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ON THE THERMAL BEHAVIOUR OF ACETYLPHENYLHYDROXYACETICACID-4-NITROBENZYL ESTERS

Th. Beyrich, M. Schleuder, G. Mietz, H. Wulff[+] *and M. Gruno*

Department of Pharmacy, Institute of Drug Control
[+]Department of Chemistry, Institute of Physical Chemistry of Ernst Moritz Arndt University of Greifswald, Germany

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Abstract

The 4-nitrobenzyl ester of acetylphenylhydroxyacetic acid differs in its melting behaviour from other nitrobenzyl esters of phenylhydroxyacetic or acetylphenylhydroxyacetic acids, the racemate having a higher melting point than the enantiomers. By means of thermal analysis, IR spectroscopy and X-ray diffractometry the ester can be shown to occur in two crystalline modifications.

In the process of solidification of the molten mass, at first a modification of higher energy is formed, obviously being caused by an excess of one enantiomer, which is then exothermally rearranged in the lattice of the racemate.

Keywords: acetylphenylhydroxyaceticacid-4-nitrobenzyl esters, enantiomer, racemat, thermal behaviour

Introduction

Racemates as mixtures of equal proportions of enantiomers differ in their physical properties from those of the single enantiomers. Their melting behaviour corresponds to that of an eutectic. Therefore the melting point of the racemate can be expected to be lower than that of the pure enantiomer [1]. Within the scope of our studies on the resolution of chiral esters by means of chiral catalysts [2] we prepared the 4-nitrobenzyl esters of (R/S)-, (R)- and (S)-acetyl phenylhydroxyacetic acid. In this process we observed a surprising thermal behaviour which will be described below.

Experimental

The esters were synthesized by reaction of the sodium salt of phenylhydroxyacetic acid and nitrobenzyl chloride [3]. 2 g of phenylhydroxyacetic-4-nitrobenzyl ester were dissolved in 5 ml pyridine without heating, 15 ml of acetic anhydride were added and the mixture brought to the boil. After cooling,

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100 ml of water were added. The initially oily, later crystalline precipitate was recrystallised from petroleum ether (50–80°C).

(R/S)-Acetylphenylhydroxyaceticacid-4-nitrobenzyl ester(I) calcd. C 62.00; H 4.59; N 4.25; found C 62.25; H 4.39; N 4.53. (R)-I found C 62.86; H 4.24; N 4.15; $[\alpha]_D^{25}$: −60.5° (C=0.1 g/ml acetone). (S)-I found C 62.43; H 4.26; N 4.08; $[\alpha]_D^{25}$: +59° (C=0.1 g/ml acetone).

Thermoanalytical studies were made by means of a Netzsch, Type 404 S, DTA instrument. Sample mass: 20 mg, heating rate 2.7 deg·min^{-1}, Ni/Cr/constantan, measuring range 20 to 160°C, sensitivity 0.2 mV, Al_2O_3 crucible.

IR analyses were made with a Perkin Elmer FTIR 1650 instrument on KBr pellets or solutions in $CHCl_3$.

X-ray diffraction studies were made by means of a HZG4/APX 63 type (Seifert-FPM) diffractometer. The measurements were made in Bragg-Brentano geometry with CuK_α radiation and follow-up graphite monochromator (GSM-6) by means of step-by-step summation (angular range 5–50°/2Θ, step width 0.02°/2Θ).

Results and discussion

The melting point of the racemic mixture of (I) is 83°C (Fig. 1), but that of the enantiomers of (I) is 56 °C (Fig. 1).

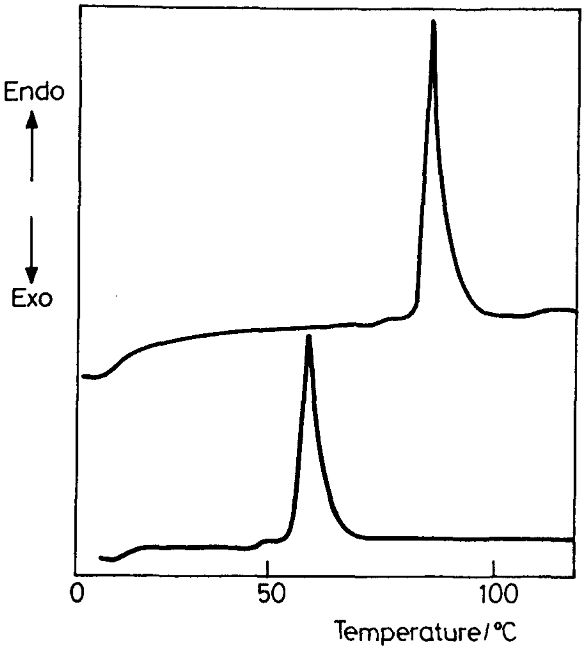

Fig. 1 DTA curves of (R/S)-4-Nitrobenzylester of acetylphenylhydroxyacetic acid (I)

