

Synthetic Studies in the Chloramphenicol Series. IV* Synthesis of *threo*-DL-Chloramphenicol Base from DL-Serine Methyl Ether**

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A synthesis of *threo*-DL-chloramphenicol base from α -bromo- β -methoxy-propionic acid, an intermediate in the synthesis of DL-serine methyl ether is described. The synthesis is essentially the same as the one previously described for the preparation of *threo*-DL-chloramphenicol from DL-serine ethyl ether. However, the over-all yield of chloramphenicol base is much higher (6.9%, based on α -bromo- β -methoxy-propionic acid) mainly due to the high yield of α -phthalimido- β -methoxy-propionophenone, which was obtained in a yield of 63.5%.

The previous papers in this series^{1,2} reported the synthesis of *threo*-DL-chloramphenicol from DL-serine ethyl ether. Evidence was presented that the synthetic approach described in these papers is capable of producing the D-(-)-*threo*-chloramphenicol if performed with the optically active intermediates. However the over-all yield of *threo*-DL-chloramphenicol, calculated on the basis of α -phthalimido- β -ethoxy-propionyl chloride, was only 2.4% and it proved difficult to prepare larger amounts of optically active intermediates.

Using reactions similar to those previously described, we are recording in this paper the synthesis of the *threo*-DL-chloramphenicol base starting with α -bromo- β -methoxy-propionic acid.

In the first part of this communication³ the preparation of α -phthalimido- β -methoxy-DL-propionic acid (I) has been described. In this paper an improved and simplified method for the preparation of the same compound is given. α -Bromo- β -methoxy-propionic acid prepared according to the method of Schiltz and Carter⁴ was ammonolyzed with a 25% ammonia solution at room temperature. The rate of ammonolysis was controlled by titration of bromide ion. Ten days were required to accomplish this reaction. After that time the ammonia solution was evaporated under reduced pressure and the dry residue containing the amino acid mixed with an equivalent amount of ammonium bromide was treated with phthalic anhydride in glacial acetic acid. The phthalimido derivative I, was thus obtained in a yield of 73.1%, calculated on the basis of α -bromo- β -methoxy-propionic acid.

* Paper III, D. Fleš, B. Balenović, R. Marušić and N. Manger, *Arhiv kem.* 27 (1955) 1.

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The α -phthalimido- β -methoxy-propionic acid was then treated with thionyl chloride and the corresponding acid chloride II was obtained in a yield of 90.7%.

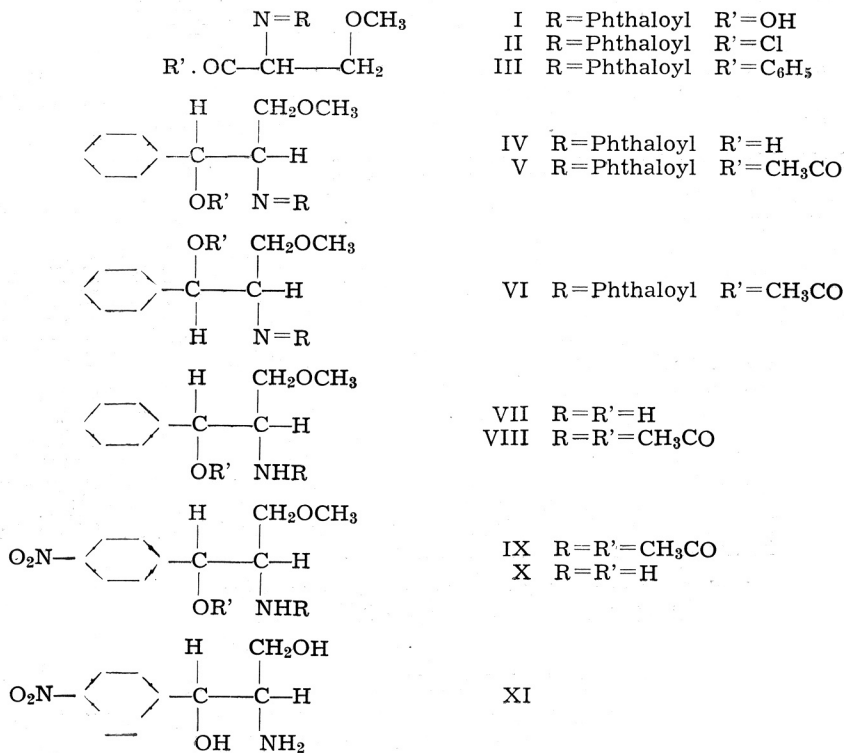
Using the usual Friedel-Crafts conditions the acid chloride II was converted to the α -phthalimido- β -methoxy-DL-propiophenone (III). In part II¹ of this communication the difficulties encountered in the preparation and isolation of α -phthalimido- β -ethoxy-propiophenone were described. The pure ketone was isolated through Girard T reagent in a yield of 2.3%. But to our surprise, when α -phthalimido- β -methoxy-DL-propionyl chloride (II) was condensed with benzene in the presence of aluminium chloride, the α -phthalimido- β -methoxy-DL-propiophenone (III) was obtained as a nice crystalline product in a yield of 63.5%. The striking difference in the reactivity of methyl and ethyl ethers is probably due to the deethoxylation reaction which occurs during the Friedel-Crafts reaction with O-ethyl-N-phthaloyl serine. The ketone III was already prepared by Mildred C. Rebstock⁵ by condensing α -bromo- β -methoxy-DL-propiophenone with potassium phthalimide in dimethylformamide as solvent.

