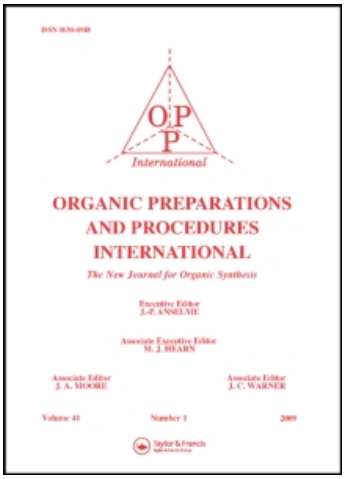

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SYNTHESIS OF [S-(R*,R*)]- ETHYL α-[(1-CARBOXYETHYL)AMINO]-BENEZENEBUTANOATE, AN IMPORTANT INTERMEDIATE IN THE SYNTHESIS OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS

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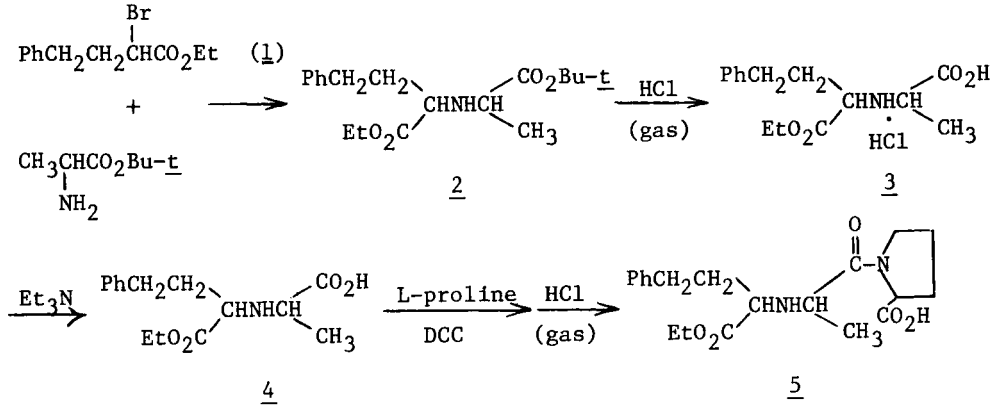
Recent work in our laboratories on the synthesis of angiotensin converting enzyme inhibitors (ACE inhibitors) required the title compound 4b as an intermediate. This paper describes an efficient synthesis of this compound, referred to in the text as the S,S-isomer. This intermediate can also be used in the synthesis of MK-421 (5), an ACE inhibitor reported by Merck, although the Merck publications[1,2] describe a different route to MK-421 (5). The synthesis is outlined below.



a) (R,S) b) (S,S)

Condensation of ethyl α-bromobenzenebutanoate 1[3,4] with the t-butyl ester of L-alanine[5,6] in acetonitrile in the presence of triethylamine gave the condensation product 2 as an oil of approximately equal amounts of diastereomers, which was used directly in the following step.

The t-butyl group could be removed with neat trifluoroacetic acid, or more conveniently, with HCl gas in dichloromethane, a process that not only cleaved the t-butyl group, but also provided a means of separating the diastereomers present.

The insoluble material from this cleavage was shown (vide infra) to be 3a, the undesired R,S-diastereomer. 3b was isolated from the dichloromethane soluble portion. Neutralization of 3b to the free amino acid followed by recrystallization from ethyl acetate provided pure 4b, the desired S,S-diastereomer.

Compound 4b was condensed with t-butyl L-proline using dicyclohexylcarbodiimide in the presence of 1-hydroxybenzotriazole. The t-butyl group of the resulting diester was cleaved with HCl gas in dichloromethane and the isolated hydrochloride salt converted to the maleate salt identical in all respects with MK-421. Since the absolute configuration of MK-421 is known,[1] this establishes the stereochemistry of the more soluble isomer 3b (and its zwitterionic form 4b) as the S,S-diastereomer. The less soluble 3a (and its zwitterionic form 4a) is thus the R,S-diastereomer.

This synthesis provides an efficient and convenient route to this important intermediate.

