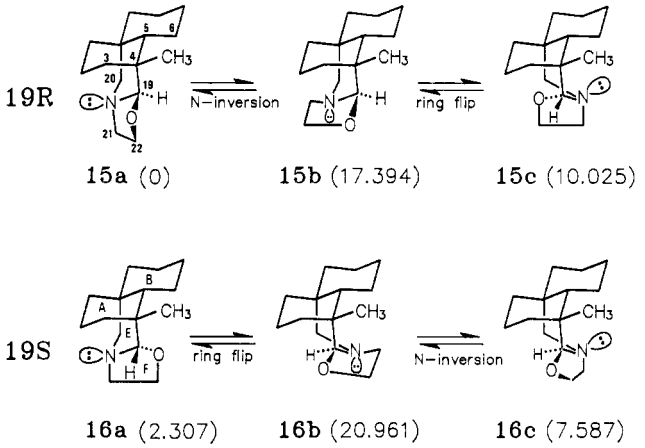
**Table II. Steric Relationships[a] in C-19 Epimers of Isoatisine**

| path | effect | relationship in 19*R* (15a) | relationship in 19*S* (16a) |
|---|---|---|---|
| O, C-19, C-4, C-5 | γ | anti | gauche |
| O, C-19, C-4, C-3 | γ | gauche | anti |
| O, C-19, N, C-20 | γ | anti | gauche |
| C-22, C-21, N, C-20 | γ | anti | gauche |
| O, C-19, C-4, C-5, C-6 | δ | extended | syn, axial |

[a] Nomenclature of ref 28.

one.[20] The absence of doubling in previous $^{13}C$ NMR spectra of isoatisine[4] may be due to the lower resolution and sensitivity with a 15- vs. a 75-MHz instrument. Alternatively, extensive recrystallization from solvents that do not permit epimerization at C-19[21] might remove the small amount of **3B** originally present from basification of the isoatisinium salt **14**. Exactly this process has been observed upon recrystallization of a C-20 epimeric mixture of homoveatchine acetates.[13] An insufficient amount of our isoatisine sample was available to permit such extensive recrystallization, which may account for its slightly lower melting point as well as the doubled $^{13}C$ signals.

Although the question of which 19-epimer of isoatisine is the most stable would seem to have been answered by X-ray analysis[9] in favor of the 19*S* isomer **15a**, as noted




above such a conclusion might be unwarranted in solution.[17,19,20] Molecular mechanics calculations[22] for the A/B/E/F ring system and the 18-methyl group of both possible C-19 epimers of isoatisine (**3**) give the relative energies shown (in kJ/mol) and indicate that E-chair conformations **15a** for the 19*R* and **16a** for the 19*S* epimers are by wide margins the lowest energy. A smaller difference in energy is calculated between the two epimers with the 19*R* isomer (**15a**) favored by only 2.3 kJ/mol over the 19*S* (**16a**). Since these correspond to trans and cis E/F ring-fusions, respectively, this relative stability is consistent with those found by experiment and calculation for other 6/5 fused ring systems such as hydrindane,[24] indolizidine,[25] and hexahydro-3*H*-oxazolo[3,4-*a*]pyridine.[26] On the other hand it is inconsistent with the suggestion that the structure of isoatisine (**3**) in the crystal (19*S*)[9] is also the more stable epimer in solution. While this discrepancy might signal the intervention of crystal packing effects, it also could reflect the accuracy limits of the molecular mechanics calculation in a heteroatom system[27] especially when the C and D rings, structural variations of which sometimes alter the chemistry of the oxazolidine ring of the C-20 diterpenoid alkaloids,[13] have been omitted from the calculations.

This ambiguity was resolved by relating the $^{13}C$ chemical shifts of **3A** and **3B** to stereochemical differences between the two most stable conformations **15a** and **16a**. As can be seen from Table II, the one δ- and four γ-effects change in a way that permits the prediction of relative chemical shifts in the two epimers. Since the *shielding* γ-effects are greater in the gauche than in the anti conformation,[28] the 19*S* epimer should have the higher field resonance at C-5, C-20, and C-22 and the lower field one at C-3. Similarly the *deshielding* δ-effect will be greatest in the synaxial conformation, thereby predicting that the 19*S* epimer will have the lower field C-6 resonance. All five of these predictions are borne out only if the 19*S* epimer is the major one in solution as well as in the crystal.[9]

In conclusion, it may be noted that the **3A**:**3B** ratio of 84:16 is very close to the 8:2 ratio reported[13] for the garryine derivatives **9**–**11**, which suggests that their major epimers might also have the 19*S* configuration. In view of the present results with isoatisine (**3**), it is probably worth reinvestigating the $^{13}C$ NMR spectra of other "nonepimeric" iso series (**5**) alkaloids such as garryine[4,13] to determine if small amounts of their 19-epimers are in fact produced if extensive recrystallization after regeneration from the iminium salts (**14** → **5**) is avoided.

