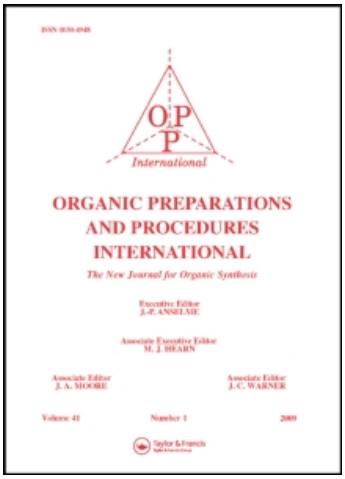

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SYNTHESIS OF 3-SUBSTITUTED-2,5-DIMETHYL-6-PYRROLIDINE-1,4-BENZOQUINONES

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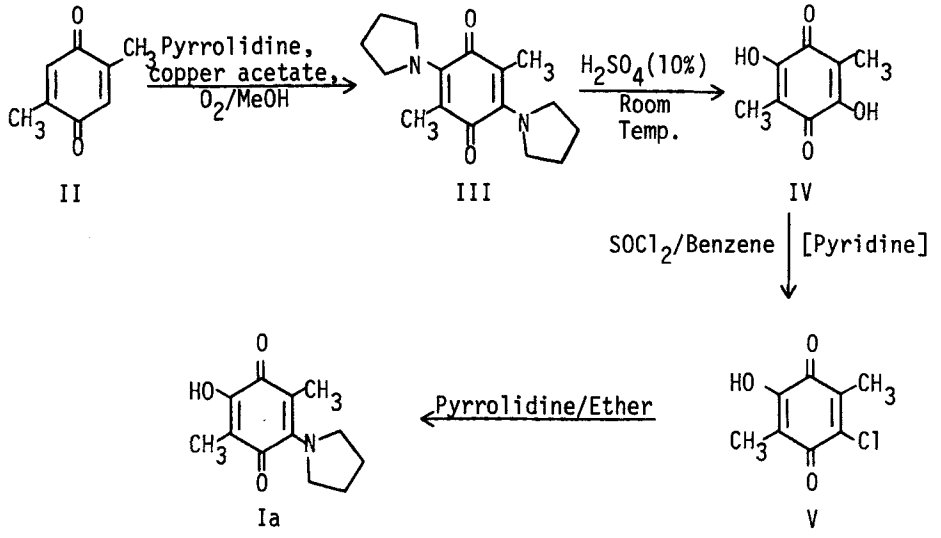
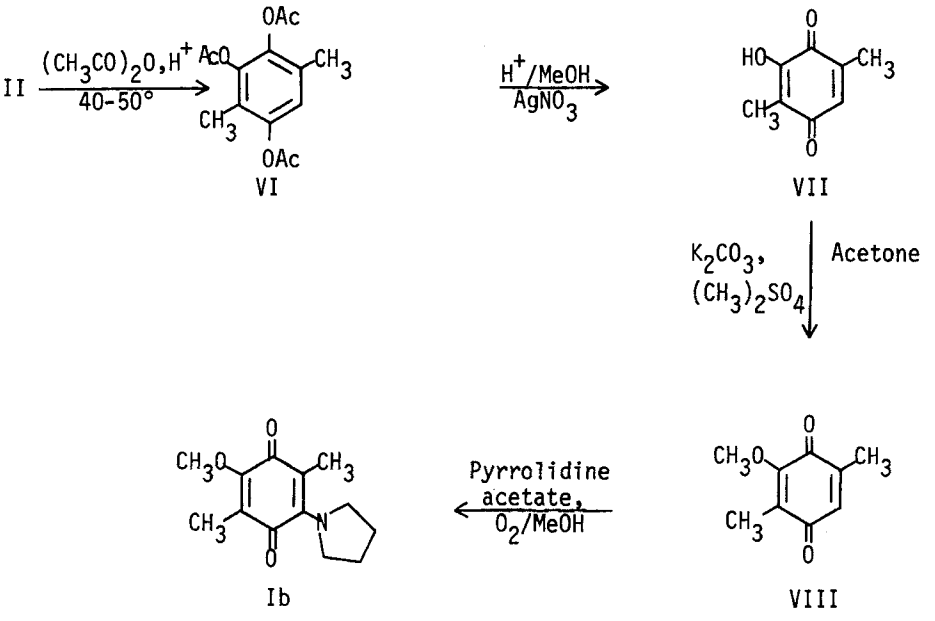
We were interested in synthesizing unsymmetrically substituted benzoquinones Ia, Ib and Ic in anticipation that these compounds could serve as useful models in degradation studies on the biosynthesis[1] of mitomycin antibiotics.

