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# DIRECT LIQUID CHROMATOGRAPHIC SEPARATION OF BENZODIAZEPINONE ENANTIOMERS

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## SUMMARY

The enantiomers of 46 3-substituted 5-phenyl-1,3-dihydro(2H)1,4-benzodiazepin-2-ones, diazepam (Valium®) analogues, have been chromatographically separated on chiral stationary phases derived from (*R*)-phenyl-glycine or (*S*)-leucine. Both analytical and preparative scale separations have been effected. The enantiomers separate readily and elute in a uniform order. Elution order is accommodated by a chiral recognition model.

## INTRODUCTION

Owing to the physiological activity of a number of benzodiazepinones, these compounds have been studied extensively[1]. One of the most important benzodiazepinones is diazepam, 7-chloro-1-methyl-5-phenyl-1,3-dihydro-(2H)1,4-benzodiazepin-2-one(1a), more generally known as Valium®. Although diazepam itself is achiral, a number of analogues bear substituents in the 3-position and are thus chiral[2,3]. The physiological activity of such benzodiazepinones has been shown to be enantiodependent and the possibility of therapeutic advantage of administration of enantiomerically pure compounds has been suggested[4].

Optically active type 1 benzodiazepinones have been obtained by coupling *o*-aminobenzophenones with N-protected amino acids followed by deprotection and cyclization[5]. Alternatively, amino acid derivatives may be condensed with *o*-aminobenzophenones directly[6].

These methods are lengthy and there is always the possibility of partial racemization which may pass unnoticed. The chiral center in a 3-monosubstituted benzodiazepin-2-one is configurationally labile, as are the chiral centers in some of the synthetic precursors. Hence, the use of an enantiomerically pure starting material does not necessarily lead to enantiomerically pure benzodiazepinone. In some cases, benzodiazepinones have been resolved by classical procedures. For example oxazepam (1q), as its succinyloxy derivative, has been resolved with ephedrine and subsequently retrieved by cleavage of the ester under anhydrous conditions[6]. Even after resolution through fractional crystallization of diastereomeric derivatives, one might well raise the issue of actual enantiomeric purity. Hence, a general and convenient

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method for determining the enantiomeric purity of type 1 benzodiazepinones is of interest and utility.

Chromatographic methods are becoming increasingly powerful and useful in the solution of stereochemical problems. However, to our knowledge, there are but two reports of the complete chromatographic resolution of a benzodiazepinone. Oxazepam has been resolved on a polymeric chiral stationary phase (CSP) into which phenylalanine was incorporated[7] and, as its O-acylated derivatives, has been resolved on immobilized human serum albumin[8].

Our previous studies on the use of CSP for the direct chromatographic separation of enantiomers have given some insight into mechanisms of chiral recognition[9]. Type 1 benzodiazepinones seemed promising candidates for resolution on N-(3,5-dinitrobenzoyl) amino acid-derived CSPs since they contain combinations of complementary functionality capable of undergoing the interactions employed by these CSPs to achieve chiral recognition.

## EXPERIMENTAL

Chromatography was performed using an Altex 100A pump, Altex 210 injector, and an Altex Model 152 dual-wavelength (254 and 280 nm) detector. Either Kipp & Zonen BD41 or Altex Model C-RIA integrating recorders were used. A Rudolph Autopol III polarimeter containing a 20-cm flow cell was used to simultaneously monitor the sign of $[\alpha]_D$. Regis covalent phenylglycine Pirkle 1-A and Baker covalent leucine columns (250 × 4.6 mm) were used to generate the data in the tables. Preparative resolutions were condicted using 250 × 10 mm Regis covalent Pirkle 1-A or covalent leucine columns. The preparation of the CSPs has been described[12,13]. Optical rotations were obtained using an Autopol III polarimeter. Melting points were obtained using a Buchi apparatus and are uncorrected.

Compounds in the tables have, for the most part, been described in the literature and were prepared by standard methods[14–24]. New compounds gave correct spectroscopic data and either elemental analyses within 0.40% of the expected values for C, H, N or, for compound 2d, the molecular weight expected from high resolution mass spectrometry.