The ketone III was then reduced with aluminium isopropoxide and DL-1-phenyl-1-hydroxy-2-phthalimido-3-methoxypropane (IV) was obtained in a yield of 53.3%. This product proved to be identical with the *threo*-DL-1-phenyl-1-hydroxy-2-phthalimido-3-methoxypropane obtained by Rebstock⁵ upon reduction of ketone III with hydrogen in the presence of palladium oxide catalyst. The mother liquor from which the *threo*-carbinol IV was obtained was evaporated under reduced pressure and the oily residue acetylated with acetic anhydride in pyridine. The *erythro*-DL-1-phenyl-1-acetoxy-2-phthalimido-3-methoxypropane (VI) was obtained in a yield of 12.1% after the acetylating agents were removed under reduced pressure, and the oily residue crystallized from ethyl acetate. The ethyl acetate mother liquor was again evaporated in vacuo, and the residue crystallized from ethanol. A yield of 9.8% of *threo*-DL-1-phenyl-1-acetoxy-2-phthalimido-3-methoxypropane (V) was obtained. The total yield of the *threo* isomer was 63.1%.

The acetylated product V was then converted to the *threo*-DL-chloramphenicol base using the method previously published.⁵ Using a somewhat different reaction scheme, the same base was prepared in comparable yield. The carbinol IV was firstly hydrazinolized and the free base (VII) acetylated with acetic anhydride in pyridine. The yield in these two reactions was almost quantitative. The diacetylated product VIII was then nitrated with fuming nitric acid at a temperature of 0° to -5°. The crude mixture of nitrated isomers was hydrolyzed with hydrobromic acid and the *threo*-DL-chloramphenicol base (XI) was thus obtained in a yield of 6.9%, based on α -bromo- β -methoxy-propionic acid. The methyl ether of the *threo*-chloramphenicol base (X) was also prepared and converted to the base XI.

Since there is evidence from the literature that all reactions used in this synthesis are applicable to an optically active preparation, we consider that the model synthesis described in this paper represents a convenient method for the preparation of optically active chloramphenicol.

Figure I



EXPERIMENTAL*

α-Phthalimido-β-methoxy-DL-propionic acid (I)

Nine hundred grams (4.92 moles) of *α*-bromo-β-methoxypropionic acid were dissolved in 9 l. of a 25% ammonia solution, kept for 8 days at room temperature (25°) and the solution was then evaporated in vacuo to dryness. The dry residue (910 g.) was mixed with 820 g. (5.54 moles) of phthalic anhydride and 1,820 ml. of warm glacial acetic acid were added. The reaction mixture was refluxed for half an hour in an oil bath, and was then poured into 3,640 ml. of water. The solution was vigorously stirred and slowly cooled with running water, and the crude *α*-phthalimido-β-methoxy-DL-propionic acid, obtained as slightly yellow, heavy precipitate, was collected on a Büchner funnel. Yield 1,010 g., m. p. 138—142°. The crude product was recrystallized from 3 l. of a mixture of methanol-water (1:2), was charcoaled and cooled slowly with stirring. A yield of 896 g. (73.1% based on *α*-bromo-β-methoxypropionic acid) was obtained, m. p. 141—145°. An analytical sample was prepared by recrystallization of a portion from a methanol-water mixture (1:2) to a melting point of 148—149°** (under previous softening at 146°).

