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Note

Gas–liquid chromatographic resolution of some racemic synthons for lamtidine analogous histamine H_2-receptor antagonists via diastereomeric amides of (1*S*)-(–)-camphanic acid

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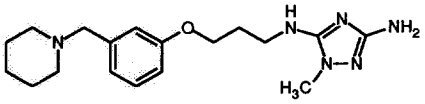
The piperidinomethylphenoxy group as a structural feature of lamtidine[1] (Fig. 1) and several other potent long-acting histamine H_2-antagonists[2,3] shows a high affinity for the histamine H_2-receptor[4]. For investigations of structure–activity relationships, the piperidino group of this moiety was replaced with racemic or enantiomeric 3-ethyl-, 3-methyl- or 2-methylpiperidines and 3-methyl- or 2-methylpyrrolidines, respectively. As a result, the enantiomeric compounds derived from these amines showed significantly different histamine H_2-antagonistic activities[5]. The cyclic secondary amines used were resolved according to known methods[6–8]. In a second approach, these amines were obtained by cleavage of the corresponding enantiomeric aminomethylphenols[9]. This paper reports the determination of the optical purity by gas chromatographic (GC) resolution after derivation of these secondary amines using (1*S*)-(–)-camphanoyl chloride[10–12].

EXPERIMENTAL

All chemicals were of analytical-reagent grade. Cyclic amines were purchased from Aldrich (Steinheim, F.R.G.) and Fluka (Buchs, Switzerland) and (1*S*)-(–)-camphanoyl chloride from Aldrich. Optically pure amines were obtained by resolution via diastereomeric salts with tartaric acid and mandelic acid[6–8]. Resolution of a cyclic aminomethylphenol intermediate with di-O-(*p*-toluoyl)tartaric acid followed by



Lamtidine

Fig. 1. Structure of lamtidine.

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cleavage of the so-obtained optically pure aminomethylphenols with hydrogen over palladium yielded optically active secondary amines[9]. The optical rotations of the isolated free amines were measured with a Perkin-Elmer 241 MC polarimeter. A Perkin-Elmer F-22 gas chromatograph equipped with a flame ionization detector was fitted with either a 25 m × 0.33 mm O.D. × 0.25 mm I.D. FS-SE-54-CB-coated fused-silica capillary column having a film thickness of 0.35 μm (Macherey, Nagel & Co., Düren, F.R.G.) or with a 25 m × 0.25 mm I.D. Chirasil-Val-coated glass column (Alltech, Belgium). The injector and detector temperatures were 280°C. The carrier gas was nitrogen at a flow-rate of 1 ml/min in both instances. Temperature programmes from 160 to 240°C at 1°C/min for the first column and from 120 to 170°C at 1°C/min for the second column were applied.

The cyclic secondary amines (0.01 m*M*) and (1*S*)-(−)-camphanoyl chloride (0.02 m*M*) were dissolved in 5 ml of dichloromethane and 0.1 ml of dry pyridine was added. After 4 h the solution was evaporated *in vacuo* and the residue was taken up in 5 ml of dichloromethane. The organic phase was washed successively with 10% aqueous $NaHCO_3$ (10 ml), 1 *M* HCl (10 ml) and twice with water (10 ml), followed by drying over anhydrous Na_2SO_4. The solution was made up to 10 ml and 1 μl of it was injected into the gas chromatograph.

RESULTS AND DISCUSSION

The resolution of racemic amines by GC can be achieved in two ways[13]: either by conversion to diastereomers with a suitable optically active reagent followed by GC under achiral conditions, or by use of a chiral stationary phase. Most popular of the chiral derivatizing reagents for amines are perfluoroacylamino acid chlorides, but they have a tendency to racemize in a short period of time or may show a high racemization rate under the reaction conditions[14,15]. Therefore, in this investigation (1*S*)-(−)-camphanoyl chloride was selected as a reagent of high optical purity and stability[10–12,16,17]. The reaction with cyclic amines proceeded smoothly and quickly