3-Alkyl derivatives were prepared by heating 2-amino-5-chlorobenzophenone and the appropriate aminoacid ethyl ester hydrochloride in refluxing pyridine[14]. 7-Chloro-1,3-dihydro-3-butyl-5-phenyl-(2H)1,4-benzodiazepin-2-one (1f) was obtained in 20% yield, m.p. 162–163°C.

3-Acyloxy derivatives were prepared by adding 1 equiv. of acid chloride in dichloromethane to a pyridine solution of oxazepam (1q)[23]. 7-Chloro-1,3-dihydro-3-(pentoxy-1-oxo)-(2H)1,4-benzodiazepin-2-one (1kk) was obtained in 40% yield, m.p. 143–146°C.

3-Alkoxy and 3-dialkylamino derivatives were prepared by allowing 3,7-dichloro-1,3-dihydro-5-phenyl-(2H)1,4-benzodiazepin-2-one to react with the appropriate alcohol or amine[21]. Thus obtained were the following derivatives, 3-propoxy (1u), m.p. 213–216°C; 3-butoxy (1v), m.p. 198–200°C; 3-pentoxy (1w), m.p. 166–168°C; 3-(3′)-methyl)-butoxy (1y), m.p. 232–234°C; 3-hexoxy (1x), m.p. 135–136°C; and 3-heptoxy (1z), m.p. 131–132°C.

1-Naphthyl-2′-N(N′-Boc-alanyl)-aminophenyl ketone (2c′) was prepared by

coupling *t*-Boc alanine and 1′-naphthyl-2-aminophenyl ketone[5]. The yield was 70%, m.p. 171–173°C.

1,3-Dihydro-3-methyl-5-(1′-naphthyl)-(2H)1,4-benzodiazepin-2-one (2c) was obtained from 2c′ by cleavage of the *t*-Boc group with HBr-HOAc and cyclization[5]. Yield 38%, m.p. 209–210°C.

2-Naphthyl-2′-N(N′-Boc-alanyl)-aminophenyl ketone was prepared in a manner analogous to the 1-naphthyl compound and was converted without isolation to 1,3-dihydro-3-methyl-5-(2′-naphthyl)-(2H)1,4-benzodiazepin-2-one (2d) in 49% overall yield.

Cyclohexyl-2′-N(N′-Boc-alanyl)-aminophenyl ketone (2e′) was similarly prepared. Yield 73%, m.p. 154–155°C.

1,3-Dihydro-3-methyl-5-cyclohexyl-(2H)1,4-benzodiazepin-2-one (2e), m.p. 203–205°C, was obtained from (2e′) in 65% yield.

## RESULTS AND DISCUSSION

The high-performance liquid chromatography (HPLC)) columns used in this study contain CSPs derived from the 3,5-dinitrobenzamides of (*R*)-phenylglycine [or (*S*)-leucine] bonded to 5 μm spherical silica particles either ionically or covalently. Such columns are now commercially available*.

Table I and Fig. 1 document the facility with which enantiomers of benzodi-

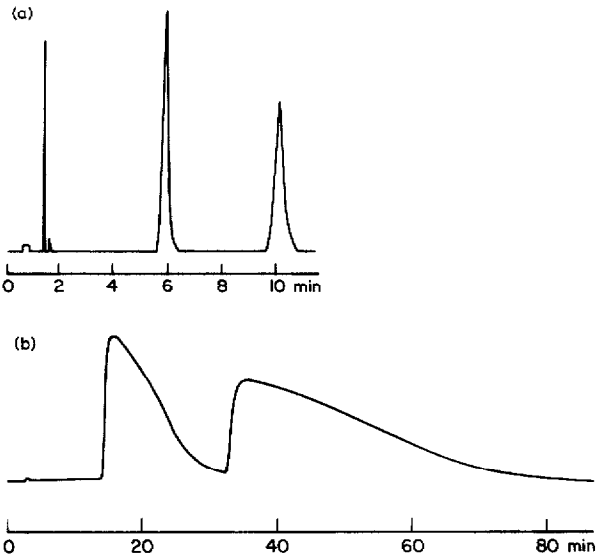
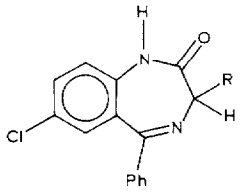



