ASYMMETRICAL DIARYLIDENEACETONES IN REACTIONS WITH o-PHENYLENEDIAMINE

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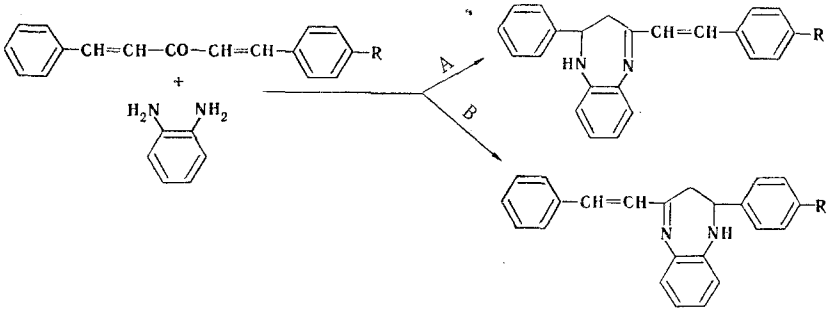
Asymmetrical diarylideneacetones were condensed with o-phenylenediamine in methanol in the presence of a tertiary amine. It is shown that the p-dimethylamino derivative does not react under these conditions, that the reaction takes place at the unsubstituted cinnamoyl fragment in the case of the p-methoxy and p-nitro-substituted compounds, and that the reaction takes place at the substituted fragment in the case of halo-containing ketones. The structures of the compounds obtained were confirmed by alternative synthesis (by the reaction of 4-methyl-2-phenyl-2,3-dihydro-1H-1,5-benzodiazepine with aromatic aldehydes), as well as by the IR, UV, and PMR spectra and the dipole moments. The principal physicochemical criteria for the identification of isomeric dihydrodiazepines were established. All of the synthesized compounds belong to the trans series.

The reaction of o-phenylenediamine (PDA) with α,β-unsaturated ketones is one of the methods for the specific synthesis of aromatic 2,3-dihydro-1,5-benzodiazepines [1]. The first step is the addition of the amine to the activated C=C bond of the ketone, after which the resulting β adduct undergoes intramolecular cyclization. Hence it is a simple matter to assume that the electronic state of the C=C bond should determine the mechanism of the entire reaction to a significant degree.

For experimental verification of this assumption, in the present research we studied dibenzylideneacetone derivatives that contain a substituent in one of the aromatic rings. This asymmetry differentiates the electronic character of the double bonds of the ketone molecules and consequently determines the specificity of their reaction with PDA.



For comparison purposes we studied the reaction of PDA with symmetrical diarylideneacetones. The experimental conditions for the synthesis are quite simple, viz., heating or maintaining in the cold equimolar amounts of PDA and the corresponding diarylideneacetone in an alcohol medium. The reaction is catalyzed by organic bases (N,N-dimethylbenzylamine or triethylamine), the amounts of which vary over a wide range. The composition of the reaction products was monitored by thin-layer chromatography (TLC).

The experiments showed that neither 4-mono- nor 4,4-bis(dimethylamino)dibenzylideneacetones react with PDA. In the remaining cases (R = OCH_3, H, and NO_2) the reaction gives only a single diazepine derivative, regardless of the temperature. The p-chloro and p-bromo derivatives of dibenzylideneacetone also react with PDA in the cold to give a single isomer (VII and VIII). However, when we carried out this reaction in refluxing methanol, we obtained mixtures of isomeric dihydrodiazepines IV and VII and V and VIII, respectively, the

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TABLE 1. 2-(4-R-Phenyl)-4-(4-R'-styryl)-2,3-dihydro-1H-1,5-benzodiazepines

