DERIVATIVES OF 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINE BASED ON SUBSTITUTED 1,2-PHENYLENEDIAMINES AND ACETYLARENES

V. D. Orlov and S. M. Desenko

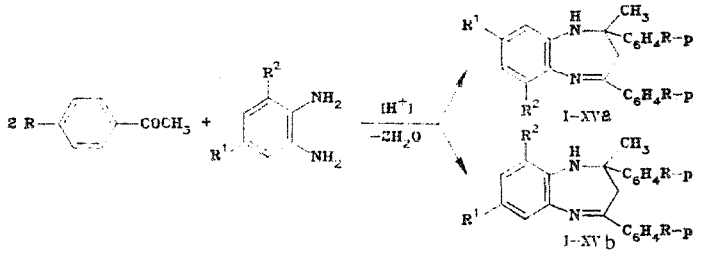
UDC 547.892.02:543.422'51.52

Derivatives of 2,3-dihydro-1H-1,5-benzodiazepine were obtained by the reaction of 4-chloro-, 4-bromo- 3,5-dichloro-, and 4-cyano-substituted ortho-phenyl-enediamines with 4-R-acetophenones in the presence of concentrated sulfuric acid. Electron-withdrawing groups R increase the reaction rate and consequently promote the formation of a mixture of isomeric products. The structure of the compounds and the composition of their mixtures were established by PMR spectroscopy. The reaction mechanism is discussed.

Earlier we developed a general method for the synthesis of 2,4-diaryl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepines by the reaction of acetylarenes with the salt form of o-phenylenediamine [1]. It was shown that the unstable intermediates are bisazomethine derivatives, while the process itself has reversible character.

In the present work we studied the reaction of acetophenone derivatives with 1,2-phenylenediamines containing electron-withdrawing groups (4-chloro, 4-bromo, 4-cyano, 3,5-dichloro, and 4-nitro). It should be noted that attempts to produce derivatives of dihydrobenzodiazepine by the reaction of the above-mentioned diamines with aromatic α, β-unsaturated ketones (and with chalcones, in particular) proved unsuccessful. In the investigated process the reactivity of the diamines also proved substantially lower compared with that of o-phenylenediamine itself. The use of a procedure in which the reaction is catalyzed by hydrogen chloride [1] did not lead to the formation of the desired products, and only boiling of alcohol solutions of the initial compounds with catalytic additions of concentrated sulfuric acid made it possible to obtain derivatives of 2,3-dihydro-1H-1,5-benzodiazepine (I-XI). However, the yields of compounds (I-XI) were low (Table 1), while 1,2-diamino-4-nitrobenzene did not enter into reaction with the acetylarenes.

The formation of compounds (I-XI) was proved unambiguously by the IR, UV, and PMR spectra and was confirmed by determination of their nitrogen contents (Tables 1 and 2). Thus, the IR spectra show clearly the bands for the stretching vibrations of the NH (3269-3386 cm^{-1}) and C=N (1606-1616 cm^{-1}) bonds. In their long-wave part the electronic absorption spectra were almost identical with the spectra of the corresponding 2,4-diaryl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepines described in [1].



I, V, VIII, XI, XII, R = H; II, XIII R = CH_3O; III, VI, IX, XIV R = Cl; IV, VII, X, XV R = NO_2; I-VII R^1 = Cl; VIII-X R^1 = C≡N; XI R^1 = Br; XII-XV R^1 = H; I-IV, VIII-XV R^2 = H; V-VII R^2 = Cl [Compounds (XII-XV) were characterized in [1]]. The signals for the protons of the

A. M. Gor'kii State University, Khar'kov. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1673-1678, December 1985. Original article submitted March 12, 1985.

