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BENZIMIDAZOLE REARRANGEMENT OF DIHYDROBENZODIAZEPINES

V. D. Orlov, N. N. Kolos, and B. M. Zolotarev

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The rearrangements of 2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepines under the influence of acids, temperature, and electron impact were studied. It is shown that the trend of the process is strictly specific for each case. The mechanism and the factors that regulate the trend of the benzimidazole rearrangement are discussed.

A peculiarity of dihydrobenzodiazepines is the ability to undergo conversion to benzimidazoles [1] both under the influence of acids and at elevated temperatures. Even the addition of catalytic amounts of acids to solutions of dihydrobenzodiazepines gives rise to this rearrangement, the general principle of which consists in retention of the substituent in the 2 position (Table 1). The reaction products are also substituted acetophenones, which were identified by chromatography and by means of 2,4-dinitrophenylhydrazine.

In the present research we studied the behavior of 2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepines I-XV in acidic media, upon heating, and under the influence of electron impact.

It is known [2, 3] that o-phenylenediamine reacts with aromatic aldehydes to give 2-arylbenzimidazoles (through the corresponding azomethines and benzimidazolines; the addition of hydride-ion acceptors promotes oxidation of the latter). One might have assumed that the rearrangement under discussion proceeds via an intermolecular mechanism that includes hydrolysis of the dihydrobenzodiazepines in acidic media to o-phenylenediamine and chalcones and subsequent reaction of the o-phenylenediamine with the aldehydes that are formed by the retroaldol process that is possible for chalcones [4]. However, this is repudiated experimentally. Thus if stoichiometric amounts of p-nitrobenzaldehyde and one to two drops of concentrated HCl are added successively to a methanol solution of II, the reaction products contain 2-phenylbenzimidazole (XVI) but do not contain even trace amounts of 2-(4-nitrophenyl)benzimidazole. Moreover, XVIII is formed in 60-80% yield in a blank experiment in which o-phenylenediamine is used in place of dihydrodiazepine II. p-Nitrobenzaldehyde is more active than benzaldehyde in reactions to form benzimidazoles [5], and the results therefore constitute evidence for the intramolecular character of the rearrangement.

It is known [6] that the optimum conditions for the synthesis of I-XV involve refluxing of alcohol solutions of o-phenylenediamine with chalcones with the addition of strong organic bases. However, if an acidic catalyst (for example, 10% HCl) is used in place of the base, exclusively benzimidazoles are obtained. However, spectral and chromatographic monitoring

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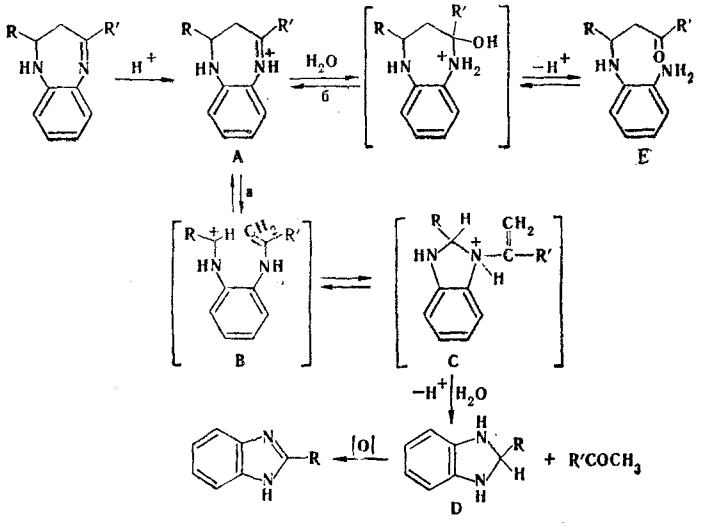
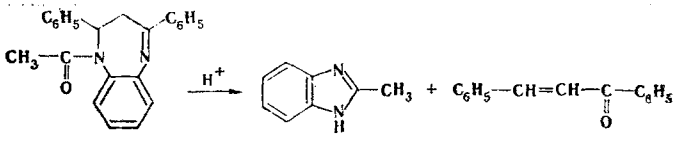
(in the case of chalcone and o-phenylenediamine) showed that very small amounts of dihydrobenzodiazepine II are observed in the mixture after refluxing for an hour. The development of benzimidazole XVI, however, is detected only after 2 h. These observations can be explained only by proceeding from the assumptions that the dihydrobenzodiazepines are absolutely necessary intermediates in the acid-catalyzed synthesis of benzimidazoles on the basis of α,β-unsaturated ketones and that the mechanism of the rearrangement under discussion is an intramolecular process.