**Acknowledgment.** This research was supported by the TCU Research Fund and the Tarrant County Charitable Foundation Trust. The Varian XL-300 NMR was purchased with a generous gift from Dr. Malcolm K. Brachman. Translations of the Chinese articles and of correspondence between our laboratories was kindly provided by Mr. Chen-yi Qian. The hospitality of the Department of Chemistry of the University of British Columbia and especially Professor James P. Kutney during the preparation of this manuscript is gratefully acknowledged.

(20) Agami, C.; Rizk, T. *Tetrahedron* **1985**, *41*, 537.
(21) While some 2-aryloxazolidines epimerize at the carbinolamine ether carbon even in nonpolar solvents,[20] there is disagreement on whether atisine-type alkaloids do[7] or do not.[4,8,11] Our sample of isoatisine was recrystallized from methanol, a solvent that probably[13] permits such epimerization.
(22) MM2 program of N. L. Allinger[23] available from Quantum Chemistry Exchange Program of Indiana University, Bloomington, IN 47401.
(23) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(24) Burkert, U.; Allinger, N. L. *Molecular Mechanics*, ACS. Monograph 177; American Chemical Society: Washington, DC, 1982; p 109, 177 and references cited therein.
(25) Reference 24, p 232 and references cited therein.
(26) Takeuchi, Y.; Chivers, P. J.; Crabb, T. A. *J. Chem. Soc., Perkin Trans. 2* **1975**, 51 and references cited therein.
(27) The standard deviation between experimental and calculated heats of formation is greater for heteroatom-containing molecules than hydrocarbons (ref 24, pp 180–183), although for the system most closely related to **3**, indolizidine,[25] the experimental and calculated differences in the cis and trans conformation differ by only 0.92 kJ/mol.
(28) Reference 16, pp 37–40.

## Practical Large-Scale Oxidation of 1,4-Hydroquinones to 1,4-Benzoquinones Using Hydrogen Peroxide/Catalytic Diphenyl Diselenide

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In connection with a synthesis project, we required an inexpensive source of a large quantity (>1 kg) of 2-meth-

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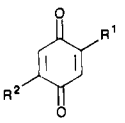
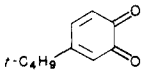
**Table I. Oxidation of Hydroquinones to Benzoquinones Using Hydrogen Peroxide and Diphenyl Diselenide**

| product | | rctn scale, mol | % yield[a] | mp, °C found | mp, °C reported |
|---|---|---|---|---|---|
|  | | | | | |
| $R^1$ | $R^2$ | | | | |
| $CH_3$ | H | 0.82 | 82 | 67.5–69.0 | 69[b] |
| $t$-$C_4H_9$ | H | 0.12 | 88 | 57.0–58.0 | 59[c] |
| $t$-$C_4H_9$ | $t$-$C_4H_9$ | 0.09 | 81 | 155.0–156.5 | 153[d] |
| Cl | H | 0.07 | 64 | 51–54 | 57[e] |
| $OCH_3$ | H | 7.25 | 90[f] | | |
|  | | 0.002 | 70[g] | 63.0–67.0 | 69[h] |

[a] Yield of recrystallized product, unless otherwise specified. All quinones were characterized by $^1H$ NMR, IR, and MS. [b] See ref 13. [c] See ref 14. [d] See ref 15. [e] See ref 16. [f] Crude yield. [g] Purified by column chromatography. [h] See ref 17.

oxy-1,4-benzoquinone for subsequent use as a Diels–Alder dienophile.[1] The only existing synthesis of this substance that might have met this need (Baeyer–Villager oxidation of vanillin to 2-methoxy-1,4-hydroquinone followed by sodium dichromate oxidation to 2-methoxy-1,4-benzoquinone[2]) afforded a crude product that was of unsatisfactory purity for this application;[3] purification of the crude 2-methoxy-1,4-benzoquinone on this scale was not practical. Other methods for the oxidation of 1,4-hydroquinones to 1,4-benzoquinones did not appear to meet our requirements, usually due to the expense of the oxidant.[4,5] We chose to develop a new method for the oxidation of 1,4-hydroquinones to 1,4-benzoquinones.