0009-3122/85/2112-1377$09.50

TABLE 1. Characteristics of Compounds (I-XI)

Compound	Ratio of isomers a : b, %	mp, °C	Heating time, h	IR spectrum (KBr), cm^{-1}		UV spectrum λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	N found, %	Molecular formula	N calc., %	Yield, %
				$\nu_{C=N}$	ν_{NH}					
I	75 : 25	117—119	3,5	1611	3346	257; 366	8,4	$C_{21}H_{19}ClN_2$	8,4	52
II	100 : 0	125—127	3,5	1606	3278	278 (17,2); 363 (7,3)	7,3	$C_{23}H_{23}ClN_2O_2$	7,1	34
III	60 : 40	152	3,5	1608	3269	263; 376	6,9	$C_{21}H_{17}Cl_3N_2$	6,9	68
IV	50 : 50	177—179	3,5	1607	3386	278; 417	13,3	$C_{21}H_{17}ClN_4O_4$	13,2	60
V	100 : 0	162—163	5	1607	3314	259 (25,6); 368 (6,2)	7,8	$C_{21}H_{18}Cl_2N_2$	7,6	44
VI	70 : 30	153—155	4	1607	3337	268; 374	6,5	$C_{21}H_{16}Cl_4N_2$	6,4	54
VII	55 : 45	205—207	4	1606	3343	277; 414	12,2	$C_{21}H_{16}Cl_2N_4O_4$	12,2	58
VIII	0 : 100	147—149	6	1616	3333	272 (31,8); 365 (6,0)	12,8	$C_{22}H_{19}N_3$	12,9	32
IX	0 : 100	178—180	5	1613	3274 3345	275 (27,9); 377 (5,4)	10,8	$C_{22}H_{17}Cl_2N_3$	10,7	51
X	0 : 100	226	5	1606	3321	263 (21,1); 417 (5,4)	16,8	$C_{22}H_{17}N_5O_4$	16,9	67
XI	100 : 0	126	3,5	1616	3349	258 (26,1); 368 (7,1)	7,4	$C_{21}H_{19}BrN_2$	7,4	59

TABLE 2. The PMR Spectra of Compounds (I-XI)

Compound	Chemical shifts of protons, δ, ppm (in $CDCl_3$)				
	CH_3, s	NH, s	H_A*, d	H_B, d	9-H†, d
Ia	1,71	3,54	2,92	3,12	6,68
Ib	1,71	3,46	2,91	3,08	6,69
IIa	1,67	3,45	2,88	3,03	6,68
IIIa	1,72	3,47	2,85	3,08	6,80
IIIb	1,72	3,37	2,83	3,35	6,70
IVa	1,81	3,37	2,98	3,29	6,87
IVb	1,81	3,75	2,97	3,05	6,79
Va	1,73	3,61	2,89	3,05	6,71
VIa	1,74	3,45	2,85	3,03	6,72
VIb	1,76	4,13	2,82	3,09	—
VIIa	1,84	3,61	2,98	3,25	6,79
VIIb	1,74	4,32	2,98	3,33	—
VIIIb	1,74	4,23	2,96	3,24	6,77
IXb	1,74	4,23	2,94	3,29	6,76
Xb	1,82	3,73	3,05	3,51	6,93
XIa	1,74	3,54	2,93	3,13	6,94

*The J_{AB} values amount to between -13.3 and -13.7 Hz.
†J = 2.0-2.5 Hz; for compounds (Ib, IIIb, IVb, VIIIb-Xb) J = 8.0-9.0 Hz.

methyl, methylene, and imino groups and also the doublet for the 9-H proton at the ortho position to the imino group were easily identified in the PMR spectra of compounds (I-XI) (Table 2).

The unsymmetrical nature of the initial diamines suggests the possibility of the formation of two isomers. An answer to the question of the direction of the process is not provided by TLC or UV and IR spectroscopy. For instance, in the region corresponding to the absorption of the amino group the IR spectrum of (IX) contains two peaks at 3274 and 3345 cm^{-1}, but a similar effect was observed for the individual dihydrodiazepine derivatives [1] and was explained by intermolecular H association. In fact, a single ν_{NH} band is observed in the spectrum of (IX) measured in carbon tetrachloride, as in the spectra of the other compounds.

