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SYNTHESIS AND CONSTANTS OF 6-NITRO-2,3-DIHYDROQUINOLIN-4(1H)-ONE

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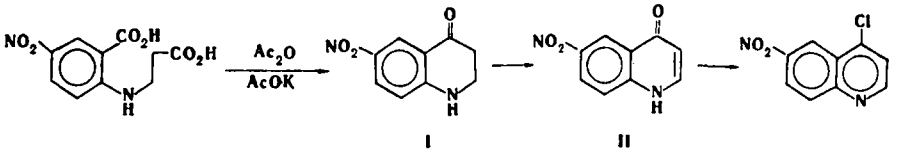
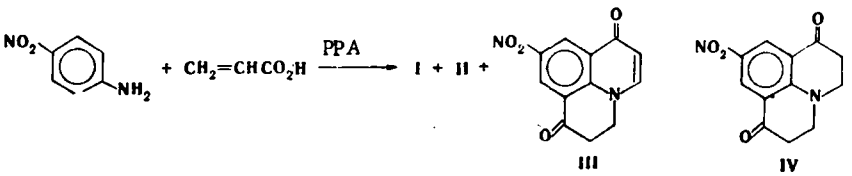
In the literature, there has appeared a communication [1] on the synthesis of 6-nitro-2,3-dihydroquinolin-4(1H)-one (I) with mp 125-126°C (2,4-dinitrophenylhydrazone, mp 269-270°C) by the reaction of p-nitroaniline with acrylic acid. Quinolinone I with mp 232-234°C (2,4-dinitrophenylhydrazone, mp 327-329°C) was obtained by us by decarboxycyclization of N-(2-carboxy-4-nitrophenyl)-β-alanine in acetic anhydride in the presence of potassium acetate [2].



I II

The structure of the product I synthesized by us was confirmed by UV and IR spectra and also by its dehydrogenation to the known 6-nitroquinolin-4(1H)-one (II) and by conversion of the latter to the also known 6-nitro-4-chloroquinoline [3].

The lack of correspondence of the published constants for quinolinone I to the obtained data induced us to repeat the work of [1]. As a result, we found that the product with mp 124-126°C mentioned in [1] was a mixture of substances, which we separated in a chromatographic column. After purification of the isolated fractions, we obtained the following substances: 4-nitroaniline, quinolinones I and II, and 2,3-dihydro-1,7-dioxo-1H, 7H-9-nitrobenzo[i,j]quinolizine (III):



III IV

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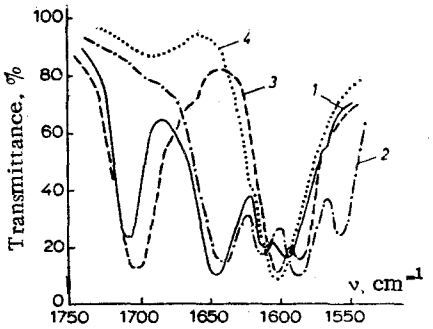

Fig. 1. IR spectra: 1) 2,3-dihydro-1,7-dioxo-1H,7H-9-nitrobenzo[i,j]quinolizine (III); 2) phenylhydrazone of quinolizine III; 3) 2,3,5,6-tetrahydro-1,7-dioxo-1H, 7H-9-nitrobenzo[i,j]quinolizine (IV); 4) phenylhydrazone of quinolizine IV.

The formation of quinolinone I was determined by thin-layer chromatography (TLC), the structure of quinolinone II was confirmed by the identity of its properties to those of the known specimen obtained by us previously [2], and the structure of quinolizine III was determined by elemental analysis and UV, IR, and mass spectra and was also confirmed by synthesizing it another way, including cyclization of N,N-bis(β-cyanoethyl)aniline [4], nitration of the resulting 2,3,5,6-tetrahydro-1,7-dioxo-1H,7H-benzo[i,j]quinolizine [5] to its 9-nitro derivative (IV), and dehydrogenation of the latter.

A comparative investigation of quinolizines III and IV showed that their UV spectra differ both in the number and location of the absorption bands; a significant difference is also observed in the IR spectra. In the region of carbonyl-group stretching-vibration frequencies, the spectrum of quinolizine IV is characterized by one intense absorption band (Fig. 1). The reactivity of the oxo groups of these compounds was also found to be different: unlike its hydrogenated analog IV, giving a phenylhydrazone at both oxo groups, quinolizine III formed a mono(phenylhydrazone) whose IR spectrum retained one low-frequency band of the carbonyl group.

The investigated quinolizines III and IV are similar in their properties and spectra to the corresponding quinolizines not containing a nitro group [5].

The formation of quinolinone II and quinolizine III can be explained by the fact that the reaction of 4-nitroaniline with acrylic acid gives two products: N-(4-nitrophenyl)-β-alanine and N,N-bis(β-carboxyethyl)-4-nitroaniline, which are cyclized to quinolinone I and quinolizine IV, and then, under the effect of the nitro group under the reaction conditions, they undergo dehydrogenation to compounds II and III, respectively. Similar aromatization was also observed during cyclization of other N-(nitroaryl)-β-alanines in polyphosphoric acid (PPA) [6, 7].