Compound	R	R'	mp, °C	UV spectra, nm (in ethanol), λ_{max} ($\varepsilon \cdot 10^{-3}$)	IR spectra (KBr), cm^{-1}			δ, ppm (2-CH)	μ_D	N found, %	Empirical formula	N calc., %	Yield, %
					$\nu_{C=N}$	ν_{N-H}	$\nu_{=CH}$						
I	H	H	136—137 [1]	392 (10,2), 300 (28,6), 223 (27,4)	1601	3337	960	5,08	3,33				50
II	H	OCH_3	138—139	384 (11,8), 330 (24,1), 236 (22,1)	1603	3339	969	5,07	—	8,03	$C_{24}H_{22}N_2O$	7,90	93
III	H	$N(CH_3)_2$	142—143	400 (13,2), 336 (27,0)	1609	3332	969	5,06	—	11,30	$C_{25}H_{25}N_3$	11,43	25
IV	H	Cl	143—144	397 (8,0), 306 (20,4), 225 sh	1602	3341	970	5,08	—	7,62	$C_{23}H_{19}N_2Cl$	7,80	30
V	H	Br	144—146	397 (8,3), 303 (21,4), 222 sh	1604	3339	974	5,07	—	6,81	$C_{23}H_{19}N_2Br$	6,94	35
VI	H	NO_2	154—155	425 (7,9), 317 (18,1), 224 sh	1599	3355	971	5,04	—	11,17	$C_{23}H_{19}N_3O_2$	11,37	42
VII	Cl	H	146	393 (9,3), 309 (24,5), 223 (27,6)	1624	3313	969	5,17	2,68	7,81	$C_{23}H_{19}N_2Cl$	7,80	72
VIII	Br	H	148—149	392 (7,5), 300 (20,4), 220 (28,0)	1622	3307	970	5,15	2,58	6,90	$C_{23}H_{19}N_2Br$	6,94	81
IX	OCH_3	OCH_3	142—143	384 (11,6), 330 (23,8), 232 (26,8)	1605	3354	960	4,94	3,62	7,10	$C_{25}H_{24}N_2O_2$	7,28	88
X	Cl	Cl	148—149	398 (8,4), 306 (24,3), 222 sh	1628	3364	972	5,17	3,14	7,19	$C_{23}H_{18}N_2Cl_2$	7,12	51
XI	2,4-di-Cl	2,4-di-Cl	111—112	409 (7,5), 297 (24,5), 227 sh	1600	3300	970	5,63	2,45	6,06	$C_{23}H_{16}N_2Cl_4$	6,09	60
XII	Br	Br	150—151	397 (9,1), 309 (24,5), 225 sh	1627	3354	970	5,16	3,12	5,70	$C_{23}H_{18}N_2Br_2$	5,81	39
XIII	NO_2	NO_2	170 (dec.)	425 (8,9), 309 (21,4), 257 (19,4)	1602	3279	974	5,32	—	13,44	$C_{23}H_{18}N_4O_4$	13,48	40
XIV	H	CH_3*	109—111	321 (3,0), 247 (11,1)	1647	3293	—	5,03	3,41	11,50	$C_{16}H_{16}N_2$	11,86	65

*The CH_3 group was taken in place of $CH{=}CH{-}C_6H_4R'$.

TABLE 2. Data from a Calculation for the Planar Model of N-(p-R-Cinnamylidene)-o-phenylenediamine

R	Electron transition	UV spectral band	Calc.		Exptl.		Localization, %					Charge transfer, eV				
			E	f	E	f	$\dot{N}$	Φ_1	N=C	C=C	Φ_2	$\dot{N}$	Φ_1	N=C	C=C	Φ_2
H	1	1	3,10	0,75	3,17	0,25	11,0	37,3	26,2	17,5	8,0	0,200	0,407	−0,280	−0,160	−0,167
	2	2	4,04	0,64	4,14	0,63	7,0	43,3	22,0	17,5	10,2	0,04	0,246	−0,252	−0,077	0,043
	3		4,53	0,003			0,2	2,0	3,4	12,0	82,4	−0,001	0,000	−0,03	−0,072	0,103
	4	3*	4,70	0,12	4,59	0,19	6,0	36,6	16,0	20,0	21,4	0,086	0,004	−0,14	−0,151	0,201
	5	4*	5,21	0,23	5,10	0,30	7,0	52,0	12,7	13,3	15,0	0,008	0,119	−0,04	−0,015	−0,144
OCH_3	1	1	3,14	1,00	3,23	0,31	7,6	29,0	27,4	20,1	15,9	0,129	0,129	−0,309	−0,082	0,133
	2	2	3,91	0,27	3,76	0,38	7,6	35,1	21,0	16,0	20,3	0,110	0,09	−0,320	−0,112	0,232
	3		4,27	0,008			0,3	3,1	9,7	17,6	69,3	−0,006	−0,06	−0,185	−0,315	0,566
	4		4,55	0,002			6,3	53,8	18,5	10,0	11,4	0,054	−0,07	−0,109	−0,119	0,244
	5	3	5,32	0,33	5,24	0,41	6,1	35,4	14,0	14,3	30,2	0,07	−0,008	−0,053	−0,028	0,019

