The Preparation of *O*-Benzyl-L-serine

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Summary The partially resolved mixture of enantiomers obtained in the Wünsch–Fürst resolution of *N*-formyl-*O*-benzyl-DL-serine may be separated by selective solubilisation without resource to a second resolving agent; this provides a more convenient and cheaper route to *O*-benzyl-L-serine.

VARIOUS esters and *N*-acyl derivatives of *O*-benzyl-L-serine are now frequently used in classical and solid-phase peptide synthesis. Their preparation is, however, laborious. Direct benzylation of L-serine derivatives leads generally to unsatisfactory products; *N*-t-butoxycarbonyl-L-serine is claimed to give *O*-benzyl-*N*-t-butoxycarbonyl-L-serine in 45% yield,[1] but in our hands the yield of pure product was much lower, and the preparation was unattractive on the large scale. The preferred route in most laboratories involves a resolution[2] of *N*-formyl-DL-serine, itself readily available from ethyl acrylate.[3,2] In this resolution, *N*-formyl-*O*-benzyl-D-serine is first separated by the use of brucine; an ethanolic solution of the racemate and brucine is cooled and the insoluble *N*-formyl-*O*-benzyl-D-serine diastereoisomeric salt is collected in 83% yield. After acidification of the ethanolic mother liquors, a product is obtained consisting of *N*-formyl-*O*-benzyl-L-serine and *N*-formyl-*O*-benzyl-DL-serine (*ca.* 2:1). By the existing procedure, the L-isomer is separated from this mixture, often with difficulty, by the use of a second resolving agent (quinine). We now find, as a further example of the general principle described by Leigh,[4] that the L-isomer may be separated without resource to a resolving agent by virtue of differences in the solubility of the two species. Several solvents capable of hydrogen bonding were investigated and n-butanol was found most satisfactory. Thus, after brief stirring of the mixture with anhydrous ether and n-butanol (2:1 v/v) only the L-isomer dissolved; evaporation led to 82% recovery of pure *N*-formyl-*O*-benzyl-L-serine.

On the scale described by Wünsch and Fürst,[2] the resolution proceeded as follows. *N*-Formyl-*O*-benzyl-DL-serine (3·8 mol) gave *N*-formyl-*O*-benzyl-D-serine brucine salt (83%) and a mixture (450 g) of *N*-formyl-*O*-benzyl-L-serine and the DL-isomer. This was suspended in anhydrous ether (9 l), n-butanol (4·5 l) was added, and the mixture was stirred at 22—24° for 30 min. The DL-isomer (210 g, 25%) was filtered off, and the filtrate was evaporated, to give *N*-formyl-*O*-benzyl-L-serine (240 g, 57%), $[\alpha]_D^{25}$ +48·4° (*c* 3·5 in 80% EtOH). The two formyl derivatives afforded *O*-benzyl-D-serine, $[\alpha]_D^{25}$ −23·3° (*c* 2 in 80% aqueous AcOH + 1 equiv. HCl) and *O*-benzyl-L-serine, $[\alpha]_D^{25}$ +22·8° (*c* 2 in 80% aqueous AcOH + 1 equiv. HCl) in 94% yield.

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