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Structural correction of the 3-methylindole oxidatively-coupled dimer

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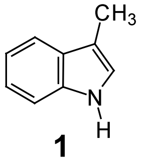
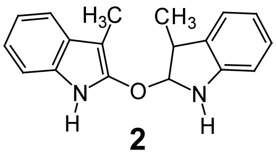
Abstract—The main product of the horseradish peroxidase-mediated oxidative coupling of 3-methylindole by H_2O_2 has been found to be the same compound previously obtained from chemical, radiolytic, and anodic oxidation of 3-methylindole and claimed to be a hexahydrofurodiindole of undefined stereochemistry (*meso* versus *d,l*). Single-crystal X-ray diffraction analysis of the compound, aimed at determining the stereochemistry, revealed that the actual product is an isomer, 7,8-dimethyl-2-oxa-4,11-diazadibenzo[*e,i*]tricyclo[5.4.0.0^{3,8}]undecane that derives from hydrolytic reorganization of the initially formed biindoline radical coupling product. © 2002 Published by Elsevier Science Ltd.

During the course of our studies on the nature of products generated in the H_2O_2-dependent oxidation of 3-alkylindoles catalyzed by horseradish peroxidase (HRP), we found that the main reaction occurring under anaerobic conditions was an oxidative coupling process. Oxidative coupling of 3-methylindole (**1**) by chemical one-electron oxidants was reported in three previous studies. In the first study (1957), oxidation by iron(III) chloride resulted in isolation of a white crystalline dimeric product analyzing for the molecular formula $C_{18}H_{18}N_2O$, and the indolinyl indolyl ether structure **2** was suggested.[1] In 1981, Tsuji and co-workers found exactly the same material from the copper(II) methoxide oxidation of 3-methylindole, but NMR characterization showed it to have a symmetrical structure.[2] The revised hexahydrofurodiindole structure **3** was claimed, and although the authors noted formation of a single diastereomer, the stereochemistry of **3** was not assigned: **3** can exist in either *meso* or *d,l* forms—both 5-5 ring fusions must be *cis*, but the relative stereochemistry off the central ring can be either *cis* (*meso*) or *trans* (*d,l*). Generation of **3** was rationalized on the basis of hydration of an initially formed 3,3′-oxidatively coupled dimer **4**, arising from coupling of two 3*H*-indol-3-yl radicals (free or metal coordinated), which in turn result from one-electron oxidation and loss of proton.[2] A decade later, pulse radiolytic one-electron oxidation of 3-methylindole was reported to give the same species **3** from hydration of **4**.[3] Recently, anodic oxidation of 3-methylindole was reported to yield the identical single diastereomer **3** (but still of undefined stereochemistry)[4] claimed to be produced from the copper(II)- and iron(III)-induced oxidations.[2]



1



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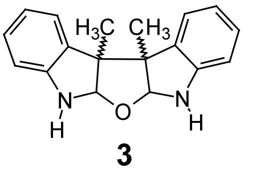

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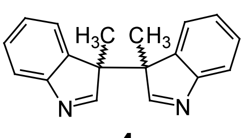

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In our own work, upon isolating once again the same dimeric product from anaerobic oxidation of 3-methylindole using HRP/H_2O_2, we endeavored to determine its stereochemistry by subjecting the readily crystallizable substance to X-ray diffraction analysis. We now report the surprising finding that the dimeric product does not have the structure **3**, but instead the isomeric structure 7,8-dimethyl-2-oxa-4,11-diazadibenzo-[*e,i*]tricyclo[5.4.0.0^{3,8}]undecane (**5**).

Thus, dropwise addition of 5 mL of 34 mM H_2O_2[5] over 1 h to a solution of **1** (65 mg, 0.5 mmol) and HRP (3 mg, 0.05 μmol) in 20 mL of a 1:1 (v/v) mixture of methanol and 0.1 M sodium phosphate (pH 7.0), followed by evaporation of methanol, extraction with

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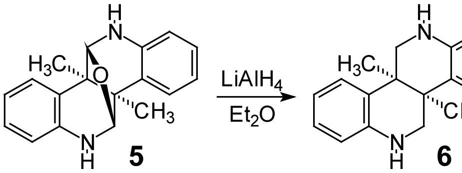
chloroform, drying (Na_2SO_4), and silica gel chromatographic separation (hexanes–EtOAc as eluant) of the evaporated residue afforded **1** (15.3 mg) and (±)-**5** (15.9 mg, 30%).[6] Further evidence for **5** derives from the finding that its reduction by $LiAlH_4$ in diethyl ether gave (±)-diamine **6**[7] in 98% yield.



Single crystals suitable for X-ray crystallographic measurement were obtained by slow evaporation of a solution of **5** in acetone–hexanes. The resulting structure is presented in Fig. 1.[8] No specific bond distances or angles warrant comment. There exists, however, weak hydrogen bonding between molecules of **5** using N(2)–H···O(1′) along the a axis (2.43 Å). The diffraction data for **5** also suggest the crystal selected for study was indeed the *S*,*S* enantiomer as shown in Fig. 1.

The latter structure may arise from equilibration of the bis-carbinolamine **7** with the bis-carbinolamine **9** via the intermediacy of ring-opened bis-aldehyde **8** (Scheme 1). Bridged ether **5** could represent a thermodynamic sink with respect to the more strained postulated ether **3**, and derives from the *d,l* diastereomer of the initial indole ring oxidatively coupled product **4**.

