OXIDATION PROCESS OF 1-(p-NITROPHENYL)-2-ACETYLAMINOETHANOL WITH OZONE

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p-Nitro- α -acetylaminoacetophenone (II) is the intermediate product in the synthesis of levomycetin, an antibiotic used for the medical treatment of infections diseases [1]. On an industrial scale (II) is obtained by oxidation of 1-(p-nitropheny1)-2-acetylamino-ethanol (I) with sodium dichromate in sulfuric acid at a temperature of 10-14°C [2]. Two significant disadvantages of this method of oxidation of (I) are formation of large amounts of acidic chromium-containing sewage and the complexity of automation of the process. These disadvantages can be removed upon using ozone as the oxidizing agent, technologically convenient and without ballast [3-6].

Results of investigation obtained during ozonization of (I) in organic solvents are presented in this paper. As is seen from Table 1, upon ozonization of (I) in glacial acetic acid, (II) is formed in 20% yield. Up to 10% p-nitrobenzoic acid (III) is contained in the oxidation products. The scheme of oxidation of (I) in glacial acetic acid can be presented in the following form:

The degree of transformation of (I) to (II) increases upon adding mineral acids to the oxidation system. Best results were obtained in the presence of hydrochloric acid. An equimolar ratio of (I) and hydrochloric acid (II) is formed in a yield of 70% (see Table 1). The role of mineral acid reduces to protonation of the amino group. Protonation prevents to a significant degree attack of ozone at the amino group, which favors more selective oxidation of (I).

To further increase the selectivity of the process in the direction of formation of (II), partial replacement of acetic acid was carried out by other solvents: chloroform, carbon tetrachloride, dichloroethane, and tetrachloroethylene. As is seen from Table 2, partial substitution of acetic acid made it possible to increase the yield of (II) from 70 to 90-100%. Quantitative yield of (II) was obtained in a mixed solvent of a 1:1 volume ratio of acetic acid and dichloroethane (see Table 2).

The quantitative transformation of (I) to (II) under these conditions is associated with prevention of the nonselective effect of the hydroxyl radical formed during oxidation of organic compounds with ozone [4]. The hydroxyl radical, the reaction rate constant of which amounts to about 10° mole·liter⁻¹·sec⁻¹ [7] with the majority of organic compounds, in the absence of dichloroethane oxidizes (I) with formation of decomposition products.

Dichloroethane, the concentration of which is six time higher than that of (I), evidently accepts attack of hydroxyl radicals on itself and in this way prevents decomposition of (I).

Rubezhanskii Branch of the Boroshilovgradskii Mechanical Engineering Institute. M. V. Lomonosov Kiev Plant of Pharmaceutical Chemistry. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 5, pp. 107-110, May, 1976. Original article submitted March 4, 1975.

This material is protected by copyright registered in the name 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 \$7.50. TABLE 1. Effect of Mineral Acids on Oxidation of (I) in Glacial Acetic Acid*

Mineral acid (mole/liter)			oxi-	II) lysis	Content of (III) in the	
sulfuric	nitric	phos- phoric	hydro- chloric	Time of dation (h)	Yield of (from anal (%)	oxidation products (%)
0,715	0,715 — — —	0,715		4,5 4,6 4,4 4,7 4,0 4,3 4,3	20 50 58 40 55 70 70 70	10,0 8,0 7,5 9,0 7,0 5,0 5,0

*Volume of solvent 500 ml, [I] = 0.72 mole/liter, productive capacity of ozonator 0.18 mole/h of ozone, temperature 10°.

TABLE 2. Effect of Solvent on Oxidation of (I)*

Solvent (vol. %)				1	Yield of	
acetic acid	dichloro- ethane	carbon tet- trachloride	chloroform	tetrachloro- ethylene	Oxida- tion time (h)	(II) from analysis (%)
98 79 49 19 0 49 49 49	19 49 79 98 	 49 			4,3 4,35 4,30 5,10 5,2 4,1 4,3 4,3	70,0 75,0 100,0 45,0 5,0 90,0 93,0 97,0

*Solvent volume 500 ml, [I] = 0.72
mole/liter, [HC1] = 0.715 mole/liter,
productive capacity of ozonator 0.18
mole/h of ozone, temperature 10°.

It was established as a result of the investigations executed that in the studied limits the initial rate of accumulation and yield of (II) do not depend on the initial concentration of (I) (see Fig. 1). Rate of accumulation of (II) increases linearly with increase in partial pressure of ozone in the ozone—air mixture and can be expressed by the equation $V = K \cdot P_{OZ}$, where V is the rate of accumulation (mole·liter⁻¹·sec⁻¹); K is the proportionality coefficient (equal to 0.375 mole/liter·sec at 10°); P_{OZ} is the partial pressure of ozone in the gas mixture (atm). A content of water in the oxidative solution of up to 3 moles/ liter virtually does not affect the yield of (II). The yield of (II) decreases and the content of (III) in the oxidation products increases at a higher water concentration (Table 3). The role of water in the oxidation process is explained as follows: In its presence, cleavage of the acyl group of (I) occurs with formation of 1-(p-nitrophenyl)-2-aminoethanol (IV), which reacts with ozone at the amino and hydroxy groups with formation of decomposition products.

