# AROMATIC DERIVATIVES OF 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINE

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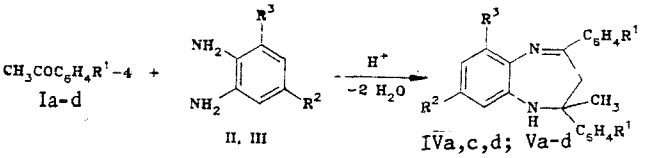
The formation of 2,2,4-trisubstituted 2,3-dihydro-1H-1,5-benzodiazepines in the reactions of acetylarenes with 4-ethoxy- and 3,5-dimethyl-1,2-phenylenediamine was studied. The effect of the substituents on the individual stages of the reactions is discussed. A quantum-chemical calculation of the relative nucleophilicity of 1,2-phenylenediamine, 2,3-diaminopyridine, and 3,4-diaminofurazan was undertaken.

In previous papers [1, 2] we showed that 1,2-phenylenediamine and its 4-chloro, 3,5-dichloro, and 4-nitrile derivatives react with aryl methyl ketones under the conditions of acid catalysis, forming the aromatic derivatives of 2,3-dihydro-1H-1,5-benzodiazepine, where the intermediates of the reaction are bisazomethine systems. Here a decrease in the reactivity of diamines containing electron-withdrawing substituents both with respect to acetylarenes and with respect to chalcones was observed.

The aim of the present work was to investigate further the reactions of aromatic ketones (I) with substituted 1,2-phenylenediamines and certain other o-diamines of the aromatic and heterocyclic series. For the case of 4-ethoxy- and 3,5-dimethyl-1,2-phenylenediamines (II, III) we investigated the effect of increase in the basicity of the diamine on its reactivity and on the regioselectivity of the formation of the dihydrodiazepine heterocycle.

The desired 2,2,4-trisubstituted 2,3-dihydro-1H-1,5-benzodiazepines (IVa, c, d, Va-d) were obtained by boiling methanol solutions of the aryl methyl ketones (Ia-d) with (II) or (III) in the presence of concentrated sulfuric acid. The exception was an attempt at the production of 2,4-di(4-ethoxyphenyl)-8-ethoxy-2,3-dihydro-1H-1,5-benzodiazepine; in this case only the initial 4-ethoxyacetophenone and 4-ethoxy-1,2-phenylene-diamine were recovered:




I, IV, V a $R^1$=H, b $R^1$=$C_2H_5O$, c $R^1$=Cl, d $R^1$=$NO_2$; II, IV $R^2$=$C_2H_5O$, $R^3$=H; III, V $R^2$=$R^3$=$CH_3$

The formation of compounds (IVa, c, d) and (Va-d) was demonstrated by IR, UV, and PMR spectroscopy and was confirmed by the presence of nitrogen (Tables 1 and 2); their spectral characteristics proved analogous with the characteristics of the previously described [1] 2-methyl-2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepines. Thus, the IR spectra clearly showed the bands for the stretching vibrations of the NH bond at 3310-3380 and the C=N bond at 1607-1613 $cm^{-1}$. In the long-wave part the electronic absorption spectra are determined by the chromophoric group N—$C_6H_2R^3R^4$—N=C—$C_6H_4R^1$ [3]. The signals for the protons of the methyl, methylene, and imino groups were identified in the PMR spectra of compounds (IVa, c, d, Va-d) together with the signals for the aromatic protons (Table 2).

