In vibrations 6b, 18b, and 11, the lines assigned to the 2-bromo and 2-iodopyrimidines have been separated out as independent groups. The frequencies of these halopyrimidines are always the lowest among the 2-substituted derivatives and serve as a reliable guide for determining the lower boundary of the frequencies of the noncharacteristic bands.

Qualitative estimates of the intensities of the noncharacteristic vibrations in the IR and Raman spectra do not basically change for the bands of vibrations 13, 9a, 10b, and 16b as compared with those of pyrimidine. In the case of vibrations 6a, 18b, and 11, the changes in intensity are more considerable than for the unsubstituted molecule. However, it is impossible to establish any quantitative correlations of the changes in intensity for the 2-monosubstituted derivatives because of the absence of information on the integral intensities of these compounds from the literature.

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# SYNTHESIS AND PROPERTIES OF 2,2,4-TRISUBSTITUTED 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINES


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General conditions for the condensation of acetylarenes with o-phenylenediamine hydrochloride, leading to the formation of 2,4-diaryl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepines, have been worked out. It has been shown that this reaction is an equilibrium one, that the equilibrium is extremely sensitive to the amount of water in the reaction medium, and that the process takes place with the formation of bisazomethines as intermediates. The UV, IR, and PMR spectra and the dipole moments of the heterocyclic compounds obtained are discussed.


The reaction of o-phenylenediamine (DPA) with ketones containing active methylene or methyl groups can take place with the formation of derivatives both of dihydrobenzimidazole and of dihydrobenzodiazepine [1-4]. The first process is favored by the presence of water in the reaction system [4] and 2,2,4-trisubstituted 2,3-dihydro-1H-1,5-benzodiazepines are obtained in good yield on catalysis with the aid of $BF_3 \cdot Et_2O$ in ethanol or when a mixture of a liquid ketone and the hydrochloride of PDA (PDA·HCl) is heated. It is also known [5] that many dihydrobenzodiazepine derivatives rearrange into benzimidazoles in the presence of even trace amounts of mineral acids.


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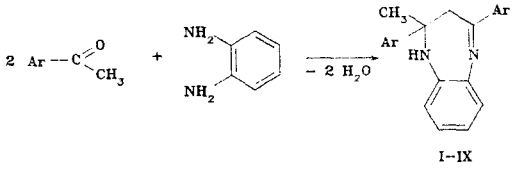
TABLE 1. Characteristics of Compounds (I-IX)

| Compound | Ar | mp, °C | IR spectrum, cm⁻¹ NH | IR spectrum, cm⁻¹ C=N | $\lambda_{max}$, nm (ε · 10⁻³) | Found, N, % | Empirical formula | Calculated, N, % | Time of boiling, h | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
| I | $C_6H_5$ | 103[a] | 3334 | 1610 | 254 (24,3), 369 (6,0) | — | $C_{22}H_{20}N_2$ | — | 1 | 72 |
| II | $p$-$CH_3C_6H_4$ | 98 | 3322 | 1610 | 267 (21,4), 364 (5,6) | 8,1 | $C_{24}H_{24}N_2$ | 8,2 | 2 | 51 |
| III | $p$-$OCH_3C_6H_4$ | 117 | 3321 | 1608 | 277 (18,3), 365 (6,4) | 7,4 | $C_{24}H_{24}N_2O_2$ | 7,5 | 2,5 | 72 |
| IV | $p$-$H_2NC_6H_4$ | 126—128 | —[b] | 1619 | 230 (20,7), 313 (14,7) | 16,7 | $C_{22}H_{22}N_4$ | 16,4 | 2,5 | 48 |
| V | $p$-$ClC_6H_4$ | 143—144 | 3336 | 1612 | 267 (21,1), 374 (5,4) | 7,5 | $C_{22}H_{18}Cl_2N_2$ | 7,5 | 1 | 85 |
| VI | $p$-$BrC_6H_4$ | 141—142 | 3331 | 1611 | 269 (22,3), 374 (5,5) | 5,9 | $C_{22}H_{18}Br_2N_2$ | 6,0 | 1 | 78 |
| VII | $m$-$NO_2C_6H_4$ | 151—153 | 3283 | 1613 | 256 (30,7), 379 (5,6) | 14,0 | $C_{22}H_{18}N_4O_4$ | 13,9 | 1,5 | 70 |
| VIII | $p$-$NO_2C_6H_4$ | 154 | 3312 | 1608 | 278 (23,9), 420 (5,2) | 14,2 | $C_{22}H_{18}N_4O_4$ | 13,9 | 1 | 75 |
| IX | 2-Furyl | 96—97 | 3224 | 1608 | 283 (14,8), 367 (7,2) | 9,4 | $C_{18}H_{16}N_2O_2$ | 9,3 | 1,5 | 71 |

