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Enzymatic Resolution of N-Acetyl p-Nitrophenylserinates

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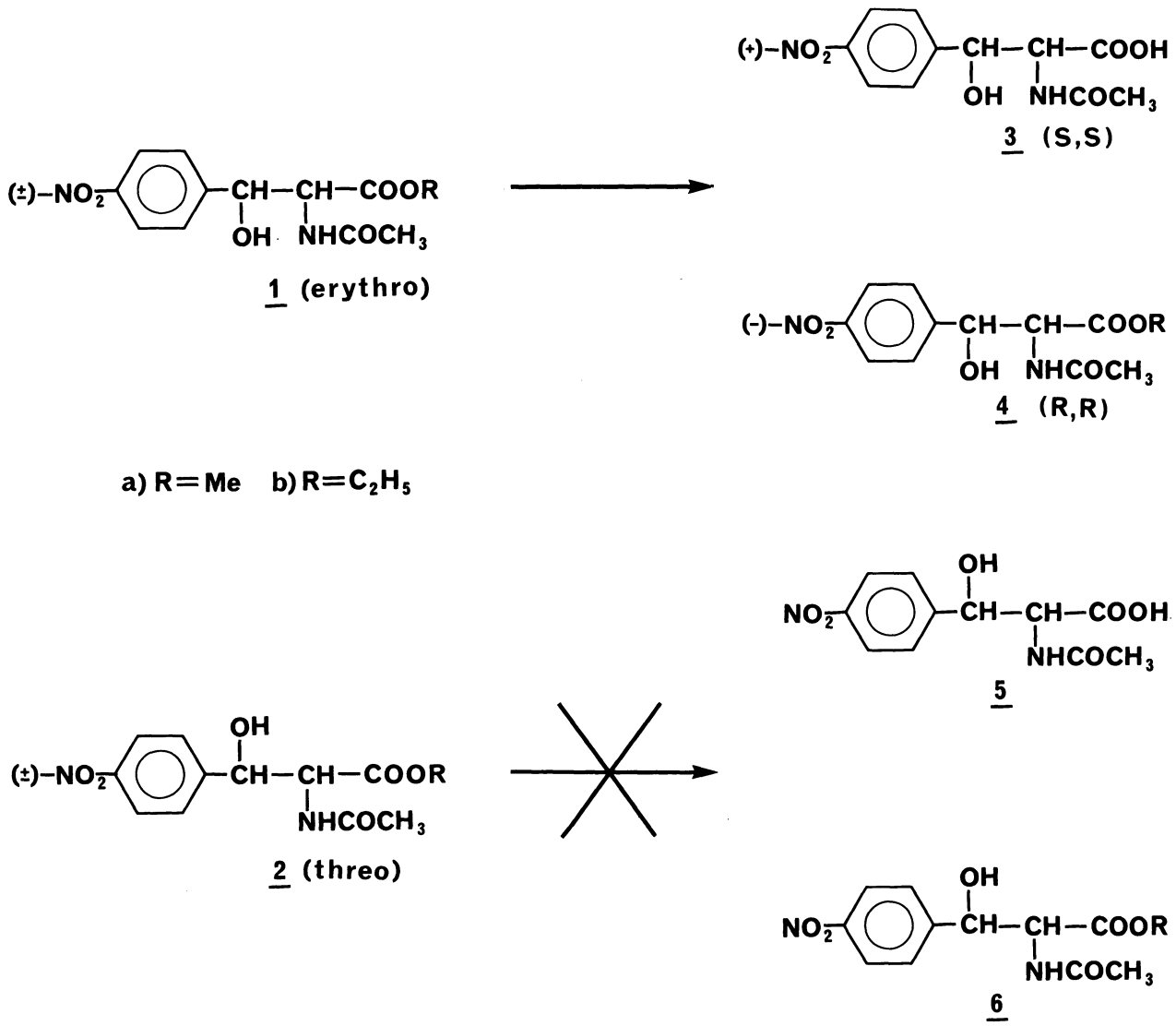
Asymmetric hydrolysis of alkyl (methyl and ethyl) (±)-erythro-p-nitrophenylserinates by α-chymotrypsin afforded optically active esters in optical purities above 95%, but alkyl (±)-threo-p-nitrophenylserinates were not hydrolyzed.