Fig. 1. (a) Analytical scale resolution of racemic benzodiazepinone (1i) on a 250 × 4.5 mm covalent 3,5-dinitrobenzoylleucine column. Mobile phase: 10% 2-propanol in hexane. The flow-rate was 2 ml/min. (b) Preparative resolution of 104 mg of racemic benzodiazepinone (1h) on a 250 × 10 mm covalent 3,5-dinitrobenzoylleucine column. Ultraviolet detector response (340 nm) was not linear with this large sample. Flow-rate was 5 ml/min. Mobile phase: 5% 2-propanol in hexane.

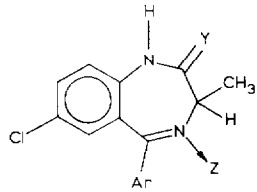
* Columns containing the phenylglycine and leucine-derived CSPs described herein are available from Regis Chemical Co., 8210 Austin Ave, Morton Grove, IL 60053 (U.S.A.), and J. T. Baker, Phillipsburg, NJ 08865 (U.S.A.).

TABLE I

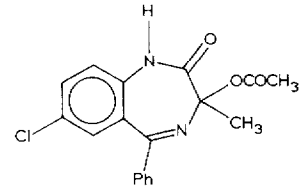
RESOLUTION OF BENZODIAZEPINONES ON CHIRAL STATIONARY PHASES



1



2



3

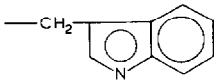
| *Compound (reference)* | *R* | *CSP* | | | | | |
|---|---|---|---|---|---|---|---|
| | | *(R)-N-3,5-Dinitrobenzoyl phenylglycine* | | | *(S)-N-3,5-Dinitrobenzoyl-leucine* | | |
| | | α* | *k'*** | *First eluting* | α | *k'*** | *First eluting* |
| 1a† (14) | –H | – | – | – | – | – | – |
| b (14) | $-CH_3$ | 1.6 | 3.2 | (−)-*R* | 4.11 | 1.8 | (+)-*S* |
| c (18) | $-CH_2CH_3$ | 1.46 | 2.3 | (−) | 2.22 | 1.9 | (+) |
| d (18) | $-CH_2CH_2CH_3$ | 1.42 | 2.2 | (−)-*R* | 2.35 | 2.7 | (+)-*S* |
| e (14) | $-CH(CH_3)_2$ | 1.92 | 2.7 | (−)-*R* | 3.53 | 1.8 | (+)-*S* |
| f | $-CH_2(CH_2)_2CH_3$ | 1.92 | 2.7 | (−) | 4.0 | 1.7 | (+) |
| g (14) | $-CH_2CH(CH_3)_2$ | 1.89 | 3.2 | (−)-*R* | 4.20 | 1.9 | (+)-*S* |
| h (14) | $-CH_2CH_2SCH_3$ | 1.57 | 4.0 | (−) | 3.0 | 2.2 | (+) |
| i (5) | $-CH_2C_6H_5$ | 1.93 | 4.0 | (−)-*R* | 4.33 | 2.2 | (+)-*S* |
| j (14) | $-CH_2C_6H_4$–OH | 1.48 | 12.3 | (−)-*R* | 2.18 | 6.3 | (+)-*S* |
| k (5) |  | 1.39 | 13.1 | (−)-*R* | 1.72 | 8.0 | (+)-*S* |
| l§§§ (15) | $-CH(CH_3)_2$ | 1.81 | 2.8 | (−) | 2.66 | 1.9 | (+) |
| m§§§ (16) | $-CH_2CH(CH_3)_2$ | 2.0 | 2.9 | (−) | 3.77 | 2.0 | (+) |
| n† (5) | $-CH_3$ | 1.11 | 3.0*** | (−)-*R* | 1.10 | 4.2*** | (+)-*S* |
| o† (5) | $-CH(CH_3)_2$ | 1.10 | 3.2*** | (−)-*R* | 1.12 | 3.0*** | (+)-*S* |
| p (21) | $CO_2CH_2CH_3$ | 1.36 | 4.4 | (−) | 1.42 | 4.3 | (+) |
