that either α-carbon radical formation via α-deprotonation does not occur or that second electron transfer from the α-carbon radical occurs faster than does cyclopropyl ring cleavage.

Incubation of purified mitochondrial MAO with *trans*-1-(aminomethyl)-2-phenylcyclopropane (1) cleanly produced only one product, identified as *trans*-2-phenylcyclopropanecarboxaldehyde, the oxidation and hydrolysis product without ring cleavage (the hydrolysis product of 3). A kinetic analysis showed that 1 is a good substrate for MAO with K_m = 1.41 mM and k_{cat} = 22 min^{-1}.[22] No inactivation of the enzyme occurred even at a concentration of 20 mM of 1 for 3 h. Chemical model studies[23] of the fate of synthesized radical 2 (in the absence of a hydrogen atom donor) showed that no 2-phenylcyclopropanecarboxaldehyde is formed, only cyclopropyl ring cleavage products. These results suggest that either radical 2 is not an intermediate in the MAO-catalyzed oxidation of 1 or, if it is, second electron transfer to the flavin semiquinone occurs at a rate considerably faster than that for the opening of the cyclopropyl ring of 2. The rate of cyclopropyl ring opening in this case, however, should be somewhat slower than that measured for the cleavage of the 2-phenylcyclopropylcarbinyl radical[21] because of the amino group stabilization energy, which has been determined to be about 10 kcal/mol.[24] Also, it has been shown by Laurie et al.[25] that cyclopropylcarbinyl radicals to which radical-stabilizing groups have been attached can be quite stable. Another possible explanation for lack of ring opening is that because of constraints at the active site of the enzyme there is improper overlap between the cyclopropane bond and the carbon radical, thereby slowing the rate of this ring cleavage.

Experimental Section

Reagents and Enzyme. All reagents are from Aldrich Chemical Co., Inc. Mitochondrial monoamine oxidase was isolated from beef liver and assayed as previously reported.[9]

General Methods. Melting points are uncorrected. Elemental analyses were done by Oneida Research Services (Whitesboro, NY).

***trans*-2-Phenylcyclopropanecarboxamide.** *trans*-2-Phenylcyclopropanecarboxylic acid (2.4 g, 14.8 mmol), anhydrous potassium carbonate (4.1 g, 30 mmol), and thionyl chloride (19.0 g 162.8 mmol) were brought to reflux for 1 h. Excess thionyl chloride was removed in vacuo, and then the resulting liquid was added dropwise over 15 min to ammonia hydroxide (10 mL) at 0-5 °C. The amide was extracted with $CHCl_3$ and dried (Drierite), and the solvent was evaporated to give the product (2.2 g, 92%) as a white solid: mp 197-198 °C; ^1H NMR (DMSO-d_6) δ 1.10-1.20 (m, 1 H), 1.40-1.50 (m, 1 H), 1.85-2.00 (m, 1 H), 2.25-2.40 (m, 1 H), 6.80 (s, 1 H), 7.10-7.40 (m, 5 H), 7.61 (s, 1 H). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.53; H, 6.83; N, 8.70. Found: C, 74.01; H, 6.97; N, 8.62.

***trans*-1-(Aminomethyl)-2-phenylcyclopropane (1).** To a solution of *trans*-2-phenylcyclopropanecarboxamide (2.2 g, 13.7 mmol) in THF (20 mL) was added $LiAlH_4$ (0.65 g, 17 mmol), and the mixture was brought to reflux. After 2 h the reaction was quenched with water (5 mL), and filtered, the THF solution was dried, and the solvent was treated with HCl gas. The solvent was removed in vacuo, and the resulting colorless solid was recrystallized twice from 1:1 ethanol-ether to give 1 as colorless crystals (2.0 g, 74%): mp 192-193 °C; ^1H NMR ($CDCl_3$-DMSO-d_6 (4:1), relative to Me_4Si) δ 1.00-1.10 (m, 1 H), 1.45-1.60 (m, 1 H), 1.90-2.10 (m, 1 H), 2.80-3.05 (m, 3 H), 7.05-7.35 (m, 5 H), 8.50 (s, 2 H); ^{13}C NMR ($CDCl_3$-DMSO-d_6 (4:1), relative to Me_4Si) δ 15, 21, 23, 45, 131, 132, 134, 148. Anal. Calcd for $C_{10}H_{14}ClN$: C, 65.40; H, 7.63; N, 7.63. Found: C, 65.26; H, 7.76; N, 7.52.

