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Short Communication

# Chiral resolution of 1,3-dimethyl-4-phenylpiperidine derivatives using high-performance liquid chromatography with a chiral stationary phase

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**Abstract**

A number of racemic 1,3-dimethyl-4-phenylpiperidines which serve as intermediates in the synthesis of opioid analgesics have been resolved on two commercially available high-performance liquid chromatography columns containing cellulose-based chiral stationary phases: Chiralcel OD and Chiralcel OJ. The resolution results were complementary between the two columns. Also, the polarity of substituents appears to play an important role on the ability of the Chiralcel OD column to resolve pairs of enantiomers.

## 1. Introduction

4-Phenylpiperidines such as meperidine, ketobemidone and prodines are opioid analgesics [1] (Fig. 1). Various structure–activity relationship studies have shown that the prodines have different pharmacological profiles compared to the analogues of ketobemidone and meperidine [2–4]. In order to test the predictions of a proposed model [5–7] which predicts the stereochemical requirements for opioid receptor activity, we initiated a project to study the effects of conformation on analgesic activity of these compounds. This study required the synthesis and resolution of $\alpha$- and $\beta$-prodines and their analogues.

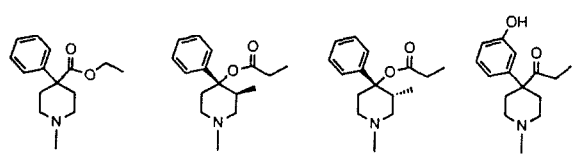


Fig. 1. 4-Phenylpiperidine opioid analgesics.

Optical resolution of prodinols, the precursor alcohols of prodines, has already been accomplished by fractional crystallization [8], but most other analogues were less amenable to this approach [9]. High-performance liquid chromatography (HPLC) with a chiral stationary phase (CSP) provides a convenient method for both analytical- and preparative-scale separation of enantiomers for all of the analogues we tested.

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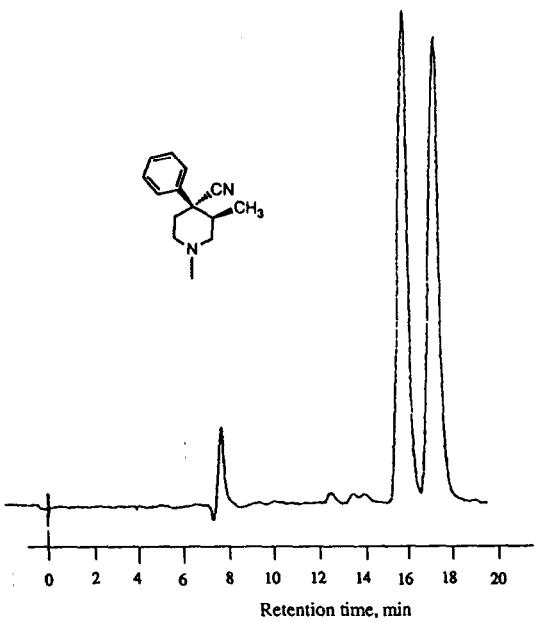



Fig. 2. Resolution of racemic β-4-cyano-1,3-dimethyl-4-phenylpiperidine on Chiralcel OD; solvent 3% isopropanol and 0.05% DEA in hexane.

However, no data concerning the resolution of the enantiomers of these compounds by HPLC on CSPs could be found in the literature.

Herein we report on the chiral resolution of α- and β-prodines, α- and β-prodinols, a ketobemidone analogue as well as precursors of two ketobemidone analogues by HPLC on two cellulose-based CSP columns viz. Chiralcel OD and Chiralcel OJ.

