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Note

High-performance liquid chromatographic resolution of propoxyphene carbinol diastereomers

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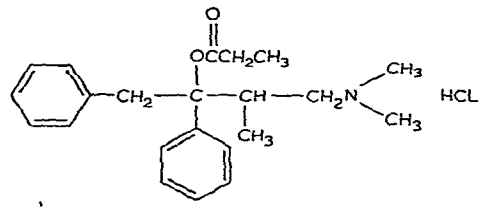
d-Propoxyphene hydrochloride is widely prescribed for relief of mild-to-moderate pain[1,2]. It was originally synthesized[3] as the *α*-racemate (*α-dl* mixture),



α-dl-1,2-diphenyl-2-propionoxy-3-methyl-4-dimethylaminobutane hydrochloride. The presence of two asymmetric centers characterizes four stereoisomers. The *β-d* and *β-l* isomers are substantially inactive[3], while the analgesic activity resides in the *α-d* isomer[4], and the *α-l* form possesses clinically useful antitussive properties[5].

In the synthesis of propoxyphene one obtains[3,6] a mixture of *α*- and *β-dl*-1,2-diphenyl-2-hydroxy-3-methyl-4-dimethylaminobutane or "crude carbinol" by reaction of benzylmagnesium chloride with *α*-methyl-*β*-dimethylaminopropiophenone. The *α*- and *β*-carbinols are separated on the basis of solubility differences, and the *α-d* and *α-l* isomers are resolved by fractional crystallization of the *d*-camphorsulfonic acid salts[7]. This technique produces pure dextropropoxyphene after esterification (propionic anhydride) and acidification.

This paper describes resolution and quantitative analysis of the *α*- and *β*-carbinol diastereomers by high-performance liquid chromatography (HPLC). Chromatographic separation of these compounds has not been reported previously. This method is valuable to check the diastereomer content of the "crude carbinol" intermediate in the synthesis of propoxyphene. Precision, linearity and sensitivity are discussed for this simple quantitative technique.

EXPERIMENTAL

Reagents

The HPLC solvent system was prepared from reagent-grade diethylamine and from distilled-in-glass *n*-butyl chloride and *n*-hexane (Burdick and Jackson Labs.,

Muskegon, Mich., U.S.A.). The α- and β-carbinols (as the free bases or as salts) were obtained from various in-house sources.

Operating conditions

A Waters Model 6000A pump (Waters Assoc., Milford, Mass., U.S.A.) was used to deliver 1.0 ml/min of a 30% diethylamine solution (0.1% diethylamine in *n*-butyl chloride) in *n*-hexane through a 25 cm × 2 mm I.D. Varian Micropak-NH_2-10μ column (Varian, Walnut Creek, Calif., U.S.A.) at ambient temperature. Using a 20-μl loop (Rheodyne injection valve No. 7120; Rheodyne, Berkeley, Calif., U.S.A.), the samples in *n*-hexane were injected onto the column and were detected at 254 nm with a Vari-Chrom detector (Varian) with an 8-nm bandwidth. Peak areas were calculated using an on-line calculation program from the expanded RTE 2100 computer system (Hewlett-Packard, Avondale, Pa., U.S.A.).

d-Camphorsulfonate salts were dissolved in water, treated with excess 50% NaOH, and extracted into *n*-hexane before injection. Nominal 50 mg samples were so treated and extracted into 5.0 ml of *n*-hexane.

RESULTS AND DISCUSSION

Figs. 1a and b indicate that the α- and β-carbinol isomers are baseline-resolved at high or low levels of β in the desired α product. Hence, a sensitive assessment of the isomeric purity is easily made.

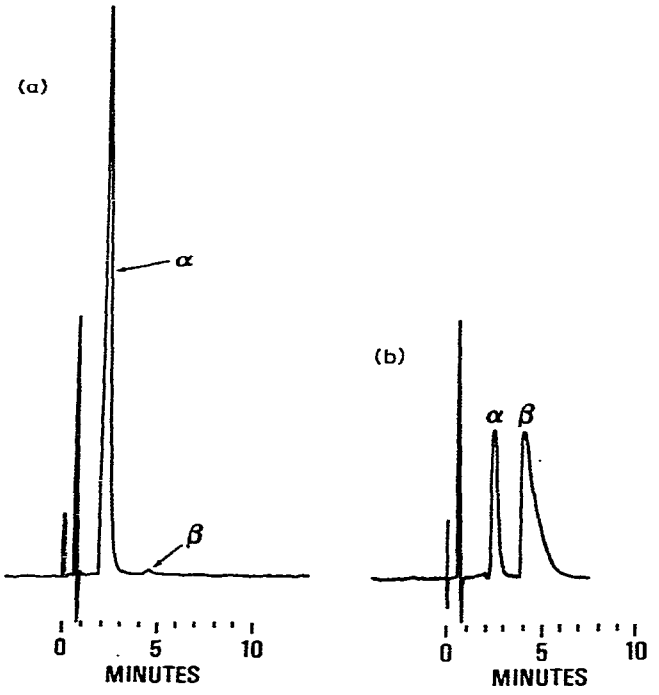


Fig. 1. (a) High-performance liquid chromatogram for 1% β-carbinol in α-carbinol. (b) High-performance liquid chromatogram for 70% β-carbinol in α-carbinol.