Incubation of Monoamine Oxidase with 1. Compound 1 (60 μL of a 25 mM solution in 250 mM Tris-HCl buffer, pH 9.0) and 2 μM MAO (60 μL in the same buffer) were incubated at room temperature. After 2 h, 60 μL of $CHCl_3$ and 60 μL of 5% HCl were added. The mixture was shaken well for 5 min and centrifuged, and the organic layer was used for GC analysis on a HP5880A GC with flame ionization detector and a HP cross-linked methyl silicone capillary column (gradient column temperature was from 50 to 250 °C at a rate of 20 °C/min; detector and injector port temperatures were 250 °C). Only *trans*-2-phenylcyclopropanecarboxaldehyde was observed. Neither of the expected ring cleavage products, 4-phenylbutanal (cleavage and reduction) or 2-hydroxy-5-phenyltetrahydrofuran[23] (cleavage and oxidation), was detected.

Attempted Inactivation of Monoamine Oxidase with 1. Compound 1 (final concentration 20 mM) was incubated with MAO (2 μM) in 100 mM sodium phosphate buffer, pH 8.0, at room temperature. Periodically over 3 h aliquots (20 μL) were removed and assayed for remaining enzyme activity.

Acknowledgment. We are grateful to the National Institutes of Health (GM32634) for financial support of this research.

(22) K_m and k_{cat} values for benzylamine, an excellent substrate for MAO B, were determined under these conditions to be 0.18 mM and 162 min^{-1}, respectively.

(23) Zelechonok, Y.; Silverman, R. B. *J. Org. Chem.*, in press.

(24) Burkey, T. J.; Castelhano, A. L.; Griller, D.; Lossing, F. P. *J. Am. Chem. Soc.* **1983**, *105*, 4701-4703.

(25) Laurie, D.; Lucas, E.; Nonhebel, D. C.; Suckling, C. J.; Walton, J. C. *Tetrahedron* **1986**, *42*, 1035-1045.

Highly Regioselective Bromination of 2,3-Dimethylanisole with *N*-Bromosuccinimide

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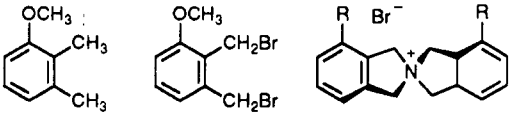
Introduction

The free-radical side-chain bromination of 2,3-dimethylanisole (1) could be a possible route to 2,3-bis(bromomethyl)anisole (2), a known precursor of the spiroindolinium salt 3 (R = OCH_3).[1] Compound 2 was



1 2 3, R = OCH_3, NO_2

prepared previously by multistep synthesis including oxidation of 1 to methoxyphthalic acid, conversion to the anhydride, and reduction of the latter to 2,3-bis(hydroxymethyl)anisole, followed by the treatment with phosphorus tribromide.[1] At the same time, the free-radical bromination of 2,3-dimethylnitrobenzene with NBS did give the corresponding bis(bromomethyl) derivative (although in low yield) which was also converted to salt 3 (R = NO_2).[1] It is for this reason that we examined the reaction of 1 with NBS expecting to obtain a mixture containing reasonable amounts of the desired compound 2. However, the experimental findings revealed rather unexpected results.

Results and Discussion

When a mixture of 1 (2 equiv), NBS (1 equiv) and benzoyl peroxide (0.01 equiv) was heated under reflux in

(1) Brewster, J. H.; Jones, R. J., Jr. *J. Org. Chem.* **1969**, *34*, 354.

0022-3263/92/1957-6374$03.00/0

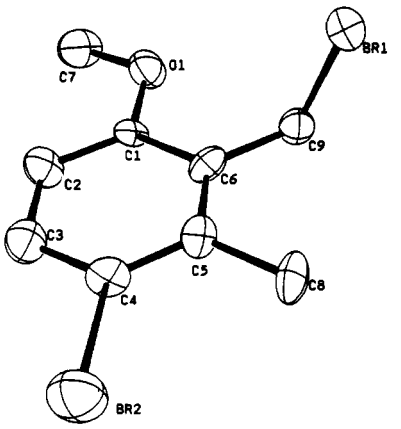
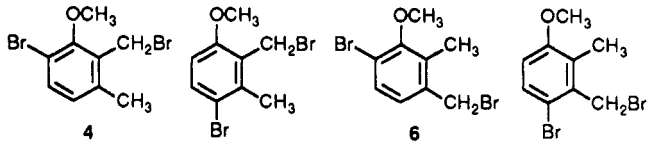


Figure 1. ORTEP diagram of **5**. Hydrogen atoms have been omitted for clarity.

