

Yunus A. Shaikh

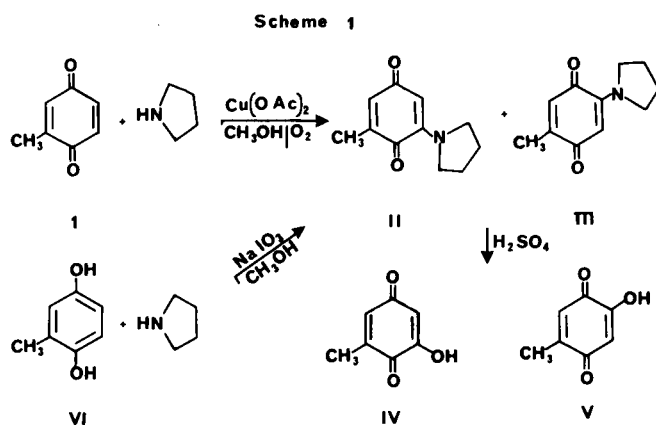
Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal  
Sciences, Purdue University, West Lafayette, Indiana 47907

Received February 7, 1977

Oxidative amination of 2-methyl-1,4-benzoquinone with pyrrolidine yielded 2-methyl-6-pyrrolidino-1,4-benzoquinone as the major product along with 2-methyl-5-pyrrolidino-1,4-benzoquinone formed as the minor product. No detectable amount of 2-methyl-3,6-bis(pyrrolidino)-1,4-benzoquinone was observed.

*J. Heterocyclic Chem.*, 14, 925 (1977)

As a part of our studies on biosynthesis of mitomycin-C and synthesis of mitomycin-C analogs, we required certain aminoquinones as model compounds. Quinones readily undergo nucleophilic attack by amines to yield aminoquinones by 1,4-addition of an amine followed by oxidation of the intermediate aminoquinol to the corresponding aminoquinone. However, when the quinone is substituted by alkyl groups amination may occur on the side chain (1) to yield aminomethylquinols. Oxidative-amination of benzoquinones has been reported by various workers (2-6), under different experimental conditions. Crosby and Lutz (7) reported the synthesis of 2,5-bis(di-alkylamino)-1,4-benzoquinones from benzoquinones by a method developed by Baltzly and Lorz (8). Using this procedure Lown and Begleiter (9) prepared bis(pyrrolidino)-1,4-benzoquinones from 1,4-benzoquinone and 2,5-dimethyl-1,4-benzoquinone.



An attempt to prepare 2-methyl-3,6-bis(pyrrolidino)-1,4-benzoquinone following the procedure of Crosby and Lutz (7) was unsuccessful. 2-Methyl-1,4-benzoquinone reacted with pyrrolidine in the presence of copper acetate and oxygen to give 2-methyl-6-pyrrolidino-1,4-benzoquinone (II) (65-70% yield) and 2-methyl-5-pyrrolidino-1,4-benzoquinone (III) (25-30% yield). Compounds II and III were characterized by acid hydrolysis to the known hydroxyquinones (IV) and (V), respectively. Alternatively, an attempt to react pyrrolidine with methylhydroquinone (VI) in the presence of sodium iodate,

according to the method of Schafer and Aguado (3) for the preparation of bis(aryl-amino)-1,4-benzoquinones, resulted in the formation of two compounds, which were identical to II and III in all respects. No detectable amount of 2-methyl-3,5-bis(pyrrolidino)-1,4-benzoquinone was thus observed, indicating that oxidative amination of 2-methyl-1,4-benzoquinone with pyrrolidine resulted in monosubstitution rather than disubstitution. The major product was the 6-substituted isomer while the 5-substituted isomer was formed as the minor product. No 3-substituted isomer was formed. The <sup>1</sup>H nmr spectra of II and III reveal that side chain amination of the quinone or methyl group displacement did not occur.

#### EXPERIMENTAL

Melting points were taken on a Fisher Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckmann IR-33 Spectrometer. <sup>1</sup>H nmr spectra were obtained on a Varian-EM-360 instrument. Chemical shifts are in ppm (δ) relative to TMS as the internal standard. Electron-impact mass spectra were obtained on a Hitachi RMV-6A mass spectrometer.

2-Methyl-6-pyrrolidino-1,4-benzoquinone (II) and 2-Methyl-5-pyrrolidino-1,4-benzoquinone (III). Method (a).

2-Methyl-1,4-benzoquinone (I) was prepared in quantitative yield from methylhydroquinone (VI) by oxidation with silver oxide in the presence of 6*N* nitric acid (10). Oxidative amination of I was carried out essentially by the procedure of Crosby and Lutz (7). A mixture of pyrrolidine (0.025 mole) and copper acetate (0.025 mole) in 50 ml. of methanol was stirred at room temperature for about 20 minutes under a stream of oxygen. A solution of I (0.01 mole) in 20 ml. of methanol was added dropwise with cooling. The reaction mixture was stirred for additional 6 hours and chromatographed (tlc) on silica gel with benzene-chloroform-methanol 80:20:10 as the eluent. The chromatogram showed two violet spots at *R<sub>f</sub>* 0.60 and *R<sub>f</sub>* 0.54.