[a] mp 102°C [4]. [b] Three peaks were observed: 3201, 3328, and 3418 $cm^{-1}$.

The aim of the present investigation was to study the mechanism of the reaction of PDA·HCl with ketones, and also the chemical and spectral properties of the heterocyclic compounds obtained. As the carbonyl components we studied aromatic ketones, among which there are fairly high-melting compounds, and, therefore, expanding the possibilities of the method proposed in [4], we carried out the reaction in methanol, since in ethanol, propanol, and other higher alcohols the solubility of the PDA salt is greatly reduced, which interferes with its condensation with ketones. The brief heating of a solution of PDA·HCl and a ketone (in a molar ratio of 1:2) in methanol following by neutralization of the solution with concentrated ammonia led to the formation of the dihydrobenzodiazepines (I-IX) with good yields (Table 1):



I-IX

As can be seen from Table 1, the yields of the dihydrobenzodiazepines (I-IX) fell in the case of the acetophenone derivatives containing electron-donating groups.

The addition of a few drops of water or hydrochloric acid completely halted the condensation process. The reaction with the participation of p-nitroacetophenone was particularly sensitive to the water content; even trace amounts of water in the mixture led to resinification.

The proposed method of synthesis permits the furan-containing compound (IX) to be obtained, while in all experiments on the condensation of 1-(2-furyl)-3-phenylpropen-3-one with PDA in the presence of a tertiary amine only resinification of the ketone was observed.

The compounds (I-IX) obtained were identified with the aid of IR, UV, and PMR spectra and the results of elementary analysis (see Tables 1 and 2).

In the IR spectra, measured in KBr tablets, the peaks of the characteristic vibrations of N–H bonds (3224-3334 $cm^{-1}$) and of C=N bonds (1608-1613 $cm^{-1}$) clearly appear. The marked decrease in the $\nu_{NH}$ frequencies for the furan derivative (IX) is apparently due to the closeness of the heteroatom of the furan ring to the hydrogen atom of the imino group, but in the IR spectra of compounds (I) and (IX) obtained in $CCl_4$ solution two bands with $\nu_{NH}$ values of 3368 and 3420 $cm^{-1}$ are observed in each case. Consequently, it can only be assumed that the packing of the molecules in the crystals of compound (IX) is determined by the existence of intermolecular hydrogen bonds.

| Compound | Chemical shifts, ppm, in $CDCl_3$ | | | | | μ, D (in benzene) |
|---|---|---|---|---|---|---|
| | $CH_3$ | $H_A$[a] | $H_B$[a] | NH | aromatic protons | |
| I[b] | 1,74 | 2,94 | 3,09 | 3,43 | 6,75—7,75 | 3,13 |
| II | 1,72 | 2,95 | 3,06 | 3,45 | 6,73—7,61 | |
| III | 1,71 | 2,90 | 3,01 | 3,39 | 6,70—7,72 | 3,39 |
| IV | 1,68 | 3,01 | | | 6,65—7,93 | |
| V | 1,72 | 2,86 | 3,04 | 3,38 | 6,72—7,58 | 3,59 |
| VI | 1,73 | 2,88 | 3,05 | 3,44 | 6,70—7,65 | |
| VII | 1,89 | 2,97 | 3,28 | 3,60 | 6,88—8,50 | |
| VIII | 1,89 | 2,97 | 3,70 | 3,60 | 7,08—8,25 | 7,75 |
| IX | 1,69 | 2,88 | 3,05 | 3,43 | 6,22—7,56 | |

[a] The constant $J_{AB}$ was 13.0 Hz for all the compounds. [b] For compound (I), according to the literature [4], the δ values are (ppm): 1.70 ($CH_3$); 2.87 ($H_A$); 3.28 ($H_B$); 4.75 (NH).