CCl_4, GC and GC/MS monitoring of the reaction showed that two bromine atoms were consecutively incorporated into **1**. The intermediate monobrominated product gradually disappeared from the reaction mixture, and eventually the sole product containing two bromine atoms (according to MS data) was isolated in 90% yield of pure material. The data for the product (see Experimental Section) show one bromine is on the ring ortho or para to the methoxy group, but one cannot distinguish among four possible isomers **4**–**7**. An X-ray determination was therefore made to unequivocally show that the product is **5**.



X-ray analysis revealed that one bromine atom is incorporated into the methyl group ortho to the methoxy group, and the second bromine is in the para position of the ring with respect to the methoxy group (Figure 1).[2] See supplementary material for crystal data, bond distances and angles, and atomic parameters (x, y, z and B_{iso}). The values of all C–C, C–O, C–Br bond distances and C–C–C, C–O–C, C–C–Br angles are in perfect agreement with those known for various bromo-, methoxy-, and bromomethyl-substituted benzenes.[3-5]

The reaction of **5** with NBS (1 equiv) in the presence of benzoyl peroxide (1 mol %) in CCl_4 at reflux temperature also occurs regiospecifically and gives rise to 4-bromo-2,3-bis(bromomethyl)anisole (**8**) in quantitative yield. The structure of **8** is confirmed by MS and NMR data (see Experimental Section). Alternatively, compound **8** can also be obtained by reacting **1** with 3 equiv of NBS. In this case, the yield of **8** is also nearly quantitative. Kinetic plots indicate that the reaction proceeds in a consecutive manner (Figure 2). As has already been mentioned, the formation of the dibromo derivative **5** also occurs through the intermediate monobrominated compound. To determine its structure, the reaction of **1** with NBS (2 or 3 equiv) was stopped when the reaction mixture

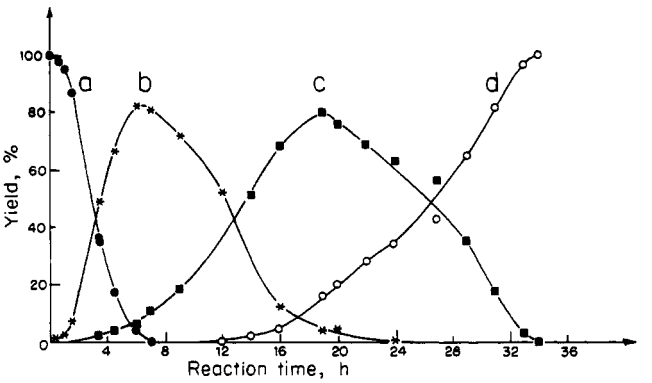
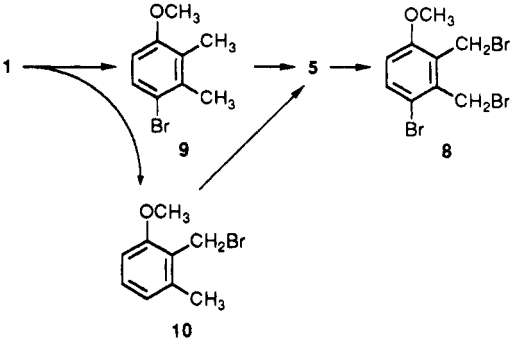


Figure 2. Free-radical bromination of 2,3-dimethylanisole (**1**) with *N*-bromosuccinimide (NBS) in CCl_4 (1:NBS:BP = 1:3:0.01) at reflux temperature: (a) **1**, (b) **9**, (c) **5**, (d) **8**.

contained mainly monobrominated product (ca. 6–7 h; see Figure 2). The ^1H NMR spectrum showed that ring bromination occurs initially, affording 4-bromo-2,3-dimethylanisole (**9**) (singlets of two nonequivalent CH_3



groups and a CH_3O group, and also doublets of the ortho aromatic protons are observed in the spectrum of **9**). The position of bromine in the ring is established on the basis that **9** is then transformed to **5**. It should be noted that according the GC/MS data, the formation of **9** is always accompanied by the parallel formation of its isomer (up to 10%). Eventually, both **9** and this isomer are converted to **5**; i.e., the impurity does not affect the selectivity for the formation of **5**. Therefore the isomeric product is, most probably, 2-(bromomethyl)-3-methylanisole (**10**). This assignment is also confirmed by the comparison of mass spectra of **9** and **10**. Unlike **9**, which has an abundant molecular ion peak [m/z 214 (^{79}Br), 100%], the intensity of the same peak in the MS of **10** is only ca. 20% and the molecular ion readily loses bromine to give an ion with m/z 135 (100%).