Anal. 14.59 mg. subst.: 30.75 mg. CO₂, 5.98 mg. H₂O

7.30 mg. subst.: 0.355 ml. N₂ (22°, 758 mm.)

C₁₂H₁₁O₅N (249.22) calc'd.: C 57.83 H 4.45 N 5.62%

found: C 57.51 H 4.58 N 5.61%

* The melting points are uncorrected.

** The earlier reported melting point³ was 140—141°.

α-Phthalimido-β-methoxy-DL-propionyl chloride (II)

Three hundred and eight grams (1.23 mole) of *α*-phthalimido-*β*-methoxy-DL-propionic acid was refluxed with 308 ml. (4.24 moles) of thionyl chloride until solution was effected (about 30 minutes). The excess of thionyl chloride was evaporated under reduced pressure and the residue dissolved in 308 ml. of benzene and crystallized with 616 ml. of petroleum ether (b. p. 40–60°). Three hundred grams of a crystalline product were obtained. Yield 90.7%, m. p. 72–74°.

α-Phthalimido-β-methoxy-DL-propiophenone (III)

In a 5 l. three-necked flask fitted with a mechanical stirrer, condenser and a dropping funnel, was placed a suspension of 375 g. (2.81 moles) of anhydrous aluminium chloride in 1,650 ml. of dry benzene. The reaction mixture was heated on a water bath to 70° and with rapid stirring, 300 g. (1.12 mole) of *α*-phthalimido-*β*-methoxy-DL-propionyl chloride dissolved in 1 l. of dry benzene were added at such a rate, as to maintain constant refluxing. The reaction mixture was then refluxed for additional three hours, cooled and hydrolyzed with a mixture of 100 ml. of concentrated hydrochloric acid and 1.5 kg. of cracked ice. The water layer was separated and extracted with three 450 ml. portions of benzene. The benzene layer was washed with three 600 ml. portions of water, then with two 250 ml. of a saturated bicarbonate solution, decolourised with 30 g. of charcoal and dried over anhydrous magnesium sulphate. The dried solution was evaporated at reduced pressure and the crystalline residue (220 g. 63.5%) melting at 126–135°, was used directly in the next conversion. An analytical sample was recrystallized from ethanol, and twice from ethyl acetate to a melting point 139–140°.* The product crystallizes in the form of nice prismatic needles.

Anal. 18.90 mg. subst.: 48.31 mg. CO₂, 8.26 mg. H₂O
 C₁₈H₁₅O₄N (309.31) calc'd.: C 69.89 H 4.89%
 found: C 69.75 H 4.89%

DL-threo-1-Phenyl-1-hydroxy-2-phthalimido-3-methoxypropane (IV)

In a 5-l. three-necked flask were placed 130 g. (0.42 mole) of *α*-phthalimido-*β*-methoxy-DL-propiophenone and 260 g. (1.27 mole) of freshly distilled aluminium isopropoxide and 2,6 l. of dry isopropanol. A mechanical stirrer and a 80-cm. Vigreux column were attached and the reaction mixture was heated with an oil bath at such a rate as to maintain a slow distillation of acetone. After 11 hours the acetone test was negative. Most of the isopropanol was removed under reduced pressure, and the residue was hydrolyzed with a solution of 330 g. of tartaric acid and 2 l. of water in the presence of 1 l. of benzene. The water layer was extracted with two 500 ml. portions of benzene, the combined benzene extracts were dried over anhydrous magnesium sulphate, and the solvent was removed in vacuo. The oily residue was dissolved in 400 ml. of ethanol (96%) and after standing for two days in a refrigerator, a crop of 60 g. of the carbinol IV separated. The mother liquor was evaporated to a syrup and redissolved in 20 ml. of benzene and 60 ml. of petroleum ether were added. After standing overnight in a refrigerator, additional 10 g. of the carbinol IV were obtained. Total yield was 70 g. (53.3%), m. p. 133–135°. An analytical sample was recrystallized from benzene and ethanol to a melting point of 137–138°.* The product crystallizes in needles from ethanol.