A similar behaviour is shown by tartaric acid (*m.p.* 170°C) and racemic acid (*m.p.* 205°C) [5] or hyoscyamine (*m.p.* 107–109°C) and atropine (*m.p.* 114–117°C), for instance. According to this atropine is a pseudo racemate and racemic mixed crystal, respectively [4].

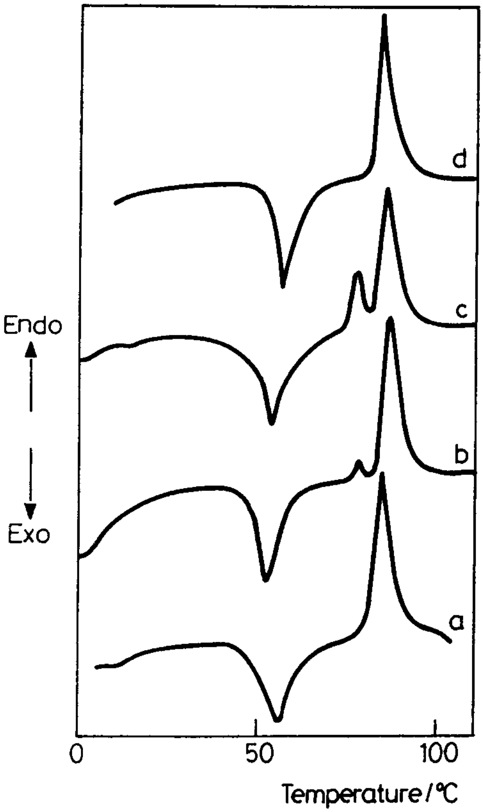

Fig. 2 Thermal behaviour of I after heating to 83° (a), 100° (b), to 105° (c) or to higher temperatures

Moreover, (I) shows a special thermal behaviour. If a sample is heated to 83°C, then rapidly cooled down to 8°C and again melted, an exothermal peak can be observed before the endothermal peak (Fig. 2a). This phenomenon is obviously based upon a lattice tension produced during crystallisation from the molten mass, which is connected with an elevated energy content and disappears with dissipation of energy before melting again [6]. A similarly polymorphic behaviour has recently been described for 2-bromothiophene, too [8].

If the molten mass is heated up to 100°C (Fig. 2b) and afterwards cooled down, an additional endothermal peak is observed, which is intensified when heating is continued up to 105°C (Fig. 2c), but cannot be found on heating up to still higher temperature (Fig. 2d). This should be a polymorphous modifica-

