Biooxidations of some *N*-Arylpiperidines and Related Compounds using *Beauveria sulfurescens*

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Beauveria sulfurescens ATCC 7159 oxidized the *N*-arylamines **3**, **4**, **7**, **13**, **18**, **20**, **22** at the 4-position with good selectivity and in 34–66% yield.

The oxidation of organic compounds at ostensibly non-activated positions using selected microorganisms is a powerful technique that has proved to be particularly useful for the introduction of additional functionality into certain structural types. For example the regio- and stereo-selective hydroxylation of steroids[1] and alkaloids[2] has been studied in some depth.

However when other, often simpler, structural types are subjected to such a biotransformation the position of oxidation is almost invariable difficult to predict[3] and only crude models of the oxidation process are available.[4] *Beauveria sulfurescens* ATCC 7159 is a microorganism that has gained popularity as an easy-to-use microbiological oxidant,[5] and we have set out to determine the rules governing the site(s) attacked by this organism for a wide range of substrates. In view of current interest in the area we report herein some initial investigations using some *N*-arylpiperidines and related compounds.

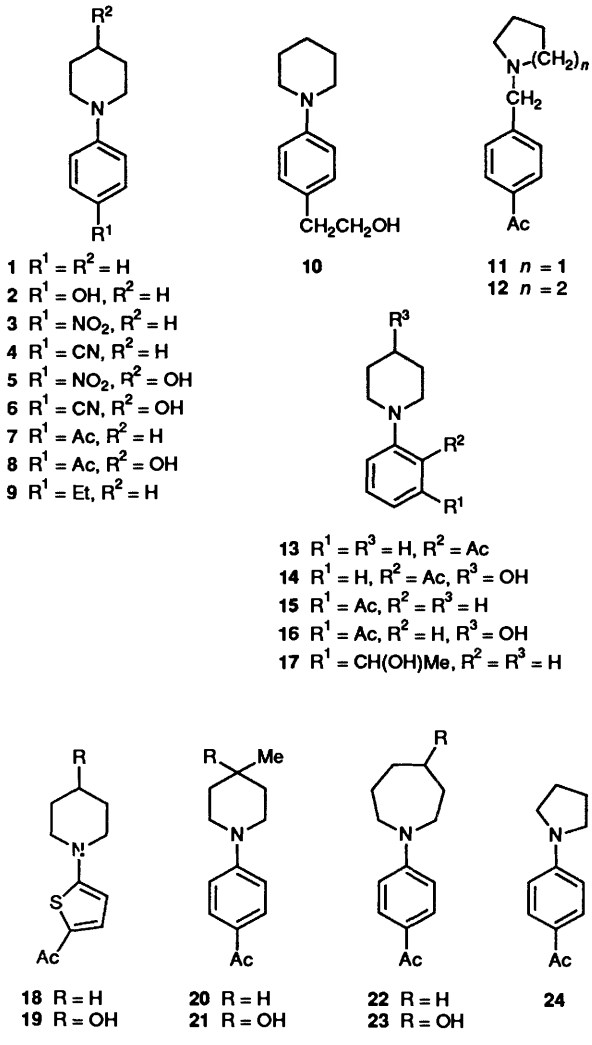
As expected[6] *N*-phenylpiperidine **1** is oxidized to the phenol **2** (27% yield†) using *B. sulfurescens* ATCC 7159. However, substitution at the *para*-position in the aromatic unit with an electron-withdrawing group leads to oxidation in the heterocyclic ring. For example, the *N*-arylpiperidines **3** and **4** form the hydroxylated derivatives **5** and **6** in 42% yield† and 34% yield,† respectively. The products **5** and **6** were identified by comparison with authentic samples[7] and no other oxidation products were isolated from these fermentations. The ketone **7** is a particularly good substrate in this biotransformation yielding the hydroxylated material **8**[7] in 66% isolated yield† (see Experimental section) which was considerably higher than in an equivalent recently reported biotransformation.[8] In contrast, the 4'-ethyl compound **9** furnished only the primary alcohol **10** in 30% yield.