A change in temperature in the range of $-10-20^{\circ}$ virtually does not have an effect on the initial rate of accumulation and yield of (II). A further increase in temperature leads to a decrease in yield of (II) as a result of its partial peroxidation to (III) (Table 4). The effective activation energy of the process calculated from kinetic data amounts to 0.5 kcal/mole.

TABLE 3. Effect of Water on the Process of Oxidation of (I)*

Water (mole/., liter)	Oxida- tion time (h)	Yield of (II) from analysis (%)	Content of (III) in oxidation products (%)
0,7	4,3	100	0,3
1,81	4,3	100	0,3
2,93	4,3	100	0,3
4,04	4,2	80	5
5,15	4,0	65	6

*Volume of solvent 500 ml, [I] 0.72 mole/liter, [HC1] = 0.715 mole/liter, productive capacity of the ozonator 0.18 mole/h of ozone, temperature 10°.



TABLE 4. Effect of Temperature on the Process of Oxidation of (I)*

Tempera- ture (deg)	Oxída- tion time (h)	Yield of (II) from analysis (%)	Content of (III) in oxidation products %
10	4,9	100	0,3
10	4,3	100	0,3
20	4,2	100	0,5
40	4,0	80	5
60	3,8	60	7

*Volume of solvent 500 ml,
[I] = 0.72 mole/liter, [HC1] =
0.715 mole/liter, productive
capacity of ozonator 0.18
mole/h of ozone.

Fig. 1. Effect of concentration of (I) on the process of accumulation of (II). Volume of solvent 500 ml, [HC1] = 0.715 mole/liter, productive capacity of the ozonator 0.18 mole/h of ozone, temperature 10°: a-c) 0.34, 0.54, 0.72 mole/liter of (I), respectively.

According to the obtained data, 1 mole of ozone is consumed for oxidation of 1 mole of (I). The degree of utilization of ozone under the experimental conditions amounts to 45%. To increase the degree of utilization of ozone, experiments were carried out in which the ozone—air mixture was passed through two consecutively connected reactors. Analysis of the gas mixture past the second reactor showed that the degree of use of ozone in the system increased to 90%.

As a result of the executed investigations, conditions of oxidation of (I) with an ozone-air mixture in a medium of organic solvents were found, making it possible to obtain (II) in a high yield.

EXPERIMENTAL

<u>p-Nitro- α -acetylaminoacetophenone (II)</u>. In a glass flask fitted with a propeller stirrer having a hydraulic seal and a bubbler for introduction of a gas mixture were placed 500 ml of solvent (234 ml of acetic acid, 234 ml of dichloroethane, 32 ml of hydrochloric acid), with a turned-on stirrer 80 g of dry technical (I) was added, and at a temperature of 10° an ozone-air mixture was passed at a rate of 300 liters/h for 4.3 h. The content of (II) (present in solution) was determined in the reaction mass. The reaction mass was evaporated at 30° and a residual pressure of 25 mm. The residue was treated with 150 ml of water cooled to 2°. The residue was filtered and dried in air. We obtained (II), mp 150-152°.

Determination of p-Nitro- α -acetylaminoacetophenone (II) in the Reaction Mass. Analysis was achieved on a FEK-56 instrument with a No. 3 light filter and a 20-mm cell. A 0.005-ml sample of reaction mass was diluted in a 100-ml measuring flask with a cooled alcoholic base solution to the mark and the optical density was measured immediately. A calibration graph was used to determine the content of (II).

<u>Generation of Ozone</u>. Ozone was obtained using an LGO-15 laboratory ozone generator. The LGO-15-type ozonator apparatus is designated for obtaining ozone in a high-voltage silent discharge from purified dry air (dew point -40°). Productive capacity of the apparatus during operation with air was 0.015 kg/h of ozone at an operating voltage of 10 kV and a supplied voltage (feed) of 220 V. Water with a temperature not above 20° was circulated to cool the ozonator. Determination of the productive capacity of the ozonator and the ozone concentration in the outgoing gases was carried out iodometrically.

Determination of p-Nitrobenzoic Acid (III) Impurity in (II). We dissolved 0.5 g of dry (II) with heating in 20 ml of ethanol and titrated the mixture with 0.1 N sodium hydroxide solution to a brown color.

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STERILIZATION OF DESALTED WATER BY AN ELECTRIC FIELD

II. A STUDY OF THE CONDITIONS OF STERILIZATION

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It has been established experimentally that in the filtration of water through polarized materials the microorganisms present in it are retained in amounts considerably exceeding the adsorption capacity of the materials [1, 2]. The process of eliminating microorganisms from a liquid is substantially affected by the nature of the packing material and, in particular, its capacity for polarization. It must also be borne in mind that in the filtration of water for the preparation of injection solutions the choice of filtering is important since its structure largely determines the efficiency of the process.

In experiments to determine the optimum conditions of sterilization we used a comparatively simple construction of the filter consisting of two current-conducting electrode plates creating an electric field in the region of the filtering material located between them. Since it was important to test the efficiency of the dielectric and electrode materials and the influence of the field strength and of the rate of flow of liquid on the sterilization process, we examined the possiblity of regulating the voltage on the electrodes within wide limits.

To perform the experiments we used three variants of sources of supply of the electrodes (Fig. 1) which ensured the production of fields without pulsations of the voltage (a), full-wave rectification without smoothing out (b), and half-wave rectification of the current

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