The Oxidation of Norbornadiene and Some Derivatives using *Pseudomonas* sp.

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Norbornadiene is oxidized by a *Pseudomonad* to give the diol (**2**) (35%) while 7-phenylnorbornadiene furnishes 3-norbornadienylcyclohexa-3,5-diene-1,2-diol (**10**) (41%) on incubation with the same organism; cyclization reactions involving the acetonide (**15**) have been investigated.
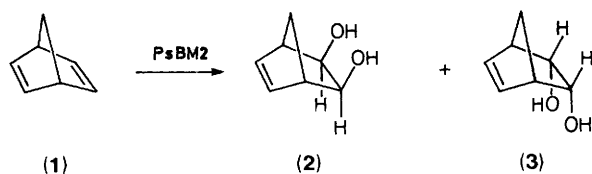
The oxidation of benzene,[1] toluene,[2] other monocyclic aromatic compounds,[3] and bicyclic aromatic substances[4] using *Pseudomonas* sp. has been the focus of much attention over the past five years.

We have found that a *Pseudomonas* sp. (strain BM2) which is capable of oxidizing various derivatives of benzene into cyclohexadienediols also oxidized norbornadiene (**1**) to give the *cis-exo*-diol (**2**) (35%) and the *cis-endo*-diol (**3**) (3%) (Scheme 1). The identity of the two diols was established by comparison of the spectral data with those from authentic samples.[5] Presumably the oxidation is accomplished by a dioxygenase enzyme within the whole cell, as in the oxidation of indene and homologues by *Pseudomonas* strains.[6,7]

Pseudomonas BM2 converted benzonorbornadiene (**4**) into the optically active phenol (**5**) and the catechol (**6**) in very low yields (>1%). Small amounts of the alcohol (**7**) were observed in some runs and from one reaction the material was isolated and identified by NMR spectroscopy.[8] The formation of the phenol (**5**) and the catechol (**6**) is easily explained if the dienediol (**8**) is an intermediate in the process. The origin of the alcohol (**7**) is more obscure. Oxidation of benzonorbornadiene with a mutant strain (87E2) of BM2 with much reduced dihydrodiol dehydrogenase activity gave the phenol (**5**) (4%), the catechol (**6**) (2%), and the dienediol (**8**) (1%).
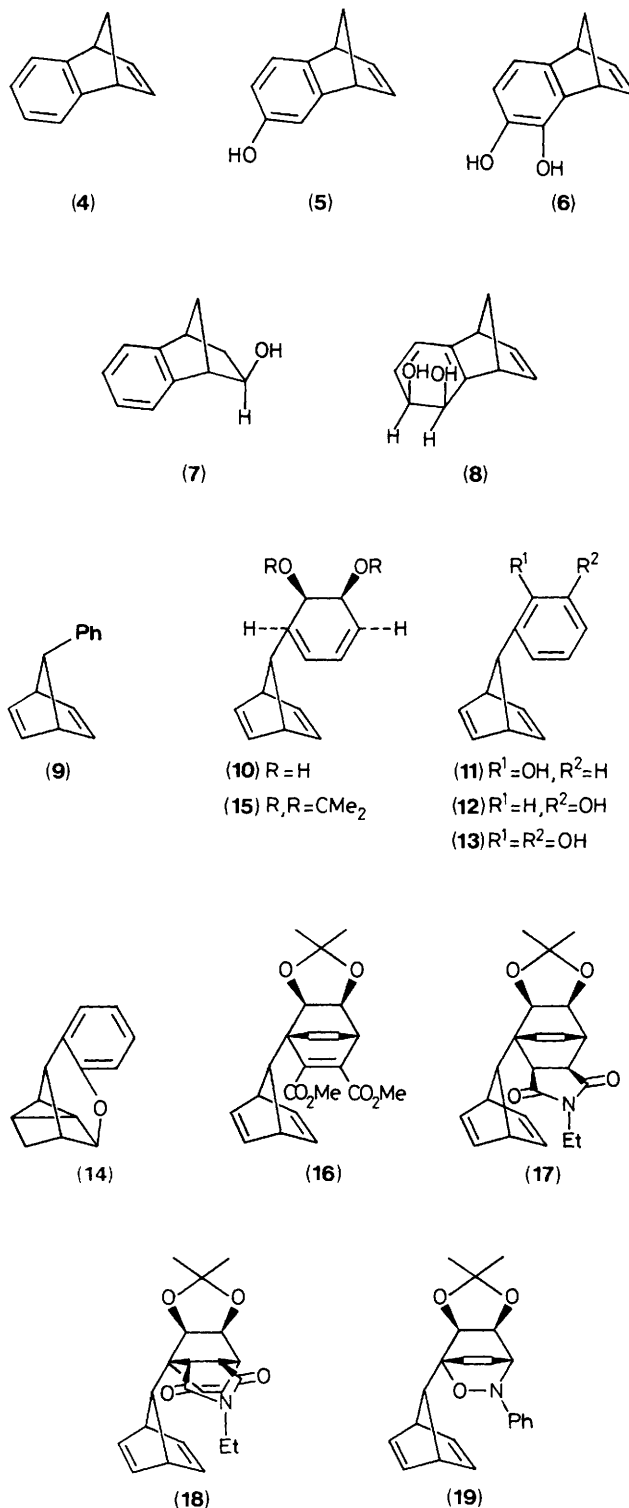
Oxidation of 7-phenylnorbornadiene (**9**) with *Pseudomonas* BM2 demonstrated that the phenyl ring was, again, the more susceptible moiety. The major products obtained from this biotransformation were 3-(norbornadien-7-yl)cyclohexa-3,5-diene-1,2-diol (**10**) (41%), the phenols (**11**) (4%) and (**12**) (1%), and the catechol (**13**) (7%). The relatively good yield of the dienediol (**10**), m.p. 90—93 °C, which could be readily purified by chromatography, allowed further chemical transformations of this chiral compound to be undertaken.