It is noteworthy that compound **7** is a vinylogous amide and it has been observed previously that amides are often good substrates in these types of biotransformation.[9] In this connection, it was of interest to find that the ketones **11** and **12** were recovered unchanged from the biotransformation.

Altering the position of the substituent in the aromatic ring led to less efficient conversions. Thus, the ketone **13** produced the keto alcohol **14** (20%) together with recovered starting material 56%). The *meta*-substituted compound **15** formed two alcohols **16** (25%)† and **17**(31%).† The thiophene derivative **18** produced the alcohol **19** (37%)† as the sole oxidation product.

Gratifyingly, when the aromatic moiety was kept constant and the heterocyclic portion of the molecule varied, the results obtained were largely in accord with expectations. For example, oxidation of the 4-methyl-*N*-arylpiperidine **20** gave the tertiary alcohol **21** (55%)† while the perhydroazepine **22** furnished the alcohol **23** (58%).† The latter alcohol was optically active {$[\alpha]_D^{27}$ −11.4 ($CHCl_3$, *c* 0.37)} and, through formation of the Mosher's ester and NMR spectroscopy, the compound was judged to be a 82:18 mixture of enantiomers. The absolute configuration of the major enantiomer was not determined. The pyrrolidine derivative **24** was not transformed under our standard conditions.

In summary, 4'-substituted *N*-arylpiperidines and related compounds are oxidized with excellent selectivity using *B. sulfurescens* ATCC 7159. In comparison, parallel experiments using *Curvularia lunata* NRRL 2380 gave less satisfactory



† Starting material (10–20%) was recovered: the yields of product(s) are calculated on the amount of starting material consumed.

results; for instance, the ketone **7** afforded the alcohol **8** in just 20% yield on incubation with the latter organism.

Experimental

Conversion of the Ketone **7** *into the Alcohol* **8** *with* Beauveria sulfurescens.—The bioconversion medium comprised corn steep liquor (20 g dm^{-3}) and glucose (10 g dm^{-3}) in water adjusted to pH 4.85 with aqueous sodium hydroxide (1 mol dm^{-3}). In a typical fermentation, the sterilized medium was inoculated with a 72 h-old vegetative culture and incubated with reciprocal shaking (28 °C, 200 rpm) in a 2 dm^{-3} conical flask filled with 1 dm^{-3} of medium. After 72 h of growth, an ethanolic solution of 4′-piperidinoacetophenone (100 mg cm^{-3}) (10% w/v) was added to the culture (100 mg dm^{-3}). After an additional 72 h period of incubation, the mycelium was filtered off and washed with water and the filtrate was continuously extracted (48 h) with methylene dichloride. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was analysed by TLC using ethyl acetate as eluent. Flash chromatography over silica gel (eluent ethyl acetate) gave the alcohol **8** (65 mg) as well as starting material (10 mg). Data for compound **8** were as follows: R_f 0.37 (ethyl acetate); m.p. 124–126 °C (lit.,[7] 123–124 °C); ν_{max}/cm^{-1}($CHCl_3$) 3625 (OH), 3030, 3010, 2980, 1665 (C=O), 1600, 1515, 1425, 1195, 1045, 780 and 665; δ_H(250 MHz, $CDCl_3$) 7.87 (2 H, d, *J* 9.8), 6.89 (2 H, d, *J* 9.8), 3.94 (1 H, tt, *J* 9, 4.5), 3.80–3.68 (2 H, m), 3.20–3.06 (2 H, m), 2.51 (3 H, s), 2.06–1.92 (2 H, m), 1.76 (1 H, s, OH) and 1.72–1.56 (2 H, m); δ_C(62.9 MHz, $CDCl_3$) 196.58 (C=O), 153.89, 130.52, 127.11, 113.47, 67.40, 45.19, 33.61 and 25.99.

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