Since in [1] the intermediate reaction product in the formation of quinolinone I should be N-(4-nitrophenyl)-β-alanine, the latter was specially obtained by us in pure form by the reaction of p-nitroaniline with propiolactone and was allowed to undergo cyclization in PPA. Quinolinones I and II were isolated from the reaction products. The first was obtained in an insignificant amount and was identified chromatographically; quinolinone II was similar in constants and properties to a known specimen [2]. In this reaction, just as in the one considered above, the resulting 2,3-dihydroquinolinone I was dehydrogenated to quinolinone II.

The obtained data show that the constants given in [1] are erroneous and do not correspond to the constants of 6-nitro-2,3-dihydroquinolin-4(1H)-one.

It should be mentioned that the method for cyclization of N-(2-carboxyaryl)-β-alanines proposed by us previously [2] is the most convenient for preparing 2,3-dihydroquinolin-4(1H)-ones, including quinolinone I.

EXPERIMENTAL

The IR spectra were measured with a UR-20 spectrophotometer (tablets with KBr), and the UV spectra of alcoholic solutions were obtained with a Specord UV-vis instrument. Silufol UV-254 plates were used under standard conditions for TLC. Preparative TLC was carried out on glass plates in an unfixed layer of Al_2O_3.

Reaction of p-Nitroaniline with Acrylic Acid in PPA [1]. To freshly prepared PPA (29 g of P_2O_5 and 21.5 g of ortho-H_3PO_4), 7 g (0.05 mole) of p-nitroaniline and 3.6 g (0.05 mole) of acrylic acid were added at 100°C with stirring. The mixture was heated at 100°C for 5 h, and the reaction material was cooled, poured into ice, and extracted with chloroform. The chloroform layer was washed with a solution of sodium bicarbonate and water and dried. After the chloroform was distilled off, 2.3 g of a solid yellow residue was obtained, which was a mixture of four substances according to TLC data, with mp 124-126°C. After chromatographic separation in a column with Al_2O_3 and crystallization from alcohol, the following were isolated from the obtained mixture: 1) p-nitroaniline, 0.9 g, mp 151-153°C, 2) 2,3-dihydro-1,7-dioxo-1H,7H-9-nitrobenzo[i,j]quinolizine (III), orange crystals, mp 252-254°C. Found: C 59.2; H 3.3; N 11.2%. $C_{12}H_8N_2O_4$. Calculated: C 59.0; H 3.3; N 11.4%. R_f 0.4 (alcohol-benzene, 1:1). IR spectrum: 1338 (NO_2), 1645, and 1708 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 232 (4.34), 267 (4.1), 340 (3.85) and 382 nm (3.97). Mass spectrum: M^+, m/e 244. Phenylhydrazone, red crystals, mp 273-275°C. Found: N 16.7%. $C_{18}H_{14}N_4O_3$. Calculated N 16.7%. IR spectrum: 1338 (NO_2), 1636 (C=O), 3251 cm^{-1} (NH); 3) 6-nitro-4-hydroxyquinoline (II), 0.15 g, yellow crystals, mp 312-314°C. R_f 0.8 (alcohol–benzene, 1:1). The melting point of a mixed sample with the known specimen [2] gave no depression; 4) 6-nitro-2,3-dihydroquinolin-4(1H)-one (I) was detected chromatographically, R_f 0.9 (alcohol–benzene, 1:1), in the alcoholic mother liquor after crystallization of 6-nitro-4-hydroxyquinoline.

N-(4-Nitrophenyl)-β-alanine. A mixture of 13.81 g (0.1 mole) of p-nitroaniline, 11.92 g (0.165 mole) of β-propiolactone, and 140 ml of acetone was heated with boiling and stirring for 15 h. The solvent was distilled off, 100 ml of water was added to the residue, and the whole was boiled and cooled. The resulting precipitate was filtered, yield 21 g, mp 135-142°C. After reprecipitation and crystallization from alcohol, 8.3 g (39%) of a product with mp 155-156°C (according to [7]) was obtained. Found: N 13.0%. $C_9H_{10}N_2O_4$. Calculated: N 13.3%. R_f 0.7 (alcohol).

Cyclization of N-(4-Nitrophenyl)-β-alanine in PPA. To PPA obtained from 7.5 g of P_2O_5 and 7.5 g of ortho-H_3PO_4, 3 g (0.142 mole) of N-(4-nitrophenyl)-β-alanine was added at 100°C with stirring, and the mixture was heated for 4 h at 100-105°C. After cooling to 50°C, the reaction material was poured into ice, a soda solution was added to pH 3-4, and the whole was extracted with chloroform. The chloroform layer was also washed with a soda solution and water and dried with sodium sulfate. The solvent was distilled off, and 1.0 g of a yellow substance with mp 150-160°C was obtained. After crystallization from alcohol, 0.3 g of a substance with mp 232-280°C was isolated, giving two spots corresponding to quinolinone I (R_f 0.9) and quinolinone II (R_f 0.8) by TLC. After purification in a column with Al_2O_3, 0.15 g of quinolinone II (R_f 0.8) (alcohol–benzene, 1:1) with mp 310-312°C was isolated; the melting point of a mixed sample with a known specimen of II [2] gave no depression.