The electronic absorption spectra of compounds (I-IX) are practically identical in their long-wave section with the spectra of the corresponding 2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepines [5] and are determined by the chromophoric grouping N—$C_6H_4$—N=C—Ar [6].

In the PMR spectrum of each of compounds (I-IX), the protons of the methylene group form a characteristic quartet for an AB system and, consequently, they are nonequivalent. An investigation of the PMR spectra of 2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepines that we performed previously showed that their seven-membered heterocycle has the rigid conformation of the "boat" type and the aryl substituent in position 2 occupies the equatorial position (in the case of the 2,4-diphenyl derivative $\delta_A$ = 2.90, $\delta_B$ = 3.08 ppm, and $J_{AB}$ = 13.6 Hz). The spectrum of the protons of the methylene groups of compounds (I-IX) confirms that the rigidity of the structure of the heterocycle is retained even when a second substituent ($CH_3$ group) is present in position 2 of the molecule. It can be seen from the figures in Table 2 that the difference in the chemical shifts of the A and B protons falls uniformly with a rise in the electron-donating properties of the aromatic nuclei; in the spectra of compound (IV) (R = p-$NH_2$-$C_6H_4$), the protons become practically equivalent because of the anisotropic influence of both aryl substituents, which also has an effect on the signal of the proton of the imino group (see Table 2); in the spectrum of compound (III) it is masked by the broad band of the protons of the methylene group.

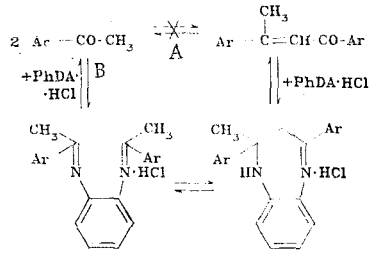
The mass-spectrometric fragmentation of compound (IX) basically coincides with the fragmentation of the 2,4-disubstituted dihydrobenzodiazepines [7]. In addition to the peaks of the molecular ions (m/z 292, 13%) and the $[M - CH_3]^+$ ion (6%), the mass spectrum contains the peaks of ions with m/z 184 (100%) and 108 (13%), which are formed in the cleavage of the diazepine ring at the $N_{(1)}$—$C_{(2)}$ and $C_{(3)}$—$C_{(4)}$ bonds, with the retention of the charge on one of the fragments formed. The process $M^+ \rightarrow 184$ is confirmed by a metastable ion with m* = 115.9.

The measured dipole moments of the individual compounds (Table 2) show a relatively high polarity of the dihydrobenzodiazepine bicyclic system. There is no doubt that a considerable contribution to the total moment of the molecule is made by the imino and azomethine groups (in particular, by the moments of the unshared electron pairs of the nitrogen atoms). However, if it is borne in mind that the values of μ for the individual fragments of the molecule of (I) — the aniline and the azomethine groupings — are relatively small (of the order of 1.7 and 1.6 D [8]), it must be assumed that the high dipole moment of the whole molecule is due to a favorable, close to parallel, orientation of the moments of these fragments.

We have studied the acetylation reaction of compound (I). It was found that acetylation under standard conditions — in particular, with acetic anhydride in pyridine and dioxane — did not give the desired product; in all cases the initial compound, contaminated with resinous substances, was recovered. In contrast to 2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine, which is readily acetylated by acetic anhydride in pyridine and dioxane [9], compound (I) did not undergo acetylation under these conditions. The electronic influence of the methyl group in position 2 on the reactivity of the imino group must be slight, and therefore the main reason for the difficulty of acetylation of compound (I) is probably steric factors — the presence of two bulky groups in position 2 of the heterocycle.

