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Note

Separation of the enantiomers of (±)-norephedrine by rotation locular counter-current chromatography

BRUNO DOMON and KURT HOSTETTMANN*
Institut de Pharmacognosie et Phytochimie, École de Pharmacie, Université de Lausanne, Rue Vuillermet 2, CH-1005 Lausanne (Switzerland)

and

KRUNOSLAV KOVAČEVIC and VLADIMIR PRELOG
Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, CH-8092 Zürich (Switzerland)

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In a recent paper, Prelog *et al.*[1] reported the separation of enantiomers by partition between two liquid phases. Racemic mixtures of salts of α-aminoalcohols, such as norephedrine, with lipophilic anions, such as hexafluorophosphate ion, could be separated by partition between the aqueous phase and the lipophilic phase (1,2-dichloroethane) containing an ester of tartaric acid (di-5-nonyl tartrate). The separation was achieved by flash partition chromatography[2], the stationary phase being the aqueous phase on a Kieselguhr support. In the present note we report a similar separation of the enantiomers of norephedrine by a support-free liquid–liquid technique using rotation locular counter-current chromatography (RLCC)[3,4].

RLCC is an adaptation of a technique based on a principle originally proposed by Signer *et al.*[5] and modified by Winistorfer and Kováts[6]. A column is constructed by placing in a glass tube multiple centrally perforated partitions which divide the tube into compartiments called loculi. It is filled with the stationary phase which can be either the lower or the upper one, depending on the separation problem. The column is then inclined from the horizontal position at an angle of 25–40° and the mobile phase is continuously introduced, from the bottom if it is the upper phase or from the top if it is the lower phase. The mobile phase displaces the stationary phase in each loculus to the level of the hole leading to the next one; it is collected at the outlet of the column. In practice several columns, which are interconnected with fine PTFE tubings, are mounted on a rotating shaft. The rotation promotes the partition of substrate between two phases and prevents the formation of emulsions.

EXPERIMENTAL

In our work a RLCC instrument (Tokyo Rikakikai Co., Tokyo, Japan) was used which consisted of 16 columns (45 cm × 11 mm I.D.) divided by centrally perforated PTFE disks into 37 loculi each. The flow-rate was 17–20 ml/h, the rotation speed was 60–70 rpm and the slope 40°. Two experiments were carried out at 2–3°C and 5–8°C, respectively.

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The stationary phase was a 0.5 *M* solution of sodium hexafluorophosphate (71.5 g) in water (850 ml) to which hydrochloric acid was added to pH 4. The mobile phase was a 0.3 *M* solution of (*R*,*R*)-di-5-nonyl tartrate in 1,2-dichloroethane. A solution of 200 mg of racemic norephedrine hydrochloride and 360 mg sodium hexafluorophosphate in 2 ml water was injected into the inlet of the apparatus and eluted in the descending mode with the lipophilic phase, which was analyzed at the outlet by determining the UV absorption spectrum. The eluate containing norephedrine was divided into four fractions, which were treated separately with 0.25 *M* sodium hydroxide, followed by extraction with 0.1 *M* hydrochloric acid. The aqueous extracts were evaporated to dryness and each residue analyzed by determining the amount of norephedrine by UV absorption on a UVIKON 810 spectrometer and its optical purity by circular dichroism on a Jobin-Yvon III Dichrograph.

RESULTS AND DISCUSSION

The results of the first separation carried out at 5–8°C are summarized in Table I. The mobile phase front was observed at 456 ml, the two maxima corresponding to the 1*S*- and 1*R*-enantiomers respectively were at 1310 and 1730 ml.

TABLE I
RLCC SEPARATION OF (±)-NOREPHEDRINE AT 5–8°C

Eluate volume (ml)	*Norephedrine hydrochloride*			
	mg	*Enantiomeric excess (%)*	*1S (%)*	*1R (%)*
821–1310	52	87	93	7
1311–1520	38	32	66	34
1521–1730	38	86	7	93
1731–2010	37	97	1	99

The results of the second experiment, which was carried out at 2–3°C, are given in Table II.

Although no baseline separation has been achieved, these results show that practically pure enantiomers can be obtained by the RLCC technique; a complete resolution could be achieved using an apparatus with more loculi.

TABLE II
RLCC SEPARATION OF (±)-NOREPHEDRINE AT 2–3°C

Eluate volume (ml)	*Norephedrine hydrochloride*			
	mg	*Enantiomeric excess (%)*	*1S (%)*	*1R (%)*
671–992	53	90	95	5
993–1146	46	45	72	28
1147–1314	41	76	12	88
1315–1650	39	99	0.5	99.5

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