The oxidation of 1,4-hydroquinones to 1,4-benzoquinones using stoichiometric quantities of benzeneseleninic anhydride has been reported by Barton and coworkers.[4f] The practicality of the latter reaction, which suffers from the expense of the organoselenium reagent, is somewhat enhanced by the report from the same group that at least one reaction of benzeneseleninic anhydride can be rendered catalytic in the organoselenium reagent if iodoxybenzene is used to regenerate the oxidant,[6] but raises new issues involving the expense and safety[7] of the latter reagent. Encouraged by reports that organoselenium reagents, which can be generated from hydrogen peroxide and diphenyl diselenide, can be used for the oxidation of alkenes and sulfides,[8] the use of this reagent combination for benzoquinone synthesis was investigated. We report herein that a two-phase reaction mixture consisting of excess aqueous hydrogen peroxide and 0.5–1.5 mol % of diphenyl diselenide containing a phase-transfer catalyst ($n$-$Bu_4N^+HSO_4^-$) will efficiently oxidize 1,4-hydroquinones to 1,4-benzoquinones.

The details of this reaction are described in the Experimental Section, but, in brief, consist of premixing 2 equiv of aqueous hydrogen peroxide, ~0.5 mol % diphenyl diselenide, tetra-$n$-butylammonium hydrogen sulfate, and methylene chloride followed by addition in portions of the hydroquinone. For reasons we have not investigated, the reaction is most efficient if two additional small aliquots of premixed hydrogen peroxide, diphenyl diselenide, and tetra-$n$-butylammonium hydrogen sulfate in water/methylene chloride are added during the reaction. Relevant data for several quinones prepared in this manner are in Table I.

Several observations made in the course of this study are of practical interest. Diphenyl diselenide is definietly required for this reaction, the starting hydroquinone being recovered unchanged in its absence. Although in some cases the phase-transfer catalyst was not absolutely required, the reaction is faster in its presence. Dilute (~0.2 M), small scale reactions were not noticeably exothermic; the more concentrated (~2 M) large-scale reactions do achieve a spontaneous gentle reflux. Electron-poor hydroquinones fail to undergo oxidation by this method, 2,3-dicyano-1,4-hydroquinone, 2-acetyl-1,4-hydroquinone, and 2-carbomethoxy-1,4-hydroquinone being recovered unchanged after exposure to these conditions.

We have not investigated the mechanism of this reaction, but note that its close relationship to oxidations in which benzeneseleninic acid[8,9] and/or benzeneperoxyseleninic acid[10] have been implicated suggest that one or both of these species may be important catalytic intermediates. In fact, the capacity of benzeneperoxyseleninic acid to effect Baeyer–Villager oxidation of aromatic aldehydes[10] can be coupled to the current reaction, as demonstrated by the one-pot conversion of vanillin to 2-methoxy-1,4-benzoquinone in 62% yield (10-g scale) as shown:

In conclusion, the procedure described herein is an inexpensive, efficient, and experimentally simple method

(1) Pratt, D. V.; Hopkins, P. B. *Tetrahedron Lett.*, submitted for publication.

(2) Jeffreys, J. A. D. *J. Chem. Soc.* **1959**, 2153.

(3) The sensitivity of the Diels–Alder reaction of 2-methoxy-1,4-benzoquinone has been previously reported: Cavill, G. W. K.; Quinn, R. J. *Aust. J. Chem.* **1973**, *26*, 595.

(4) (a) Cason, J. *Org. React. (N.Y.)* **1948**, *4*, 305. (b) Patai, S. *The Chemistry of Quinoid Compounds, Part I*; Wiley: New York, 1974; p 111. (c) Ulrich, H.; Richter, R. In *Methoden der organischen Chemie*, 4th ed.; Müller, E., Ed.; Verlag: Stuttgart, 1977, p 44. (d) Barton, D. H. R.; Magnus, P. D.; Rosenfeld, M. N. *J. Chem. Soc., Chem. Commun.* **1975**, 301. (e) Durst, H. D.; Mack, M. P.; Wade, F. *J. Org. Chem.* **1975**, *40*, 269. (f) Barton, D. H. R.; Brewster, A. G.; Ley, S. V.; Read, C. M.; Rosenfeld, M. N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1473. (g) Barton, D. H. R.; Godfrey, C. R. A.; Morzycki, J. W.; Motherwell, W. B.; Stobie, A. *Tetrahedron Lett.* **1982**, *23*, 957. (h) Takata, T.; Tajima, R.; Ando, W. *J. Org. Chem.* **1983**, *48*, 4764. (i) Gupta, D. N.; Hodge, P.; Davies, J. E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2970.