It has been mentioned above that one of the characteristic properties of the dihydrobenzodiazepines is their acid-catalyzed rearrangement into benzimidazoles. At the same time, heating compounds (I-IX) in ethanol with the addition of 2-3 drops of concentrated HCl or heating their hydrochlorides in aqueous methanol led to the formation of the initial ketones and PDAs. A back-reaction has been observed previously [3] also for the dihydrobenzodiazepine synthesized from PDA and cyclohexanone. The combination of these facts shows, in the first place, the reversible nature of the process of forming the seven-membered heterocycle.

Two alternative mechanisms of the reaction of PDA with ketones have been discussed in the literature. According to one point of view (3), the first act is the formation of an α,β-unsaturated ketone followed by its interaction with the PDA (route A). According to another opinion [4], a bisazomethine is first formed and cyclization then follows (route B).



Under the conditions of the reaction of PDA·HCl with acetylarenes that we have performed, just as in the hydrolysis of the dihydrobenzodiazepine (I-IX), it was impossible to detect intermediate compounds, even though for this purpose we used electronic, IR, and PMR spectrometry, thin-layer chromatography, and the reaction with 2,4-dinitrophenylhydrazine. In all cases, only the starting materials and the final dihydrobenzadiazepines were detected, in various ratios depending on the time of occurrence of the process. This is probably explained by the instability of the intermediates, which increases with a rise in the concentration of acid in the mixture.

We performed a series of experiments to elucidate the nature of the intermediates. Thus, β-dypnone and its 4,4'-dibromo derivative were brought to react with PDA·HCl. It was found the β-dypnone formed compound (I) with yields of 50-55%, i.e., almost 20% lower than acetophenone. 4,4'-Dibromo-β-dypnone did not react with PDA·HCl at all.

It appeared possible that PDA hydrochloride catalyzed the self-condensation of acetophenone. Consequently, in some experiments acetophenone and its p-Br- and p-$NO_2$ derivatives were boiled with an ethanolic solution of the hydrochloride of o-toluidine (the basicity of this amine is comparable with that of o-PDA: $pK_a$ values 4.57 and 4.47, respectively [10]). Regardless of the time of heating, no traces of the formation of β-dypnones were observed. At the same time, it was found that β-dypnone and its 4,4'-dibromo derivative did not undergo the retroaldol reaction even on prolonged boiling in methanol acidified with HCl (both with additions of and in the absence of o-toluidine). It follows from this that under the conditions of the main method of synthesizing the dihydrobenzodiazepines (I-IX), β-dypnones are not formed as intermediates (route A is not followed).

Route B could not be subjected to direct experimental confirmation, since it was impossible to obtain the bisazomethines at any pH values of the medium. At the same time, there is a number of indirect confirmations of this direction of the process. It is known that azomethines are formed in the first stage of the acid-catalyzed rearrangement of the 2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepines and benzimidazoles [7]. The conditions for this rearrangement are identical with the conditions for performing the hydrolysis of compounds (I-IX); consequently, the presence of voluminous methyl groups in the bisazomethine derivatives of ketones apparently prevents their cyclization into benzimidazoles, and under the conditions of the reaction that we are studying they are not formed even in trace amounts, while with PDA hydrochloride aromatic aldehydes form dihydrobenzimidazole systems in high yields [9].

In conclusion, we must give the results of two other experiments which, on the one hand, agree with route B and, on the other hand, characterize the thermodynamic stability of individuality of dihydrobenzodiazepine derivatives. Analysis of an ethanolic solution of the hydrochloride of compound (I) and 4-nitroacetophenone (molar ratio 1:2) after it had been boiled for an hour showed that it contained a very small amount (∿10-15%) of compound (I), 30-35% of its nitro derivative (VIII), a certain amount of acetophenone and p-nitroacetophenone (identi-

fied in the form of their dinitrophenylhydrazones), and resinous substances. When an ethanolic solution of the hydrochloride of compound (VIII) and acetophenone was boiled, only slight resinification took place; compound (I) and p-nitroacetophenone could not be detected under these conditions. From this it is possible to arrive at the conclusion that the thermodynamic stability of the 2,4-diaryl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepines rises with an increase in the electron-accepting nature of the aromatic nuclei. In our opinion, an important role is played by the fact that electron-accepting substituents in the phenyl nucleus favor the appearance of conjugation effects in the azomethine fragment of a dihydrobenzodiazepine molecule.