Anal. 18.59 mg. subst.: 47.45 mg. CO₂, 9.12 mg. H₂O
 12.269 mg. subst.: 0.4802 ml. N₂ (23°, 767 mm)
 C₁₈H₁₇O₄N (311.32) calc'd.: C 69.44 H 5.50 N 4.50%
 found: C 69.65 H 5.49 N 4.55%

DL-erythro-1-Phenyl-1-acetoxy-2-phthalimido-3-methoxypropane (VI)

The benzene-petroleum ether mother liquor from which the *threo*-1-phenyl-1-hydroxy-2-phthalimido-3-methoxypropane (IV) was separated, was evaporated in vacuo and the remaining oil (60 g.) was acetylated with 240 ml. of acetic anhydride

* The earlier reported melting point⁵ was 137–138°.

SYNTHESIS OF *threo*-DL-CHLORAMPHNICOL BASE

in 120 ml. of dry pyridine. After standing overnight at room temperature, solvents were removed under reduced pressure and the semi-crystalline residue recrystallized from 250 ml. of ethyl acetate. Eighteen grams of a product melting at 160—162° were obtained. Yield 12.1%. An analytical sample was recrystallized from ethyl acetate and finally from ethanol to a melting point of 165—166°.*

Anal. 11.76 mg. subst.: 29.21 mg. CO₂, 5.54 mg. H₂O
C₂₀H₁₉O₅N (353.36) calc'd.: C 67.98 H 5.42%
found: C 67.78 H 5.27%

DL-*threo*-1-Phenyl-1-acetoxy-2-phthalimido-3-methoxypropane (V)

An additional quantity of the *threo*-isomer was obtained from the mother liquor after the erythro isomer was separated. The ethyl acetate was evaporated to dryness and the residue was crystallized from 50 ml. of ethanol. A crop of 14.5 g. of V, representing a yield of 9.8% was obtained, m. p. 113—124°. The product was recrystallized from ethanol to a melting point of 129—132°. No melting point depression was observed on admixing with a sample obtained by acetylation of DL-*threo*-1-phenyl-1-hydroxy-2-phthalimido-3-methoxypropane, according to the procedure described by Rebstock⁵.

DL-*threo*-1-Phenyl-1-hydroxy-2-amino-3-methoxypropane (VII)

Fifty two grams (0.167 mole) of the *threo*-carbinol IV were refluxed for 1.5 hour with 175 ml. (0.175 mole) of a N-hydrazine hydrate in absolute ethanol. The reaction mixture was cooled and the crystalline precipitate removed by filtration. The crystalline product was refluxed with three 250 ml. portions of methylene chloride. The combined alcohol and methylene chloride solutions were evaporated under reduced pressure to give 29.5 g., representing a 97.5% yield of the base VII, m.p. 60—63°. An analytical sample was purified by distillation at a temperature of 80—90° at a pressure of 0.03 mm. as colourless oil which solidified very soon and had a melting point 65°. The yield of the phthalyl hydrazide was quantitative.

Anal. 13.31 mg. subst.: 32.19 mg. CO₂, 9.65 mg. H₂O
C₁₀H₁₅O₂N (181.23) calc'd.: C 66.27 H 8.34%
found: C 66.00 H 8.11%

DL-*threo*-1-Phenyl-1-acetoxy-2-acetamido-3-methoxypropane (VIII)

Twenty five grams (0.138 mole) of the base VII were dissolved in 40 ml. of dry pyridine and acetylated with 30 ml. of acetic anhydride. After standing overnight at room temperature the solvents were removed under reduced pressure. The traces of acetic acid were removed by repeating evaporation with water, and the slightly yellow oil was triturated with petroleum ether (b. p. 40—60°). The oil solidified very soon to a crystalline mass with a melting point at 80—82.5°. Yield 36.4 g., 99.4%. A sample was recrystallized from ether to a melting point of 83—84°, and finally distilled for analysis at a temperature of 120—130° and a pressure of 0.05 mm.