It has been previously shown [7] that various o-aminophenyleneazomethine systems, including dihydrobenzodiazepines, are protonated primarily at the nitrogen atom of the azomethine group. The resulting for A is the nitrogen analog of a protonated aldol molecule, the dissociation of which in an acidic medium is realized exclusively at the β bond (retroaldol condensation) [4]. This analogy makes it possible to assume the possibility of the formation of intermediate B. The assumption of the existence of intermediate C is in agreement with the data in [8, 9], in which 1-isopropenylbenzimidazol-2-one was isolated in the rearrangement of 4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one; this product is readily hydrolyzed in acidic media to give benzimidazolin-2-one and acetone. The fact that intermediate dihydrobenzimidazoles D were not detected under the experimental conditions reflects their well-known tendency to undergo aromatization [2].



It should be noted that we were unable to isolate a β-addition product (E) in any of the experiments. However, process b may, in principle, occur, as evidenced, for example, by the nitration of II and its reaction with phenylhydrazine and 2,4-dinitrophenylhydrazine, which leads to chalcone derivatives [1]. However, under the conditions described here the benzimidazole rearrangement competes successfully with process b.

A change in the trend of the rearrangement is observed for 1-acetyl-2,4-diphenyl-2,3-dihydro-1,5-benzodiazepine (XV). In acidic media the principal products of its chemical transformations are 2-methylbenzimidazole XXII and chalcone; the products also contain trace amounts (∿2%) of 2-phenylbenzimidazole XVI.



The electron-acceptor group conjugated with the N_1 atom probably has a destabilizing effect on intermediate B. This in turn favors process b.

The thermal rearrangement of the dihydrobenzodiazepines was investigated in ethylene glycol and napththalene at 180-200°C, since preliminary studies showed that they are quite stable at temperatures below 170°C. Thus the development of even trace amounts of 2-phenylbenzimidazole XVI [as monitored by thin-layer chromatography (TLC)] is not observed when II is refluxed in o-xylene (bp 144°C) for 10 h. This pattern is retained in naphthalene thermostated at 160-170°C, while the formation of benzimidazole XVI is complete after ∿5 h in naphthalene at 200°C.

TABLE 1. Data on the Rearrangement of 2-R-4-R'-2,3-Dihydro-1H-1,5-benzodiazepines (I-XV) and 2-X-Benzimidazoles (XVI-XXII)

Compound	R	R′	Acidic catalysis			Thermolysis in naphthalene*		
			compound	X	yield, %	compound	X	yield, %
I	C_6H_5	CH_3	XVI	C_6H_5	80	XXII	CH_3	18
II	C_6H_5	C_6H_5	XVI	C_6H_5	60	XVI	C_6H_5	15
III	C_6H_5	C_6H_4Cl-*p*	XVI	C_6H_5	72	XVI	C_6H_5	17
IV	C_6H_5	C_6H_4Br-*p*	XVI	C_6H_5	63	—	—	—
V	C_6H_5	$C_6H_4NO_2$-*p*	XVI	C_6H_5	48	XVI	C_6H_5	10
VI	C_6H_5	$C_6H_4OCH_3$-*p*	XVI	C_6H_5	74	XVI	C_6H_5	5
VII	C_6H_5	2-Thienyl	XVI	C_6H_5	76	XVI	C_6H_5	33
VIII	C_6H_5	$HC{=}CHC_6H_5$	XVI	C_6H_5	70	XVI	C_6H_5	25
IX	C_6H_4Cl-*p*	C_6H_5	XVII	C_6H_4Cl-*p*	78	XVI	C_6H_5	21
X	$C_6H_4NO_2$-*p*	C_6H_5	XVIII	$C_6H_4NO_2$-*p*	59	XVI	C_6H_5	18
XI	$C_6H_4NO_2$-*o*	C_6H_5	XIX	$C_6H_4NO_2$-*o*	58	XVI	C_6H_5	12
XII	$C_6H_4OCH_3$-*p*	C_6H_5	XX	$C_6H_4OCH_3$-*p*	69	XVI	C_6H_5	5
XIII	2-Thienyl	C_6H_5	XXI	2-Thienyl	64	—	—	—
XIV	C_6H_4Cl-*p*	C_6H_4Cl-*p*	—	—	—	XVI	C_6H_5	5
XV †	C_6H_5	C_6H_5	XXII	CH_3	90	—	—	—

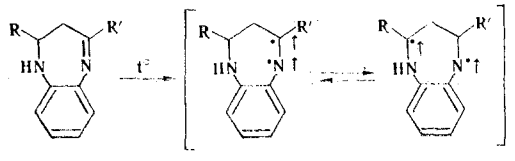
*In ethylene glycol III and V form XVI in 44 and 25% yields, respectively, while X forms XVIII in 33% yield.
†The N-acetyl derivative of II was investigated.

