SYNTHESIS OF DIBAZOL IN ANHYDROUS MEDIUM

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Dibazol (2-benzylbenzimidazole) is an original native preparation having hypotensive effect [1] and finds wide use in medical practice. According to literature data [2], the industrial method of dibazol synthesis is based on condensation of phenylacetic acid, formed as a result of acidic hydrolysis of benzyl cyanide, witho-phenylenediaminein the presence of hydrochloric acid at a temperature of 225°C.

It is known that benzylimidazoles can be obtained upon direct reaction of nitriles with aromatic diamines [3] in the presence of an acidic catalyst.

We investigated the condensation reaction of o-phenylenediamine (I) with benzyl cyanide (II) in anhydrous medium using acids of various strengths. The reaction was carried out in a melt at a temperature of 190° and an equimolar ratio of reagents and acid. In all cases dibazol (IV) was isolated as the main reaction product. The obtained results are presented in Table I.

It is seen from Table I that the yield of (IV) increases upon increasing the acidic properties of the acid. The effect of acid evidently reduces to activation of the nitrile and its transformation to the activated form [4], which reacts with the amine. The fraction of the active intermediate form of the nitrile increases with increasing strength of the acid. It can be postulated that an intermediate product is present in the reaction mass having an amidene nature, since it is known that under analogous conditions N-substituted amidines [5] are obtained in good yields from aromatic amines and nitriles. However, only (I), (II), and (IV) were detected in all cases upon chromatographic analysis of the reaction mass and the oxidation product of (I) was detected in a small amount. We synthesized N^2-(o-aminophenyl) phenylacetamidine (III) from (I) and (II) in the presence of phenyllithium by the known method. The obtained amidine base has a spectrum in the ultraviolet region characteristic for substituted phenylacetamides. It closes easily to (IV) already upon weak heating. Amidine hydrochloride (II), upon boiling in acetone, also closes to (IV) with liberation of ammonium chloride. Consequently, it can be proposed that the formed amidine (III) closes rapidly under the reaction conditions to (IV). The following scheme can be presented in connection with the proposed reaction between (I) and (II) in the presence of acids.

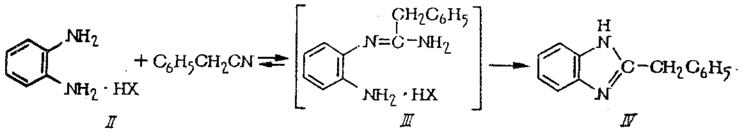

TABLE 1. Experimental Rate Constants of the Dibazol (IV) Formation Reaction and Yields as a Function of Added Acids

Acids	$K \cdot 10^{-3}$, liter/mole · sec	Yield, %, $\tau = 2$ h
Hydrogen chloride	20	85
Aluminum chloride	18,4	74
p-Toluenesulfonic acid	12,7	58,2
Phosphorus pentoxide		46
Boric acid	1,8	17
Ammonium chloride		Traces

As a rule, the limiting stage of an acidic catalytic process is transformation of the active form of the nitrile to the reaction product. Since under the reaction conditions the concentration of intermediate product is significantly lower than the concentration of initial reagents, the reaction can be characterized as an equilibrium process. In this case the experimental rate constant can be determined from the change in concentration of either the initial or final products. The rate of change in concentration of (I) in the reaction was controlled colorimetrically from formation of the colored condensation product of (I) with

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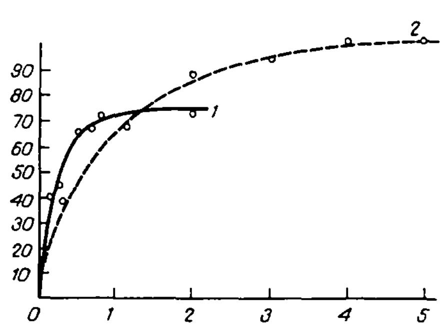

Fig. 1

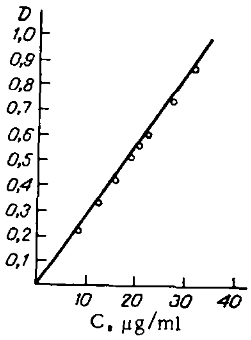

Fig. 2

Fig. 1. Dependence on degree of transformation of o-phenylenediamine (I) on amount of acidic catalyst. Molar ratios of acid and (I) on the abscissa axis; degree of transformation of (I) in 2 h (%) on the ordinate axis. 1) p-Toluenesulfonic acid; 2) hydrogen chloride.

Fig. 2. Dependence of degree of transformation (η) of o-phenylenediamine on temperature.

acetylacetone in acidic medium (1,4-benzdiazepine) [6]. Under the conditions of carrying out the analysis, (IV) and amidine (III), the intermediate reaction product, do not form colored products with acetylacetone.

Values of reaction rate constants are presented in Table 1. They are in agreement with yields of the final product. The error in determining reaction rate constants, calculated by the method of mathematical statistics [7], amounts to 2-3%. It is seen from Table 1 that in the case of strong acids, both protic and aprotic, the values of rate constants are significantly higher than in the case of weak acids. The reaction proceeds most readily in the presence of hydrogen chloride and p-toluenesulfonic acid. Experimental rate constants do not make it possible to evaluate ratios of constants of individual reaction steps; however, on the whole they agree with the proposed scheme. We did not determine the true rate constant of the acid-catalyzed process, since it is not possible to establish the fraction of active form of nitrile. The effect of amount of acid on reaction rate was investigated for the case of p-toluenesulfonic acid and hydrogen chloride. Upon increasing the amount of acid the reaction rate increased, which evidently is associated with an increase in the amount of active form of nitrile (Fig. 1). An attempt to decrease the temperature of the reaction mass leads to a decrease in yield of final product (Fig. 2).