TABLE I

RESOLUTION CONDITIONS FOR DIASTEREOMERIC AMIDES OF (1*S*)-(−)-CAMPHANIC ACID ON AN SE-54-CB-COATED FUSED-SILICA CAPILLARY COLUMN AND A CHIRASIL-VAL-COATED GLASS COLUMN

Amide derived from (according to elution sequence)	*Separation factor*	
	SE-54-CB	*Chirasil-Val*
R-(−)-2-Methylpyrrolidine *S*-(+)-2-Methylpyrrolidine	1.013	1.040
R-(+)-3-Methylpyrrolidine *S*-(−)-3-Methylpyrrolidine	1.0	1.0
R-(−)-2-Methylpiperidine *S*-(+)-2-Methylpiperidine	1.016	1.033
S-(+)-3-Ethylpiperidine *R*-(−)-3-Ethylpiperidine	1.005	1.030
R-(−)-3-Methylpiperidine *S*-(+)-3-Methylpiperidine	1.013	1.033

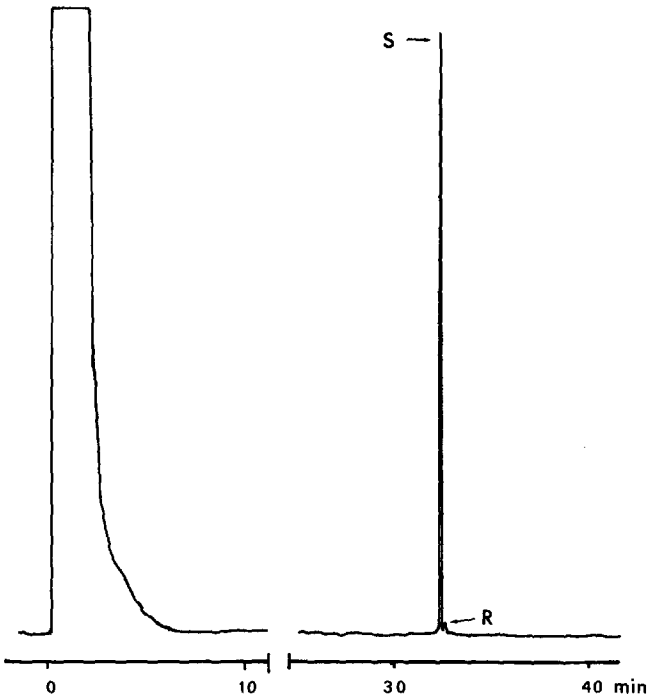

Fig. 2. Chromatogram of (*S*)-(+)-3-ethylpiperidine derivative containing 1% of the (*R*)-(−)-enantiomer on a Chirasil-Val-coated glass column.

within 4 h under ambient conditions. Byproducts did not occur. The addition of pyridine was necessary to shorten the reaction time, as without it more than 36 h were needed to complete the reaction. Heating, although it reduces the reaction time, should be avoided because of the formation of byproducts. During the derivation of the racemic amines, no kinetic or thermodynamic differentiation was observed, as the peak areas of the corresponding diastereomeric amides were equal. The optical impurities of all resolved amines listed in Table I were less than 1%. The solutions in dichloromethane were stable at room temperature for at least 48 h. The separation factors of the diastereomeric amides after chromatography on SE-54-CB-coated fused-silica capillary columns and Chirasil-Val-coated glass columns are listed in Table I.

With an SE-54-CB-coated fused-silica capillary column shorter retention times and good separations down to the baseline were obtained. As expected, the separation factors were better (with slightly longer retention times) for all amides, except the 3-methylpyrrolidine derivative, when the Chirasil-Val-coated column was used[18–21]. For both columns the retention sequence was the same. It was not possible to resolve racemic 3-methylpyrrolidine by this method, as in all instances only a single, sharp peak was observed. For this substance the use of N-trifluoroacetyl-(*S*)-prolyl chloride under the same chromatographic conditions gave clearly separated peaks[22,23]. With the described method an optical impurity of 1% can be determined easily (see Fig. 2).

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