In ethylene glycol the rearrangement is realized in the same way as the acid-catalyzed process, i.e., substituent R is retained in the final benzimidazoles, and the secondary products are acetophenone derivatives. The residual water in the ethylene glycol probably participates in the process, and this is to a certain degree responsible for the identical character of the mechanisms of the thermal and acidic rearrangement processes.

Heating I-XII and XIV in naphthalene in air leads to a complex mixture of products; however, only one of the two possible benzimidazoles, in the molecule of which the substituent with lower mass is always retained (see Table 1), can be isolated from it. Heating deoxygenated (by purging with nitrogen) naphthalene solutions of the dihydrobenzodiazepines in sealed ampuls makes it possible to increase the yields of the desired benzimidazoles somewhat.

Complete isolation of the benzimidazoles from the reaction mixtures is achieved by treating them with ether, in which these compounds are virtually insoluble. o-Phenylenediamine and polymeric compounds were detected in the ether extracts. Thus, in addition to the benzimidazole rearrangement, more profound destruction of the dihydrobenzodiazepine molecules also occurs here.

The trend of the rearrangement here can probably be explained by the fact that it proceeds via a radical mechanism:



The subsequent processes are determined by cleavage of the C–N and C–C bonds to give benzimidazoles (or o-phenylendiamine); of the two possible intermediate styrene radicals, primarily that which is stabilized by the substituent in the aromatic ring is formed. Processes involving recombination of the intermediate radicals explain the absence of unsaturated hydrocarbons in the reaction mixtures.

Gas–liquid chromatography (GLC) of the mixtures of compounds obtained in the thermolysis of the dihydrobenzodiazepines in naphthalene confirmed the presence of o-phenylenediamine in them. A number of unidentified signals that characterize the nonvolatile products are observed on the chromatograms. These data do not contradict the results of the chemical experiments.

The benzimidazole rearrangement of dihydrobenzodiazepines is also one of the principal

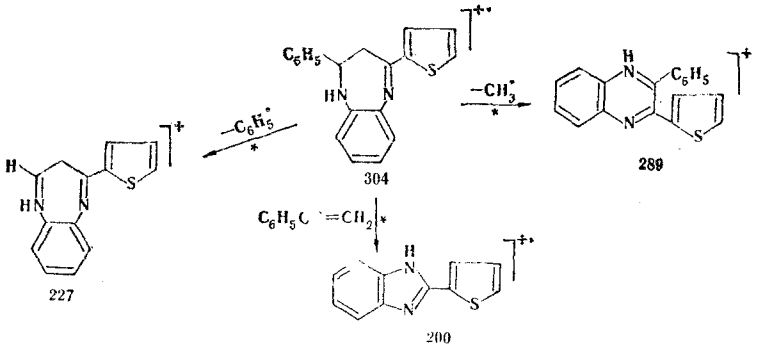
TABLE 2. Mass Spectra of 2-R-4-R'-2,3-Dihydro-1H-1,5-benzodiazepines

