

SYNTHESES OF MACROCYCLES FROM L-AMINO ACID (II)

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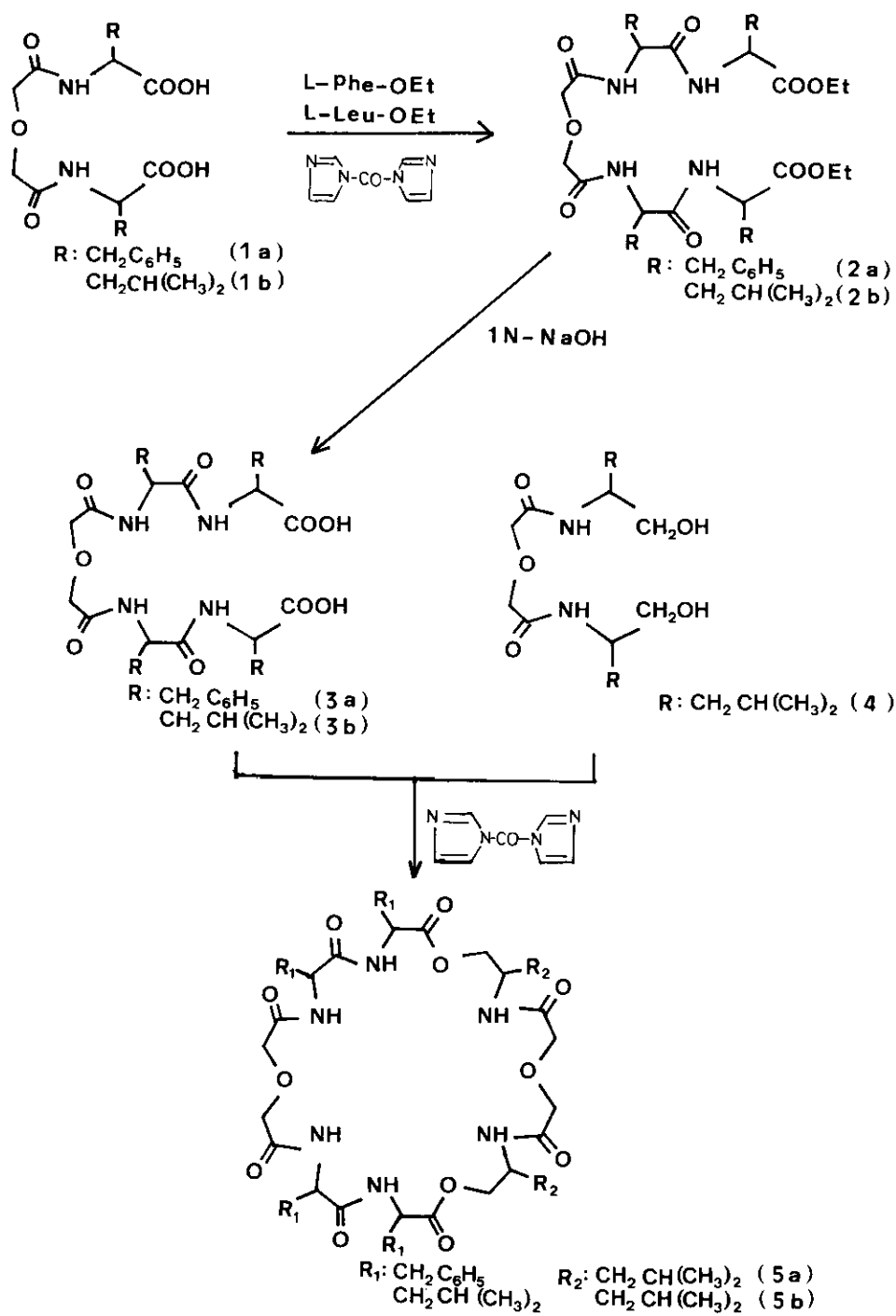
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Abstract - Syntheses of 30-membered macrocycles were achieved by using diglycolic acid, L-phenylalanine and L-leucine as constituents.

We previously reported the syntheses of 24-membered macrocycles using L-phenylalanine and L-leucine¹ which were then used to study the transport of some amino ester salts through an organic liquid membrane². When used as a carrier, they slightly increased the transport rate of L-phenylalanine methyl ester compared with 18-crown-6, but had little effect on the transport of other amino ester salts. This suggested that their ring size was not sufficient to bind the primary ammonium cation.

In this study, we prepared 30-membered macrocycles with similar structures. The reaction of dicarboxylic acid (1a)^{1,3} with L-phenylalanine ethyl ester or dicarboxylic acid (1b)¹ with L-leucine ethyl ester in anhydrous tetrahydrofuran using N,N'-carbonyldiimidazole gave ethyl diester (2a) or (2b), respectively. Hydrolysis of these ethyl diesters with a slight excess of 1 N NaOH in methanol with stirring at 40°C gave the dicarboxylic acid (3a) and (3b).

To the dicarboxylic acid (3b) in anhydrous tetrahydrofuran, was added an equivalent of N,N'-carbonyldiimidazole under ice-cooling and stirring. After 1 hour, the diol (4)¹ in anhydrous tetrahydrofuran was added gradually and stirring was continued for 1 day. Next, the mixture was treated in the usual way, the crude product was purified by silica gel column chromatography. Elution with diethyl ether afforded the pure 30-membered macrocycle (5b). Macrocycle (5a) was similarly prepared from dicarboxylic acid (3a) and diol (4), but the yield was very poor. Therefore, cesium chloride was added before the gradual addition of diol (4) in anhydrous tetrahydrofuran. The reaction mixture was stirred for



3 days. An additional half equivalent of N,N'-carbonyldiimidazole was added to the mixture, and the stirring was continued for another day. After the general treatment of the mixture, the crude product was purified by silica gel column chromatography using ethyl acetate as the eluent to obtain compound (5a). The structures of the compounds were confirmed from elemental analyses (for 2a, 3a, 3b, 5a, 5b) and mass spectral data (for 2a, 2b, 3b, 5b).