| q (17) | OH | 1.20 | 16.9 | (−)-*R* | 1.13 | 11.7 | (+)-*S* |
| r (21) | Lorazepam§§ | 1.21 | 7,6§ | (−) | – | – | – |
| s (21) | $OCH_3$ | 1.33 | 10.0 | (−) | 1.19 | 11.0 | (+) |
| t (17) | $OCH_2CH_3$ | 1.30 | 9.0 | (−) | 1.44 | 5.7 | (+) |
| u | $O(CH_2)_2CH_3$ | 1.72 | 2.9 | (−) | 1.51 | 4.4 | (+) |
| v | $O(CH_2)_3CH_3$ | 1.72 | 3.1 | (−) | 1.60 | 3.6 | (+) |
| w | $O(CH_3)_4CH_3$ | 1.72 | 2.5 | (−) | 1.59 | 3.5 | (+) |
| x | $O(CH_2)_5CH_3$ | 1.71 | 2.4 | (−) | 1.68 | 3.1 | (+) |
| y | $OCH_2CH_2CH(CH_3)_2$ | 1.67 | 2.4 | (−) | 1.67 | 3.3 | (+) |
| z | $O(CH_2)_6CH_3$ | 1.77 | 2.3 | (−) | 1.61 | 2.8 | (+) |
| aa (22) | $O(CH_2)_3OH$ | 1.28 | 15.1 | (−) | 1.30 | 15.5 | (+) |
| bb (17) | $OCOCH_3$ | 1.27 | 7.4 | (−) | 1.62 | 3.8 | (+) |
| cc† (17) | $OCOCH_3$ | 1.07 | 5.5 | (−) | – | – | – |
| dd§§§ (17) | $OCOCH_3$ | 1.41 | 5.6 | (−) | 1.68 | 3.5 | (+) |
| ee (17) | OCOPh | 1.87 | 3.1 | (−) | 2.84 | 2.3 | (+) |
| ff (23) | $OCOCH_2CH_3$ | 1.71 | 2.4 | (−) | 2.30 | 1.9 | (+) |
| gg (23) | $OCO(CH_2)_2CH_3$ | 1.77 | 1.8 | (−) | 2.74 | 1.5 | (+) |
| hh (23) | $OCOCH(CH_3)_2$ | 1.66 | 1.5 | (−) | 2.89 | 1.3 | (+) |
| ii (23) | $OCOC(CH_3)_3$ | 2.05 | 1.0 | (−) | 3.69 | 0.7 | (+) |

TABLE I *(continued)*

| *Compound (reference)* | *R* | *CSP* | | | | | |
|---|---|---|---|---|---|---|---|
| | | *(R)-N-3,5-Dinitrobenzoyl phenylglycine* | | | *(S)-N-3,5-Dinitrobenzoyl-leucine* | | |
| | | $\alpha$* | *k'*** | *First eluting* | $\alpha$ | *k'*** | *First eluting* |
| jj (23) | $OCOCH_2CH(CH_3)_2$ | 1.73 | 1.5 | (−) | 3.18 | 1.2 | (+) |
| kk | $OCO(CH_2)_3CH_3$ | 1.69 | 1.6 | (−) | 3.26 | 1.1 | (+) |
| ll (23) | $OCO(CH_2)_3Ph$ | 1.81 | 2.4 | (−) | 2.78 | 1.8 | (+) |
| mm (24) | $NEt_2$ | 1.21 | 1.9 | (−) | 1.44 | 4.3 | (+) |
| nn (24) |  | 1.12 | 5.6 | (−) | 1.45 | 2.7 | (+) |
| oo (24) |  | 1.16 | 2.9 | (−) | 1.21 | 2.3 | (+) |
| pp (24) | $N(CH_3)Ph$ | 1.38 | 1.3 | (−) | 1.50 | 2.1 | (+) |
| | *Z Y Ar* | | | | | | |
| 2a (19) | O O Ph | 1.18 | 11.5 | | 1.21 | 8.0 | |
| b (20) | − S Ph | 1.18 | 2.1 | | 1.75 | 1.4 | |
| c§§§ | − O 1-Naphthyl | 1.31 | 6.3 | | 1.62 | 7.2 | |
| d§§§ | − O 2-Naphthyl | 1.69 | 3.5 | | 2.10 | 3.5 | |
| r§§§ | − O Cyclohexyl | No resolution | | | No resolution | | |
| 3 (21) | | 1.38 | 2.0 | (−) | 2.37 | 1.7 | (+) |

