DEVELOPMENT OF METHODS FOR OBTAINING CERTAIN INTERMEDIATES OF THE SYNTHESIS OF CHLORAMPHENICOL

G. F. Gavrilin, L. U. Bykova, UDC 615.332(LAEVOMYCETINUM).012.1.002.62
T. D. Rogachkova, É. I. Novikova, and G. S. Savel'eva

Of the numerous methods of synthesis of the widely known antibiotic chloramphenicol, its synthesis from ω -nitroacetophenone [1] seemed of particular interest. This method makes it possible to consider the prospect of a significant increase in yield and a simplification of the technology in comparison with the methods of synthesis used in manufacture.

In this work we present our results on the development of conditions for the synthesis of certain intermediate products according to the scheme

$$C_{6}H_{5}-CH = CH_{2} \rightarrow C_{6}H_{5}-CH - CH_{2} \rightarrow NO \qquad NO_{2}$$

$$I \qquad II \qquad II$$

$$\rightarrow C_{6}H_{5}-C - CH_{2} - NO_{2} \rightarrow C_{6}H_{5} - C - CH_{2} - NH_{2} \cdot HCI \rightarrow 0$$

$$III \qquad IV$$

$$\rightarrow C_{6}H_{5}-C - CH_{2} - NH - C - C_{6}H_{5} \rightarrow C_{6}H_{5} - C - CH - CH_{2}OH = 0$$

$$V \qquad 0 \qquad V$$

The conversion of styrene (I) into styrene pseudonitrosite (II), which has been described previously, consisted of treatment of (I) with nitrogen trioxide in ether solution or with sodium nitrite in acetic acid [2]. We have shown that (II) was formed in higher yield by the reaction of (I) with sodium nitrite in the presence of hydrochloric acid in a water—benzene medium. The conversion of (II) into ω -nitroacetophenone (III) was accomplished by various methods: either by the isomerization of (II) into the oxime of (III) and subsequent hydrolysis in an acidic medium [2] or by the direct hydrolysis of (II) by boiling in dilute hydrochloric acid [3]. Other methods of obtaining (III) are known, for example, by the condensation of benzaldehyde with nitromethane and subsequent oxidation of the resulting nitro alcohol [4].

We have established that carrying out the hydrolysis of (II) with dilute hydrochloric acid at 75° gave better results. The synthesis of (III) by this method seemed more economical to us. Known methods of obtaining ω -aminoacetophenone hydrochloride (IV) from ω -haloacetophenones through the hexamethylenetetramine complex [5, 6] have several disadvantages such as the high toxicity of the raw material. Consequently we have developed a synthesis of (IV) by the reaction of (III) with powdered iron in a medium consisting of dichloroethane and hydrochloric acid. Previously the expensive stannous chloride was used for this purpose [1]. Benzoylation of (IV) with benzoyl chloride in the presence of sodium hydroxide led to the formation of ω -benzamidoacetophenone (V). We have found that effecting this reaction in a medium

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• 1974 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for \$15.00. consisting of dilute isopropyl alcohol gave a higher grade crude product requiring no further purification. Hydroxymethylation of (V) with paraformaldehyde in methyl alcohol [1] we have superceded by hydroxymethylation with an aqueous solution of formaldehyde in dilute isopropyl alcohol. α -Benzamido- β -hydroxypropiophenone (VI) formed in this way did not require subsequent recrystallization. It is interesting to note that during the preparation of (II) the formation of small amount of ω -nitrostyrene (VII) took place. When necessary, (VII) can be obtained in high yield by heating (II) in the presence of basic catalysts in alcoholic medium.

EXPERIMENTAL

Styrene Pseudonitrosite (II). To a stirred and cooled (5-10°) mixture consisting of benzene (120 ml), 36% concentrated hydrochloric acid (100 ml), water (300 ml), and styrene (52.08 g) was added a solution of sodium nitrite (75.9 g) in water (100 ml) over 1-1.5 h. At the end of the addition the temperature of the reaction mixture was maintained within the same limits for a further half hour. The resulting (II) was filtered off, washed with water (200 ml), then with isopropyl alcohol (150 ml), and air dried. The yield of (II) was 81-85 g (90-94%).