N,N-Bis(β-cyanoethyl)aniline, mp 79-80°C, was obtained by the method of [4], and by cyclization it was converted to 2,3,5,6-tetrahydro-1,7-dioxo-1H,7H-benzo[i,j]quinolizine, mp 145-146°C [4], as a result of whose nitration 9-nitroquinolizine IV was isolated [5].

Dehydrogenation of 2,3,5,6-Tetrahydro-1,7-dioxo-1H,7H-9-nitrobenzo[i,j]quinolizine (IV). Preparation of Compound III. A mixture of 0.8 g (3.3 mmoles) of quinolizine IV, 0.8 g of a Pd/C catalyst, and 25 ml of xylene was boiled for 15 h. The catalyst was filtered off, the filtrate was evaporated, and the residue was purified by crystallization from alcohol and preparatively on Al_2O_3. The yield of compound III was 0.4 g (51.5%), mp 252-254°C. Found: C 59.3; H 3.2; N 11.2%. $C_{12}H_8N_2O_4$. Calculated: C 59.0; H 3.3; N 11.4%. IR spectrum: 1338 (NO_2), 1645 and 1707 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 232 (4.34), 267 (4.10), 340 (3.85), 382 nm (3.97). The melting point of a mixed sample with quinolizine III isolated from the reaction gave no depression. The phenylhydrazone was red crystals with mp 272-274°C. IR spectrum: 1338 (NO_2), 1636 (C=O), 3251 cm^{-1} (NH).

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REACTIONS OF 2-METHYLENE-3-OXOQUINUCLIDINE WITH BIFUNCTIONAL NUCLEOPHILIC REAGENTS

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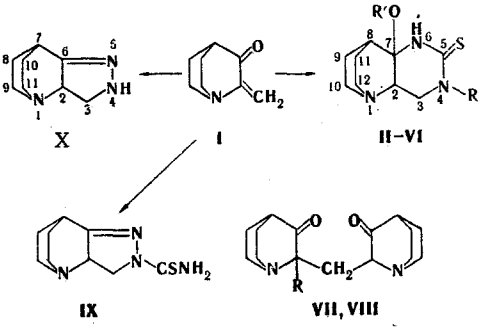
The synthesis of certain condensed heterocyclic quinuclidine derivatives has been accomplished by the reaction of 2-carbethoxy-3-oxoquinuclidine with bifunctional nucleophilic reagents [1-3], by reaction of 3-carbethoxy-Δ^2 dehydroquinuclidine with diazomethane or phenylazide [1], or on the basis of addition products of malonic ester or phenol to 2-methylene-3-oxoquinuclidine [4,5].

To enlarge the possibilities of preparing condensed derivatives of quinuclidine from the readily available 2-methylene-3-oxoquinuclidine (II), we have studied the reactions of ketone I with various bifunctional nucleophilic reagents: thioureas, hydrazine, or thiosemicarbazide.

On reaction of ketone I with thiourea or N-phenylthiourea, compounds of the general formula II-VI are formed. Depending on the reaction conditions, 5-thio-7-oxy-1,4,6-triazatricyclo[4.2.2.$0^{2,7}$]dodecane (II, IV) or their 7-alkoxy derivatives (III, V, VI) are formed.



II R=R′=H; III R=H, R′=C_2H_5; IV R=C_6H_5, R′=H; V R=C_6H_5, R′=C_2H_5; VI R=H, R′=CH_3; VII R=CH_2OH; VIII R=H

Regardless of the catalyst used (sodium hydroxide, sodium alcoholates) or of the solvent (water, methanol, ethanol) the 7-hydroxy derivatives (II, IV) are formed at room temperature. On heating compounds II or IV with sodium alcoholates, a replacement of the hydroxyl group in the 7 position by an alkoxy group takes place; thereupon the compounds III, V, or VI are formed. The 7-alkoxy derivatives can also be obtained directly from ketone I and thiourea (or N-phenylthiourea) with alcoholic solutions of sodium alcoholates. Formation of the tricyclic compounds is facilitated by the introduction of a phenyl residue into the thiourea molecule, which agrees well with the effect of an electron-acceptor grouping on the ability to form N,O-hemiketals.

On treatment of the tricyclic compounds III and V with an alcoholic hydrogen chloride solution at room temperature, the ethoxy group is hydrolyzed, which leads to the hydrochlorides of the 6-hydroxy derivatives II and IV. In aqueous solution, the hydrochloride of compound II is converted into an equilibrium mixture of tricyclic compound II and the product of its ring-opening at the N_6—C_7 bond — N-(3-oxoquinuclidyl-2-methyl)-thiourea.

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