* Chromatographic separation factor.
** Unless otherwise indicated, mobile phase was 10% 2-propanol in hexane.
*** Mobile phase was 2% 2-propanol in hexane.
§ Mobile phase was 25% 2-propanol in hexane.
§§ Lorazepam has structure 1q, but with a second chloric on the *ortho* position of the phenyl substituent.
§§§ Chlorine free.
† The amide nitrogen is N-methylated.

azepinones are resolved upon the covalent columns (the ionic columns afford similar results but with somewhat lower separability factors). One immediately notes that all the compounds in the table are readily resolvable, with the leucine-derived CSP generally affording better results. Elution orders are, when known, invariant, the (*R*)-enantiomer of the benzodiazepinone being initially eluted from the (*R*)-phenylglycine CSP; the (*S*)-enantiomer from the (*S*)-leucine CSP. The signs of rotation at 589 nm (determined with a polarimetric detector) correlate with elution order and, when known, with absolute configuration. We infer that elution order and sign of rotation can be used to assign absolute configuration to those type 1 benzodiazepinones in the table for which absolute configurations have not been previously reported.

The extent of separation of the benzodiazepinone enantiomers on these CSPs makes preparative resolution facile. For example, by chromatographing 25–40 mg

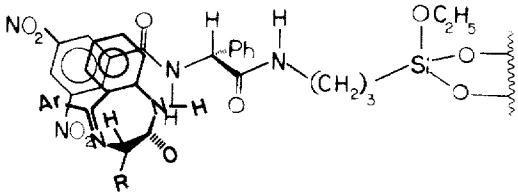


Fig. 2. Chiral recognition model for selective retention of one benzodiazepinone enantiomer by the chiral stationary phase. The depicted configurations lead to the most stable diastereomeric adsorbate.

samples of racemate on a 25 × 1 cm semipreparative phenylglycine column, we obtained: 7-chloro-1,3-dihydro-3-methyl-5-phenyl-(2H)1,4-benzodiazepin-2-one (1b) [(*R*)-enantiomer, m.p. 203–205°C (ref. 5: 200–203°C), $[\alpha]_D^{25} = -158.4°$ (c 2.38, $CHCl_3$): (*S*)-enantiomer, m.p. 204–205°C, $[\alpha]_D^{25} = +158.6°$ (c 1.95, $CHCl_3$)] and 7-chloro-1,3-dihydro-3-isopropyl-5-phenyl-(2H)1,4-benzodiazepin-2-one (1e) [(*R*)-enantiomer, m.p. 191–192°C (ref. 5: 192–194°C), $[\alpha]_D^{25} = -119.3°$ (c 1.54, $CHCl_3$); (*S*)-enantiomer, m.p. 191–193°C $[\alpha]_D^{25} = +122.4°$ (c 0.62, $CHCl_3$)].

Owing to the larger separability factors afforded by the leucine-derived CSP, larger quantities can be resolved on a semipreparative column of this type. For example, a 100-mg sample of the 3-benzyl compound, 1i, was resolved to give the high $R_F$ (*S*)-enantiomer (>99% ee) and the low $R_F$ (*R*)-enantiomer (98.6% ee). For the 3-(2'-methylthio)-ethyl analogue, 1h, the corresponding values are high $R_F$ (*S*)-enantiomer 99.3% ee, low $R_F$ (*R*)-enantiomer 97.2% ee. Enantiomeric purities of the enantiomers (each of the two chromatographic bands was collected as a single fraction) were determined using the chiral analytical columns and an integrating recorder.