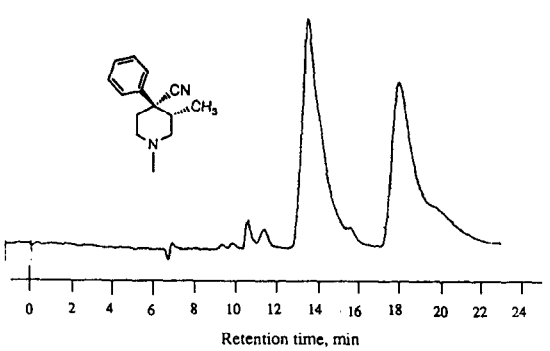



Fig. 3. Resolution of racemic α-4-cyano-1,3-dimethyl-4-phenylpiperidine on Chiralcel OD; solvent 10% isopropanol and 0.1% DEA in hexane.

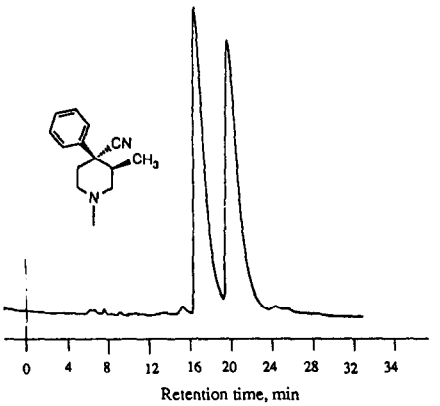



Fig. 4. Resolution of racemic β-4-cyano-1,3-dimethyl-4-phenylpiperidine on Chiralcel OJ; solvent 10% isopropanol and 0.1% DEA in hexane.

## 2. Experimental

### 2.1. Chromatography

Chromatography was performed using a Waters Model 590 pump, an U6K injector, a Model 450 variable-wavelength UV detector detecting at 254 nm and a Fisher Recordall recorder. Chiralcel OD and Chiralcel OJ (both 25 × 0.46 cm, 0.5-μm particles, from Daicel) were used. The flow-rate was 0.5 ml/min.

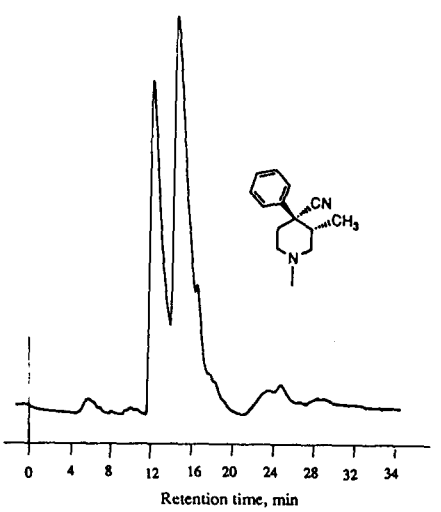



Fig. 5. Resolution of racemic α-4-cyano-1,3-dimethyl-4-phenylpiperidine on Chiralcel OJ; solvent 10% isopropanol and 0.1% DEA in hexane.

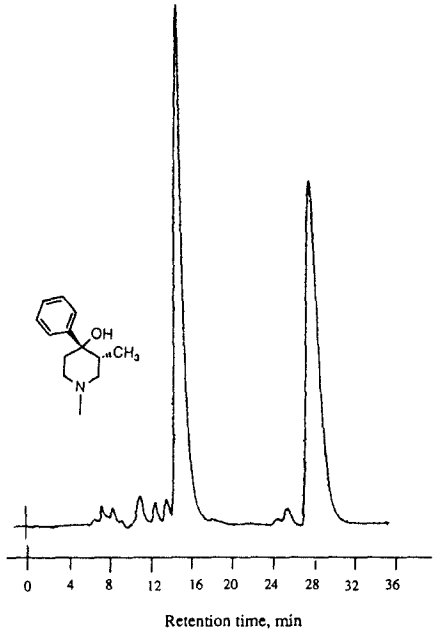



Fig. 6. Separation of enantiomers of α-prodinol on Chiralcel OD; solvent 10% isopropanol and 0.1% DEA in hexane.