The PMR spectra provide an unambiguous answer to the question. Thus, the spectra of compounds (I, III, IV, VII) show the splitting of signals of the same type. This corresponds to the formation of these compounds as mixtures of a and b isomers, whereas in other cases [compounds (II, V, VI, VIII-XI)] the PMR spectra correspond to the appearance of the individual compounds (Table 2).

TABLE 3. The Dipole Moments (D) of Compounds (I, III, XII-XV)

Compound	μ_{expt} [lit]	μ_{calc}	
		μ_1	μ_2
Ia	—	3,45	
Ib	—	4,56	
75% Ia+25% Ib	3,77	3,76	
IIIa	—	2,54	2,75
IIIb	—	3,82	4,30
55% IIIa+45% IIIb	3,61	3,18	3,53
XII	3,13 [1]	3,30	
XIII	3,39 [1]	2,84	3,24
XIV	3,59 [1]	2,67	3,91
XV	7,75 [1]	3,05	7,49

The signals for the protons of the methylene groups form a typical AB quartet with J_{AB} = 13.3-13.7 Hz, where the difference $\delta_{H_B} - \delta_{H_A}$ increases with increase in the electron-withdrawing characteristics of the substituents at positions 2 and 4 of the heterocycle. The observed nonequivalence of the methylene protons is undoubtedly due to their different anisotropic screening by the aromatic rings. This is consistent with theories about the preferred existence of the dihydrodiazepine ring as a single conformer of the "boat" type [2].

On account of the strong electron-donating effect of the imino group the signals for the 9-H proton of the o-phenylene ring are shifted upfield (6.70-6.94 ppm, Table 1) compared with the spectra of the remaining aromatic protons, and this simplifies their analysis. The spectrum of the 9-H proton represents a doublet, the spin–spin coupling constant of which will be either an ortho constant (8-9 Hz) or a meta constant (2.0-2.5 Hz), depending on the position of the substituents R^1 and R^2 in the o-phenylene ring; coupling with the proton at the para position (0.2-0.5 Hz [3]) does not appear in the spectra. This made it possible to determine unambiguously the structure of the obtained compounds and in the case of the formation of mixtures of isomers to establish their composition (Table 1); here the integral intensities of the spectra of the 9-H, H_B, and NH protons were compared. It should also be noted that considerable change in the δ_{NH} value is observed in the PMR spectra of compounds (VIb) and VIIb) containing substituents at the ortho position to the imino group [compounds (VIb) and (VIIb), Table 2].

The structure of dihydrobenzodiazepine derivatives I, III, XII-XV was also analyzed by measuring their dipole moments. The values of μ_{max} for these compounds are given (Table 3).

In the calculation of the dipole moments μ_1 and μ_2 were used the standard moments of the substituents in aromatic rings [4] and also the data from [2], in which the coordinates of the atoms of the bicycle and the magnitude and direction of its dipole moment are given.

In the 2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepine molecules the heterocycle has the form of a slightly distorted boat, where the 2-aryl radical occupies the equatorial position [2]. The appearance of a bulky methyl group at position 2 of the heterocycle can be reflected in the stereochemical orientation of the geminal aryl ring. For compounds (XII-XV) the calculation was therefore performed for each of the possible conformers [with the equatorial (μ_1) and axial (μ_2) positions of the aromatic ring (Tabel 3)]. The Calculation gives good agreement between the μ_2 and μ_{expt} values, i.e., predicts a preference for the conformer in which the methyl group occupies the equatorial position while the aromatic ring occupies the axial position. The accuracy of this conclusion is confirmed by calculation of the dipole moments of compounds (I, III) (Table 3), which was made with allowance for the ratio of the a and b isomers (Table 1); in this case good agreement is observed between μ_{expt} and μ_2 (calculated by means of the equation $\mu_2^2 = \Sigma N_i \mu_i^2$ [4]).

The fact that the phenyl group is in the axial position in the presence of a geminal methyl group is somewhat unexpected, but it has an analogy in the cyclohexane series [5].

