and **10** showed strong antimicrobial activities. The results may be useful to researchers attempting to gain more understanding of the antimicrobial activity of 2,5-substituent hydroquinone compounds.

ACKNOWLEDGEMENTS

This work was co-financed by grants from the Natural Science Foundation of Weifang (No. 2012098) and National Torch Project, P.R. China (No. 2012GA740034).

REFERENCES

1. H. Itokawa, N. Totsuka, K. Nakahara, M. Maezuru, K. Takeya, M. Kondo, M. Inamatsu and H. Morita, *Chem. Pharm. Bull. (Tokyo)*, **37**, 1619 (1989).
2. J.S. Swenton, S. Patai and Z. Rappoport, The Chemistry of the Quinonoid Compounds; Vol. 2, Wiley, New York (1988).
3. A. Sato, T. Shindo, N. Kasanuki and K. Hasegawa, *J. Nat. Prod.*, **52**, 975 (1989).
4. T. Yamamura, K. Nishiwaki, Y. Tanigaki, S. Terauchi, S. Tomiyama and T. Nishiyama, *Bull. Chem. Soc. Jpn.*, **68**, 2955 (1995).
5. (a) D.M. Dooley, M.A. McGuirl, D.E. Brown, P.N. Turowski, W.S. Mclntire and P.F. Knowles, *Nature*, **349**, 262 (1991); (b) D.M. Dooley, R.A. Scott, P.F. Knowles, C.M. Colangelo, M.A. McGuirl and D.E. Brown, *J. Am. Chem. Soc.*, **120**, 2599 (1998).
6. (a) J.P. Klinman, *Chem. Rev.*, **96**, 2541 (1996); (b) W.S. McIntire, *Annu. Rev. Nutr.*, **18**, 145 (1998).
7. R. Calvo, E.C. Abresch, R. Bittl, G. Feher, W. Hofbauer, R.A. Isaacson, W. Lubitz, M.Y. Okamura and M. Paddock, *J. Am. Chem. Soc.*, **122**, 7327 (2000); C.W. Hoganson, *Science*, **277**, 1953 (1997).
8. (a) D.G. Nichols and S.J. Ferguson, Bioenergetics 2, Academic Press, New York (1992); (b) S. Iwata, Science, **281**, 64 (1998).
9. S.X. Wang, M. Mure, K.F. Medzihradsky, A.L. Burlingame, R.A. Brown, D.M. Dooley, A.J. Smith, H.M. Kagan and J.P. Klinman, *Science*, **273**, 1078 (1996).
10. C. Basavaraja, N.R. Kim, H.T. Park and D.S. Huh, *Bull. Korean Chem. Soc.*, **30**, 907 (2009).
11. T. Bánsági and O. Steinbock, *Chaos*, **18**, 026102 (2008).
12. P. Cao, X.F. Huang, H. Ding, H.M. Ge, H.Q. Li, B.F. Ruan and H.L. Zhu, *Chem. Biodivers.*, **4**, 881 (2007).
13. J. Meletiadis, J.F. Meis, J.W. Mouton, J.P. Donnelly and P.E. Verweij, *J. Clin. Microbiol.*, **38**, 2949 (2000).