The nonequivalence of the amino groups in the initial diamines raises the question of the direction of the heterocycle formation process. A similar problem had been encountered before [2] and was solved by PMR spectroscopy on the basis of analysis of the signals for the 9-H proton of the bicycle. The introduction of electron-donating substituents into the

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TABLE 1. Characteristics of Compounds (IVa, c, d, Va-d)

| Compound | mp, °C | IR spectrum, $cm^{-1}$ | | $\lambda_{max}$, nm ($\varepsilon \cdot 10^{-3}$) | N found, % | Molecular formula | N calculated, % | Boiling time, h | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
| | | NH | C=N | | | | | | |
| IVa | 91 | 3368 | 1612 | 247 (19,3), 268 (19,2), 368 (8,3) | 7,9 | $C_{24}H_{24}N_2O$ | 7,9 | 6 | 52 |
| IVc | 131—133 | 3337 | 1611 | 249 (18,7), 271 (21,8), 374 (9,0) | 6,7 | $C_{24}H_{22}Cl_2N_2O$ | 6,6 | 6 | 52 |
| IVd | 152—154 | 3380 | 1607 | 250 (19,0), 275 (24,1), 421 (7,2) | 14,6 | $C_{24}H_{22}N_4O_5$ | 14,3 | 4 | 65 |
| Va | 116—117 | 3310 | 1619 | 267 (20,9), 367 (6,7) | 8,1 | $C_{24}H_{24}N_2$ | 8,2 | 1 | 72 |
| Vb | 82 | 3335 | 1610 | 267 (22,1), 365 (5,2) | 6,5 | $C_{28}H_{32}N_2O_2$ | 6,5 | 2 | 57 |
| Vc | 178—180 | 3323 | 1609 | 269 (20,8), 373 (5,8) | 6,9 | $C_{24}H_{22}Cl_2N_2$ | 6,8 | 0,5 | 80 |
| Vd | 202—203 | 3336 | 1613 | 251 (18,7), 275 (21,0), 423 (5,6) | 15,0 | $C_{24}H_{22}N_4O_4$ | 14,9 | 0,5 | 85 |

TABLE 2. Chemical Shifts (ppm) of the Protons in Compounds (IVa, c, d, Va-d)

| Compound | $CH_3$, s | $CH_2$ | | NH, s | 6-H ($J$=8 Hz) | 7-H** | 9-H |
|---|---|---|---|---|---|---|---|
| | | $H_A$*, d | $H_B$, d | | | | |
| IVa | 1,70 | 2,91 | 3,08 | 3,55 | —*** | 6,53 | 6,29 |
| IVc | 1,63 | 2,79 | 3,01 | 3,44 | 7,10 | 6,55 | 6,30 |
| IVd | 1,73 | 2,93 | 3,32 | 3,25 | 7,20 | 6,54 | 6,31 |
| Va | 1,73 | 2,84 | 2,98 | 3,18 | — | 6,75 | 6,47 |
| Vb | 1,64 | 2,74 | 2,86 | 3,08 | — | 6,63 | 6,40 |
| Vc | 1,68 | 2,75 | 2,89 | 3,09 | — | 6,75 | 6,44 |
| Vd | 1,75 | 2,86 | 3,09 | 3,25 | — | 6,78 | 6,49 |

*The $J_{AB}$ values for all the compounds (IVa, c, d, Va-e) amount to −13.0 to −13.6 Hz.
**Quartet for compounds (IVa, c, d) (J = 8 and 2.5 Hz) and doublet for compounds (Va-d) (J = 2.5 Hz).
***The signal is overlapped by the signals of the other aromatic protons.

benzene ring [compounds (IVa, c, d, Va-d)] shifts the signals of practically all the protons 6-H to 9-H upfield, and this makes it possible to identify them easily [except for the 6-H signal in the spectra of compounds (IVa, Va-d)], since they do not overlap with the signals for the remaining aromatic protons (Table 2). Here the 9-H proton at the ortho position to the imino group resonates in the strongest fields, while the 6-H proton resonates in the weakest fields. The spectrum of the 9-H proton in compounds (IVa, c, d, Va-d) represents a doublet with J = 2-2.5 Hz, i.e., with a meta spin—spin coupling constant [4]. This indicates position 8 for the $R^2$ substituent in compounds (IVa, c, d, Va-d) and, consequently, position 6 for $R^3$ in (Va-d). This conclusion is confirmed by analysis of the spectra of the 7-H [compounds (IVa, c, d, Va-d)] and 6-H [compounds (IVc, d), Table 2] protons. Such a structure for the obtained compounds corresponds to realization of the reaction path in which the azomethine bond in the heterocycle is formed with the participation of the most basic nitrogen atom of the initial diamine, and this is consistent with published data [2].