## EXPERIMENTAL

The IR spectra of compounds (I-VIII) were measured in KBr tablets on a Specord IR-75 spectrophotometer; electronic absorption spectra in ethanolic solutions with a concentration of the substances of $2.3 \cdot 10^{-5}$ M on a Specord UV-Vis instrument; PMR spectra in $CDCl_3$ solutions on a Tesla BS-2487-B instrument (with TMS as internal standard); the mass spectrum of compound (VIII) on a Varian MAT 212 instrument (ionizing voltage 70 eV); and dipole moments in benzene at 25°C as described by Tsukerman et al. [11]. The individuality of compounds (I-VIII) and the compositions of the reactions mixtures were monitored by thin-layer chromatography on Silufol UV-254 plates with chloroform as the eluent.

2,4-Diphenyl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (I). A. A solution of 0.5 g (3.5 mmole) of PDA·HCl and 0.84 g (7 mmole) of acetophenone in 15 ml of methanol was boiled under reflux for 1 h. Then the reaction mixture was neutralized with 0.3-0.5 ml of a concentrated solution of ammonia. Three quarters of the volume of the solvent was distilled off in a rotary evaporator, and the remainder was cooled and the crystals that deposited were filtered off. Yield 0.79 g (72%), mp 103°C (from aqueous methanol).

Compounds (II-IX) (Table 1) were obtained similarly; in the synthesis of compounds (VII) and (VIII) appreciable resinification was observed.

B. A solution of 0.5 g (3.5 mmole) of PDA·HCl and 0.7 g (3.5 mmole) of 1-methyl-1,3-diphenylpropen-3-one (β-dypnone) in 15 ml of ethanol was treated under conditions similar to those of method A. This gave 0.57 g (52%) of compound (I) with mp 103°C.

Hydrolysis of 2-Methyl-2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (I). A solution of 0.3 g of compound (I) in 10 ml of methanol was treated with 0.3 ml of hydrochloric acid (1:2). The solution was boiled for 3 h, cooled to room temperature, and mixed with a methanolic solution of 0.5 g of 2,4-dinitrophenylhydrazine (DNPH). The precipitate that deposited (0.35 g, 59%) consisted of acetophenone DNPH (checked by a mixed melting point, mp 232°C, $\lambda_{max}$ 377 nm in methanol and $R_f$ 0.75). The excess of the hydrazine was eliminated by the addition of acetone and the residual filtrate (after the removal of the acetone DNPH) was neutralized with ammonia and analyzed by TLC: PDA and compound (I) were identified, with $R_f$ 0.15 and 0.4, respectively).

The hydrolysis of compounds (II-IX) was studied similarly; in all cases the DNPHs of the corresponding acetylarenes, with yields of 50-60%, PDA, and initial compounds were isolated.

Reaction of 2-Methyl-2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (I) with p-Nitroacetophenone. A solution of 0.7 g (2 mmole) of the hydrochloride of compound (I) in 15 ml of methanol was treated with 0.67 g (4 mmole) of p-nitroacetophenone and the mixture was heated under reflux for 1 h. Then the solution was neutralized with concentrated ammonia, part of the solvent (0.5% by volume) was distilled off and the remainder was cooled, which led to the deposition of 0.26 g (32%) of orange crystals of compound (VIII), mp 154°C. The filtrate was treated with an excess of 2,4-dinitrophenylhydrazine and the crystals that precipitated were identified by TLC as a mixture of the DNPHs of acetophenone and of p-nitroacetophenone ($R_f$ 0.75 and 0.5).

The reaction of compound (VIII) with acetophenone was studied under analogous conditions. The formation of resinous substances in the reaction mixture was observed, but no indications of the formation of compound (I) or of p-nitroacetophenone were detected.

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