*Chiral recognition rationale*

Previous experience with these CSPs suggests that the chiral recognition mechanism shown in Fig. 2 is likely to be operative. The benzodiazepinone is shown in the conformation that it adopts both in solution[10] and in ther crystalline state[11] (*i.e.* the 3-substituent in a quasi-equatorial position). The phenylglycine CSP is shown in the conformation previously suggested to be important to chiral recognition[12].

For the relative configurations shown, we envision three simultaneous bonding interactions: (a) $\pi$–$\pi$ interaction between the 3,5-dinitrobenzoyl group of the CSP and the benzo ring of 1, (b) hydrogen bonding between the 3,5-dinitrobenzamide hydrogen and the carbonyl oxygen of 1, (c) hydrogen bonding of the amide hydrogen of 1 to the C-terminal carboxamide oxygen of the CSP. These interactions cannot occur simultaneously for the other set of relative configurations. The benzodiazepinone enantiomer depected in Fig. 2 will be the last to elute from the depicted CSP. The data in Table I are in accord with this model. Methylation of the amide nitrogen dramatically reduces the separability of benzodiazepinone enantiomers as an important hydrogen bond is (presumably) replaced with a less efficient electrostatic interaction (between the positive end of the amide dipole of the benzodiazepinone and the negative end of the carboxamide dipole of the CSP). Similarly, replacement of the carbonyl oxygen of compound 1b with a less electronegative sulfur (compound 2b) results is hastened elution and reduced chiral recognition just as one would expect if the carbonyl oxygen was involved in hydrogen bonding. The observation that

TABLE II

TEMPERATURE EFFECTS

Column: covalent leucine. Solvent: isopropyl alcohol–hexane (10:90). The column used to generate this data differs from the one used to generate data in Table I in that it utilizes a different type of silica support.

| *Compound* | *Temperature (°C)* | $\alpha$ | $k'$ | $R_S$ |
|---|---|---|---|---|
| 1b | 20°C | 2.65 | 1.21 | 3.32 |
| | 0°C | 3.40 | 1.68 | 4.55 |
| | −20°C | 4.21 | 2.42 | 3.78 |
| 1i | 20°C | 3.32 | 1.42 | 3.72 |
| | 0°C | 4.42 | 2.04 | 4.35 |
| | −20°C | 5.53 | 2.81 | 3.36 |

enhancing the $\pi$-basicity of the 5-aryl substituent (as in naphthyl bearing benzodiazepinones, 2c or 2d) does not increase $\alpha$ values is consistent with the benzo ring serving as the site of $\pi$–$\pi$ interaction.

The lesser separability of the enantiomers of $\alpha$-naphthyl-substituted compound 2c, as compared to $\beta$-naphthyl-substituted compound 2d, is presumed to stem from an increase in the dihedral angle between the aromatic rings. This angle change occurs owing to the presence of the *peri* hydrogen. A large dihedral angle will prevent close approach of the CSP to the "bottom" face of the benzodiazepinone (as depected in Fig. 2). The failure of cyclohexyl-bearing compound 2e, to resolve is attributed to the same cause. The observation that increased length of the 3-alkyl substituent does not diminish the magnitude of $\alpha$ suggests that this substituent is not directed toward the underlying silica support. If it were, steric interactions would interfere with the chiral recognition process. Interestingly, compound 3, which bears both 3-methyl and 3-acetoxy substituents, resolves easily and shows the expected relationship between elution order and sign of rotation. However, absolute configuration cannot be assigned from this data. In the case of monosubstituted compounds, the substituent, as already mentioned, occupies the quasi-equatorial position thus determining the sense in which the 7-membered ring folds. Thus, in turn, controls both elution order and sign of rotation at 589 nm. In the case of compound 3, one does not know which substituent preferentially occupies the quasi-equatorial position.

*Temperature effects*

The diastereometric adsorbate having the greatest degree of simultaneous bonding, apart from being more stable, is also expected to have fewer degrees of freedom. Hence, one expects and finds that temperature reduction substantially enhances the magnitude of $\alpha$ (Table II). The attendent reduction in mass transfer rates degrades column efficiency, however, and tends to somewhat offset the expected gain in resolution, $R_S$.