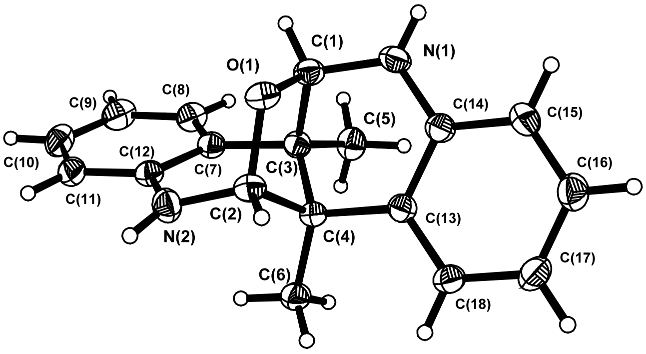


Figure 1.

The *meso* versus *d,l* nature of initial dimer **4** is permanently established at the point of C–C bond formation in the indole ring oxidative coupling. This coupling could well be diastereoselective to favor *d,l*-**4**, which can be transformed to **5** (note that the *meso* analog of **5** is geometrically forbidden). However, at least some *meso*-**4** in the initial oxidative coupling should be generated. In fact, the crude NMR spectrum of the product mixture before chromatographic separation indicated that **5** was indeed the major product, but that a minor product was also present,[9] exhibiting ^1H NMR resonances consistent with the meso diastereomer of carbinolamines **7** or **9**. No evidence for the previously claimed structure **3** (either diastereomer) could be found.

In summary, we report here a correction to the literature in regard to the nature of the common crystalline product formed from oxidation of 3-methylindole by one-electron oxidants. It should be noted that the chemistry considered here relates only to this structural question—the overall nature of reaction products, which becomes quite complicated in the presence of O_2, will be discussed later.

Acknowledgements

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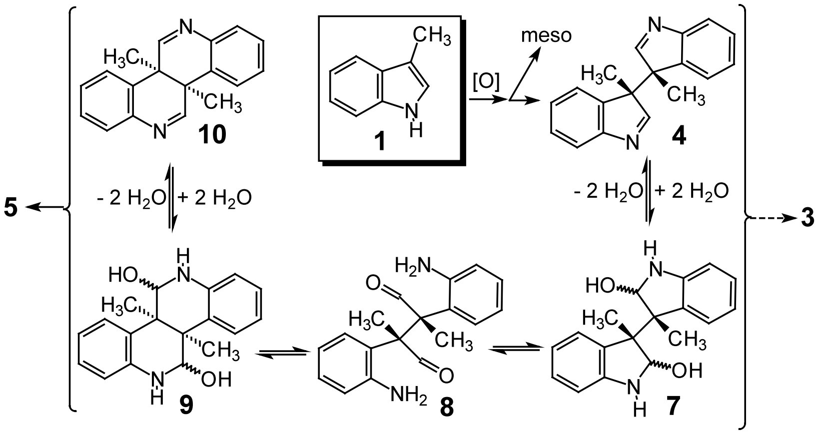

Scheme 1.

6. **5**: mp 202–203°C [lit.[2] 202°C]; ^{1}H NMR (CDCl$_3$) δ 1.35 (s, 6H), 4.93 (br d, 2H, $J=4.3$ Hz, exchangeable, NH), 4.99 (d, 2H, $J=4.3$ Hz, becomes a singlet on adding D$_2$O), 6.57 (dd, 2H, $J=1.5$, 8.0 Hz), 6.84 (dt, 2H, $J=1.5$, 8.0 Hz), 7.12 (dt, 2H, $J=1.5$, 8.0 Hz), 7.29 (dd, 2H, $J=1.5$, 8.0 Hz); ^{13}C NMR (APT, CDCl$_3$) δ 13.2 (–), 43.6 (+), 95.7 (–), 115.1 (–), 119.5 (–), 126.5 (–), 128.0 (–), 128.8 (+), 141.6 (+); HRMS (FAB) calcd for $C_{18}H_{19}N_2O$ (M+1) 279.1497, found 279.1504.
7. **6**: colorless viscous oil that solidified on standing; ^{1}H NMR (CDCl$_3$) δ 1.39 (s, 6H), 3.01 (d, 2H, $J=12.0$ Hz), 3.66 (d, 2H, $J=12.0$ Hz), 3.98 (br, s, 2H, NH), 6.50 (d, 2H, $J=7.5$ Hz), 6.71 (t, 2H, $J=7.5$ Hz), 7.04 (t, 2H, $J=7.5$ Hz), 7.28 (d, 2H, $J=7.5$ Hz); ^{13}C NMR (APT, CDCl$_3$) δ 21.1 (–), 37.1 (+), 52.8 (+), 114.2 (–), 117.3 (–), 126.6 (+), 127.2 (–), 127.5 (–), 143.4 (+); HRMS (FAB) calcd for $C_{18}H_{20}N_2$ 264.1626, found 264.1626.
8. Crystal data for **5**: $C_{18}H_{18}N_2O$, $M=278.34$, orthorhombic, $Pna2(1)$, $a=8.9399(8)$, $b=20.4379(19)$, $c=7.5443(7)$ Å, $V=1378.4(2)$ Å^3, $Z=4$, $D_{\text{calcd}}=1.341$ g/cm^3, Final R indices $[I>2\sigma(I)]$ $R_1=0.0303$, $wR_2=0.0683$, GoF = 1.017. Full crystallographic details have been deposited with the Cambridge Crystallographic Data Centre: CCDC reference number 190245.
9. The minor product was found with the NH and CH signals appearing at 5.27 (br, s) and 5.31 (s) in CDCl$_3$, and the CH signal appearing at 5.11 ppm (d, $J=2.4$ Hz) in DMSO-d_6, respectively. The ratio of **5** versus the minor product was ~10:1.