Several procedures for the preparation of <u>para</u> disubstituted 1,4-benzoquinones having identical secondary amine substituents are known.[2] However, there appears to be a paucity of reports concerning the preparation of 1,4-benzoquinones having different <u>para</u> substituents with one or both of these substituents being amine functions.[2] The starting benzoquinone II was prepared from the reaction of 2,5-dimethylphenol with sodium nitrite in an ethanolic-HCl solution in the presence of a copper powder.[3] Separate routes to the title compounds had to be developed since attempts to achieve interconversions of these compounds proved unsuccessful.

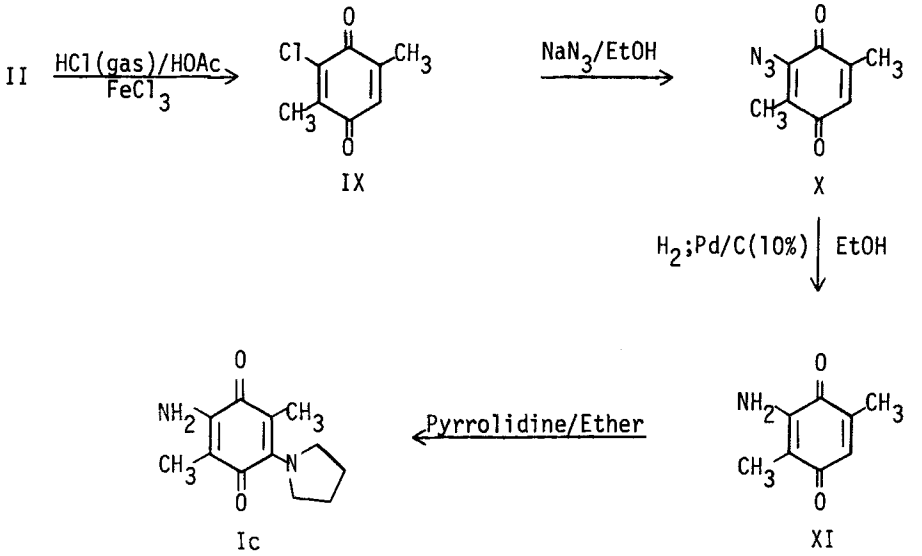
Synthesis of 3-hydroxy-2,5-dimethyl-6-pyrrolidine-1,4-benzoquinone Ia was achieved from II by way of the known intermediates III-V.[4-6] Attempts to convert III directly into Ia by partial acid hydrolysis were unsuccessful. Condensation of 2,5-dimethyl-3-hydroxy-1,4-benzoquinone VII with pyrrolidine yielded Ia in traces. Attempts to convert Ib into Ia by refluxing with 2% K_2CO_3 for twelve hours was unsuccessful, while treating it with 2% NaOH at room temperature for twelve hours yielded IV.



Synthesis of 3-methoxy-2,5-dimethyl-6-pyrrolidine-1,4-benzoquinone Ib was achieved from II by way of the known intermediates VI-VIII.[7,8] Treatment of Ia with diazomethane to get Ib, yielded several unidentified products as indicated by tlc.