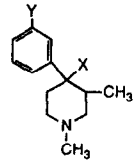
### 2.2. Reagents and materials

The compounds used in this study were synthesized in our laboratory following literature procedures. The racemic diastereomers were first separated and purified by column chromatography before injecting into the chiral HPLC columns. The solvents used were HPLC grade. Diethylamine (DEA) used as a modifier was of analytical-reagent grade.

## 3. Results and discussion

Chiralcel OD and Chiralcel OJ are derivatized cellulose stationary phases. Although the mechanism of chiral recognition by this kind of CSP is not quite clear, there are numerous examples demonstrating the wide range of solutes which have been resolved [10,11]. Since we were interested in direct resolution of our analogues as free bases without derivatization, we chose Chiralcel

Table 1
Resolution of 1,3-dimethyl-4-phenylpiperidine derivatives




| Compound | | | Chiralcel OD | | | | Chiralcel OJ | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| X | Y | 3-Me/4-Ph | $k'_1$ | $k'_2$ | α | Solvent | $k'_1$ | $k'_2$ | α | Solvent |
| OH | H | (±) α | 1.70 | 5.89 | 3.45 | A | 1.38 | 1.50 | 1.09 | A |
| | | (±) β | 1.17 | 4.35 | 3.70 | A | – | – | – | |
| CN | H | (±) α | 1.00 | 1.95 | 1.95 | A | 0.87 | 1.25 | 1.42 | B |
| | | (±) β | 0.97 | 1.12 | 1.15 | A | 1.56 | 2.02 | 1.32 | B |
| OCOEt | H | (±) α | 1.04 | 1.14 | 1.09 | C | 1.38 | | 1.00 | A |
| | | (±) β | 0.62 | 0.74 | 1.19 | C | 1.31 | 2.00 | 1.53 | A |
| COEt | H | (±) α | 0.88 | 0.98 | 1.12 | A | 0.56 | 0.68 | 1.22 | A |

Solvents: A = 5% isopropanol and 0.1% DEA in hexane; B = 10% isopropanol and 0.1% DEA in hexane; C = 3% isopropanol and 0.05% DEA in hexane.

OD and Chiralcel OJ [12,13], which are thought to be the best and the most practical among this type of CSPs.

The retention time could be adjusted by modifying the percentage of isopropanol in the mobile phase. Also a small amount of DEA was used as a modifier to decrease peak broadening and tailing. We found that increasing the proportion of DEA in the mobile phase did not influence the retention time dramatically, but more than 0.5% DEA caused disturbance of the baseline.

The resolution data for prodines and their analogues on Chiralcel OD and Chiralcel OJ columns are summarized in Table 1. From these data it is clear that the resolution abilities of the two columns are quite different. The best resolution on Chiralcel OD column was obtained when X = OH (for both $\beta$ and $\alpha$ isomers); $\alpha$ = 3.70 for the $\beta$ and $\alpha$ = 3.45 for the $\alpha$ diastereomer. However, the $\alpha$ diastereomer showed very poor resolution on Chiralcel OJ column. When X = CN, both $\beta$ and $\alpha$ isomers had good resolutions on either columns. The best separation on Chiralcel OJ was obtained for $\beta$-prodine which showed much less satisfactory resolution on Chiralcel OD. For all the compounds that were tested, the (+)-enantiomer had a shorter retention time than the (−)-enantiomer. Overall, better resolutions were obtained on Chiralcel OD compared to Chiralcel OJ. It appears that for the Chiralcel OD column polarity is a key factor in the chiral recognition; the more polar the substituents, the better the resolution.

The resolution results of compounds described above indicated that the two columns, Chiralcel OD and Chiralcel OJ, perform in a complementary fashion. As a result, we were able to resolve all of the racemic diastereomers synthesized in our laboratory. Some of these compounds were also resolved on a preparative scale using a semipreparative Chiralcel OD column.

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