

Synthetic Studies in the Chloramphenicol Series, II.* Synthesis of β -Ethoxy- α -Phthalimido-DL-Propiophenone**

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When β -ethoxy- α -phthalimido-DL-propionyl chloride [I] was condensed with benzene in the presence of anhydrous aluminum chloride, β -ethoxy- α -phthalimido-DL-propiophenone [II] was obtained in a yield of 2.3%. Melting point 110° (under previous softening at 106°). [I] gave with diphenylcadmium the same ketone, which was isolated in the form of 2,4-dinitrophenylhydrazone, in a yield of 3.5%. Melting point 192—195°.

In the course of our studies on the configuration of chloramphenicol, we have outlined a synthesis starting from optically active serine. In the model synthesis we have prepared the key intermediate i. e. β -ethoxy- α -phthalimido-DL-propiophenone. This ketone was prepared by condensation of β -ethoxy- α -phthalimido-DL-propionyl chloride^{1, 2} via Friedel-Crafts reaction with benzene and with diphenylcadmium. In the first reaction the pure ketone was obtained in a yield of 2.3%. 2,4-Dinitrophenylhydrazone was also prepared. When β -ethoxy- α -phthalimido-DL-propionyl chloride was condensed with diphenylcadmium, the ketone was isolated in the form of 2,4-dinitrophenylhydrazone in a yield of 3.5%. The preparation of diphenylcadmium was essentially the same as the one described by Cason³ and Cason and Proot⁴.

EXPERIMENTAL***

β -Ethoxy- α -phthalimido-DL-propiophenone.

A. Via the Friedel-Crafts Reaction: A mixture of 130 ml. of dry benzene and 24 g. (0.18 mole) of anhydrous aluminum chloride was placed in a 500 ml. three-necked flask equipped with a mercury-sealed stirrer, a reflux condenser, and a dropping funnel. The reaction mixture was heated on a water bath to 60°, and, with rapid stirring, 28 g. (0.1 mole) of β -ethoxy- α -phthalimido-DL-propionyl chloride dissolved in 90 ml. of dry benzene was added dropwise in the course of one and a half hour. After adding the acid chloride, the reaction mixture was refluxed for additional 3 hours. The mixture was cooled and hydrolysed with a mixture of 16 ml. of concentrated hydrochloric acid and 100 g. of cracked ice. When the ice had melted, the aqueous part was separated and extracted with 50 ml. portions of benzene. The benzene layer was washed with water until all the unreacted acid chloride was hydrolysed. Benzene was dried over magnesium sulfate, and evaporated in vacuo to give 24.6 g. of a dark viscous oil. Five grams of this oil was treated with 5 g. of

* Paper I, N. Štimac and B. Gašpert, *Arhiv kem.* 26 (1954) 105.

** D. Fleš, M. Brajdić and N. Štimac, *Yugoslav Patent Application*, June 28, 1954.

*** The melting points are uncorrected.

Girard T reagent in 50 ml. of absolute ethanol and 1.17 g. of ketonic material was obtained. The crude ketonic fraction was dissolved in 10 ml. of benzene and treated with 10 ml. of a 10% sodium bicarbonate solution. The benzene layer was dried over magnesium sulfate and evaporated in vacuo. 325 mg. of an oily residue was obtained. After recrystallization from ethanol, 150 mg. of a white crystalline product, m. p. 107—108°, was obtained. A sample purified for analysis melted at 110° (under previous softening at 106°). The yield of the product with m. p. 107—108° was 2.3%, based on the acid chloride used.

Anal. 5.718 mg. subst.: 14.79 mg. CO₂, 2.76 mg. H₂O
 4.205 mg. subst.: 0.1564 ml. N₂ (22°, 751 mm)
 C₁₉H₁₇O₄N (323.33) calc'd.: C 70.57; H 5.30; N 4.33%
 found: C 70.58; H 5.40; N 4.25%

2,4-Dinitrophenylhydrazone was prepared in quantitative yield in alcoholic solution. It crystallized from a mixture of ethanol-ethyl acetate in the form of orange needles. M. p. 191—194° (under previous softening at 185°).

Anal. 3.677 mg. subst.: 0.452 ml. N₂ (23°, 765 mm)
 C₂₅H₂₁O₇N₅ (503.46) calc'd.: N 14.27%
 found: N 14.04%

B. *Via Diphenylcadmium**: The reaction was performed in a 500 ml. three-necked flask, equipped with a mercury-sealed stirrer, a reflux condenser, a dropping funnel and a gas inlet tube. The Grignard solution prepared from 480 mg. (0.02 mole) of magnesium turnings and 3.15 g. (0.02 mole) of bromobenzene in 10 ml. of dry ether was cooled in an ice-bath. The reaction mixture was stirred vigorously and after removing the ice-bath, 2 g. (10% excess) of anhydrous, finely divided cadmium chloride was added at once. The solution darkened in colour and after about 15 minutes the Gilman test was negative. The ether was distilled rapidly from the solution, and 10 ml. of dry benzene was added. 5.6 g. (0.02 mole) of β-ethoxy-α-phthalimido-DL-propionyl chloride dissolved in 15 ml. of dry benzene was added dropwise under continuous stirring. The reaction mixture was refluxed for 2 hours, cooled and hydrolysed with an ice-cold solution of 10 g. of tartaric acid in 50 ml. of water. The water layer was separated and extracted with three 30 ml. portions of ether, the organic layer was washed twice with 20 ml. of water and dried over magnesium sulfate. After evaporating the solvent in vacuo 3.7 g. of a dark, viscous oil was obtained. The crude product was dissolved in ethanol and an ethanolic solution, containing 10% excess of 2,4-dinitrophenylhydrazine, was added. After standing for two days at room temperature, 370 mg. of crude 2,4-dinitrophenylhydrazone, m. p. 175—182°, was obtained. After two recrystallizations from ethanol containing a few drops of chloroform, a pure product m. p. 192—195° was obtained. The product was identical with 2,4-dinitrophenylhydrazone previously described. The yield of crude 2,4-dinitrophenylhydrazone calculated on the basis of acid chloride was 3.5%.

Anal. 10.412 mg. subst.: 22.90 mg. CO₂, 3.77 mg. H₂O
 C₂₅H₂₁O₇N₅ (503.46) calc'd.: C 59.64; H 4.20%
 found: C 60.01; H 4.05%

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4. J. Cason and F. S. Proot, *J. Am. Chem. Soc.* **66** (1944) 46.

* In collaboration with V. Jagodić.

IZVOD

**Sintetske studije u redu kloramfenikola. II.
Sinteza β -etoksi- α -ftalimido-DL-propiofenona***D. Fleš, M. Brajdić i N. Štimac*

Sinteza β -etoksi- α -ftalimido-DL-propiofenona, međuprodukta u sintezi kloramfenikola, provedena je kondenzacijom β -etoksi- α -ftalimido-DL-propionil klorida sa benzenom u prisutnosti bezvodnog aluminijskog triklorida i s difenil kadmijem. U prvom slučaju izoliran je slobodni keton u iskorištenju od 2,3%; priređen je k tome pripadni 2,4-dinitrofenilhidrazon; u drugom slučaju izoliran je nastali keton u obliku 2,4-dinitrofenilhidrazona s iskorištenjem od 3,5%.

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