PREPARATION OF CERTAIN INTERMEDIATE PRODUCTS IN THE PRODUCTION OF CHLOROMYCETIN. II. SYNTHESIS OF n-NITROACETOPHENONE

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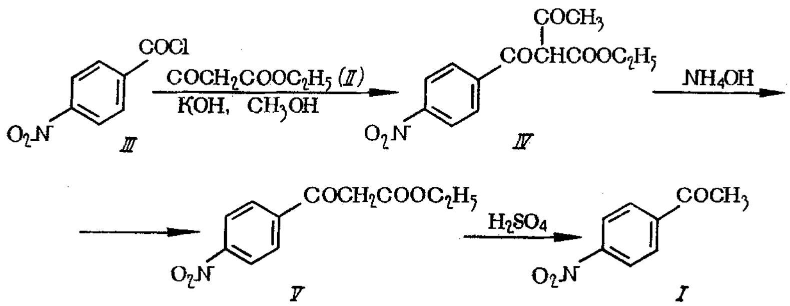
With the object of searching for an economical and technologically convenient method of preparing n-nitroacetophenone (I), a comparative study was conducted of methods for preparing this compound by condensation of the ethyl ester of acetoacetic acid (II) and the acid chloride of n-nitrobenzoic acid (III), and by the hydrolysis of the resultant n-nitrobenzoyl acetoacetate ester (IV) into the n-nitrobenzoyl acetic ester (V) with subsequent saponification and decarboxylation of the latter into n-nitroacetophenone (I).

According to data in the literature, condensation of the acetoacetate ester with the acid chloride of the acids is conducted in the presence of metallic sodium [1] or magnesium [2] and in a medium of absolute ethyl alcohol, and in an analogous manner the diethyl ester of malonic acid is condensed with the acid chloride of n-nitrobenzoic acid [3]. The disadvantages of the described methods are the necessity of using metallic sodium or magnesium and the fact that the alcohol used must be in an extremely anhydrous state. When an attempt was made to repeat certain of the experiments described in the literature for preparing the ester IV it was impossible to reproduce the results, and maximum yields of the ester IV obtained by us varied from 65-70% (according to data in the literature [4] the yield was 90%).

Having commenced to study the reaction, an attempt was made firstly to obtain the magnesium derivative of the acetoacetate ester in a medium of liquid ammonia [5], after which the ammonia was replaced by benzene, in which the condensation was conducted. The method was not very suitable, firstly on account of the difficulties associated with the use of liquid ammonia and secondly on account of the inadequate yield of the ester IV (not more than 55%).

Further, a study was made of the possibility of conducting the condensation in an aqueous medium in the presence of sodium hydroxide [6]. Compound II and a benzene solution of compound III were simultaneously added dropwise to a concentrated aqueous solution of sodium hydroxide at a temperature of approximately 10° when the pH of the medium was approximately 11.0. The yield of compound IV with a mp of 54-55° was equivalent to 40-50%. Simultaneously n-nitrobenzoic acid was isolated with a yield of approximately 40%. One might suggest that in the heterogeneous medium the rates of condensation and hydrolysis of the acid chloride III are almost identical. In order to inhibit hydrolysis, the condensation was conducted in a homogeneous medium, a solution of methanol with potassium hydroxide as the condensing agent. A decrease in temperature of the reaction led to a subsequent decrease in rate of hydrolysis of the acid chloride of n-nitrobenzoic acid. At −5° in a methanolic solution of potassium hydroxide the condensation of acetoacetic ester with n-nitrobenzoyl chloride proceeds with a yield of 95% for the technical product and 90-92% for the recrystallized substance with a mp of 56°.



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Hydrolysis of the n-nitrobenzoyl acetoacetate ester IV may be achieved by the action of ammonium chloride and ammonia in an aqueous medium or ammonia in an alcoholic medium with approximately the same yields. An advantage of the latter method is the possibility of conducting the condensation and hydrolysis in one stage without extracting the intermediate product, IV. By heating the ethyl ester of n-nitrobenzoyl acetic acid, V, with a 20% solution of sulfuric acid n-nitroacetophenone was obtained with a yield of 90%.