(5) Similar in simplicity and economy to the method described herein is oxidation with sodium hypochlorite (Ishi, F.; Kishi, K. I. *Synthesis* **1980**, 706). Although we experienced difficulty in initial attempts to use the hypochlorite procedure for the preparation of 2-methoxy-1,4-benzoquinone, subsequent to the completion of these studies we learned that by adhering carefully to the advice of the latter authors to carefully control the pH of the hypochlorite reaction, it is comparable to the procedure herein.

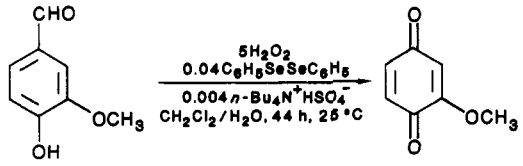
(6) Barton, D. H. R.; Morzycki, J. W.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1981**, 1044.

(7) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 511.

(8) Reich, H. J.; Chow, F.; Peake, S. L. *Synthesis* **1978**, 299.

(9) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978** *43*, 1689.

(10) Syper, L.; Mlochowski, J. *Tetrahedron* **1987**, *43*, 207.




for the oxidation of 1,4-hydroquinones to 1,4-benzoquinones on a milligram to kilogram scale.

## Experimental Section[11]

**2-Methyl-1,4-benzoquinone.** To a 1-L, three-neck flask equipped with a reflux condenser (open to atmosphere), thermometer, and magnetic stirring bar were added 0.80 g (2.5 mmol) of diphenyl diselenide, 110 mg (0.33 mmol) of tetra-*n*-butylammonium hydrogen sulfate, and 500 mL of $CH_2Cl_2$. Aqueous hydrogen peroxide (180 mL, 1.8 mol, 30%) was added and the solution was stirred vigorously until the yellow color was discharged. 2-Methyl-1,4-hydroquinone (33.3 g, 268 mmol) was added in a single portion, and the mixture was stirred vigorously for 1 h, during which time the mixture spontaneously gently refluxed and at the end of which time thin-layer chromatography (TLC) indicated complete consumption of the hydroquinone. A fresh portion of organoselenium catalyst, prepared by admixture and stirring until colorless in a separate vessel of 0.22 g (0.7 mmol) of diphenyl diselenide, 1.1 mL (11 mmol) of 30% aqueous hydrogen peroxide, 0.022 g (0.06 mmol) of tetra-*n*-butylammonium hydrogen sulfate, and 17 mL of $CH_2Cl_2$, was added to the main reaction vessel, followed by addition of 33.4 g (269 mmol) of 2-methyl-1,4-hydroquinone. After 1 h of vigorous stirring, TLC analysis again indicated consumption of the hydroquinone, and a final portion of organoselenium catalyst (again from 0.22 g of diphenyl diselenide, 1.1 mL of 30% aqeous hydrogen peroxide, 0.022 g of tetra-*n*-butylammonium hydrogen sulfate, and 17 mL of $CH_2Cl_2$) was added, followed by a final 33.3 g (268 mmol) portion of 2-methyl-1,4-hydroquinone. After 1 h of vigorous stirring, TLC analysis indicated consumption of the hydroquinone, and the reaction mixture had spontaneously cooled to 25 °C. The $CH_2Cl_2$ layer was separated, washed sequentially with three 100-mL portions of saturated aqueous sodium bicarbonate and three 200-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo. The resulting yellow solid was recrystallized from 60% aqueous ethanol to afford a first crop of yellow plates, 67.7 g, mp 67.5–69.0 °C (lit.[12] mp 69 °C), and second crop of yellow plates, 14.7 g, mp 67–68 °C, combined yield 82.4%. 2-Methyl-1,4-benzoquinone: $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.78 (1 H, d, $J$ = 10 Hz), 6.73 (1 H, dd, $J$ = 10 and 3 Hz), 6.64 (1 H, brs), 2.08 (3 H, d, $J$ = 1 Hz); IR ($CHCl_3$) 1658 $cm^{-1}$ (C=O); MS (low-resolution, EI), $m/e$ 123 ($M^+ + 1$), 122 ($M^+$), 94, 82 (100).