The great potential of enzymes as catalysts in synthetic organic chemistry is now well recognized.[1] In recent years, several hydrolytic enzymes have been used for the resolution of racemates[2] or the enantiotopic group differentiation in meso compounds.[3] We report here a study on the resolution of N-acetyl p-nitrophenylserinates by α-chymotrypsin[4] and esterase.[5] Derivatives of phenylserinates are intermediates in synthesis of natural compounds such as chloramphenicol,[6] chiral auxiliaries, resolving reagents, and precursors to chiral 2-oxazolines.[7]

The preparation of racemic alkyl (methyl and ethyl) p-nitrophenylserinates, suitably derivatized for enzymatic resolution, was accomplished in two steps according to known procedures. In the first step, p-nitrobenzaldehyde and alkyl glycinates were condensed to give alkyl p-nitrophenylserinates.[8,9] Azeotropic condensation of the two reactants led to the erythro configuration, but use of an excess of the glycine esters gave the threo compounds.[10,11] Acetylation with acetic anhydride and sodium acetate[12] gave racemic alkyl N-acetyl p-nitrophenylserinates 1 and 2 (Scheme 1).[13] A representative experimental procedure of enzymatic hydrolyses is the following: α-chymotrypsin (30 mg) in saline water (10 ml, 0.125 M in NaCl) was added at 25 °C to a magnetically stirred solution of N-acetyl p-nitrophenylserinate (2.25 mmol) in 0.125 M NaCl aqueous solution (100 ml). The pH of the reaction was immediately adjusted by the addition of 0.1 M aqueous sodium hydroxide to pH 7.8 and then maintained at this pH by further addition of base. This process was done manually using a burette. When the hydrolysis had virtually stopped (49% of the ester hydrolyzed and 98 ml of base consumed), the unhydrolysed ester was extracted with ether. The erythro compounds 1a and 1b were hydrolysed after ≈ 28 h. α-Chymotrypsin is inactive on threo compounds and esterase (pH 7.0, 25 °C, aqueous KCl 0.1 M as solvent) is inactive on both series. The acid 3 was not recuperated and enantiomeric composition of the unhydrolysed erythro esters 4a and 4b were determined by nmr analysis using tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato] europium (III) as a chiral shift reagent.[14] Figure 1A shows the well resolved signals for the methyl



Scheme 1.

group ($\underline{CH_3}CONH$-) of racemic 1b in the presence of 0.1 equiv. of $Eu(hfc)_3$. The partial spectrum (Fig. 1B) of the hydrolysis product shows a large singlet for one enantiomer and a small singlet for the other one. The optical purity is 96%. The same method was applied for compound 1a using the signals of methyl ester group ($COO\underline{CH_3}$). In this case, a signal due to the shift reagent interfere somewhat and the optical purity is $\geqslant$ 95% (Fig. 2). Chymotrypsin catalyses the hydrolysis of the enantiomer having the same configuration on carbon two (S or L) as the natural standard amino-acids. Specific rotations of each enantiomer of ethyl ester are known[15] and correlation between methyl and ethyl ester was established by transesterification.

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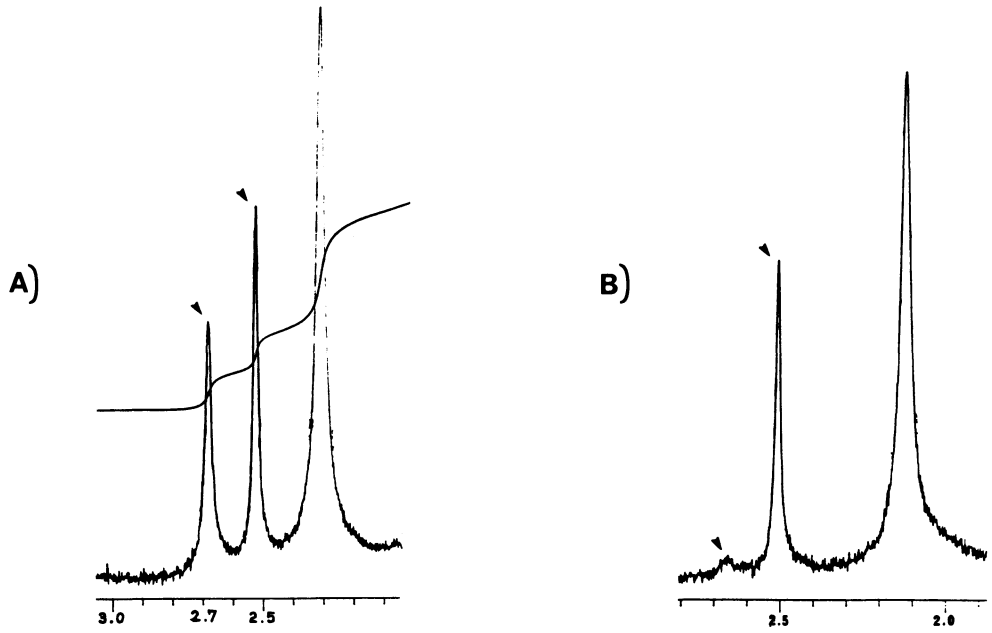

Fig. 1. 200-MHz ^{1}H-NMR spectra of a solution prepared from (A) racemic ethyl p-nitrophenylserinate and (B) the product obtained by enzymatic resolution, in the presence of Eu(hfc)$_3$.