EXPERIMENTAL

Preparation of n-Nitrobenzoyl Acetoacetate Ester (IV).

A. In Liquid Ammonia. A 150 ml volume of liquid ammonia was added to a heat-insulated, triple-necked flask provided with a stirrer. During slow agitation 2.5 g of magnesium filings were then added, and finally 13 g of the acetoacetate ester were added dropwise. The mixture was stirred for 1 hour, and the ammonia was removed by evaporation at room temperature and then vaccum. A 20 ml volume of dry benzene was added to the residue of the magnesium derivative of the acetoacetate ester, and then with stirring at room temperature a solution of 14 g of n-nitrobenzoyl chloride in 80 ml of benzene was added dropwise. The mixture was heated for 1 hour at 90°, cooled, and treated with 200 ml of a 5% solution of sulfuric acid. The benzene layer was separated and dried, the solvent was removed by distillation, and the residue was recrystallized. The yield of the ester IV was 15.5 g (55%), mp 53-55°.

B. In Aqueous Medium. A 20 g quantity of acetoacetate ester and a solution of 30 g of n-nitrobenzoyl chloride in 15 ml benzene were simultaneously added dropwise over a two hour period from two dropping funnels into 80 ml of a 15% solution of sodium hydroxide cooled to 0°. The mixture was stirred for a further 2 h at room temperature, after which a solution of hydrochloric acid was added until the pH value was adjusted to 2.0. The mixture was twice extracted with benzene, the organic layer was dried, the solvent was removed by distillation on a water bath, and the residue was recrystallized from alcohol. The yield of ester IV was 21 g (50%), and the crystals had a mp of 54-55°.

C. In Methanol. A 30.6 g quantity of acetoacetate ester was added dropwise over a 15-minute period to a solution of 11.2 g potassium hydroxide in 160 ml methanol cooled to −5°. At the same temperature a solution of 37 g of n-nitrobenzoyl chloride in 100 ml benzene was added to the above mixture over a one-hour period. The mixture was stirred for a further 10 hours, after which the temperature was allowed to rise to room temperature. A 200 ml volume of water was added, the reaction mixture was acidified to pH 2.0, the benzene layer was separated, the water layer was twice extracted with benzene, and the benzene extracts were combined and dried, and the benzene was removed by distillation on a water bath. The residue was recrystallized from 30 ml of ethyl alcohol. The yield of the ester IV was 55 g (96%), mp 55-56°.

Preparation of n-Nitrobenzoyl Acetic Ester (V).

A. In Aqueous Medium. A 50 g quantity of freshly-ground n-nitrobenzoyl acetoacetate ester IV was added with stirring to a solution of 32 g of ammonium chloride and 10 ml of a 25% solution of ammonia in 400 ml water. The mixture was subsequently stirred for several minutes in order to achieve complete dispersion, and it was then heated in a water bath to 40° and rapidly cooled to 10°, when crystallization commenced. Yield of ester V 36 g (85%), mp 75° (from alcohol).

B. In Methanol. A mixture of 30 g ester IV 30 ml methyl alcohol and 30 ml concentrated ammonia was heated for 3 hours in a reflux condenser. On cooling the mixture to 0° crystals of n-nitrobenzoyl acetate ester V separated out. Yield, 22 g (87%), mp 74-75°.

A mixture of 50 g n-nitrobenzoyl acetate ester V and 130 ml of a 20% solution of sulfuric acid was stirred at 100° for one hour, and 30 ml of concentrated sulfuric acid was added dropwise from a dropping funnel. The mixture was stirred during heating for a further 4 hours, 500 ml water was added, and then the mixture was cooled and the separated crystals of n-nitroacetophenone were recrystallized from alcohol. Yield, 32 g (92%), mp 79-80°.

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