Compound	m/z values (intensities, %)*
I	**236 (9)**, 221 (6), 159 (20), 132 (100), 131 (20), 130 (6), 119 (14), 118 (7), 104 (14), 103 (9), 91 (19), 90 (7), 89 (6), 77 (20), 65 (11)
II	**298 (25)**, 283 (10), 221 (25), 219 (5), 195 (25), 194 (100), 193 (11), 165 (5), 119 (19), 104 (13), 103 (14), 92 (8), 91 (9), 77 (20), 65 (9)
III	**332 (50)**, 331 (11), 317 (19), 257 (7), 255 (26), 230 (33), 229 (20), 228 (100), 221 (9), 195 (17), 193 (13), 119 (46), 138 (7), 137 (8), 103 (5), 102 (6), 92 (11), 77 (9), 65 (13)
VII	**304 (3)**, 303 (10), 289 (3), 221 (2), 200 (5), 195 (17), 194 (100), 193 (8), 119 (6), 110 (5), 104 (5), 91 (6), 77 (10), 65 (8)
VIII	**324 (60)**, 309 (10), 247 (10), 233 (15), 220 (24), 219 (100), 144 (10), 129 (18), 119 (17), 103 (9), 102 (8), 92 (11), 77 (16), 65 (16)
XI	**343 (50)**, 326 (8), 308 (8), 296 (14), 295 (27), 221 (16), 194 (100), 193 (25), 192 (10), 165 (20), 119 (16), 103 (45), 102 (40), 91 (19), 77 (20), 65 (19)
XIII	**304 (58)**, 289 (23), 227 (26), 200 (100), 194 (10), 129 (10), 119 (32), 109 (34), 104 (14), 103 (9), 102 (10), 92 (16), 91 (17), 77 (27), 65 (33)
XIV	**332 (19)**, 317 (9), 255 (5), 229 (5), 221 (12), 194 (100), 193 (11), 119 (19), 103 (11), 102 (9), 92 (6), 77 (11), 65 (6)
XV	**340 (37)**, 325 (4), 298 (17), 297 (98), 282 (11), 263 (10), 236 (10), 221 (36), 220 (4), 195 (57), 194 (100), 165 (13), 119 (20), 103 (37), 92 (21), 77 (50), 65 (20)

*The masses of the molecular ions are printed in boldface.

processes that occurs under the influence of electron impact, and we therefore studied the mass spectra of a number of compounds. The characteristics of the principal ions and ion radicals are presented in Table 2.

The peak of the 2-R-benzimidazole ion radical has the greatest intensity (100%) in the mass spectra of the dihydrobenzodiazepines, while the intensity of the molecular ion ranges from 3 to 60%. These data satisfactorily reflect the stabilities of the corresponding ion radicals. The principal fragmentation pathways are general in character and are presented in the case of VII:



The formation of the $(M-15)^+$ ion is most likely due to contraction of the benzodiazepine ring to a quinoxaline ring. Ejection of a methyl group is confirmed by measurements of the high-resolution mass spectrum of II.† This process is general in character, and the scheme of the fragmentation of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine [11] that assumes splitting out of only the CH_3 substituent does not, in our opinion, sufficiently completely reflect the process that occurs.

A characteristic secondary process is also detachment of the substituent from the 2 posi-

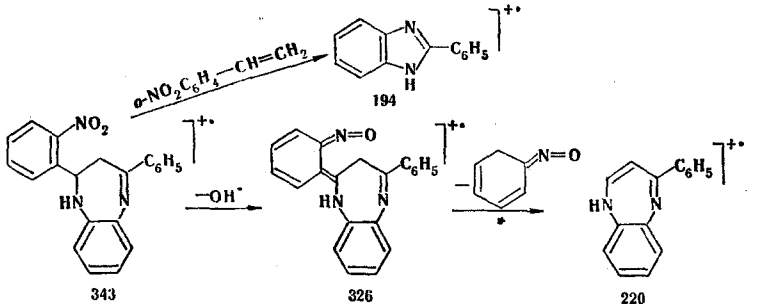
*Metastable transitions.

†The empirical formulas of some of the ions of II were obtained with a JEOL JMS-01FG-2 mass spectrometer by V. A. Zamureenko (VNIVI), for which we express our gratitude.

tion. This regularity is probably due to the differences in the energies of the C–C bonds that join the R and R' groups to the heteroring. Inclusion of the R' group in the conjugation chain increases the energy of the corresponding C–C bond, whereas this effect is absent in the case of substituent R.

Another regularity in the fragmentation of the dihydrobenzodiazepines is the strict trend of the benzimidazole rearrangement: an $R-CH=CH_2$ fragment is split out from the M^+ ion under the influence of electron impact. The fact that the C–N and C–C bonds undergoing cleavage are not included in the conjugation system, and, consequently, their cleavage requires smaller energy expenditures, also plays a definite role here. As in the preceding processes the rearrangement is confirmed by the corresponding peak of a metastable ion.

It should be noted that weak peaks of alternative 2-phenylbenzimidazoles are observed in the mass spectra of I-III, VII, VIII, XI, and XIII (i.e., the R substituent is retained). The intensities of these peaks increase as the temperature at which the samples are heated is increased, and this directly indicates thermolysis as the reason for their formation.



In the case of N-acetyl derivative XV splitting out of the acetyl group (m/z 259.4) precedes the above-described fragmentation processes; the corresponding $(M-43)^+$ ion is one of the most intense in the spectrum.