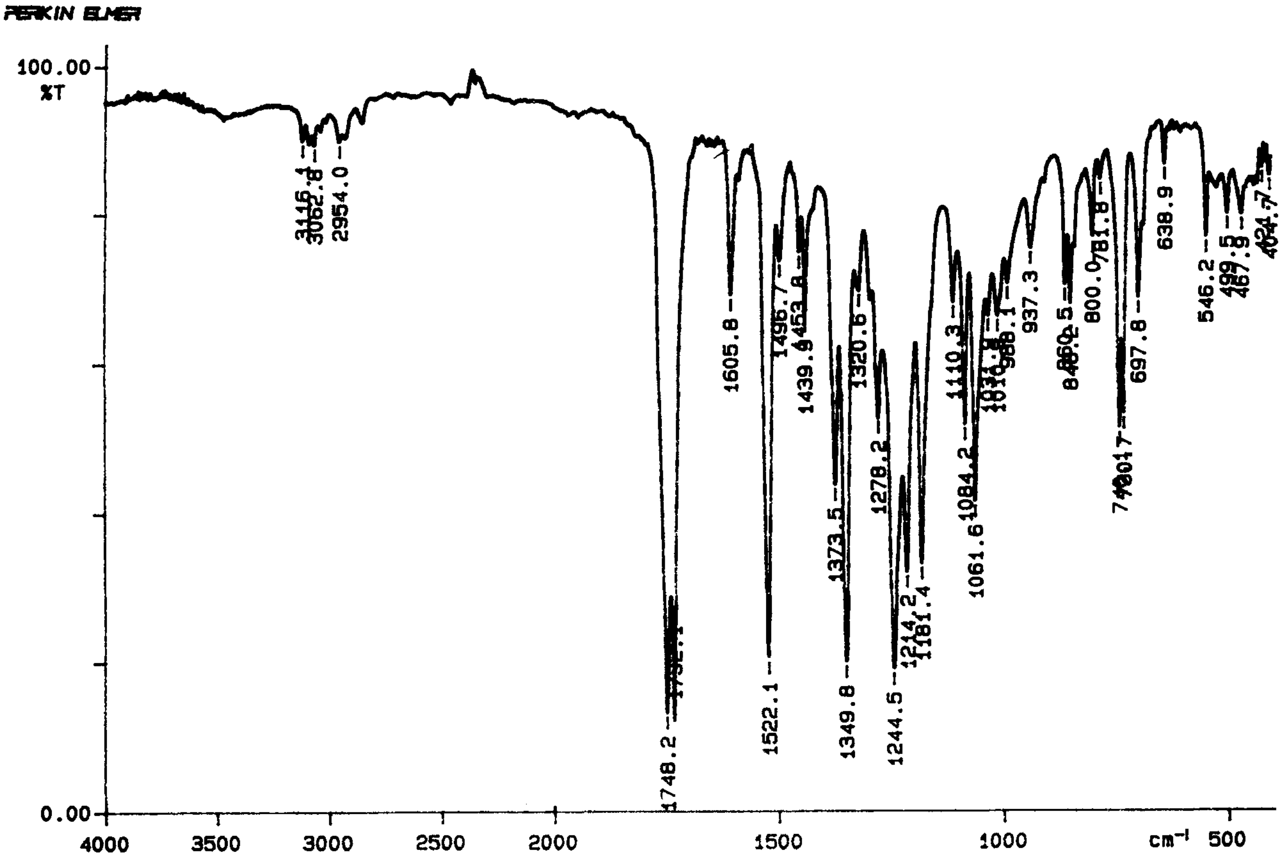

Fig. 3a IR spectrum of (I) after recrystallisation from petroleum ether

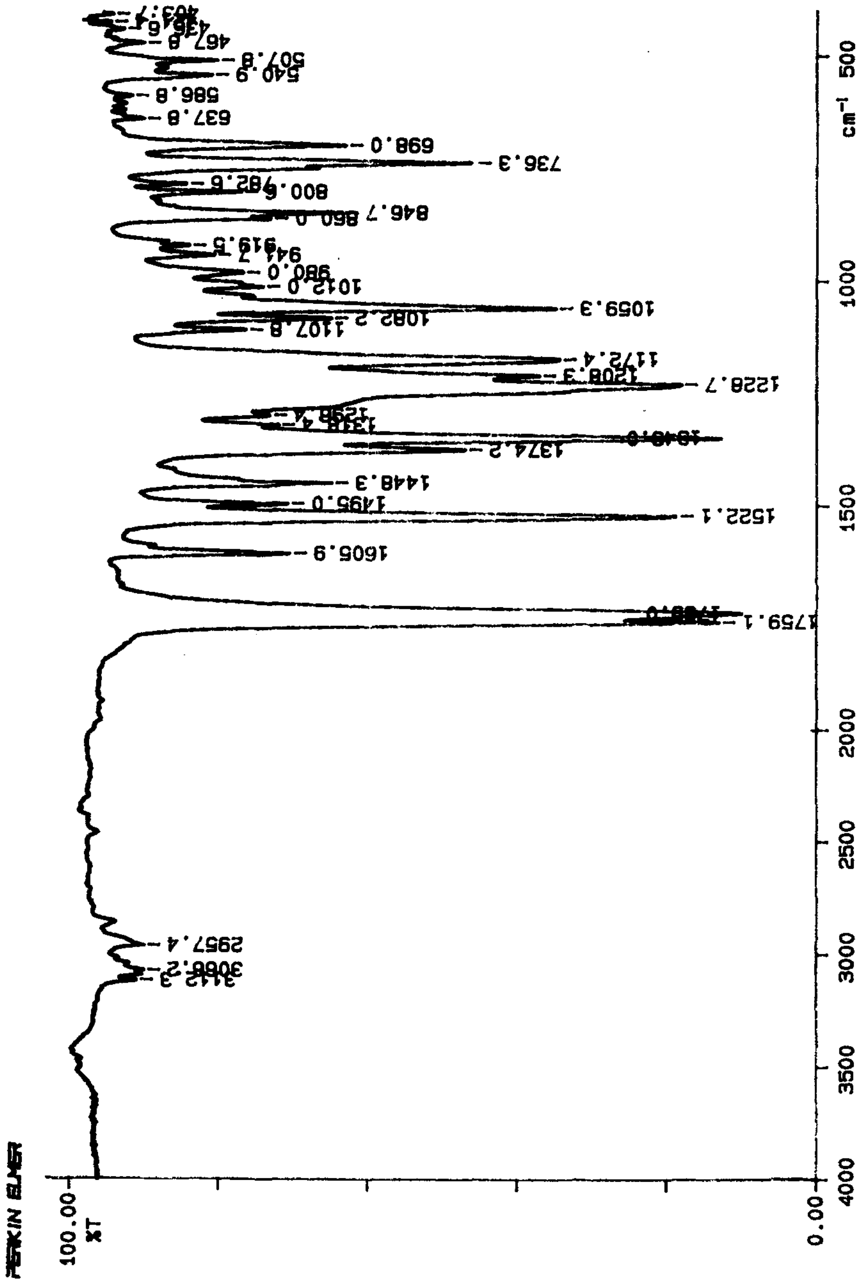

Fig. 3b IR spectrum of (I) after recrystallisation from the molten mass

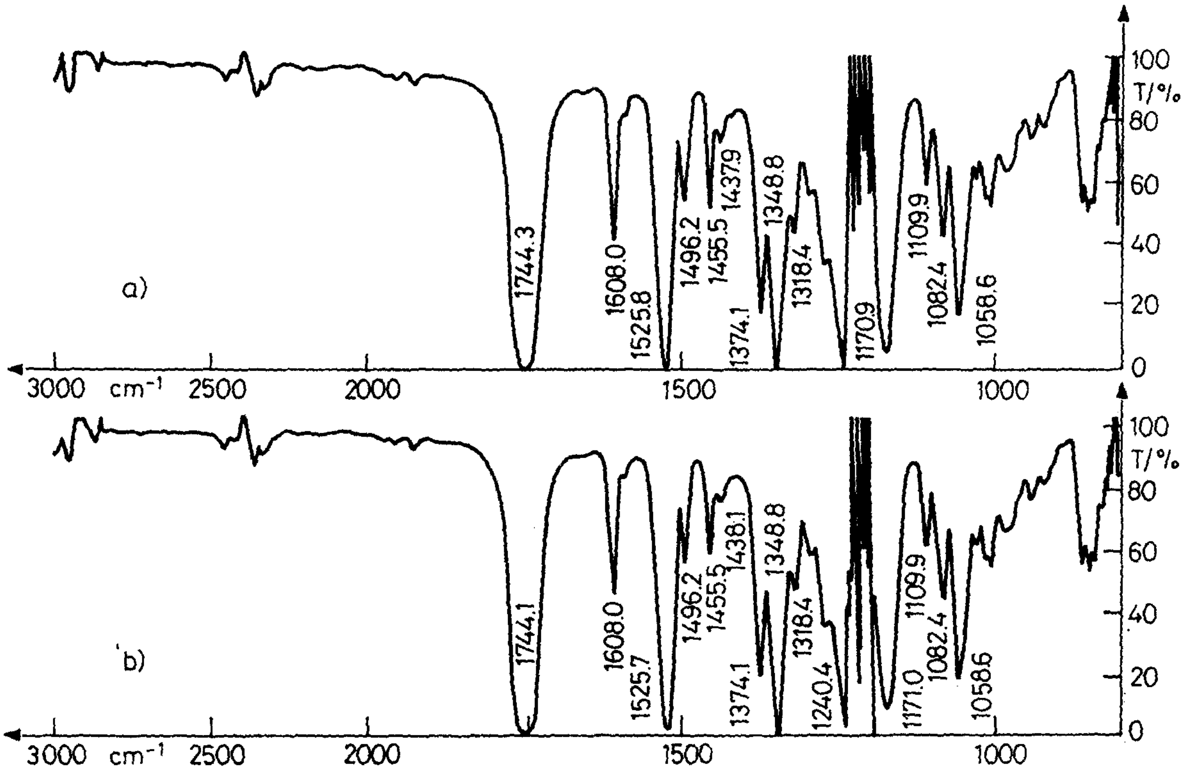

Fig. 4 IR spectra of both modifications of (I) in $CHCl_3$

tion, because this peak occurs on heating as well as on cooling, in opposite directions [6]. As the melting behaviour is reproducible even after repeated heating and cooling, chemical decomposition can be excluded.

This phenomenon, however, can only be observed in connection with crystallisation from the molten mass, and it is the more obvious the more rapidly crystallisation proceeds. As an exothermic peak accompanies the conversion, the process must be classified as an enantiotropic change of state [7].