Synthesis of 3-amino-2,5-dimethyl-6-pyrrolidine-1,4-benzoquinone Ic was carried out from II via the known intermediates IX-XI.[9,10] The synthesis of Ic was also attempted by treatment of Ib with methanolic ammonia under a variety of conditions. In all the above cases Ib was recovered unchanged. Intermediates IX-XI were prepared by modification of previous procedures.[9-11]



EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 Spectrometer. Nuclear magnetic resonance spectra were obtained using a Varian A-60A instrument and TMS as the internal standard. Chemical shifts are reported in δ values in parts per million (ppm) downfield from the TMS signal. Mass spectra were obtained on a Hitachi RMV-6A and on a DuPont CEC 121 B10 instrument.

2,5-Dimethyl-1,4-benzoquinone (II). - 2,5-Dimethylphenol (6.1 g, 50 mmoles) in 60 ml of ethanol was mixed with 50 ml of conc. hydrochloric acid under stirring and cooling. Sodium nitrite (3.8 g) in 10 ml of water was added dropwise (30-40 min.) at 0-5° and the mixture was allowed to stir for 1 hr. at this temperature. Copper powder (3.25 g) was then

added and the mixture was stirred for an additional 20 min. at 0-5° and allowed to reach room temperature. Steam distillation gave a yellow crystalline product which was filtered and dried to give 4.8 g (70%), mp. 118-120°, lit.[12] mp. 123-125°. IR (nujol): 1650 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.06 (d, 6H, J = 1.5 cps), 6.68 (m, 2H, J = 1.5 cps).

3-Hydroxy-6-pyrrolidine-2,5-dimethyl-1,4-benzoquinone (Ia). - V (46 mg, 0.25 mmole) in 10 ml of ether was added to 10 ml of ether containing pyrrolidine (25 mg, 0.36 mmole). A violet colored solution resulted which was kept in the dark at room temperature for 12 hrs. A violet solid separated from the solution which was washed twice with 5 ml of ether and filtered to give 40 mg (72%) of the desired product, which darkens above 125° and melts at 148-150°. IR (nujol): 3260 (OH), 1645, (quinone, C=O), 1615 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 1.75 (s, 3H, Me), 2.05 (s, 3H, Me), 1.78-2.10 (m, 4H, $-CH_2-$), 3.10-3.45 (m, 4H, -N-methylene), 7.35 (s, 1H, OH). MW (mass spec.) Calcd. for $C_{12}H_{15}NO_3$: 221·105; Found, 221·105.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65·13 ; H, 6·78 ; N, 6·33. Found: C, 64·85 ; H, 6·90 ; N, 6·18.

3-Methoxy-6-pyrrolidine-2,5-dimethyl-1,4-benzoquinone (Ib). - A-pyrrolidine acetic acid salt was prepared by neutralizing pyrrolidine solution to ether with glacial acetic acid. The resulting colorless oil was separated and washed twice with ether to remove unreacted acid or base. Then it was distilled under high vac. and the colorless oil which distilled at 55-60° at 0.2-0.5 mm. was collected. B-VIII (166 mg, 1 mmole), copper acetate (200 mg) and pyrrolidine acetic acid salt (260 mg, 2 mmole) bp. 55-60° at 0.2-0.5 mm. prepared as described[13] were dissolved in anhydrous methanol (6 ml). Oxygen was bubbled through the mixture for 3 hrs. at room temperature. The solvent was evaporated and the

resulting dark brown solid was washed well with hexane (15 ml x 5) and filtered. The hexane was evaporated to give a reddish violet oil showing a yellow and a violet spot on tlc on silica gel in methylene chloride. The yellow spot corresponded to starting material. The mixture was chromatographed on an alumina (basic) column, which was eluted first with petroleum ether then with petroleum ether:ether (1:1) and finally with ether. The first fraction gave 33 mg (20%) of the starting material, the second fraction gave Ib as a violet oil (35 mg in 19% yield). ^{1}H NMR ($CDCl_3$):δ 1.86 (s, 3H, Me), 2.03 (s, 3H, Me), 1.73 - 2.06 (m, 4H, $-CH_2-CH_2$), 3.36 - 3.86 (m, 4H, $-N-CH_2-$) 4.03 (s, 3H, CH_3). MW (mass spec.) Calcd. for $C_{13}H_{17}NO_3$: 235·1208; Found, 235·1220.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66·38 ; H, 7·23 ; N, 5·96. Found: C, 66·50 ; H, 7·12 ; N, 5·80.