The solvent was completely removed on a rotatory evaporator at room temperature and the residue was extracted with ether. Evaporation of the solvent gave a residue, which was chromatographed on a neutral silica gel-60 column and developed with benzene-chloroform (8:2). Compound II was isolated in 65-70% yield from the violet fraction which eluted first. Repeated recrystallization from ethyl acetate-petroleum ether gave an analytically pure sample, m.p. 95-97° dec. A single component was observed in the foregoing solvent system at *R<sub>f</sub>* 0.60; nmr (deuteriochloroform): δ 1.95 (4H, m, -CH<sub>2</sub>-CH<sub>2</sub>-), 2.10 (3H, d,

$J = 2$  cps,  $\text{CH}_3\text{-}\overset{|}{\underset{|}{\text{C}}}\text{=}\overset{|}{\underset{|}{\text{C}}}\text{-H}$ ), 3.3 to 3.90 (4H, m,  $2\text{-CH}_2\text{-N}\langle$ ), 5.50

(1H, s,  $\text{-CH=}\overset{|}{\underset{|}{\text{C}}}$ , quinonoid proton at position 3); ir (nujol): showed absorption at 1645 and 1665  $\text{cm}^{-1}$  (quinone  $\text{>C=O}$ )

1560  $\text{cm}^{-1}$  ( $\text{>N-}\overset{|}{\underset{|}{\text{C}}}\text{=}\overset{|}{\underset{|}{\text{C}}}$ ). MW (mass spectrum): Calcd. for  $\text{C}_{11}\text{H}_{13}\text{O}_2\text{N}$ : 191.094. Found: 191.094.

Anal. Calcd. for  $\text{C}_{11}\text{H}_{13}\text{O}_2\text{N}$ : C, 69.10; H, 6.80; N, 7.32. Found: C, 68.84; H, 7.05; N, 7.03.

Compound III was similarly isolated in 25-30% yield from a second violet fraction which was eluted with benzene-chloroform-methanol (8:2:1). It was recrystallized from hexane, m.p. 103-107° dec. It was homogenous (tlc) in the foregoing system at  $R_f$  0.54; nmr (deuteriochloroform):  $\delta$  1.90 (4H, m,  $\text{-CH}_2\text{-CH}_2\text{-}$ ), 2.05 (3H, d,  $J = 2$  cps,  $\text{CH}_3\text{-}\overset{|}{\underset{|}{\text{C}}}\text{=}\overset{|}{\underset{|}{\text{C}}}\text{-H}$ ), 3.30 to 3.80 (4H, m,  $2\text{-CH}_2\text{-N}\langle$ ), 5.50 (1H, s,  $\text{-CH=}\overset{|}{\underset{|}{\text{C}}}$ , quinonoid proton at

position 6), 6.50 (1H, q,  $\text{-CH-}\overset{|}{\underset{|}{\text{C}}}\text{=}\overset{|}{\underset{|}{\text{C}}}\text{-CH}_3$ , quinonoid proton at position 3); ir (nujol): showed strong absorption at 1700  $\text{cm}^{-1}$

(quinone  $\text{>C=O}$ ), 1560  $\text{cm}^{-1}$  ( $\text{>N-}\overset{|}{\underset{|}{\text{C}}}\text{=}\overset{|}{\underset{|}{\text{C}}}$ ). MW (mass spectrum): Calcd. for  $\text{C}_{11}\text{H}_{13}\text{O}_2\text{N}$ : 191.094. Found: 191.094.

Anal. Calcd. for  $\text{C}_{11}\text{H}_{13}\text{O}_2\text{N}$ : C, 69.10; H, 6.80; N, 7.32. Found: C, 68.85; H, 7.05; N, 7.30.

#### Acid Hydrolysis of II and III.

Compounds II and III (0.5 g.) in 30 ml. of methanol on refluxing with 15 ml. of 10% sulfuric acid in methanol (1:1) gave the reported hydroxyquinone (IV), m.p. 115-127° dec., lit. (11) 117-127° dec., and V m.p. 127-141° dec., lit. (12) 127-141° dec. Each reaction mixture was poured into water and extracted with chloroform. The chloroform layer was separated, dried over sodium sulfate and evaporated. The resulting hydroxyquinones were purified by sublimation under vacuum.

Method (b) for the Synthesis of II and III.

2-Methylhydroquinone (VI) and pyrrolidine were allowed to react in the presence of sodium iodate (3). The reaction product was chromatographed (tlc) along with II and III as references. Chromatograms were developed using benzene-chloroform-methanol, 8:2:1. Two violet spots were observed having  $R_f$  values corresponding to II and III. The compounds were isolated on a column as described earlier and were found to be identical to II and III in all respects.

#### Acknowledgements.

The author gratefully acknowledges all the facilities rendered by Dr. Ulfert Hornemann, present department, in carrying out this work which was supported by NIH grant CA 14378-07.

#### REFERENCES AND NOTES

- (1) D. Cameron, P. Scott and L. Todd, *J. Chem. Soc.*, 42 (1964).
- (2) S. Srivastava and U. Hornemann, *Angew. Chem. Int. Ed. Engl.*, 15 109 (1976).
- (3) W. Shafer and A. Aguado, *ibid.*, 10, 405 (1971).
- (4) T. Zinke, *Ber.*, 16, 1555 (1883).
- (5) H. Suida and W. Suida, *Ann. Chem.*, 416, 113 (1918).
- (6) J. Kumanotani, F. Kagawa, A. Hikosaka and K. Sugita, *Bull. Chem. Soc. Japan*, 41, 2118 (1968).
- (7) A. Crosby and R. Lutz, *J. Am. Chem. Soc.*, 78, 1233 (1956).
- (8) R. Baltzby and E. Lorz, *ibid.*, 70, 861 (1948).
- (9) J. Lown and A. Begleiter, *Can. J. Chem.*, 52, 2331 (1974).
- (10) C. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, 94, 227 (1972).
- (11) H. Musso, *Chem. Ber.*, 91, 349 (1948).
- (12) R. Woodward, F. Sondheimer, D. Taub, K. Hensler and W. McLamore, *J. Am. Chem. Soc.*, 74, 4223 (1952).