*The bands were isolated graphically.

separation of which is difficult. The structures of the synthesized II and VI-VIII were established by both chemical (alternative synthesis) and physical [from the UV, IR, and PMR spectra and the dipole moments (Table 1)] methods.

To carry out the alternative syntheses we used the data in [2], according to which a methyl group in the 4 position of the diazepine is quite activated and is capable of undergoing condensation with aromatic aldehydes. As the starting compound we obtained 4-methyl-2-phenyl-2,3-dihydro-1H-1,5-benzodiazepine (XIV), information regarding which is not available in the literature. Ried and Stahlhofen [3] and Nawojska and Nawrocka [4] have described only a β adduct based on PDA and benzylideneacetone but with different characteristics in each case. It has been shown [5] that the condensation of the same starting substances in the case of heating in methanol leads to 2,2-dimethyl-2,3-dihydroimidazo[4,5-b]-phenazine in low yields (6-8%). The dihydrodiazepine (XIV) synthesized in the present research was identified by means of its IR, UV, and PMR spectra (Table 1) and also from its mass spectrum (the presence of M^+ 236 and ions with m/e 195, 159, 132, 119, and 118 is in agreement with the general character of the fragmentation of the 2,3-dihydro-1,5-diazepines examined in [6]). The dihydrodiazepine is not very stable (for example, upon prolonged heating in methanol it undergoes complete hydrolysis), and one should note particularly that its synthesis must be carried out at room temperature. In order to accelerate its condensation with aromatic aldehydes we carried out this reaction in triethylamine with the addition of sodium methoxide. Under these conditions various 4-R-benzaldehydes, including the 4-dimethylamino derivative, undergo the reaction. Compounds I-V were obtained by this method (Table 1). We noted that the rates of the reaction and the yields of products increase appreciably as the electron-acceptor properties of the substituent increase.

A comparison of the properties of the compounds obtained by specific synthesis with the properties of the products of the condensation of asymmetrical diarylideneacetones showed that monomethoxy- and mononitrodibenzylideneacetones react with o-phenylenediamine to give II and VI via Scheme A, whereas the halogen-containing ketones react via Scheme B (VII and VIII). The unequivocal character of this solution of the problem makes it possible to also note those principal physical characteristics that can serve as independent criteria in the interpretation of the isomeric dihydrodiazepines.

It follows from the data in Table 1 that a number of characteristic bands ($\nu_{C=N}$, ν_{N-H}, and $\gamma_{=CH}$) are observed in the IR spectra; however, because of their insufficient sensitivity to the electronic character of the substituent, these spectra cannot be used for the identification of the isomers. At the same time, the presence in the spectra of all of the compounds of a distinctly expressed ν_{CH} band of a vinylene group at 960-974 cm^{-1} makes it possible to assign them to the trans series.

The UV spectra give a more unambiguous answer to the question of the position of the substituent in the dihydrodiazepines. A peculiarity of their UV spectra is the presence in the near-UV region of at least three absorption bands.