EXPERIMENTAL

HPLC analyses were carried out on a C18 Reverse Phase Alltech Column using 40% acetonitrile/60% 0.005 M Pic A as the solvent. Peaks were detected by UV at 210 nm.

Ethyl α-[[1-[(1,1-dimethylethoxy)carbonyl]ethyl]amino]benzenebutanoate (2).- A solution of 40.0 g (0.148 mole) of ethyl α-bromobenzene butanoate 1, 22.5 g (0.148 mole) of the 1,1-dimethylethyl ester of L-alanine, and 20.6 ml (0.148 moles) of triethylamine in 400 ml of acetonitrile was heated at reflux for 40 hours. The solvent was removed under reduced pressure and the residue was taken up in ether. The ether suspension was washed with H_2O, sat. $NaHCO_3$, and again with H_2O. After drying over $MgSO_4$ the solvent was removed under reduced pressure. The oily residue was taken up in 500 ml of hexane, charcoaled, filtered through Celite, and evaporated under reduced pressure to give 48.4 g (98% yield) of 2 as a pale yellow oil. VPC analysis showed this to be 88% pure as an approximately equal mixture of diastereomers. $[\alpha]_D^{23}$ -20.2° (c = 1.17, MeOH). NMR ($CDCl_3$): δ 7.2 (s, 5H, phenyl), 4.15 (q, 2H, $C\underline{H}_2CH_3$), 3.25 (m, 2H, C<u>H</u>), 2.7 (m, 2H, $C_6H_5C\underline{H}_2$), 2.0 (m, 3H, $C\underline{H}_2$ and N<u>H</u>), 1.45 (s, 9H, $(C\underline{H}_3)_3$), 1.3 (m, 6H, $CH_3C\underline{H}_2$ and $C\underline{H}_3$).

Cleavage of 2 and Separation of the Diastereomers

A. [R-(R*,S*)]- Ethyl α-[(1-Carboxyethyl)amino]benzenebutanoate·HCl. (The R,S-isomer, 3a).- A solution of 43.4 g (0.116 mole) of 2 in 430 ml of dichloromethane containing 7.5 ml of tetrahydrofuran was saturated with HCl gas and stirred at room temperature for 1.5 hours. The mixture was then resaturated with HCl gas, at which time a solid began to precipitate. The mixture was stirred at room temperature overnight. The precipitated solid was collected, washed with CH_2Cl_2 and then ether. There was obtained 17.0 g (93% yield) of 3a as a white solid, mp. 202-204° (dec.), $[\alpha]_D^{23}$ - 28.1° (c = 1.04, MeOH). HPLC analysis showed this to be 98.9% of the R,S isomer.

NMR (DMSO-d_6): δ 7.2 (s, 5H, phenyl), 4.2 (q, 2H, $CH_3\underline{CH_2}$), 4.05 (m, 2H, $\underline{CH}$), 2.7 (m, 2H, $C_6H_5\underline{CH_2}$), 2.2 (m, 2H, $\underline{CH_2}$), 1.5 (d, 3H, $\underline{CH_3}$), 1.25 (t, 3H, $\underline{CH_3}CH_2$).

Anal. Calcd. for $C_{15}H_{22}ClNO_4$: C, 57.05 H, 7.02 N, 4.44

Found: C, 56.97 H, 7.08 N, 4.37

A small sample, recrystallized twice from MeOH/Et_2O had mp. 203-205° (dec.), $[\alpha]_D^{23}$ - 29.7° (c = 1.11, MeOH). HPLC analysis showed 100% of the R,S-isomer.

B. [S-(R*,R*)]- Ethyl α-(1-Carboxyethyl)amino]benzenebutanoate·HCl. (The S,S-isomer, 3b).- The filtrate from the preparation of 3a was evaporated under reduced pressure and the residue taken up in 70 ml of CH_2Cl_2. The hazy solution was filtered, diluted with 70 ml of CH_2Cl_2, and 400 ml of ether added to the cloud point. The mixture was seeded with a crystal of 3b and allowed to crystallize overnight. The product was collected, washed with ether, and dried to give 18.3 g (99% yield) of 3b as a white solid, mp. 127-128°, $[\alpha]_D^{23}$ + 25.6° (c = 1.03, MeOH). HPLC analysis showed this to be 92.3% of the S,S-isomer.