As one should have expected [11], the fragmentation of XI has its own peculiarities due to the ortho effect of the nitro group.

EXPERIMENTAL

The mass spectra were obtained with a Varian MAT CH-6 spectrometer with direct introduction of the samples into the ion source; the ionization chamber temperature was 180°C, the ionizing voltage was 70 eV, and the emission current was 100 μA. The temperature at which the samples was heated was varied as a function of their volatilities over the 50-120°C range.

The experiments involving GLC of the mixtures of thermolysis products (in naphthalene) were carried out with a Pye-Unicam chromatograph with glass columns packed with a Diatomit gA/W DMS solid support (100-120 mesh) at 250°C. The experiments were conducted by A. A. Reznichenko, for which we express our gratitude.

The individuality of the substances in all cases was monitored by TLC on Silufol UV-254 plates (elution with chloroform).

Acidic Rearrangement of 2,4-Diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (II). A) Three drops of 10% HCl were added to a solution of 0.5 g (1.7 mmole) of II in 25 ml of methanol, and the reaction mixture was heated with a reflux condenser for 2 h. It was then mixed with an alcohol solution of excess 2,4-dinitrophenylhydrazine, and the resulting precipitate was removed by filtration to give 0.31 g (64%) of acetophenone 2,4-dinitrophenylhydrazone. The excess 2,4-dinitrophenylhydrazine was removed by means of acetone, the filtrate was evaporated, and the oily residue was crystallized from toluene to give 0.2 g (60%) of 2-phenylbenzimidazole (XVI) with mp 289°C (sublimation). The rearrangement was realized similarly for I and III-XV.

B) Four drops of 10% HCl were added to a solution of 0.5 g (1.7 mmole) of II and 0.25 g (1.7 mmole) of p-nitrobenzaldehyde in 30 ml of methanol, and the mixture was refluxed for 2 h. The solvent was removed by distillation, and the residue was crystallized from toluene to give 0.2 g (60%) of 2-phenylbenzimidazole (XVI) with mp 289°C.

2-(p-Nitrophenyl)benzimidazole (XVIII). Equimolar amounts (3.3 mmole) of p-nitrobenzaldehyde (0.5 g) and o-phenylenediamine (0.36 g) in 20 ml of methanol were heated with four

drops of 10% HCl for 40 min, after which the mixture was cooled, and the precipitated XVIII [0.48 g (60%)], with mp 300°C (mp 298-299°C [12]), was removed by filtration.

Condensation of Chalcone with o-Phenylenediamine in an Acidic Medium. Equimolar amounts (5 mmole) of chalcone (1.04 g) and o-phenylenediamine (0.54 g) were dissolved in 15 ml of methanol, and four to five drops of HCl were added. A spot due to dihydrobenzodiazepine II (R_f 0.2) was observed on the chromatogram after refluxing for 1 h, while a spot of benzimidazole XVI (R_f 0.1, elution with chloroform) also appeared after 2 h. The mixture was refluxed for 7 h. Evaporation of the solvent (50% by volume) yielded 0.05 g (3%) of II with mp 127°C. The solvent was removed by evaporation to dryness, and the oily residue was crystallized from toluene to give 0.26 g (27%) of XVI with mp 289°C.

Thermal Rearrangement of 2,4-Diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (II). A) In Naphthalene. A mixture of 0.3 g (1 mmole) of II and 1 g of naphthalene was heated in a sealed ampul on a sand bath at 200°C for 5 h, after which the contents of the ampul were dissolved in 20 ml of ether, and the undissolved XVI [0.03 g (15%)], with mp 289°C, was removed by filtration. The thermolysis of II, III, V-XII, and XIV was carried out similarly.

B) In Ethylene Glycol. A 0.5-g (1.7 mmole) sample of II was dissolved in 15 ml of ethylene glycol, and the solution was heated at 190°C for 10 h. The solvent was removed by distillation, the residue was dissolved in methanol, and the solution was mixed with an alcohol solution of 2,4-dinitrophenylhydrazine. Workup gave 0.14 g of acetophenone 2,4-dinitrophenylhydrazone. The excess 2,4-dinitrophenylhydrazine was removed by means of acetone, the filtrate was evaporated, and the oily product was crystallized from toluene to give 0.1 g (30%) of benzimidazole XVI with mp 289°C. The rearrangement of dihydrobenzodiazepines III, V, and X was carried out similarly.

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