**2-Methoxy-1,4-benzoquinone, 1-kg Scale.** The oxidation of 2-methoxy-1,4-hydroquinone[2] on a 1-kg scale was accomplished essentially as described above for the oxidation of 2-methyl-1,4-hydroquinone, with the following changes: A 22-L, three-neck flask equipped with thermometer, reflux condenser, and overhead stirrer was charged with 7 g (22 mmol) of diphenyl diselenide, 0.7 g (2 mmol) of tetra-*n*-butylammonium hydrogen sulfate, and 4 L of $CH_2Cl_2$ and treated with 1.6 L (15.7 mol) of 30% aqueous hydrogen peroxide. After the solution was stirred vigorously until colorless, 333 g (2.4 mol) of 2-methoxy-1,4-hydroquinone was added over a period of 1.25 h at a rate sufficient to maintain gentle reflux. If the reaction became undesirably vigorous, it could be slowed by stopping or slowing the stirring rate. After an additional 1.5 h, TLC analysis indicated consumption of the hydroquinone. Fresh organoselenium catalyst, prepared by stirring in a separate vessel until colorless 4.0 g (12 mmol) of diphenyl diselenide, 20 mL (196 mmol) 30% aqueous hydrogen peroxide, 0.4 g (1 mmol) tetra-*n*-butylammonium hydrogen sulfate, and 300 mL $CH_2Cl_2$, was added, followed by 334 g (2.4 mol) of 2-methoxy-1,4-hydroquinone again over 1.25 h (to maintain reflux), with an additional 1.5 h to complete consumption of hydroquinone. A final addition of fresh organoselenium catalyst (from 4.0 g of diphenyl diselenide, 20 mL of 30% aqueous hydrogen peroxide, 0.4 g tetra-*n*-butylammonium hydrogen sulfate, and 300 mL of $CH_2Cl_2$) was added, followed by addition over 1.25 h of the final 333 g of 2-methoxy-1,4-hydroquinone and stirring an additonal 1.5 h. The $CH_2Cl_2$ layer was separated from the aqueous layer, which was extracted with four 1.6-L portions of $CH_2Cl_2$. The organic extracts were combined with the original $CH_2Cl_2$ layer, dried ($MgSO_4$), and concentrated in vacuo to afford 888 g (90%) of 2-methoxy-1,4-benzoquinone as a brown amorphous solid[12] suitable for use in Diels–Alder cycloadditions: $^1H$ NMR (80 MHz, $CDCl_3$) $\delta$ 6.7 (2 H, m), 5.9 (1 H, brs), 3.8 (3 H, s); IR ($CHCl_3$) 1680, 1650, 1595 $cm^{-1}$; MS (low resolution, EI), $m/e$ 138, 110, 108, 69 (100).

**2-Methoxy-1,4-benzoquinone from Vanillin.** A solution of 0.78 g (2.5 mmol) of diphenyl diselenide, 0.078 g (0.23 mmol) of tetra-*n*-butylammonium hydrogen sulfate, 40 mL of $CH_2Cl_2$, and 31 mL (0.30 mol) of 30% aqueous hydrogen peroxide was stirred until the yellow color was discharged (ca. 10 min) and then treated with 10 g (66 mmol) of vanillin. The mixture was stirred and cooled (ice bath) as necessary to maintain a gentle reflux. After the initially exothermic reaction subsided, the mixture was stirred for 44 h at 25 °C, at which time the layers were separated, and the organic layer was washed sequentially with 100 mL of saturated aqueous sodium bicarbonate and two 100-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo to afford 6.2 g (62%) of 2-methoxy-1,4-benzoquinone as a dark solid, mp 129–140 °C (lit[2] mp 142 °C).

**Acknowledgment.** This work was generously supported by the Searle Scholars Program and Research Corporation.

**Registry No.** 2-Methyl-1,4-hydroquinone, 95-71-6; 2-*tert*-butyl-1,4-hydroquinone, 1948-33-0; 2,5-di-*tert*-butyl-1,4-hydroquinone, 88-58-4; 2-chloro-1,4-hydroquinone, 615-67-8; 2-methoxy-1,4-hydroquinone, 824-46-4; 4-*tert*-butyl-1,2-hydroquinone, 98-29-3; 2-methyl-1,4-benzoquinone, 553-97-9; 2-*tert*-butyl-1,4-benzoquinone, 3602-55-9; 2,5-di-*tert*-butyl-1,4-benzoquinone, 2460-77-7; 2-chloro-1,4-benzoquinone, 695-99-8; 2-methoxy-1,4-benzoquinone, 2880-58-2; vanillin, 121-33-5.

(11) General procedures are described in detail elsewhere: Shea, R. G.; et al. *J. Org. Chem.* **1986**, *51*, 5243.

(12) Attempts to purify 2-methoxy-1,4-benzoquinone by recrystallization resulted in considerable decomposition. The crude product described herein sufficiently pure for use in subsequent transformations; for example, affording an 80–90% yield of the Diels–Alder adduct upon heating with excess 1,3-butadiene in benzene[3].

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(16) Clark, T. H. *Am. Chem. J.* **1892**, *14*, 553.

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