NMR (DSMO-d_6): δ 7.2 (S, 5H, phenyl), 4.2 (q, 2H, $CH_3\underline{CH_2}$), 4.1 (m, 2H, $\underline{CH}$), 2.7 (m, 2H, $C_6H_5\underline{CH_2}$), 2.2 (m, 2H, $\underline{CH_2}$), 1.5 (d, 3H, $\underline{CH_3}$), 1.25 (t, 3H, $\underline{CH_3}CH_2$).

Anal. Calcd. for $C_{15}H_{22}ClNO_4$: C, 57.05 H, 7.02 N, 4.44

Found: C, 56.74 H, 6.98 N, 4.36

A small sample, prepared from 4b and recrystallized from acetone/Et_2O had mp. 139-141°, $[\alpha]_D^{23}$ +33.3° (c = 1.03, MeOH). HPLC analysis showed 100% of the S,S-isomer.

Conversion to the Zwitterions and Purification of the Separated Isomers.

A. [R-(R*,S*)]- Ethyl α-[(1-Carboxyethyl)amino]benzenebutanoate. (The R,S-isomer, 4a). A solution of 9.7 g (31 mmoles) of 3a in 120 ml of H_2O was cooled to 5° and treated with 4.3 ml (31 mmoles) of triethylamine. After stirring for two minutes, the mixture was extracted four times with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with H_2O and dried over $MgSO_4$. Removal of the solvent under reduced pressure left 6.5 g of crude 4a. Recrystallization from 80 ml of ethyl acetate gave 4.5 (53% yield) of 4a as a white solid, mp. 135-137°, $[\alpha]_D^{23}$ - 24.9° (c = 0.83, MeOH). HPLC analysis showed this to be 98.4% of the R,S-isomer.

NMR (DMSO-d_6): δ 7.2 (S, 5H, phenyl), 4.1 (q, 2H, CH_3CH_2), 3.2 (m, 2H, CH), 2.7 (m, 2H, $C_6H_5CH_2$), 1.8 (m, 2H, CH_2), 1.2 (m, 6H, CH_3, CH_3CH_2).

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.49 H, 7.58 N, 5.01

Found: C, 64.52 H, 7.58 N, 4.95

A small sample, recrystallized from ethyl acetate had mp. 136-137°, $[\alpha]_D^{23}$ -27.1° (c = 1.09, MeOH). HPLC analysis showed 100% of the R,S-isomer.

B. [S-(R*,R*)]- Ethyl α-[(1-Carboxylethyl)amino]benzenebutanoate. (The S,S-isomer, 4b). A solution of 18.2 g (57.8 mmoles) of 3b in 180 ml of tetrahydrofuran was filtered to remove traces of 3a. To this solution was then added 8.1 ml (57.8 mmoles) of triethylamine and the mixture stirred for five minutes. The precipitated triethylamine hydrochloride was collected and washed with tetrahydrofuran. The tetrahydrofuran was removed under reduced pressure and the residue recrystallized

from 160 ml of ethyl acetate to give 13.2 g (82% yield) of 4b as a white solid, mp. 148-150°, $[\alpha]_D^{23}$ + 28.6° (c = 1.07, MeOH). HPLC analysis showed this to be 99% of the S,S-isomer.

NMR (DMSO-d_6): δ 7.2 (S, 5H, phenyl), 4.1 (q, 2H, $CH_3\underline{CH_2}$), 3.2 (m, 2H, $\underline{CH}$), 2.7 (m, 2H, $C_6H_5\underline{CH_2}$), 1.8 (m, 2H, $\underline{CH_2}$), 1.2 (m, 6H, $\underline{CH_3}$ and $\underline{CH_3}CH_2$).

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.49 H, 7.58 N, 5.01

Found: C, 64.20 H, 7.34 N, 4.95

A small sample recrystallized twice from ethyl acetate had mp. 150-151°, $[\alpha]_D^{23}$ +29.1° (c = 1.03, MeOH). HPLC analysis showed 100% of the S,S,-isomer.

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