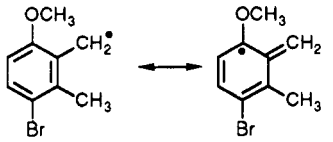
The reaction of **1** with NBS (1 equiv), carried out under the same conditions but in the absence of the radical initiator, occurs at an appreciably lower rate and gives the ring-brominated product **9**[6] contaminated with a small amount of **10** (ca. 10%). In this case, the subsequent side-chain bromination to **5** and **8** does not occur. The isomeric **9** and **10** display very similar chromatographic behavior, and it is therefore difficult to separate them. However, the admixture of aryl halide **10** can be easily removed from aryl halide **7** by reacting the mixture of these compounds with pyridine in diethyl ether at reflux temperature, thus enabling one to obtain pure **9**.

The selective conversion of **9** to **5** may be due to resonance stabilization of the radical intermediate (**11**) by the

(2) Krigbaum, W. R.; Chatani, Y.; Barber, P. G. *Acta Crystallogr.* **1970**, *B26*, 97.
(3) Milledge, H. J.; Plant, L. M. *Acta Crystallogr.* **1960**, *13*, 285.
(4) Marsau, M. P. *Acta Crystallogr.* **1965**, *18*, 851.
(5) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(6) Electrophilic bromination of **1** with NBS catalyzed by $HClO_4$ also gives **9** in almost quantitative yield: Goldberg, Yu.; Alper, H. *J. Org. Chem.*, submitted.

methoxy group. Radical generation at the methyl group located ortho to bromine would result in a less favored situation.



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In conclusion, the reaction of 2,3-dimethylanisole with NBS in the presence of benzoyl peroxide proceeds with remarkable regioselectivity and results in the formation of **5** or **8** in almost quantitative yield using 2 or 3 equiv of NBS, respectively. Mono-ring-brominated derivative **9** can also be obtained in high yield by carrying out the reaction of **1** with NBS in the absence of a radical initiator.

Experimental Section

2,3-Dimethylanisole, NBS, and benzoyl peroxide were purchased from Aldrich Chemical Co. and were used as received. CCl_4 was dried over 4A molecular sieves. Amberlyst 15 (Fluka) was dried in vacuo (0.2 mmHg) at 50 °C for 4 h prior to use.

^1H NMR spectra were obtained at 200 MHz in $CDCl_3$, and GC analyses were carried out on a column packed with 1.5% OV-17 + 1.95% OV-210 on Chromosorb W-HP (100–120 mesh). Melting points are uncorrected.

4-Bromo-2-(bromomethyl)-3-methylanisole (5). A stirred mixture of 2,3-dimethylanisole (6.8 g, 0.05 mol), NBS (17.8 g, 0.1 mol), and benzoyl peroxide (121 mg, 0.5 mmol, 1 mol %) in CCl_4 (70 mL) was refluxed until complete consumption of the starting material (ca. 6 h) and intermediate mono-ring-brominated product **9** (ca. 28 h, GC monitoring). The reaction mixture was cooled to rt, succinimide was filtered, and the solvent was removed on a rotary evaporator at rt to give 13.9 g (95%) of crude **5**. Recrystallization of the latter from a 9:1 hexane–diethyl ether mixture afforded 13.1 g (yield: 90%) of **5** as slightly yellowish needles: mp 72–73 °C; ^1H NMR δ 2.45 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 4.63 (s, 2 H, CH_2Br), 6.62 (d, 2 H, J = 8.4 Hz), 7.45 (d, 1 H, J = 8.4 Hz; MS m/z (rel abundance) 292 [8, M^+ (^{79}Br)], 213 (100, M^+ – Br), 183 (42), 104 (51), 103 (20), 91 (32), 89 (10), 77 (14), 65 (20), 63 (14), 51 (14), 39 (18). Anal. Calcd for $C_9H_{10}Br_2O$: C, 36.77; H, 3.43. Found: C, 36.73; H, 3.40. Note: compound **5** is a rather strong lachrymator.