Treatment of the dienediol (**10**) with Amberlyst 15 resin in diethyl ether gave the phenols (**11**) and (**12**) (ratio 10 : 1, yield 56%) and also the interesting polycyclic compound (**14**) (42%). The structure of the compound (**14**) [which was also formed in 49% yield on treatment of the phenol (**11**) with Amberlyst 15 resin] was established by NMR spectroscopy: δ_H (CDCl$_3$) 7.14—6.72 (4H, m, aromatic C–H), 4.48 (1H, dd, *J* 1.6, 1.5 Hz, 2-H), 2.78 (1H, t, *J* 1.5, 1.5 Hz, 7-H), 2.04 (1H, m, *J* 1.6, 1.5, 1.5, 1.2, 1.0, 0.8 Hz, 1-H), 1.8—1.7 (2H, m, 6 *exo*-H and 4-H), 1.67 (1H, dt, 6 *endo*-H), 1.4—1.3 (2H, m, 3-H and 5-H); δ_C (CDCl$_3$) 152.9, 127.9, 127.7, 126.5, 119.7, and 115.4 (aromatic C); 81.0 (2-C), 43.7 (7-C), 31.1 (6-C), 30.6 (1-C), 22.8 (4-C), 14.9 (3-C), 14.1 (5-C).

(4)   (5)   (6)

(7)   (8)

(9)   (10) R = H   (11) R^1=OH, R^2=H
             (15) R,R=CMe$_2$ (12) R^1=H, R^2=OH
                                  (13) R^1=R^2=OH

(14)   (16)   (17)

(1)   (2)   (3)

PsBM2 = *Pseudomonas* BM2

Scheme 1

(18)   (19)

Formation of the acetonide (**15**) (65%) followed by reaction of this compound with dimethylacetylene dicarboxylate in water[9] furnished the polycyclic compound (**16**) (65%). The Diels–Alder products (**17**) (42%) and (**18**) (27%) were isolated following reaction of the acetonide (**15**) with *N*-ethylmaleimide in water while under similar reaction conditions nitrosobenzene and the acetonide (**15**) combined to afford the adduct (**19**) (66%). The structures of compounds (**17**)—(**19**) were confirmed by NOE experiments.