Comparison of the yields of the desired compounds and the reaction times (Table 1) with the data in [1, 2] shows that the introduction of the two methyl groups into 1,2-phenylenediamine accelerates the reaction a little. At the same time the yields of compounds (IVa, c, d) (Table 1) are 20-25% lower than the yields of the corresponding dihydrobenzodiazepines from o-phenylenediamine or even its 4-halogen derivatives [1, 2]. Here the reaction time is increased to 4-6 h (from 1-2.5 h for o-phenylenediamine [1]).

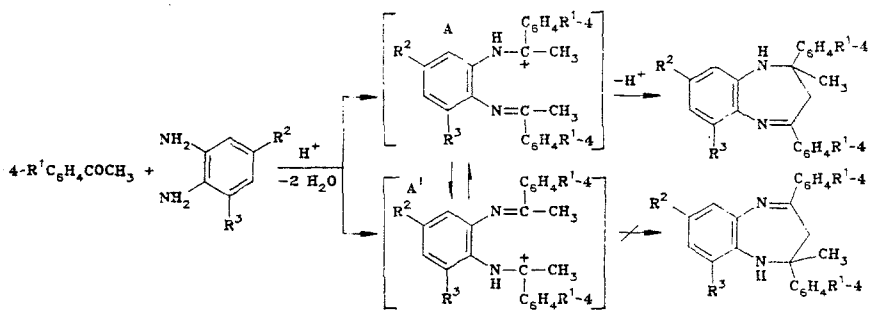
Thus, the substituted 1,2-phenylenediamines are characterized by a dual effect from the substituents $R^2$ and $R^3$ on the reactivity of the diamine toward aryl methyl ketones. On the one hand, the formation of the heterocycle is hindered with decrease in the basicity of the diamine component [2]; on the other, the introduction of the electron-donating ethoxy group into 1,2-phenylenediamine also leads to a decrease in the yields of the desired dihydrobenzodiazepines (IVa, c, d).

TABLE 3. Data from the Quantum-Chemical Calculation of the o-Diamines*

| Compound | $q$ | | $q_\pi$ | | $E_{HOMO}$, eV | $C_N^2$ | |
|---|---|---|---|---|---|---|---|
| | $N_{(1)}$** | $N_{(2)}$ | $N_{(1)}$ | $N_{(2)}$ | | $N_{(1)}$ | $N_{(2)}$ |
| 1,2-Phenylenediamine | 0,212 | | 1,59 (1,72) | | −5,72 (−6,50) | 0,135 (0,30) | |
| 3,4-Diaminofurazan | 0,205 | | 1,60 (1,74) | | −8,40 (−7,27) | 0,037 (0,31) | |
| 2,3-Diaminopyridine | 0,190 | 0,195 | 1,57 (1,65) | 1,58 (1,67) | −5,79 (−10,90) | 0,128 (0,24) | 0,139 (0,40) |

*By the CNDO/2 method, in parentheses by the PPP method.
**The nitrogen atom of the 2-amino group of the diaminopyridine.

These facts can be explained in the following way. The mechanism proposed in [2] for the reaction of acetylarenes with 1,2-phenylenediamines includes the formation of the bis-azomethine carbocation A as one of the intermediates, which then undergoes cyclization to the seven-membered heterocycle. It must be expected that cyclization of the isomeric carbocations A and A' leads to the appearance of the regioisomeric dihydrobenzodiazepines:



The substituents $R^2$ and $R^3$ in the diamine component must have an effect both on the formation of the azomethines [5] and on the ability of the carbocations A and A' to undergo cyclization. The first factor explains the decrease in the reactivity of the o-diamine with decrease in its basicity. At the same time, although it should, according to data in [5], facilitate the formation of the azomethine systems, the presence of the ethoxy group in the diamine can at the same time promote delocalization of the charge in the carbocations A and A', thereby hindering their cyclization. In our opinion, it is this which explains the decrease in the yield of the desired dihydrobenzodiazepines (IVa, c, d). The negative result obtained during an attempt to bring 4-methoxy-1,2-phenylene-diamine into reaction with 4-ethoxyacetophenone becomes understandable if account is taken of the fact that the electron-donating substituents $R^1$ must have an analogous effect on the intermediates A and A'.

