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PREPARATIVE OPTICAL RESOLUTION OF CHLORMEZANONE ON MICROCRYSTALLINE TRIACETYLCELLULOSE

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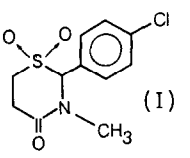
SUMMARY: Direct optical resolution of the drug chlormezanone (2-(4-chlorophenyl)-tetrahydro-3-methyl-4H-1,3-thiazin-4-one 1,1-dioxide) (I) by preparative chiral chromatography on microcrystalline triacetylcellulose is described together with an analytical technique to monitor the enantiomeric purity. The enantiomers are characterized by physical and chromatographic data.

Chlormezanone (I) is a muscle relaxant of broad therapeutic use (1). It is administered as the racemate, and its two optically active forms have not previously been isolated and studied. The absence of groups permitting separation of the enantiomers via formation of diastereomers by reaction with an optically active reagent, necessitates the use of chiral chromatography for optical resolution. In this communication we describe the direct liquid chromatographic separation of I into its antipodes on a preparative scale by the use of a column packed with microcrystalline triacetylcellulose (MCTA) (2,3).

Application of 250 mg of I (dissolved in 2 ml of a mixture of methanol and 95% ethanol) on 60 g MCTA in a 25x360 mm column followed by elution with 95% ethanol at 1.0 ml/min and continuous monitoring of the optical rotation at 546 nm via polarimetry, yielded the chromatogram shown in Fig 1. During the elution the UV-absorbance at 226 nm was followed simultaneously and 11 fractions (of 25 or 12.5 ml volume) were collected. The large amount of I applied resulted in some peak overlap and therefore the collected fractions were analyzed with respect to optical purity with the use of a Resolvosil analytical chiral LC column (4,5)



(I)

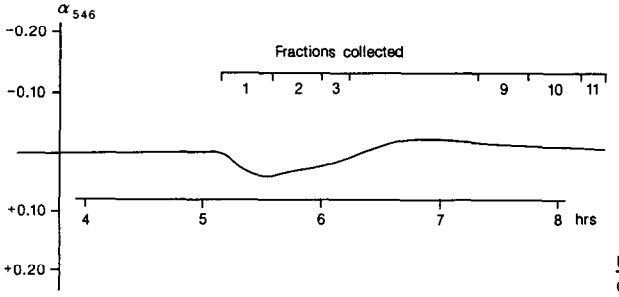


Fig 1. Polarimetric recording of the eluted enantiomers of I.

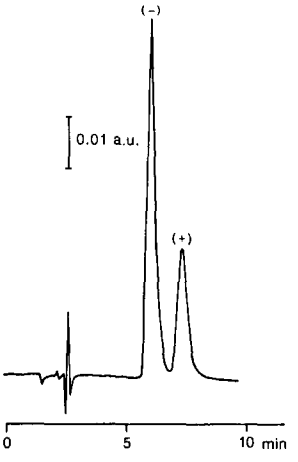


Fig 2. Determination of the enantiomeric purity of fraction 5 (diluted 1/100) by optical resolution on a 4.6x150 mm Resolvosil analytical BSA-silica column. Mobile phase: Phosphate buffer (40 mM, pH 6.95, 2% 1-propanol). Flow rate: 0.8 ml/min. UV 228 nm.

This procedure gave the results shown in Table I. High enantiomeric purity (>93%) is found in fractions 1-3 and 10-11, respectively. The performance of the analytical determination is illustrated by Fig 2, which shows the presence of 67.5% of (-)-I in fraction 5.

Fractions 1+2 and 10+11, respectively, were pooled and the ethanol removed in a rotary evaporator. This gave 58 mg (46%) of optically pure >99% (+)-I and 17.5 mg (14%) of almost pure >93.5 (-)-I, respectively. The physical and chromatographic data of the enantiomers obtained are given in Table II.

While the (+)-enantiomer was the least retained on the MCTA-column, an opposite elution order was found on the Resolvosil column. On the latter, retention of both enantiomers increased with decreasing pH of the mobile phase.

The possible different pharmacological effect of the two antipodes will be investigated.

Table I. Enantiomeric purity of fractions collected from the MCTA column (Results obtained from analytical LC as described under Fig 2).

Fraction no	1	2	3	4	5	6	7	8	9	10	11
Volume, ml	25	25	12.5	12.5	12.5	12.5	12.5	12.5	25	25	12.5
Enantiomeric purity, %	100	99.2	96.0	38.2	35.1	61.9	70.6	83.0	84.6	>93.2*	>94.3*
Enantiomer	+	+	+	+	-	-	-	-	-	-	-

* A slight tailing of main (-) peak exaggerates the integration result from superimposed minor peak.

Table II. Data obtained for the enantiomers of chlormezanone

M.p.*, °C	$[\alpha]_{546}^{25}$	Enantiomeric purity, %	Retention values k'(MCTA)	α	k'(Resolvosil)	α
149.5-50.5	+23.8 (MeOH, c.1.1) +38.8 (CH_2Cl_2, c.0.7)	>99	2.31	1.35	2.03	1.34 (0.74)
147-50	-18.5 (MeOH, c.0.4)** -33.1 (CH_2Cl_2, c.0.4)**	>93.5	3.12		1.51	

* M.p. of rac. I: 114-5 °C (lit. (6): 116.2-8.2 °C)

** The discrepancy between the optical and enantiomeric purity found for (-)-I is probably due to a slight contamination with material liberated from the MCTA.

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References and Notes

1. K. Adam and I. Oswald, Br. J. Clin. Pharmacol., 14, 57 (1982).
2. MCTA (25-40 μ), obtained from Merck Co., Darmstadt, GFR, was swollen in ethanol before use.
3. A. Mannschreck, H. Koller and R. Wernicke, Kontakte (Merck), 1, 40 (1985).
4. Available from Macherey-Nagel GmbH, Düren, GFR.
5. S. Allenmark, B. Bomgren and H. Borén, J. Chromatogr., 264, 63 (1983).
6. Merck Index, 10th Ed., Merck & Co., Inc., Rahway, N.J., USA, 1983.

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