EXPERIMENTAL

All melting points were measured with a Yanaco MP-S3 apparatus and are uncorrected. Mass spectra were taken with a Hitachi RMU-6MG spectrometer.

Ethyl diester (2a)

The dicarboxylic acid (1a) (7.71 g) was dissolved in anhydrous tetrahydrofuran (150 ml), and N,N'-carbonyldiimidazole (6.42 g) was added to this solution under ice-cooling. After the effervescence had ceased, the solution was stirred for 1 h and then L-Phe-OEt HCl (8.27 g) was added. Next, triethylamine (5.02 ml) in anhydrous tetrahydrofuran was added dropwise over a period of 1 h under stirring at 0°C. The reaction mixture was stirred for 20 h at room temperature. The solvent was evaporated in vacuo and to the residue was added a large amount of ethyl acetate. This solution was washed with 10% hydrochloric acid, aqueous 10% sodium bicarbonate solution and brine, then dried over anhydrous magnesium sulfate and evaporated in vacuo.

Recrystallization of the residue from ethanol gave ethyl diester (2a) (11.92 g, 85.0%), mp 175.0-177.0°C, MS m/e: 778(M⁺). Anal. Calcd for C₄₄H₅₀O₉N₄: C, 67.85; H, 6.47; N, 7.19. Found: C, 67.45; H, 6.50; N, 7.02.

Ethyl diester (2b)

The above procedure gave an oily residue (an almost quantitative yield), a portion of which was purified by column chromatography on silica gel. Elution with ethyl acetate afforded the pure oily ethyl diester (2b), MS m/e: 642(M⁺). The crude product was used for the next step without further purification.

Dicarboxylic acid (3a)

The ethyl diester (2a) (1.11 g) was dissolved in 60 ml of hot methanol. To the

solution was added dropwise 1 N NaOH solution (5.7 ml) at 40°C under vigorous stirring for 1 h and then with stirring for 7 h. The methanol was evaporated in vacuo, then the remaining aqueous solution was extracted with ethyl acetate. The aqueous layer was acidified with 10% hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo.

Usually the crude residue was sufficiently pure to be used for the next step (1.02 g, 99.1%), mp 166.0-167.0°C. For analysis, a portion of the dicarboxylic acid was recrystallized from tetrahydrofuran-benzene. Anal. Calcd for $C_{40}H_{42}O_9N_4$: C, 66.47; H, 5.86; N, 7.75. Found: C, 66.28; H, 5.92; N, 7.46

Dicarboxylic acid (3b)

The crude ethyl diester (2b) (5.01 g) was dissolved in methanol (20 ml), and then 1 N NaOH (23.4 ml) was added at 0°C, followed by stirring for 7 h at 40°C. The same treatment of (3a) gave a residue which was recrystallized from ethyl acetate, yielding dicarboxylic acid (3b) (2.98 g, 65.2%), mp 110.0-112.0°C, MS m/e: 586:(M⁺). Anal. Calcd for $C_{28}H_{50}O_9N_4$: C, 57.32; H, 8.59; N, 9.55. Found: C, 57.27; H, 8.96; N, 9.42.

30-membered macrocycle (5a)

To a solution of dicarboxylic acid (3a) (6.17 g) in anhydrous tetrahydrofuran (85 ml) was added N,N'-carbonyldiimidazole (2.76 g) at 0°C. The solution was permitted to stand for 1 h after the effervescence had subsided, and then cesium chloride (14.3 g) and a solution of the diol (4) (2.83 g) in anhydrous tetrahydrofuran (40 ml) were added. The reaction mixture was stirred for 3 days. Next, N,N'-carbonyldiimidazole (1.38 g) was added, and the mixture was stirred for an additional day. The solution was filtered, the filtrate was evaporated in vacuo, and a large amount of ethyl acetate was added to the residue. The mixture was washed with 10% hydrochloric acid, aqueous 10% sodium bicarbonate solution and brine, then dried over anhydrous magnesium sulfate and evaporated in vacuo.

The crude product was purified by column chromatography on silica gel. Elution with ethyl acetate afforded the pure 30-membered macrocycle (5a) (1.51 g, 17.4%), mp 105.0-106.0°C. Anal. Calcd for $C_{56}H_{70}O_{12}N_6 \cdot 1/2H_2O$: C, 65.42; H, 6.96;

N, 8.17. Found: C, 65.39; H, 7.08; N, 8.26.

30-membered macrocycle (5b)

To a solution of dicarboxylic acid (3b) (5.00 g) in anhydrous tetrahydrofuran (85 ml) was added N,N'-carbonyldiimidazole (2.76 g) at 0°C. The solution was left standing for 1 h after the effervescence had subsided, and then a solution of the diol (4) (2.83 g) in anhydrous tetrahydrofuran (40 ml) was added. After stirring for 1 day, the solvent was evaporated in vacuo and the residue was taken up in ethyl acetate. The mixture was washed with 10% hydrochloric acid, aqueous 10% sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate and evaporated in vacuo.

The crude product was purified by column chromatography on silica gel using diethyl ether as an eluent to afford the pure 30-membered macrocycle (5b) (1.65 g, 22.0%) mp 104.5-106.5°C, MS m/e: 883(M⁺). Anal. Calcd for C₄₄H₇₈⁰₁₂N₆•1/2H₂O: C, 59.24; H, 8.93; N, 9.42. Found: C, 59.22; H, 9.23; N, 9.31.

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