The high regioselectivity of the formation of the heterocycle during the synthesis of compounds (IVa, c, d) and (Va-d) is also explained well by the decrease in the ability of the carbocations A and A' to undergo cyclization with the introduction of the electron-donating substituents $R^2$ and $R^3$. In fact, in most cases halogen-substituted 1,2-phenylene-diamines in reactions with acetylarenes form mixtures of the isomeric dihydrobenzodiazepines differing in the positions of the substituents $R^2$ and $R^3$ in the condensed benzene ring [2]. In the case of the synthesis of compounds (IVa, c, d, Va-d), however, the retardation of the cyclization of the carbocations A and A' on account of their stabilization by the electron-donating substituents $R^2$ and $R^3$ makes the process as a whole more of an equilibrium process, and the effect of $R^2$ and $R^3$ on the azomethine fragment, situated at the para (or ortho) position, is so substantial that the carbocation A' becomes incapable of subsequent cyclization.

We also set up a series of experiments on the synthesis of aromatic derivatives of 2,3-dihydro-1H-1,5-benzodiazepine by the reaction of the diamines (II) and (III) with chalcone or 4-chloro and 4,4'-dichloro derivatives. Earlier [6] it had been established that

unsubstituted o-phenylenediamine and chalcone readily form 2,4-diphenyl-2,3-dihydro-H-1,5-benzodiazepine when their methanol solutions are boiled with additions of triethylamine. However, neither the diamine (II) nor the diamine (III) entered into reaction with chalcone and its derivatives under these conditions. Attempts to realize the reaction in pure triethylamine or in methanol acidified with hydrochloric acid were also unsuccessful — the initial substances were recovered in all cases.

A negative result was also obtained when 2,3-diamino-anthraquinone, 2,3-diaminopyridine, and 3,4-diaminofurazan were used as diamine components. The above-mentioned diamines did not react with chalcones and acetylarenes (Ia-d) either under the conditions of base catalysis or under the conditions of acid catalysis. This is probably explained by the reduced nucleophilicity of these compounds.

In order to determine the relative nucleophilicity of the above-mentioned heterocyclic diamines we undertook a quantum-chemical calculation of the molecular diagrams and molecular orbital energies. The calculation was made by the CNDO/2 method; in addition, the calculation of the π-electron densities, the HOMO energies, and the frontier electron densities was duplicated by the LCAO-MO SCF-CI method in the PPP variant with the usual set of parameters [7]. The results are given in Table 3.

In terms of the perturbation molecular orbital theory the energy of the nucleophile–electrophile interaction is determined by the expression:

$$\Delta E = -q_N q_E / r_{NE} + \beta_{NE}^2 C_N^2 C_E^2 / (E_{\text{LUMO}} - E_{\text{HOMO}}) \quad [8],$$

where ΔE is the change of energy during the formation of the bond between the reaction centers of the molecules, $q_E$ and $q_N$ are the electron densities at the reaction centers of the electrophile and nucleophile molecules respectively, $E_{HOMO}$ and $E_{LUMO}$ are the energies of the HOMO of the nucleophile and the LUMO of the electrophile, $C_N$ and $C_E$ are the coefficients in the frontier molecular orbitals at the orbitals of the atoms directly participating in the formation of the new bond, $r_{NE}$ is the distance between the interacting atoms, and $\beta_{NE}$ is the change of the resonance integral during the interaction of the orbitals of the nucleophile and electrophile.