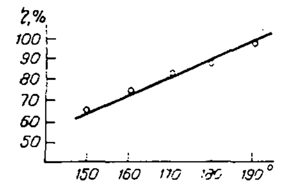

Fig. 3. Dependence of optical density (D) of solution of reaction products of o-phenylenediamine (I) with acetylactone on concentration of (I) (C).

Thus, the found optimal conditions of synthesizing (IV) in anhydrous medium are: temperature 190°, length 2 h, ratio of (I) base: (I) dihydrochloride: (II) 0.5 : 0.5 : 1.

EXPERIMENTAL

The following materials were used: (I) base (pure), (I) dihydrochloride (pure), aluminum chloride (very pure); p-toluenesulfonic acid (pure), dried in vacuum over phosphorus pentoxide; (II) distilled in vacuum at 170° (12 mm), boric acid (chemically pure), ammonium chloride (chemically pure), triethylamine (chemically pure).

Synthesis of Dibazol (IV) in Anhydrous Medium. A mixture of (I) base, (I) dihydrochloride, and (II) in a molar ratio of 0.5 : 0.5 : 1 was melted at a temperature of 190° in a sealed ampoule or a flask having an air condenser and stirrer in a stream of inert gas for 2 h. At the end of holding the mass was cooled and the obtained product was transformed to the hydrochloride (IV) by boiling with 5% hydrochloric acid for 10 min. Purification of (IV) was carried out by recrystallization from water. Yield of (IV) hydrochloride was 85%. The product was a white powder with a slightly yellow tinge, mp 184-186°.

Synthesis of N^2-(o-aminophenyl)phenylacetamidine (III). To 0.2 g-atom of lithium in absolute ether was added in drops 0.1 mole of bromobenzene with stirring. After maintaining for 30 min 0.1 mole of (I) was added; again after 30 min (II) was added gradually. The reaction mass was decomposed with water and the layers were separated. The solvent was distilled from the ether layer in vacuum without heating. We obtained (III) in a yield of 40%. The product was white crystals, soluble in ether, alcohol, and slightly soluble in water. Upon heating in hydrochloric acid it hydrolyzes to (I), giving a positive reaction with acetylacetone. It starts to melt at 110° with liberation of ammonia and closing to (IV). Upon lengthy standing of the product in air the odor of ammonia is also perceived, which indicates the gradual closing of (III) to (IV). Therefore, it is not possible to purify the obtained product by recrystallization. An alcoholic solution of (III) in the UV region has a dropping spectrum with absorption maxima in the region of 220-320 nm, which is characteristic for substituted phenylacetamidines. Hydrochloride (III) is obtained by passing a calculated amount of hydrogen chloride into an ether solution of base. The product does not submit to purification and closes to (IV) upon boiling in acetone.

Kinetic Investigations

A. Construction of a Calibration Graph. To construct a calibration graph of the dependence of optical density on the concentration of 1,4-benziazepine, formed upon reaction of (I) with acetylacetone in a 5% hydrochloric acid medium, into 25-ml measuring flasks were placed 2, 1.5, 1, 4, . . . 0.5 ml of prepared solution of (I) of a determined concentration (0.00395 mole/liter). The contents of the flask were mixed, 0.5 ml of a 20% acetylacetone solution in alcohol was added, and solutions were brought to the mark with hydrochloric acid. The optical density of solutions was measured after 3 min on an FÉK-M with a yellow-green filter. Solutions obeyed the Lambert–Bouguer–Beer law (Fig. 3).

B. Kinetics of Disappearance of o-Phenylenediamine (I) in Reaction with Benzyl Cyanide (II). In ampoules were placed 0.02 mole each of (I) and (II) acid. The reaction was carried out at a temperature of 100° (± 1 deg). The amount of unreacted (I) was controlled after each 30 min photocolorimetrically analogously to that described above.

Effect of Amount of Acid on Rate of Disappearance of o-Phenylenediamine (I) in Reaction with Benzyl Cyanide (II)

A. p-Toluenesulfonic Acid. In ampoules were placed 0.001 mole each of (I) base and (II). The amount of p-toluenesulfonic acid amounted to 0.0002, 0.0005, 0.0001, 0.002, 0.003, 0.004, and 0.005 mole. The ampoules were heated on an oil bath at a temperature of 190° for 2 h. At the end of reaction the contents of the ampoule were dissolved in 5% hydrochloric acid. The amount of remaining amine was determined at the corresponding dilution analogously to that described above.

B. Hydrogen Chloride. In ampoules were placed (I) base in amounts of 0.004, 0.0035, 0.003, 0.002, 0.0015, 0.001 mole; (I) dihydrochloride in amounts of 0.0005, 0.001, 0.002, 0.0025, 0.003, 0.004 mole; (II) in an amount of 0.004 mole. The amount of unreacted free (I) was determined analogously to that described above.

Effect of Temperature on Rate of Disappearance of o-Phenylenediamine (I) in Reaction with Benzyl Cyanide (II)

In ampoules were placed 0.001 mole of (I) base, 0.001 mole of (II), and 0.004 mole of p-toluenesulfonic acid, and they were heated to temperatures of 190, 180, 170, 160, 150°. The amount of unreacted (I) was determined analogously to that described above.

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