2,5-Dimethyl-3-chloro-1,4-benzoquinone (IX). - To a suspension of II (3.4 g, 25 mmoles) in glacial acetic acid (40 ml), HCl gas was bubbled for 5 to 7 min. Excess of HCl was removed by bubbling nitrogen. Ferric chloride (35 ml, 30%) was added; the reaction mixture was stirred for an additional 2 to 3 min. It was poured into ice-cold water and the separated solid was collected by filtration. The dried solid was chromatographed on silica gel column using CH_2Cl_2 as eluting solvent. Elution of the red band gave 3.3 g of IX in 77% yield. It was recrystalized from ethanol as orange needles, mp. 46-47°, lit.[14] mp. 48°. IR (nujol): 1650 and, 1640 (quinone, C=O), 1610 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$): δ 2.10 (d, 3H, Me, J = 1.5 cps), 2.16 (s, 3H, Me), 6.61 (m, 1H, >C=CH<, J = 1.5 cps).

2,5-Dimethyl-3-azido-1,4-benzoquinone (X). - IX (500 mg, 3 mmoles) was dissolved in the minimum amount of boiling 95% ethanol. Then the solution was cooled under running water. Sodium azide (500 mg, 7 mmoles)

in 15 ml of water was added in one portion at room temperature. On cooling in ice there was a solid obtained, which when filtered and recrystalized from hot ethanol gave 217 mg of X in 41% yield, mp. 85-87° (dec), lit.[9] mp. 87° (dec). IR (nujol): 2100 (N≡N), 1665 (quinone, C=O), 1605 cm^{-1} (C=C); ^1H NMR ($CDCl_3$):δ 1.80 (s, 3H, Me), 2.10 (d, 3H, Me, J = 1.5 cps), 6.61 (m, 1H, Ethylene, J = 1.5 cps).

2,5-Dimethyl-3-amino-1,4-benzoquinone (XI). - X (115 mg, 0.65 mmole) was dissolved in 25 ml of 95% ethanol. Pd/C (5 mg, 10%) was added and hydrogenation was carried out at room temperature for approximately 1½ hrs. in a Parr hydrogenator. The catalyst was removed by filtration. The crude product was recrystalized from benzene/pet. ether, (97 mg, 64% yield), mp. 179-181°, lit.[10] mp. 183°. IR (nujol): 3460 and, 3360 (N<H H), 1655 and 1640 (quinone, C=O), 1605 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 1.86 (s, 3H, Me), 2.03 (d, 3H, Me, J = 1.5 cps), 4.5-4.9 (broad hump, 2H, NH_2), 6.45 (m, 1H, Ethylene).

3-Amino-2,5-dimethyl-6-pyrrolidine-1,4-benzoquinone (Ic). - A solution of XI (75 mg, 0.5 mmole) in ether (10 ml) was added to a solution of pyrrolidine (44 mg, 0.62 mmole) in ether (10 ml) and allowed to stand at room temperature in the dark for four days. The violet brown sediment that formed was washed by decantation with ether. The residue was dissolved in a minimal amount of chloroform and chromatographed on a neutral alumina column. The column was eluted with petroleum ether and finally with methylene chloride. Ic elutes first as a blue violet zone, the solvent was removed under vacuum to give 15 mg of Ic in 13% yield. ^1H NMR ($CDCl_3$):δ 1.82 (s, 3H, Me), 2.02 (s, 3H, Me), 1.74 - 2.08 (m, 4H, methylene) 3.25 - 3.64 (m, 4H, -N-methylene), 4.3 - 4.6 (broad hump, 2H, NH_2). MW (mass spec.) Calcd. for $C_{12}H_{16}N_2O_2$: 220·1212; Found, 220·1220.

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.45 ; H, 7.27 ; N, 12.72. Found: C, 65·50 ; H, 7·10 ; N, 12·38.

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