The enantiomers R-(I) and S-(I) melt at 53–54°C. If they are mixed in a proportion of 1:1, this racemic mixture melts at 83°C. The enantiomers not showing any polymorphy, the phenomenon observed in R/S-(I) can be reproduced with the mixture. As the exothermic conversion temperature which can be recorded in the molten racemate and the melting temperatures of the enantiomers are identical, it can be supposed that the structure forming from the molten mass at first partially corresponds to the single optical antipodes from which the stable mixed crystal of the racemic form is produced.

To prove the polymorphic behaviour of (I), the molten mass was studied by IR spectroscopy. The spectrum obtained thereby (Fig. 3b) actually differs from that produced by the substance obtained after acetylisation of 4-nitrobenzyl ester of phenylhydroxyacetic acid (Fig. 3a). For the molten mass the double band of the carbonyl group is obviously higher. Striking differences in this range were observed with various modifications of hyoscyamine, too [4].

It can be concluded from the position of the carbonyl band that the carbonyl structure is more pronounced in the modification crystallising from the molten mass. On heating it is transformed to the stable structure by rearrangement. The spectra of the samples in chloroform are identical (Fig. 4).

Table 1 Melting ranges of phenylhydroxyacetic acid-nitrobenzyl esters

	m.p./°C	ΔH/kJ·mol^{-1}
(R/S)-Mandelic acid-4-nitrobenzylester	122–124	32.2
(R)-Mandelic acid-4-nitrobenzylester	143–145	46.6
(S)-Mandelic acid-4-nitrobenzylester	143–145	43.2
(R/S)-Mandelic acid-2-nitrobenzylester	88–91	32.4
(S)-Mandelic acid-2-nitrobenzylester	101–103	30.8
(R/S)-Acetylmandelic acid-4-nitrobenzylester	82–83	32.02
(R)-Acetylmandelic acid-4-nitrobenzylester	53–54	18.3
(S)-Acetylmandelic acid-4-nitrobenzylester	53–54	19.5
(R/S)-Acetylmandelic acid-2-nitrobenzylester	68–69	29.8
(S)-Acetylmandelic acid-2-nitrobenzylester	fl.	