Analysis of the isomeric composition of compounds (I-XI) (Table 1) shows primarily that it depends on the electronic character of the substituents R, R^1, and R^2. As we established [1], increase in the electron-withdrawing character of the substituent R in the acetophenone component accelerates the formation of the dihydrobenzodiazepines and increases the thermodynamic stability of the desired heterocycle. The fact that the probability of

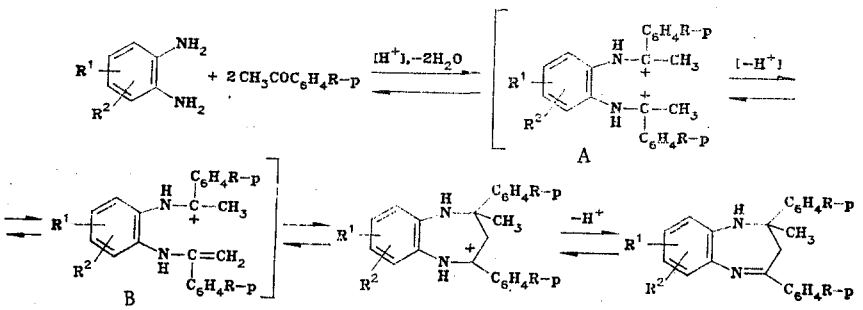
the formation of the two isomers is leveled out here shows that the reversibility of the process is lost and the reaction is subject to kinetic control. For this reason increase in the boiling time of the reaction mixture from 3.5-5 to 25-30 h in the reactions of the diamines with 4-nitroacetophenone does not change the isomeric position of the obtained dihydrobenzodiazepines.

On the other hand, if in the initial ketone R = H or CH_3O, the reaction is retarded and becomes thermodynamically controlled. As a result, even with small differences in the characteristics of the amino groups of the o-phenylenediamine component either one of the isomers or their mixture is formed but with a preferential content of one of them [compounds (I, II, V, VIII, IX), Table 1].

These conclusions agree well with the results from the experiment, where compound (Va) was brought into reaction with 4-nitroacetophenone under the conditions of acid catalysis. Here the thermodynamically more stable [compared with (Va)] 2-methyl-2,4-di(4-nitrophenyl) derivatives (VIIa, b) were formed. Although one isomer was brought into the reaction, the final product was a mixture of the isomers (VIIa) and (VIIb) with the same content (55:45, %) as in the product from the reaction of 4-nitroacetophenone with 3,5-dichloro-1,2-phenylenediamine (Table 1).

The effect of the substituents R^1 and R^2 in o-phenylene-diamine is also extremely significant. From Table 1 it is seen that the selectivity of the process increases with increase in their electron-withdrawing effect. Thus, whereas the ratio of the isomers a and b is approximately the same in the case of compounds (III) and (IV) (R^1 = Cl, R^2 = H) for (IX) and (X) (R^1 = C≡N, R^2 = H) the direction of the reaction becomes quite well defined, and the azomethine bond in the dihydro-diazepine molecules is formed with the participation of the more basic amino group.

All these observations can be explained on the basis of the following mechanism for the process:*



As shown earlier [1], the intermediate compound in the reaction is a bisazomethine, the diprotonated form of which is shown in the scheme. Its deprotonation must lead to the formation of the intermediate B, for which two cyclization paths are possible, i.e., with attack by the carbocation at the nitrogen atom or at the methylene group. The first path is realized in the absence of a methyl group and reflects the acid-catalyzed in the absence of a methyl group and reflects the acid-catalyzed transformation into benzimidazoles characteristic of 2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepines [6]. In our case the second cyclization path is realized in the carbocation B, leading to the formation of a seven-membered dihydrodiazepine ring; the steric effects of the bulky groups at the carbocationic center probably hinder its reaction with the nitrogen atom.