2,3-Bis(bromomethyl)-4-bromoanisole (8). A mixture of **5** (2.94 g, 10 mmol), NBS (1.78 g, 10 mmol), and benzoyl peroxide (24 mg, 0.1 mmol, 1 mol %) in CCl_4 (15 mL) was stirred and heated under reflux. After reaction was complete (ca. 3 h, GC monitoring), the mixture was cooled to rt, succinimide was filtered, and CCl_4 was evaporated in vacuo to afford 3.71 g (99%) of crude **8**. Recrystallization from hexane gave 3.65 g (98%) of **8**: mp 98–99 °C; ^1H NMR δ 3.87 (s, 3 H, OCH_3), 4.72 (s, 2 H, CH_2Br), 4.75 (s, 2 H, CH_2Br), 6.74 (d, 1 H, J = 8.4 Hz), 7.49 (d, 1 H, J = 8.4 Hz); MS m/z (rel abundance) 370 [M^+ (^{79}Br), 3], 291 (50), 212 (48), 182 (12), 169 (15), 103 (50), 90 (27), 89 (28), 77 (11), 63 (23), 51 (14). Anal. Calcd for $C_9H_9Br_3O$: C 28.99; H, 2.43. Found: C, 28.98; H, 2.46. Alternatively, compound **8** was obtained by reaction **1** (1.36 g, 10 mmol), NBS (5.34 g, 30 mmol), benzoyl peroxide (24 mg, 0.1 mmol), and CCl_4 (15 mL) for 34 h at reflux temperature. Yield: 3.49 g (94%).

4-Bromo-2,3-dimethylanisole (9). A mixture of **1** (1.36 g, 10 mmol), NBS (1.78 g, 10 mmol), and CCl_4 (15 mL) was stirred and heated under reflux for 36 h. After cooling to rt, succinimide was filtered and CCl_4 was removed under vacuum. The residue (2.1 g) containing ca. 90% of **9** and ca. 10% of **10** (GC data) was dissolved in diethyl ether (20 mL) and pyridine (1 mL) was added. The mixture was stirred at reflux temperature for 4 h. A white solid (the quaternary salt derived from **10** and pyridine) was filtered, and the solvent was evaporated in vacuo. To the solution of the residue in acetone (10 mL) was added Amberlyst 15 (3 g)[7] in order to remove excess pyridine. The mixture was stirred at room temperature for 30 min and filtered, acetone was evaporated, and the residue was distilled under vacuum to give 1.75 g (81%) of **9**: bp 58–59 °C/0.2 mmHg; ^1H NMR δ 2.18 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 6.57 (d, 1 H, J = 9.0 Hz), 7.32 (d, 1 H, J = 9.0 Hz); MS m/z (rel abundance) 214 [M^+ (^{79}Br), 100], 199 (M^+ – Me, 51), 171 (16), 135 (37), 120 (15), 105 (44), 104 (11), 103 (15), 92 (53), 91 (56), 79 (11), 77 (18), 62 (21), 61 (13), 51 (18). Anal. Calcd for $C_9H_{11}BrO$: C, 50.26; H, 5.16. Found: C, 50.34; H, 4.99. **10**: MS m/z (rel abundance) 214 [M^+ (^{79}Br), 20], 135 (M^+ – Br, 100), 105 (75), 103 (14), 91 (26), 79 (22), 77 (16), 65 (11). A white solid resulted from the quaternization of pyridine with **10**: mp 205–207 °C dec; ^1H NMR (DMSO-d_6/TMS) 2.45 (s, 3 H), 3.76 (s, 3 H), 5.85 (s, 2 H), 7.0–7.4 (m, 3 H), 8.1–9.0 (m, 5 H). Anal. Calcd for $C_{14}H_{16}BrNO$: C, 57.16; H, 5.48. Found: C, 57.50; H, 5.62.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for support of this research.

Supplementary Material Available: Table of crystal data, stereoview of the packing diagram, and experimental details of X-ray analysis of **5** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) Amberlyst 15 is a registered trade mark of Rohm and Haas; exchange capacity: 4.6 mg-equiv of H^+/g.