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pinones that led to this investigation, and to Richard Heier for conducting the temperature studies described in Table II.

## REFERENCES

1 L. H. Sternbach, *J. Med. Chem.*, 22 (1979) 1.
2 B. E. Reitter, Y. P. Sachdeva and J. F. Wolfe, *J. Org. Chem.*, 46 (1981) 3945.
3 V. Sunjic, M. Oklobdzija, A. Lisini, A. Sega, F. Kajfez, D. Srzic and L. Klasinc, *Tetrahedron*, 35 (1979) 2531.
4 V. Sunjic, R. Dejanovic, A. Palkovic, L. Klasinc and F. Kajfez, *Tetrahedron Lett.*, (1976) 4493.
5 V. Sunjic, F. Kajfez, I. Stromar, N. Blazevic and D. Kolbah, *J. Heterocycl. Chem.*, 10 (1973) 591.
6 A. Corbella, P. Gariboldi, G. Jommi, A. Forgione, F. Marcucci, P. Martelli, E. Mussini and F. Mauri, *J. Chem. Soc. Chem. Commun.*, (1973) 721.
7 G. Blaschke and H. Markgraf, *Chem. Ber.*, 113 (1980) 2031.
8 I. Fitos, M. Simonyi, Z. Tegyey, L. Ötvös, J. Kajtár and M. Kajtár, *J. Chromatogr.*, 259 (1983) 494.
9 W. H. Pirkle, J. M. Finn, B. C. Hamper, J. Schreiner and J. R. Pribish in E. L. Eliel and S. Otsuka (Editors), *ACS Symp. Ser. No. 185, Asymmetric Reactions and Processes in Chemistry*, American Chemical Society, Washington, DC, 1982, Ch. 18, and refs. cited therein.
10 V. Sunjic, A. Lisini, A. Sega, T. Kovac, F. Kajfez and B. Ruscic, *J. Heterocycl. Chem.*, 16 (1979) 757.
11 G. Gilli, V. Bertolasi, M. Sacerdoti and P. A. Borea, *Acta Crystallogr. Sect. B*, B33 (1977) 2664.
12 W. H. Pirkle, D. W. House and J. M. Finn, *J. Chromatogr.*, 192 (1980) 143.
13 W. H. Pirkle and C. J. Welch, *J. Org. Chem.*, 49 (1984) 138.
14 L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy and A. Stempel, *J. Org. Chem.*, 27 (1962) 3788.
15 A. V. Bogatskii, S. A. Andronati, V. P. Gultyai, Yu I. Vikhlyaev, A. F. Galatin, Z. I. Zhilina and T. A. Klygul, *Zh. Obshch. Khim.*, 41 (1971) 1358.
16 Masamichi, Kawai, *Patent Japan 6,926,302, C.A.*, 72 (1970) 43752a.
17 S. C. Bell and S. J. Childress, *J. Org. Chem.*, 27 (1962) 1691.
18 A. V. Bogatskii, S. A. Andronati, Yu. I. Vikhlyaev, Z. I. Zhilina, T. A. Klygul and V. F. Ryakhin, *Khim.-Farm. Zh.*, 8(5) (1974) 13.
19 S. C. Bell, T. S. Sulkowski, C. Gochman and S. J. Childress, *J. Org. Chem.*, 27 (1962) 562.
20 J. B. Hester, A. D. Rudzik and P. F. von Voigtlander, *J. Med. Chem.*, 23 (1980) 392.
21 S. C. Bell, R. J. McGaully, C. Gochman, S. J. Childress and M. I. Gluckmann, *J. Med. Chem.*, 11 (1968) 457.
22 W. A. Khan and P. Singh, *Org. Prep. Proced. Int.*, 10 (1978) 105.
23 G. Maksay, Z. Tegyey and L. Otvos, *J. Med. Chem.*, 22 (1979) 1443.
24 F. Gatta, M. R. Del Giudice and G. Settimj, *Synthesis*, (1979) 718.