CLEAVAGE OF ARYLHYDRAZONES OF α-HYDROXYKETONES AT THE N–N BOND WITH ACETIC ACID IN THE PRESENCE OF o-PHENYLENEDIAMINE

FORMATION OF QUINOXALINES

K. M. Ermolaev

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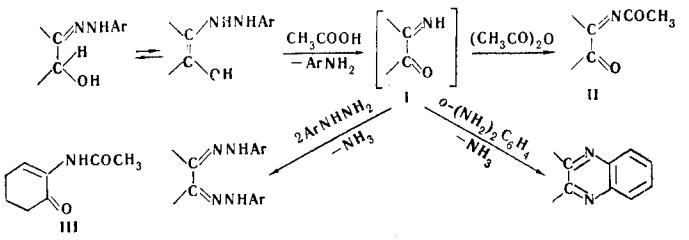
The corresponding quinoxalines are formed by the reaction of arylhydrazones of α-hydroxyketones with o-phenylenediamine in glacial acetic acid. The basis for the reaction is the ability of arylhydrazones of α-hydroxycarbonyl compounds to undergo cleavage at the N–N bond in carboxylic acid media to form an arylamine and an α-diketone monoimine.

In connection with a study of the chemical properties of the arylhydrazones of α-hydroxycarbonyl compounds [1], several of them were subjected to reaction with o-phenylenediamine in acetic acid. The arylamine and the corresponding quinoxaline were isolated as the reaction products, and ammonia was detected in the reaction mixture. To carry out the reaction, equimolar ratios of the reagents were held in glacial acetic acid at a fixed temperature. The instant at which the temperature of the reaction mixture again becomes equal to the bath temperature after reaching a maximum value served as a sign of completion of the reaction, which proceeds with a small amount of heat evolution. After removal of the solvent, the reaction products were separated by the usual methods. The starting arylhydrazones, the reaction conditions, and the compounds obtained are presented in Table 1.

The problem of the mechanism of this reaction can apparently be solved if one takes into account the ability of arylhydrazones of α-hydroxyketones to undergo cleavage at the N–N bond in carboxylic acid media to form an arylamine and an α-diketone monoimine (I) [1, 2]. In particular, if this sort of cleavage occurs in the presence of a twofold excess of arylhydrazine, an osazone is formed [2]. An N-acetyl-α-iminoketone (II) can be isolated when the cleavage is carried out in a mixture of acetic acid and acetic anhydride. In this reaction, however, the α-iminoketone (I) obtained during the cleavage of the arylhydrazone and the nitrogen analog of the α-diketone react with o-phenylenediamine to form a quinoxaline* (see [3]).



As seen from the data presented in Table 1, the ease with which the α-hydroxyketone arylhydrazones enter into this reaction depends on the character of the aryl radical of the hydrazine residue, which can be followed in the case of 2-hydroxycyclohexanone. Thus, while the phenylhydrazone of this compound reacts

*The α-iminocarbonyl compounds were earlier identified as quinoxaline derivatives; for example, in the thermolysis of some organic azides [4].

Institute of Biological and Medicinal Chemistry, Academy of Medical Sciences of the USSR, Moscow.
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TABLE 1. Reaction of Arylhydrazones of α-Hydroxyketones with o-Phenylenediamine

Starting hydrazone	Bath temp. °C	Max. temp. of reaction mixture, °C	Reaction time, h	Reaction products* (yield, %)
2-Hydroxycyclohexanone phenylhydrazone	25	40- 50	15-20	1,2,3,4-Tetrahydrophenazine (85) and aniline (70)
2-Hydroxycyclohexanone p-nitrophenylhydrazone	70	75- 80	15-20	1,2,3,4-Tetrahydrophenazine (80) and p-nitroaniline (60)
2-Hydroxycyclohexanone 2,4-dinitrophenylhydrazone (mp 152-153°)	100	105-106	20-25	1,2,3,4-Tetrahydrophenazine (70) and 2,4-dinitroaniline (60)
2-Hydroxycyclohexanone 2,4-dinitrophenylhydrazone (mp 194-195°)	100	104-105	20-25	1,2,3,4-Tetrahydrophenazine (65) and 2,4-dinitroaniline (55)
Acetoin p-nitrophenylhydrazone	70	75- 80	15-20	2,3-Dimethylquinoxaline (80) and p-nitroaniline (80)
Acetoin 2,4-dinitrophenylhydrazone	100	103-104	30-40	2,3-Dimethylquinoxaline (35) and 2,4-dinitroaniline (40)
2-Hydroxycyclopentanone p-nitrophenylhydrazone	100	105-107	10-15	2,3-Trimethylquinoxaline (70) and p-nitroaniline (60)
Benzoin p-nitrophenylhydrazone	100	102-103	30-40	2,3-Diphenylquinoxaline (70) and p-nitroaniline (85)

*Aniline and p-nitroaniline were isolated as the N-acetyl derivatives.

with o-phenylenediamine at room temperature, the p-nitrophenylhydrazone requires heating to 70°, while the 2,4-dinitrophenylhydrazone, regardless of which of the two modifications [1] is used in the reaction, reacts at a sufficient rate only at 100°. A similar regularity was also observed in the cleavage of the same compounds in a mixture of acetic acid and acetic anhydride and resulted in the formation of 2-acetamido-2-cyclohexenone (III) and the corresponding arylamine. However, in this case the low-melting form of 2-hydroxycyclohexanone 2,4-dinitrophenylhydrazone was more reactive than the high-melting form [1].