Anal. 13.25 mg subst.: 30.68 mg. CO₂, 8.40 mg. H₂O
C₁₄H₁₉O₄N (265.30) calc'd.: C 63.38 H 7.22%
found: C 63.19 H 7.09%

DL-*threo*-1-*p*-Nitrophenyl-1-acetoxy-2-acetamido-3-methoxypropane (IX)

Hundred and five milliliter of the fuming nitric acid were placed in a 1-l. round bottomed flask equipped with a mechanical stirrer and a thermometer. The flask was immersed in an ice-salt bath and the diacetylated product VIII (24 g., 0.09 mole) was added in the course of 15 minutes, with constant stirring. The inside temperature was kept between 0 and —5°. After the addition of VIII was completed, the flask was kept for a further 30 minutes at room temperature. The reaction mixture was then quenched on 300 g. of ice and neutralized with solid sodium bicarbonate. The oily product which separated was extracted with three 100 ml.

* The earlier reported melting point⁵ was 165—166°.

portions of ethyl acetate. The dried solution was evaporated in vacuo to a crystalline product (24 g.) which was immediately used in the next conversion.

DL-threo-1-p-Nitrophenyl-1-hydroxy-2-amino-3-methoxypropane (X)

The crude nitrated product IX (24 g.) was heated for two and a half hours on the water bath with 240 ml. of a 5% hydrochloric acid. The hydrochloric acid was evaporated under reduced pressure, the semi-crystalline product dissolved in 100 ml. of water, charcoaled, and the solution was adjusted to pH 10 with a concentrated ammonia solution. The crystalline precipitate was collected by filtration and washed with two 10 ml. portions of cold water. A yield of 12.5 g. (61.1% based on diacetyl VIII) was obtained, m. p. 120—125°. A portion was purified for analysis by recrystallization from ethanol, ethylene dichloride and water. Needles with a melting point 134—136°* The product sublimed unchanged at 140—143° at a pressure of 0.35 mm.

Anal. 16.52 mg. subst.: 32.01 mg. CO₂, 8.96 mg. H₂O
3.06 mg. subst.: 0.3332 ml. N₂ (30°, 754 mm)
C₁₀H₁₄O₄N₂ (226.23) calc'd.: C 53.09 H 6.24 N 12.38%
found: C 52.88 H 6.07 N 12.17%

DL-threo-1-p-Nitrophenyl-2-amino-1,3-propanediol (XI)

The crude nitrated product IX (6.7 g.) was heated with 67 ml. of 48% hydrobromic acid in a sealed tube at 130° for half an hour and at 120° for one hour. The heating was discontinued and the tube cooled overnight. The acid was removed under reduced pressure by repeating evaporation with three 20 ml. portions of water, the residue dissolved in 70 ml. of water, charcoaled, and adjusted to pH 11 with a concentrated ammonium hydroxide solution. The crystalline product which separated on cooling, was filtered off and washed with a small amount of cold water. Yield 2.1 g., m. p. 127—131°. The product was recrystallized from 6 ml. of water to give 1.46 g. (27.2% based on VIII) of the base melting at 136—139°, undepressed upon admixture with an authentic specimen of the DL-threo-chloramphenicol base.

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IZVOD

Sintetske studije u redu kloramfenikola. IV. Sinteza DL-treo-kloramfenikolske baze iz metilnog etera DL-serina

D. Fleš i B. Balenović

U prije objavljenim publikacijama^{1, 2} opisana je sinteza DL-treo-kloramfenikola iz etilnog etera DL-serina s iskorištenjem od 2,7% računato na α -ftalimido- β -etoksi-DL-propionil klorid. Upotrebivši slične reakcije, u ovoj publikaciji je opisana sinteza DL-kloramfenikolske baze iz α -bromo- β -metoksi-propionske kiseline, intermedijera u sintezi metilnog etera serina. Iskorištenje na kloramfenikolskoj bazi iznosi 6,9%, računato na α -brom- β -metoksi-propionsku kiselinu.

Smatramo da je opisana sinteza vrlo pogodna za pripremu optički aktivnog kloramfenikola uz upotrebu optički aktivnih intermedijera.

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* The earlier reported melting point⁵ was 132—133°.