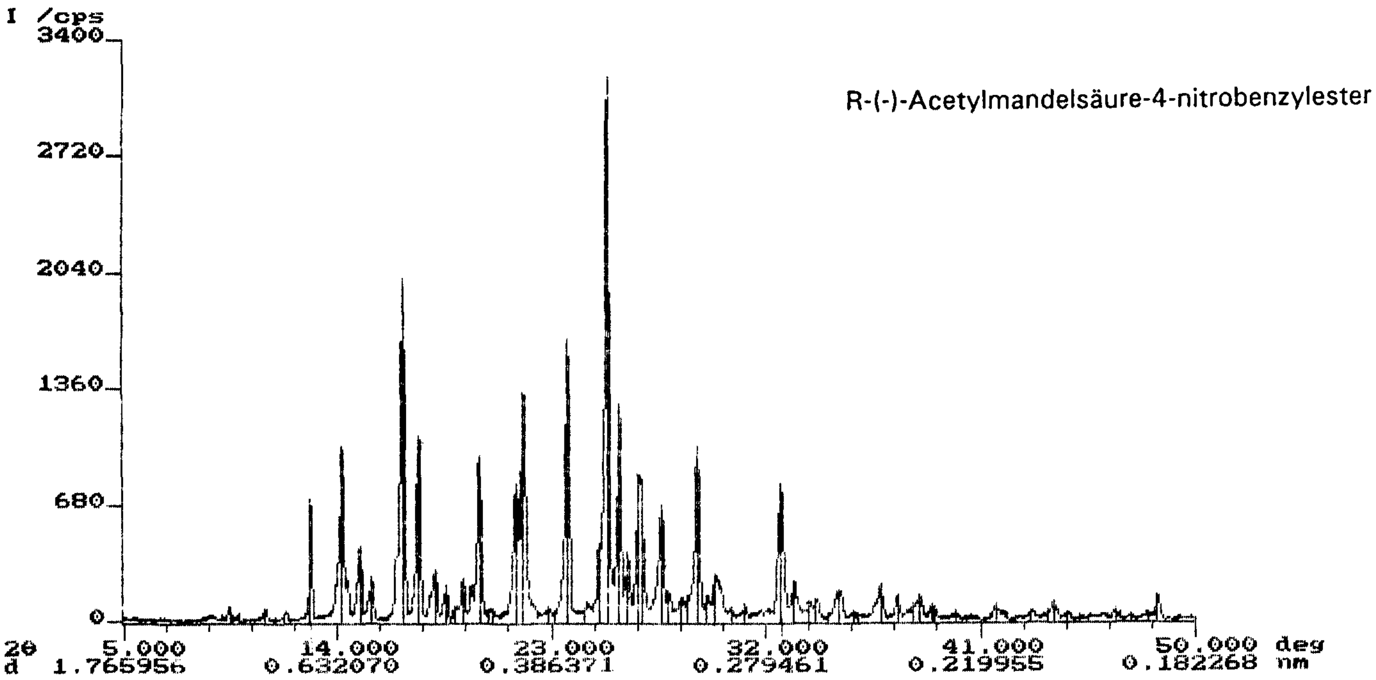

Fig. 5a X-ray diffractogram of R-(–)-(I) enantiomer

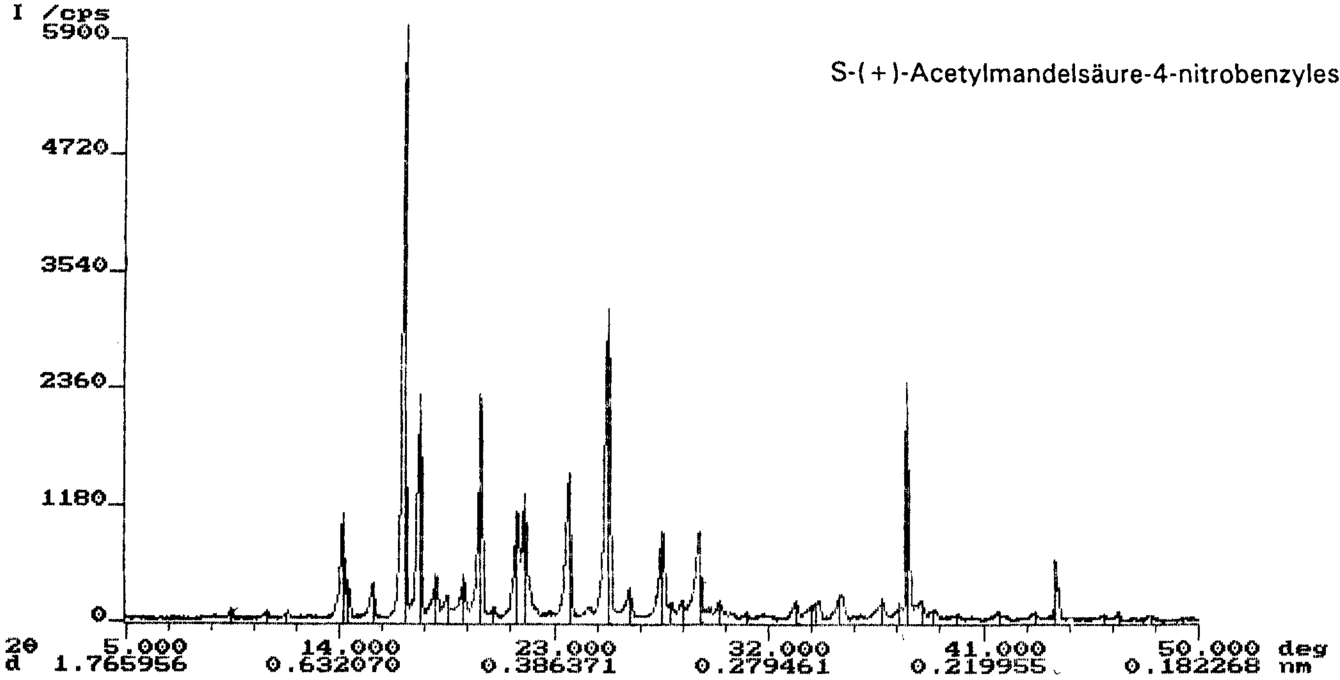

Fig. 5b X-ray diffractogram of S-(+)-(I) enantiomer

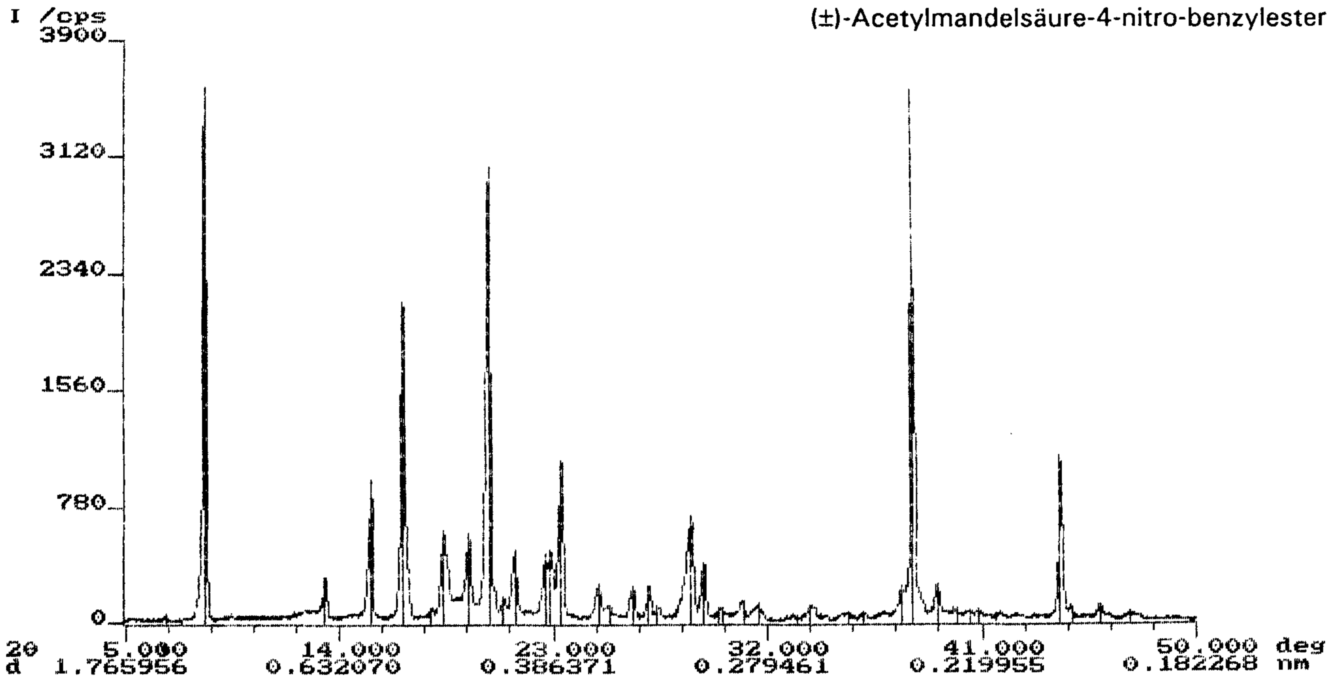

Fig. 5c X-ray diffractogram of (I) racemate from the molten mass

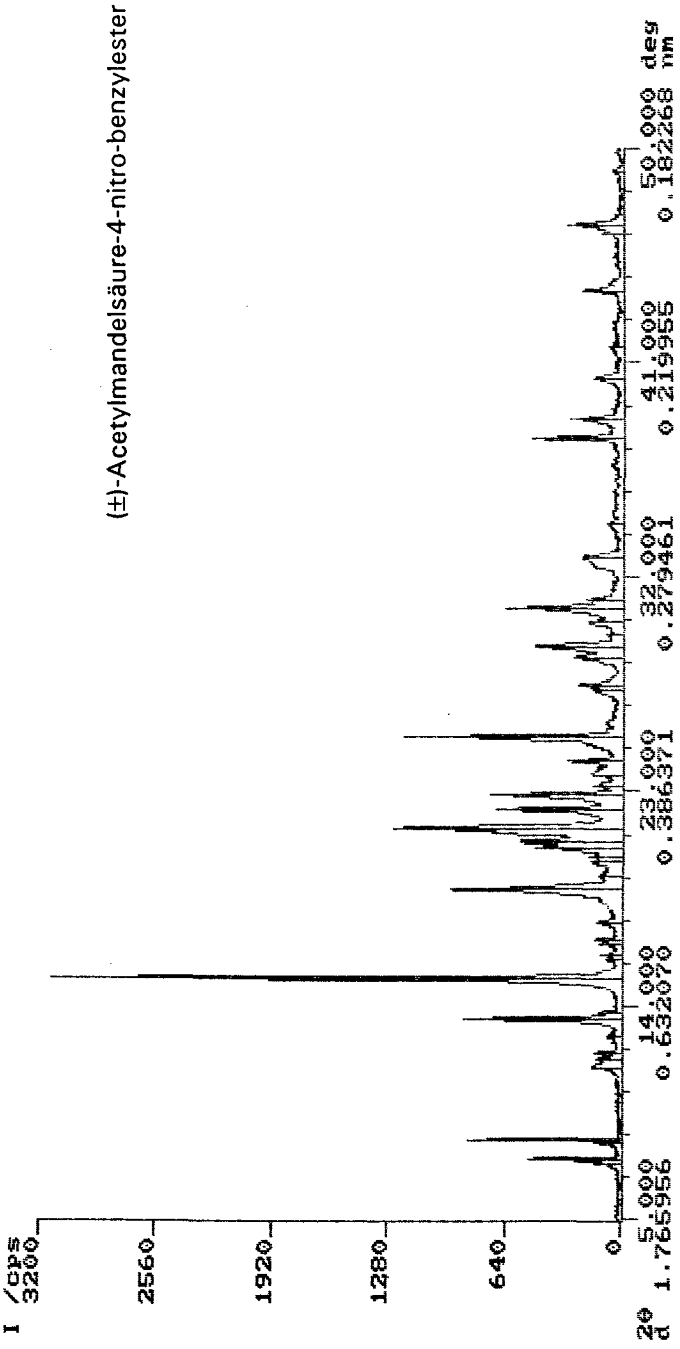

Fig. 5d X-ray diffractogram of (I) racemate after recrystallisation

Not only the enantiomers (Figs 5a and b) differ crystallographically from the racemic mixture, but also the modification produced from the molten mass (Fig. 5c) shows a crystal structure differing from that of the stable racemate (Fig. 5d). The formation of the stable modification is disturbed when, during crystallisation from the molten mass, one enantiomer temporarily dominates.

The phenomena mentioned can only be observed with (R/S)-I; neither the 2-nitrobenzyl ester of acetyl phenylhydroxyacetic acid nor the 4-nitrobenzyl ester of phenylhydroxyacetic acid produce any conversion points in the cooled molten mass. With these esters the racemic mixtures melt as eutectics, lower than their enantiomers (Table 1).

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Zusammenfassung — Der 4-Nitrobenzylester der Acetylmandelsäure zeigt im Gegensatz zu anderen Nitrobenzylestern der Mandel- oder Acetylmandelsäure ein abweichendes Schmelzverhalten, indem das Racemat höher schmilzt als die Enantiomeren. Mittels thermischer Analyse, IR-Spektroskopie und Röntgendiffraktometrie kann nachgewiesen werden, daß der Ester in zwei kristallinen Modifikationen auftritt. Beim Erstarren der Schmelze bildet sich zunächst eine energiereiche Modifikation, offensichtlich durch das Überwiegen eines Enantiomeren bedingt, die sich exotherm in das Gitter des Racemates umlagert.