The yields of the quinoxalines also depend on the character of the aryl radical, as indicated by experiments with the arylhydrazones of 2-hydroxycyclohexanone and, especially, acetoin. In a preparative respect, it is expedient to use the p-nitrophenylhydrazones of the starting compounds (which is natural when the α-hydroxyketones are more accessible than the corresponding α-diketones). The p-nitrophenylhydrazones more sufficiently reactive, and the reaction products are isolated more simply and completely than in the case of phenyl- and 2,4-dinitrophenylhydrazones after preliminary acetylation of the p-nitroaniline formed with acetic anhydride. In conclusion, it should be noted that the investigated reaction is apparently general for the arylhydrazones of α-hydroxycarbonyl compounds.

EXPERIMENTAL

Acetoin p-Nitrophenylhydrazone. A mixture of 15.3 g (0.1 mole) of p-nitrophenylhydrazine and 9.0 ml (0.102 mole) of acetoin in 100 ml of methanol was stirred at 60° until a solution formed. The solution was cooled carefully to prevent the formation of an emulsion and diluted with an equal volume of water. After 10-12 h, the hydrazone was filtered, washed with water, and dried in a vacuum desiccator over sulfuric acid to give 90-95% of yellow crystals with mp 125-127° (from toluene at 100°) which were soluble in most organic solvents and almost insoluble in ether. Found %: C 54.0; H 6.2; N 18.9. $C_{10}H_{13}N_3O_3$. Calculated %: C 53.7; H 5.9; N 18.8.

Acetoin 2,4-Dinitrophenylhydrazone. A total of 9.0 ml (about 0.102 mole) of acetoin was added carefully (boiling over is possible) to a refluxing suspension of 19.8 g (0.1 mole) of 2,4-dinitrophenylhydrazine in 200 ml of anhydrous ethyl acetate. The resulting solution was vacuum evaporated to about one third of its initial volume and held at 0° for 10-12 h. The hydrazone was filtered, washed with ether (14.5 g were obtained), and the filtrate was evaporated almost to dryness. The residue was stirred with ether, and 8-9 g of the hydrazone was separated. The overall yield of orange crystals with mp 109-110° (from methanol) was 85-90%. The product was soluble in most organic solvents and almost insoluble in ether and carbon tetrachloride. Found %: C 45.0; H 4.6; N 21.0. $C_{10}H_{12}N_4O_5$. Calculated %: C 44.8; H 4.5; N 20.9.

2-Hydroxycyclopentanone p-Nitrophenylhydrazone (see [5]). A mixture of 11.9 g (0.1 mole) of 2-chlorocyclopentanone [6] and 11.0 g (about 0.55 mole) of barium carbonate in 50 ml of water was refluxed until carbon dioxide evolution ceased (1.5-2 h). A solution of 18.90 g (0.1 mole) of p-nitrophenylhydrazine hydrochloride in 150 ml of water was added to the filtered solution containing 2-hydroxycyclopentanone. The precipitated hydrazone was filtered, washed with water until it gave a neutral reaction to Congo, and dried in a vacuum desiccator over sulfuric acid to give 85-90% of orange crystals with mp 194-195° (from acetonitrile, 1:20). The product was soluble in hot ethanol and ethyl acetate and almost insoluble in ether. Found %: C 56.4; H 5.6; N 17.9. $C_{11}H_{13}N_3O_3$. Calculated %: C 56.2; H 5.6; N 17.9.

Reaction of α-Hydroxyketone Arylhydrazones with o-Phenylenediamine. A mixture of 0.01 mole of the arylhydrazone and 0.01 mole of o-phenylenediamine in 15 ml of glacial acetic acid was held under the conditions indicated in Table 1. The p-nitrophenylhydrazones of 2-hydroxycyclohexanone and acetoin gave as side products about 0.1-0.2 g of the corresponding osazone, which should be removed by filtration. The acetic acid was removed by vacuum distillation (7-10 mm); the bath temperature at the end of the distillation should not exceed 60-65°, since otherwise considerable losses of ammonia and aniline are possible. The residue is then treated as follows. In the case of 2-hydroxycyclohexanone phenylhydrazone, the residue was stirred with 10 ml of acetic anhydride, the solution was vacuum evaporated after 1 h (toward the end on a boiling-water bath), and 1,2,3,4-tetrahydrophenazine was extracted with boiling hexane. After evaporation of the hexane extracts to dryness, the crystalline residue was triturated with 10-15 ml of water, and the tetrahydrophenazine was separated, washed with water, and dried. The hexane-insoluble residue was triturated with 3-5 ml of ice water to isolate the acetanilide. The acetamide can be isolated after evaporation of the aqueous filtrates.

In the case of p-nitrophenylhydrazones, the residue was also treated with acetic anhydride, the p-nitroacetanilide thus formed was separated, and the filtrate was evaporated as described above. The residue was stirred with 25-30 ml of ether, the p-nitroacetanilide was additionally filtered, the precipitate was washed thoroughly with ether, and the filtrate was vacuum evaporated. To isolate the 2,3-diphenylquinoxaline, the residue obtained was immediately crystallized from ethanol. In the formation of 1,2,3,4-tetrahydrophenazine, 2,3-dimethylquinoxaline, and 2,3-trimethylenequinoxaline, these compounds are extracted with boiling hexane, and the solutions are handled as described above. Both p-nitroacetanilide fractions were washed with water and dried. Acetamide was isolated from the aqueous filtrates. In the case of 2,4-dinitrophenylhydrazones of 2-hydroxycyclohexanone and acetoin, the quinoxalines were extracted with hexane after evaporation of the acetic acid solution, and the residue was triturated with 5 ml of ethanol to isolate 2,4-dinitroaniline. All of the quinoxalines except 2,3-diphenylquinoxaline were purified by vacuum sublimation (85-90°, 0.1 mm). The isolated quinoxalines were identical to those synthesized by the condensation of o-phenylenediamine with the appropriate α-diketones in acetic acid (identification by mixed-melting point determination) [7-10].

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