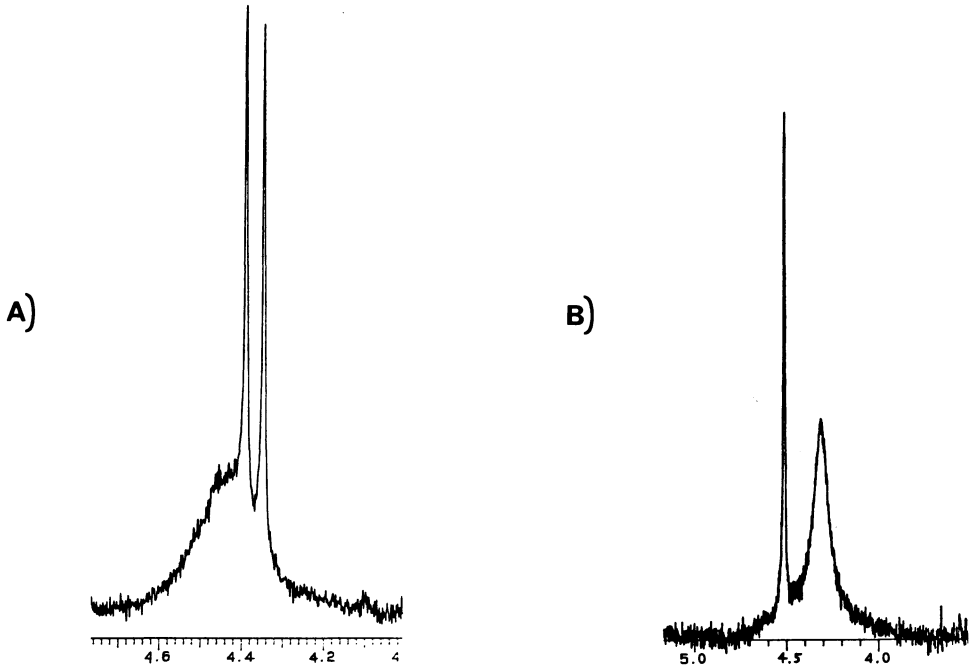

Fig. 2. 200-MHz ^{1}H-NMR spectra of a solution prepared from (A) racemic methyl p-nitrophenylserinate and (B) the product obtained by enzymatic resolution, in the presence of Eu(hfc)$_3$.

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13) All compounds of the ethyl series have been previously reported[15] but in view of the fact that spectroscopic data are limited, we checked their structures by modern techniques (200 MHz NMR, IR, MS). Compounds 1a and 2a gave satisfactory elemental analysis and their spectroscopic data are the following: compound 1a: mp 179-181 °C; IR (KBr) 3300, 3500-3100, 1735, 1635, 1500, 1328, 1200 cm^{-1}; ^1H NMR (DMSO-D_6) 1.73 (3H, s, NH-$\underline{COCH_3}$), 3.59 (3H, s, $COO\underline{CH_3}$), 4.52 (1H, t, J = 8.5 Hz, $\underline{CH}COO$), 4.85 (1H, dd, J_1= 8.5 Hz, $\underline{CH}OH$), 6.14 (1H, d, J = 6.9 Hz, $\underline{OH}$), 7.62 (2H, d, J = 8.5 Hz, H meta to NO_2 group), 8.18 (2H, d, J = 8.5 Hz, H ortho to NO_2 group), 8.43 (1H, d, J = 8.5 Hz, $\underline{NH}$); MS (70 e.v.) 282 (M^+). Compound 2a: mp 195-197 °C; IR (KBr) 3360, 1745, 1650, 1608, 1520, 1340, 1215 cm^{-1}; ^1H NMR (DMSO-D_6) 1.74 (3H, s, $NHCO\underline{CH_3}$), 3.65 (3H, s, $COO\underline{CH_3}$), 4.73 (1H, dd, J_1= 3.4 Hz, J_2= 8.8 Hz, $\underline{CH}COO$), 5.29 (1H, d, J = 3.4 Hz, $\underline{CH}OH$), 6.21 (1H, d, J = 5.0 Hz, $\underline{OH}$), 7.70 (2H, d, J = 8.8 Hz, H meta to NO_2 group), 8.16 (2H, d, J = 8.8 Hz, H ortho to NO_2 group), 8.27 (1H, d, J = 8.8 Hz, $\underline{NH}$); MS (70 e.v.) 282 (M^+).

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