

Preparation of O-Alkyl-N-acyl-DL-serines

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N-Phthaloyl amino acids have proved to be very useful for the syntheses of peptides¹, diazoketones², homologous optically active β -amino acids^{3,4,5,6}, optically active α -amino aldehydes⁷, aminoalkylglyoxals^{8,9} and vinyls of naturally occurring amino acids¹⁰.

As no description has hitherto been given of the N-phthaloyl derivatives of O-alkyl-DL-serine* which would enable the above mentioned syntheses to be carried out with serine, we prepared O-methyl-N-phthaloyl-DL-serine by reacting O-methyl-DL-serine and O-ethyl-DL-serine respectively with phthalic anhydride. Furthermore, O-ethyl-N-p-tosyl-DL-serine and N-carbobenzoxy-O-ethyl-DL-serine were also prepared.

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EXPERIMENTAL**

O-methyl-N-phthaloyl-DL-serine

A finely ground mixture of O-methyl-DL-serine prepared according to Schiltz and Carter¹¹ (11.9 g., 0.1 mole) and phthalic anhydride (14.8 g., 0.1 mole) was heated to 160°, and kept at that temperature for half an hour with occasional stirring. The cooled mixture was dissolved in methanol (50 ml.), treated with charcoal, and the solution filtered. Water (200 ml.) was then added to the filtrate and the mixture left overnight in an ice-box. The crystals which separated were collected, the filtrate evaporated and cooled and a further crop of crystals obtained. Yield of crude O-methyl-N-phthaloyl-DL-serine 21.5 g., (85%). Recrystallization from methanol-water (1:3) gave white needles with the m. p. 140—141°.

Anal. 10.960 mg. subst.: 23.17 mg. CO₂, 4.35 mg. H₂O
C₁₂H₁₁NO₅ (249.22) calc'd: C 57.83; H 4.45%
found: C 57.69; H 4.44%

The anilide O-ethyl-N-phthaloyl-DL-serine was prepared for characterization from α -phthalimido- β -ethoxypropionyl chloride and aniline in benzene. After several recrystallizations from ether, colorless crystals, m. p. 100° were obtained.

Anal. 6.705 mg. subst.: 16.60 mg. CO₂, 3.17 mg. H₂O
C₁₉H₁₈N₂O₄ (338.35) calc'd: C 67.44; H 5.36%
found: C 67.56; H 5.29%

* When this work was completed, a description of some derivatives of N-phthaloyl-DL-serine was published by Rinderknecht and Niemann¹², and therefore we did not include the preparation of these compounds in the experimental part, as we had contemplated. They were prepared a year ago by M. Brajdić, to whom we are indebted for some of the starting materials.

** The melting points are uncorrected.

1-Bromo-4-ethoxy-3-phthalimidobutan-2-one

To a solution of 1-diazo-4-ethoxy-3-phthalimidobutan-2-one¹⁴ (4.9 g., 0.017 mole) in glacial acetic acid (20 ml.), 48% hydrobromic acid (5 ml.) was added with cooling and stirring. The mixture was left at room temperature for an hour, and diluted with water (200 ml.). The dilution must be carried out gradually, otherwise an oil separates. Yield of crude *1-bromo-4-ethoxy-3-phthalimidobutan-2-one* 5.2 g. (90%), m. p. 50—62°. Several recrystallizations from dichloromethane-petroleum ether gave clusters of colorless needles, m. p. 91—95°.

Anal. 10.237 mg. subst.: 18.56 mg. CO₂, 3.75 mg. H₂O
 C₁₄H₁₄BrNO₄ (360.16) calc'd: C 49.43; H 4.14%
 found: C 49.48; H 4.09%

O-Ethyl-N-p-tosyl-DL-serine

To a solution of α -amino- β -ethoxypropionic acid (O-ethoxy serine) (1.33 g., 0.01 mole) in 2N sodium hydroxide, a solution of an equimolar quantity of p-tosyl chloride (1.9 g.) in ether (10 ml.) was added. The mixture was left at room temperature, with stirring, for 48 hours. The ethereal layer was discarded, and the water layer acidified with 2N hydrochloric acid. *O-ethyl-N-p-tosyl-DL-serine* (1.85 g., 64.5%) separated, m. p. 121—124°. Recrystallization from water gave colorless leaflets, m. p. 131—132°.

Anal. 9.360 mg. subst.: 17.16 mg. CO₂, 4.83 mg. H₂O
 C₁₂H₁₇NO₅S (287.31) calc'd: C 50.16; H 5.96%
 found: C 50.02; H 5.78%

N-Carbobenzoxy-O-ethyl-DL-serine

To a suspension of α -amino- β -ethoxypropionic acid (6.7 g., 0.05 mole) and magnesium oxide (5.95 g., 0.14 mole) in water (75 ml.), ether (25 ml.) was added, and the mixture cooled to 0°. Carbobenzoxy chloride (16.7 g., 0.098 mole) was then gradually added during 30 minutes. The stirring was continued six hours more, and the whole mixture filtered through a Whatman No. 1 filter paper. The ethereal layer was then discarded, and the water layer freed from excess carbobenzoxy chloride by extracting it with ether two times. The aqueous solution was acidified with 2N hydrochloric acid, and crude oily *N-carbobenzoxy-O-ethyl-DL-serine* separated. This oil was collected, and a further quantity of oil extracted from the aqueous layer with ethyl acetate. This ethyl acetate extracts were combined with the oil and repeatedly washed with 5% hydrochloric acid, and finally with water; after drying these extracts over sodium sulphate and removing the ethyl acetate by evaporation, 11.5 g. (85.6%) of oil remained, which solidified to a crystalline mass, m. p. 63—67°. Recrystallized from ethyl acetate-petroleum ether, colorless leaflets, m. p. 73—74.5°.

Anal. 9.580 mg. subst.: 20.49 mg. CO₂, 5.35 mg. H₂O
 C₁₃H₁₇NO₅ (267.26) calc'd: C 58.43; H 6.40%
 found: C 58.35; H 6.25%

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IZVOD

Priprema O-alkil-N-acil-DL-serina

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Pokazalo se, da su N-ftaloil aminokiseline vrlo prikladne za sintezu peptida¹, diazoketona², homologa optički aktivnih aminokiselina^{3,4,5,6}, optički aktivnih α -aminoaldehyda⁷, aminoalkilglioksala^{8,9} i viniloga prirodnih aminokiselina¹⁰.

Budući da se dosad te sinteze nisu mogle provoditi sa serinom, jer N-ftaloil derivati serina nisu bili opisani priredili smo O-metil-N-ftaloil-DL-serin, O-etil-N-p-tosil-DL-serin i N-karbobenzoksi-O-etil-DL-serin.

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