<u>Nitroacetophenone (III)</u>. Compound (II) (90.08 g) was added to a mixture of 36% concentrated hydrochloric acid (54 ml) and water (400 ml). The reaction mass was heated with vigorous stirring at 75° for 4-6 h until complete conversion of the amorphous solid (II) into crystalline (III). After cooling, the precipitate was filtered off and the damp (III) was recrystallized from 80% isopropyl alcohol (100 ml). After concentrating the mother liquor to 1/3 volume the additional precipitate which separated was filtered off and air dried. The overall yield was 74-76 g (90-92%) of mp 104-106°. According to literature data [1] mp $105-105.5^{\circ}$.

<u> ω -Aminoacetophenone Hydrochloride (IV)</u>. To a mixture of 36% concentrated hydrochloric acid (600 ml), dichloroethane (250 ml), and (III) (82.6 g) was added grade PZh4MZ iron powder (150 g) with vigorous stirring in small portions over 4 h while keeping the reaction mixture at a temperature of 40-45°. The reaction mass was kept without stirring for a further 10 h after which time dichloroethane was distilled off in vacuum (200-300 mm) with heating on a water bath at 80°. After removal of the dichloroethane, water (35 ml) was added to the reaction mass which was then cooled to room temperature. Crude (IV) was filtered off and dissolved in water (250 ml) at 50°; the the solution was treated with activated charcoal A (2.5 g) and filtered. The aqueous solution of (IV) obtained was suitable for the preparation of (V). In order to isolate pure (IV) the filtrate was cooled to 0°, and the precipitate which separated was filtered off and washed with water (20 ml) which had been cooled to 5°. The product was dried at 40-50°. Yield of (IV) was 60.0 g (70%) mp 186-187°. According to literature data [5] mp 187°.

<u> ω -Benzamidoacetophenone (V)</u>. To the aqueous solution of (IV) obtained in the previous experiment (about 500 ml) was added isopropyl alcohol (250 ml); the solution was cooled to -5°, and 98% benzoyl chloride (71 ml) was added. A solution of sodium hydroxide (20 g in 100 ml) was added to the mixture obtained during 2 h with vigorous stirring, the reaction mass temperature being kept below 0° until the formation of a stable green coloration as a result of the separation of iron hydroxide present as an impurity. About 320 ml sodium hydroxide solution was consumed by this. At the end of the addition of alkali the reaction mixture was kept a further 1.5 h at 0°, then concentrated hydrochloric acid (35 ml) was added and the mixture was stirred at room temperature until the green color was transformed into a light yellow. The precipitate was filtered off and washed with isopropyl alcohol (70 ml) and with water (300 ml). A paste of (V) (250 g) was obtained which was used for the preparation of (VI) without preliminary drying. The yield of dry (V) was 101-102 g [85% calculated on (III)] of mp 122-124°. According to literature data [1] mp 123°.

 α -Benzamido- β -hydroxypropiophenone (VI). To the paste of (V) obtained as described above, amounting to 59.8 g calculated on dry product, was added isopropyl alcohol (130 ml), 36% formaldehyde solution (20 ml), and sodium bicarbonate (6 g) and the reaction mixture was heated with stirring for 3 h at a temperature of 50-55°. After cooling, the precipitate of (VI) was filtered off, washed with isopropyl alcohol (20 ml) and with water (100 ml), and then dried at 70°. The yield of (VI) was 57-58 g (85%) mp 140-143°. According to literature data [1] mp 142-143°.

<u> ω -Nitrostyrene (VII)</u>. To (II) (45 g) was added 95% ethyl alcohol (70 ml) and triethylamine (0.5 ml) and the mixture then heated at 60° until complete dissolution of the solid. As soon as the solution became transparent, concentrated hydrochloric acid (0.5 ml) was quickly added and the solution was cooled to 5°.

The crystals which precipitated were filtered off, washed with a little cold alcohol, and air dried. The yield of (VII) was 35.5 g (95%) mp 57-58°. According to literature data [7] mp 57-58°.

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