The first term is determining in charge-controlled reactions and the second in orbital controlled reactions. We will examine chalcone as the electrophilic component of reactions with diamines. According to published data [9-11], the characteristics of an ambident electrophile must be expected from chalcone, as from an α,β-unsaturated ketone, and addition of the nucleophile at the C=C bond (1,4-addition) must take place preferentially under orbital control and at the C=O group (1,2-addition) under charge control. Earlier [6, 12] one of the present authors established that the first stage in the reaction of chalcone with 1,2-diamines can take place in both directions, and this depends on the nature of the nucleophile and on the reaction conditions. However, the unidirectional change of $q_N$ and $E_{HOMO}$ in the case of the 1,2-diamines makes it possible to consider the change in their nucleophilicity, irrespective of which type of interaction predominates (i.e., irrespective of the nature of the electrophilic reaction center).

From the calculated data (Table 3) it is seen that the transition from o-phenylenediamine to diaminopyridine and diaminofurazan leads to a decrease in the overall electron density at the nitrogen atoms of the amino groups. As far as the π-electron density is concerned, it is enhanced somewhat in the case of 3,4-diaminofurazan. Such a dual effect from the furazanyl radical in aminofurazans (π-donating and, to a greater degree, σ-accepting) has been mentioned in the literature [13].

The values of the frontier electron densities at the nitrogen atoms of the amino groups calculated by the two methods show on the whole a weak dependence on the nature of the 1,2-diamine. The exception is the result for $C_N$ of the diaminofurazan, obtained by the CNDO/2 method. The value $C_N^2 = 0.037$ does not contradict the experimental data on the reduced nucleophilicity of the diaminofurazan, but its clear departure from the $C_N^2$ value in the remaining diamines must, in our opinion, be attributed rather to errors in the given method of calculation. Calculation by the PPP method gives for 3,4-diaminofurazan a frontier electron density at the nitrogen atoms of the amino groups close to the corresponding values for other investigated diamines (Table 3).

As far as the HOMO energies of the o-diamines, which must have a deciding effect both on the magnitude of their orbital interaction with the electrophile and on the proportion of such interaction [6], are concerned, it is seen from Table 3 that there is a significant decrease in the $E_{HOMO}$ value of the heterocyclic diamines, and this applies particularly to the values obtained in the π-electron approximation (Table 3).

Thus, the decrease in the basicity of the amino groups and the HOMO energy of 3,4-diaminofurazan and 2,3-diaminopyridine compared with 1,2-phenylenediamine must lead to a decrease in the reactivity of the diamines both in 1,4-addition and in 1,2-addition to α,β-unsaturated ketones. As shown by experiment, such processes do become impossible in the case of chalcones.

## EXPERIMENTAL

The IR spectra of the compounds were measured in tablets with potassium bromide on a Specord IR-75 spectrophotometer. The electronic spectra were recorded in solutions in methanol ($c = 4 \cdot 10^{-5}$ M) on a Specord UV-vis instrument. The PMR spectra were obtained in deuterochloroform solutions on a Tesla BS-2487-B instrument at 80 MHz with TMS as internal standard. The individualities of the compounds and the compositions of the reaction mixtures were monitored by TLC on Silufol UV-254 plates with chloroform as eluant.

2-Methyl-2,4-diphenyl-8-ethoxy-2,3-dihydro-1H-1,5-benzodiazepine (IVa). To a solution of 0.45 g (3 mmole) of 4-ethoxy-1,2-phenylenediamine and 0.72 g (6 mmole) of acetophenone in 30 ml of methanol we added one drop of sulfuric acid. The solution was boiled under a reflux condenser for 6 h and filtered. The filtrate was mixed with 50 ml of water, and after cooling the crystals were filtered off. The yield was 0.55 g (52%); mp 91°C (from aqueous methanol). Compounds (IVc, d, Va-d) were obtained similarly (Table 1).

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