Linearity of absorbance response to α-*d*-carbinol concentration at 254 nm was found to extend from 0 to at least 11 mg/ml in *n*-hexane. This maximum concentration sample represents about 220 μg of α-*d*-carbinol injected onto the column with the 20-μl loop.

The most sensitive detection wavelength was found to lie between 250 and 260 nm. Detection was done at 254 nm for all measurements, using a 8-nm bandwidth. At 254 nm, the absorbance-per-milligram of the α- and β-carbinol isomers was found to be the same within experimental error.

Since both isomers give the same absorbance/weight response, a single isomer may be used as the standard to quantitate both in a mixture. A description of quantitative work follows. Eight consecutive injections of an α-*d*-carbinol solution were made with the injection loop to determine its reproducibility, which proved to be 0.6%. With such good injection precision and because (a) this method might be adapted for quick control assays of isomer content not requiring extreme precision and (b) some "crude carbinol" samples contain a variety of impurities, an internal standard was not chosen and tested for these experiments.

Using triplicate determinations for three separate crude carbinol sample lots, it was found that the α-isomer content could be determined with a precision essentially that of the injection loop reproducibility (0.6%, 0.5%, and 0.3% R.S.D. values; av. = 0.5%).

In a typical chromatogram of crude carbinol presented as Fig. 2, α- and β-carbinol contents were determined (in triplicate) with precisions of 0.5 and 2.9%, respectively. The higher R.S.D. value for the β isomer is to be expected since the peak is broader and is partially overlapped by an unknown impurity.

Carbinol isomer contents of the *d*-camphorsulfonic acid salts may also be determined by this HPLC method. Neutralized salts are extracted with *n*-hexane and injected. Such treatment in triplicate was done for one lot and the α isomer content was determined with a precision of 0.7%. To quantitatively assay such salt samples

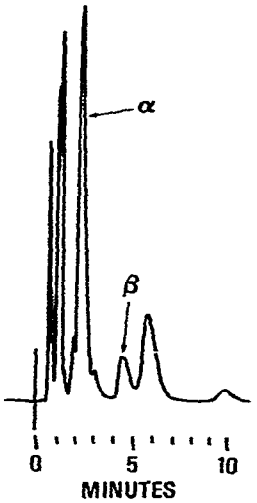


Fig. 2. High-performance liquid chromatogram for "crude carbinol" sample.

the extraction efficiency must be determined for the conditions used, and the appropriate corrections made.

Using one carbinol diastereomer as the standard (α-*d* in this work), the α and β isomer contents may be simply determined as follows:

1. *Total isomer content in samples*

A. Calculate $\dfrac{\text{sample } (\alpha + \beta) \text{ area}}{\text{sample weight}}$ for each sample replicate.

B. Calculate $\dfrac{\text{standard } (\alpha\text{-}d) \text{ area}}{\text{standard weight}}$ for each standard replicate.

C. Average the replicates in 1A to give the sample factor.

D. Average the replicates in 1B to give the standard factor.

E. Calculate: $\% (\alpha + \beta) = \dfrac{\text{sample factor}}{\text{standard factor}} \times \%$ purity standard (α-*d*).

2. *Individual isomer content in samples*

A. $\% \alpha = \% (\alpha + \beta) \times \dfrac{\text{av. area } (\alpha)}{\text{av. area } (\alpha + \beta)}$.

B. $\% \beta = \% (\alpha + \beta) \times \dfrac{\text{av. area } (\beta)}{\text{av. area } (\alpha + \beta)}$.

CONCLUSIONS

A simple rapid HPLC method is described for the quantitative determination of diastereomeric α- and β-carbinols from the synthesis of propoxyphene. This method yields good precision even without the added complication of an internal standard. This is the first reported chromatographic separation of these important diastereomers. This procedure is useful to assess isomeric purity in a variety of carbinol samples.

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REFERENCES

1 W. Modell, H. Schild and A. Wilson, *Applied Pharmacology*, Saunders, Philadelphia, Pa., 1976, p. 392.
2 K. Melmon and H. Morrelli (Editors), *Clinical Pharmacology, Basic Principles in Therapeutics*, Macmillan, New York, 1972, p. 492.
3 *U.S. Pat.*, 2,728,779 (Dec. 27, 1955).
4 *Codeine and Certain Other Analgesic and Antitussive Agents: A Review*, Medical Literature Dept., Merck Sharp and Dohme Laboratories, Merck and Co., Rahway, N.J., 1970. p. 2.
5 H. A. Bickerman, *Med. Clin. N. Amer.*, 45 (1961) 805.
6 A. Pohland and H. Sullivan, *J. Amer. Chem. Soc.*, 75 (1953) 4458.
7 A. Pohland and H. Sullivan, *J. Amer. Chem. Soc.*, 77 (1955) 3400.