By counteracting the delocalization of the charge at the α-carbon atom of the intermediates A and B, electron-withdrawing substituents R [compounds (III, IV, VI, VII)] greatly accelerate the deprotonation and cyclization processes. Against the background of these effects the electronic effect of the substituents R^1 and R^2 must decrease regularly, which leads (as seen from Table 1) to a decrease in the selectivity of the reaction in the case of compounds (III, IV, VI, VII). On the other hand, if the substituent R is an electron-donating group, the charge in the carbocation A is delocalized, the stability of the ion increases, the deprotonation rate decreases, and the process as a whole acquires more clearly defined

*The authors convey their gratitude to Prof. Yu. S. Shabarov (Moscow State University) for useful consultations in the discussion of the mechanism.

equilibrium character. Under these conditions the differences in the characteristics of the azomethine fragments, due to the electronic effect of the substituents R^1 and R^2, become perceptible. The preferential formation of the isomer *a* in the syntheses of compounds I-VII, XI and of isomer b in the other cases, corresponds to the higher probability of deprotonation at the methyl group in the intermediate A due to the more basic imino group.

The proposed mechanism also explains why the reaction of the halogen and cyano derivatives of o-phenylenediamine with acetylarenes requires a stronger acid than the unsubstituted diamine (concentrated sulfuric acid instead of hydrogen chloride) and why the process stops even with small additions of water [1]. The introduced substituents R^1 and R^2 are characterized by an over all electron-withdrawing effect, the basicity of the amino groups as a whole is therefore reduced, and the processes presented in the scheme require protons with higher activity.

EXPERIMENTAL

The IR spectra of compounds (I-XI) were measured on a Specord IR-75 spectrophotometer for tablets with potassium bromide. The electronic absorption spectra were obtained on a Specord UV-vis instrument in methanol at concentrations of $3\text{-}4\cdot10^{-5}$ M. The PMR spectra were obtained on a Varian XL-100 instrument in deuterochloroform with TMS as internal standard. The dipole moments were measured in benzene at 25°C by the method in [7].

The individualities of compounds (I-XI) 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(7)-chloro-2,3-dihydro-1H-1,5-benzodiazepines (I). To a solution of 0.5 g (3.5 mmole) of 4-chloro-1,2-phenylenediamine and 0.84 g (7 mmole) of acetophenone in 10 ml of methanol we added one drop of concentrated sulfuric acid. The reaction mixture was boiled for 3.5 h, added to 50 ml of water, and left overnight at 20-25°C, and 0.6 g (52%) of compound (I) was filtered off; mp 117-119°C (from a 2:1 mixture of methanol and water). Compounds (II-XI) were obtained similarly (Table 1).

Reaction of 2-Methyl-2,4-diphenyl-6,8-dichloro-2,3-dihydro-1H-1,5-benzodiazepine (Va) with 4-Nitroacetophenone. To a solution of 0.8 g (2 mmole) of (Va) in 20 ml of methanol we added 0.67 g (4 mmole) of 4-nitroacetophenone and one drop of sulfuric acid. The mixture was heated under a reflux condenser for 6 h. After cooling 0.5 g (51%) of orange crystals was filtered off; mp 205-207°C. The product was a mixture of the isomers (VIIa) and (VIIb) in a ratio of 55:45 (PMR).

LITERATURE CITED

1. V. D. Orlov, S. M. Desenko, and N. N. Kolos, Khim. Geterotsikl. Soedin., No. 1, 126 (1984).
2. V. D. Orlov, N. N. Kolos, and B. A. Abramov, Khim. Geterotsikl. Soedin., No. 12, 1662 (1984).
3. A. Junke, Nuclear Magnetic Resonance in Organic Chemistry [Russian translation], Mir, Moscow (1974), p. 84.
4. V. I. Minkin, O. A. Osipov, and Yu. A. Zhdanov, Dipole Moments in Organic Chemistry, Khimiya, Leningrad (1968), p. 79.
5. V. M. Potapov, Stereochemistry [in Russian], Khimiya, Moscow (1976), p. 350.
6. V. D. Orlov, N. N. Kolos, and B. M. Zolotarev, Khim. Geterotsikl. Soedin., No. 3, 390 (1983).
7. S. V. Tsukerman, V. D. Orlov, Yu. N. Surov, and V. F. Lavrushin, Zh. Strukt. Khim., 9, 67 (1968).