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Note

Semipreparative separation of cyclic carbamates of beta-blocking agents by liquid chromatography on swollen microcrystalline triacetylcellulose

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Awareness of the different biological activities of enantiomers of chiral drug compounds has undoubtedly contributed to the development of chromatographic methods for the analysis as well as the preparation of stereoisomers[1]. In the future, chiral, pharmacologically active compounds will need to be developed and marketed as pure stereoisomers.

Among beta-blocking drugs of general formula $ArOCH_2CHOHCH_2NHR$, in which Ar denotes an aromatic group and R an aliphatic group, usually isopropyl, the *S*-forms are found to be more active than the *R*-forms[2].

Direct resolution of the enantiomers of these compounds has been carried out by ion-pair chromatography using a chiral additive in the mobile phase[3]. Chiral[4] as well as achiral derivatization reagents[5–10] for high-performance liquid chromatography (HPLC) and gas chromatography (GC) have also been employed successfully for enantiomeric resolutions of beta-blockers on an analytical scale.

We now report a convenient method for the separation of two representative beta-blockers in clinical use, namely, metoprolol (Ar = p-$CH_3OCH_2CH_2C_6H_4$) (Ia) and propranolol (Ar = α-naphthyl) (Ib) as their cyclic carbamates, and two oxazolidinones IIa and IIb on a semipreparative scale by liquid chromatography on swollen microcrystalline triacetylcellulose (TAC). The individual enantiomers thus obtained can easily be hydrolysed with hydroxide ion[11] to liberate the amino alcohols (Fig. 1).

EXPERIMENTAL

The conversion of the beta-blockers into oxazolidinones and subsequent hydrolysis is illustrated in Fig. 1. After reaction of I with phosgene[6], followed by vacuum evaporation of the volatiles, the authenticity of the residue, II, was verified by ^1H NMR spectroscopy. The crude product was dissolved in 95% ethanol and used for chromatography without further purification. The chromatographic set-up and method has been reported recently by one of us[12]. In each run, about 10 mg of

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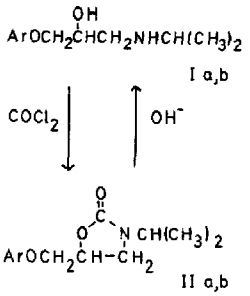

Fig. 1. Derivatization and hydrolysis of beta-blockers. Ar denotes (a) *p*-$CH_3OCH_2CH_2C_6H_4$, (b) α-$C_{10}H_7$.

racemate was dissolved in 4 ml of 95% ethanol and injected on the first one of two TAC columns, 600 mm × 10 mm I.D., coupled in series via a switching valve. Elution was made with the same solvent at a flow-rate of 70 ml/h, which produced a pressure of about 5 bar.

The *R*-antipode was eluted first in either case, as could be shown by comparison with the authentic *S*-enantiomers. These were available from another source [reaction between (5*S*)-3-isopropyl-5-*p*-toluenesulphonyloxymethyl-oxazolidin-2-one (Kanegafuchi Chemical Industry, Japan) and the respective phenolates].

RESULTS AND DISCUSSION

The chromatograms of IIa and IIb show almost complete baseline separation (Fig. 2). The chromatographic data are given in Table I. The α-naphthoxy compound (IIb) is much more retained on the TAC column than the *p*-(2-methoxyethyl)phenoxy compound (IIa). Benzene moves slower than 1,3,5-tri-*tert.*-butylbenzene, which is supposed to be unretained on TAC[13]. Probably, the *para* substituent in IIa fends the compound off better than is the case with the flat IIb structure.

The fact that the cyclic carbamates II are better separated than I may be rationalized in several ways. Rigid, cyclic compounds normally give better resolution

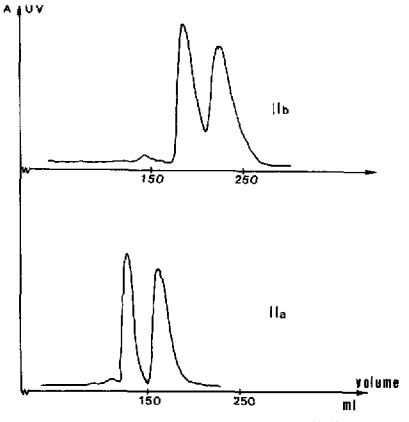

Fig. 2. Chromatograms of oxazolidinones.

TABLE I

CAPACITY FACTORS (k') AND SEPARATION FACTORS (α) FOR OXAZOLIDINONES

*Compound**	k'_R	k'_S	α
IIa	0.74	1.36	1.84
IIb	1.77	2.47	1.39

* See Fig. 1: in a, Ar = *p*-(2-methoxyethyl)phenyl; in b, Ar = α-naphthyl.

than flexible, open-chain analogues. Perhaps more important is the diminished hydrogen bonding between the solute and the eluent going from I to II. Compounds with hydroxyl, carboxyl and amino groups generally show none or very poor separation on TAC columns[12]. The dipole–dipole interaction between the ester carbonyl groups of TAC and the oxazolidinones may also contribute to chiral recognition. In a study of 1,2-glycerol carbonates, it was found that the effect caused by introduction of the dipolar carbonyl group close to the asymmetric centre is even more important than the effects of aromaticity and hydrogen bonding[14].

Apart from its analytical value in determining the enantiomeric purity of beta-blocking drugs, the above method is of obvious interest for the separation of small amounts of compounds, *e.g.* for screening purposes. A valuable application is to separate the antipodes of beta-blockers labelled at the asymmetric carbon atom with deuterium or tritium. Such compounds are prepared through borodeuteride or borotritide reduction of prochiral ketones, yielding racemic material[15]. It is difficult to envisage simple, enantiospecific routes to the *S*- and *R*-forms.

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