Note that the absolute configuration of compounds (**5**)—(**8**) and the enantiomeric excesses (e.e.) (if any) are, as yet, unknown. One enantiomer is depicted here for the sake of clarity. From the precedent in the literature[10] it is likely that the diol (**10**) [CD: (0.24 mM in methanol) $\Delta\varepsilon$ +2.75 (272 nm), −1.14 (237 nm) shoulder, −6.15 (209.5 nm); $\lambda_{max.}$ 271 (ε 5420)], and hence the compounds (**15**)—(**19**), possess the absolute configurations depicted in the formulae. The optical purities of the diol (**10**), the acetal (**15**), and the adduct (**17**) were judged to be >95% e.e. by a combination of ^{1}H NMR experiments using tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) as the chiral shift reagent. Significant downfield shifts were observed for some protons [*e.g.* the NCH_2CH_3 signal in adduct (**17**)], but no evidence for the formation of diastereoisomeric complexes could be found. The tricyclic compound (**14**) was not optically active, as expected if the phenol (**11**) is an intermediate in the cyclization process.

This study shows firstly, that dioxygenase enzymes in some *Pseudomonas* sp. are capable of oxidizing the alkene unit in norbornadiene. Secondly, that in two norbornadiene derivatives which contain an aryl ring, the aromatic unit is attacked preferentially. Thirdly, 7-phenylnorbornadiene is oxidized to the corresponding cyclohexadienediol quite efficiently and the latter compound undergoes a variety of inter- and intramolecular cyclisation reactions.

References

1 S. V. Ley and F. Sternfeld, *Tetrahedron Lett.*, 1988, **29**, 5305; S. V. Ley, M. Parra, A. J. Redgrave, F. Sternfeld, and A. Vidal, *ibid.*, 1989, **30**, 3557.

2 T. Hudlicky, H. Luna, G. Barbieri, and L. D. Kwart, *J. Am. Chem. Soc.*, 1988, **110**, 4735.

3 I. C. Cotterill, C. A. Pittol, R. J. Pryce, S. M. Roberts, G. Ryback, V. Sik, and J. O. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1160; H. G. Davies, R. H. Green, D. R. Kelly, and S. M. Roberts, 'Biotransformations in Preparative Organic Chemistry: the Use of Isolated Enzymes and Whole Cells in Organic Synthesis,' Academic Press, London, 1989, pp. 195—6; T. Hudlicky, H. Luna, J. D. Price, and F. Rulin, *Tetrahedron Lett.*, 1989, **30**, 4053.

4 D. R. Boyd, R. A. S. McMordie, H. P. Porter, H. Dalton, R. O. Jenkins, and O. W. Howarth, *J. Chem. Soc., Chem. Commun.*, 1987, 1722.

5 Y. F. Shealy and J. D. Clayton, *J. Am. Chem. Soc.*, 1969, **91**, 3075.

6 D. R. Boyd, R. A. S. McMordie, N. D. Sharma, H. Dalton, P. Williams, and R. O. Jenkins, *J. Chem. Soc., Chem. Commun.*, 1989, 339.

7 L. P. Wackett, L. D. Kwart, and D. T. Gibson, *Biochemistry*, 1988, **27**, 1360.

8 D. J. Sandman, K. Mislow, W. P. Giddings, J. Dirlam, and G. C. Hanson, *J. Am. Chem. Soc.*, 1968, **90**, 4877.

9 P. A. Grieco, K. Yoshida, and P. Garner, *J. Org. Chem.*, 1983, **48**, 3137; R. Breslow, U. Maitra, and D. Rideout, *Tetrahedron Lett.*, 1983, **24**, 1901.

10 H. Ziffer, K. Kabuto, D. T. Gibson, V. M. Kobal, and D. M. Jerina, *Tetrahedron*, 1977, **33**, 2491.