A quantum-mechanical calculation shows (Table 2) that the long-wave band in these spectra is a one-electron 0→1 transition that is primarily localized on the N—Φ_1—N=C—C=C

fragment. The transition is accompanied by a small degree of charge transfer (0.2 eV) from the amino group to the conjugated chain. Thus the calculation predicts a hypsochromic shift of this band when an electron-donor substituent is introduced and a bathochromic shift when an electron-acceptor substituent is introduced in the styryl grouping of the dihydrodiazepine. In agreement with this conclusion is a calculation of the spectrum of the conjugated system of II, from which it additionally follows that the character of the electron transitions does not change when this substituent is introduced. Although the 2 band (the 0—2 transition) is characterized by preferred localization on the same fragment (Table 2), charge transfer in this case is substantially less pronounced, and, consequently, this band is less suitable for identification of diazepines. This is especially true for the remaining electron transitions, the bands of which are, in addition, mutually overlapped.

It should be noted that the conclusion drawn on the basis of the calculation are in complete agreement with the spectral characteristics of I-VI and IX-VIII, in which the substituent is known to be incorporated in the overall conjugated system of the molecule. Insofar as the spectra of dihydrodiazepines VII and VIII, which were obtained from asymmetrical ketones, are concerned, the adequacy of the long-wave part of their absorption spectra makes it possible to identify these compounds as products of reaction B.

In the PMR spectra of the investigated dihydrodiazepines the signals of the protons of the aryl ring should be sensitive to whether or not the aryl group is part of the conjugated system. Unfortunately, measurements at 100 MHz give a complex picture in the aromatic proton region (15 protons absorb here), and it is therefore difficult to interpret them rigorously. In this region one can reliable identify only doublets of the α and β protons of the vinylene group. The vicinal constant for spin—spin coupling of this pair of protons is 16.0 Hz, and the conclusion regarding the trans structure of this grouping that was drawn above in the analysis of the IR spectra is consequently confirmed. At the same time, it is apparent from Table 1 that the electronic effect of the 2-aryl group is reflected distinctly in the magnitude of the chemical shift of the proton of the adjacent CH group; an increase in the electronegativity of the aryl group is accompanied by an increase in the δ value of this proton. Since its signal is readily identified in the PMR spectra measured at frequencies above 40 MHz, it may serve as a good criterion in the study of alternative dihydrodiazepines.

The dipole moments give extremely valuable information regarding the structures of the benzodiazepines. We found that 2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepine and its vinylog I have close dipole moments, viz., 3.37 and 3.39 D, respectively. This correspondence is also retained for other pairs of vinylogs. On the other hand, the μ values of isomeric compounds that differ with respect to the position of the substituent in one or another aromatic ring differ by more than 1 D; for example, 2-(p-bromophenyl)-4-phenyl- and 2-phenyl-4-(p-bromophenyl)-1,5-benzodiazepines have μ values of 2.55 and 3.90 D, respectively. The dipole moments of VII and VIII (Table 1) confirm unambiguously that the 4-chloro(bromo)phenyl group is attached to the C_2 atom of the two-ring system.

Thus the entire set of experimental data obtained is in complete agreement with the structure of the compounds that is reflected in Table 1.

In addition, it should be noted that in conformity with the general rules [7] that are operative in A_N reactions of enones, electron-donor aryl groups in the β position of a ketone should slow down the addition process, whereas electron-acceptors should accelerate it. In the case of asymmetrical diarylideneacetones this should be manifested in the different competitive capacities of the double bonds. If the process has equilibrium character, the cinnamoyl fragment, which is maximally stabilized by the mesomeric effect of the electron-donor substituent, should be retained. Strict observance of this rule was noted in [8] in the case of the Knoevenagel reaction. Clear deviations from the rule occur in the present research in the synthesis of dihydrodiazepines that contain acceptor groups (Cl, Br, and NO_2). There is no doubt that the formation of the thermodynamically less favorable IV-VI in the reaction of asymmetrical ketones with PDA is due to intensification of the role of kinetic factors. Either conformational changes in the ketone molecule (for example, the nonplanar s-trans structure is more characteristic for a cinnamoyl fragment that contains an acceptor substituent) or a change in the ratio of the rates of the I (addition) and II (condensation) steps may serve as a direct reason for this. A more detailed response to this question requires studies of the mechanism of the addition of amines to unsaturated ketones, which has not been adequately elucidated in the literature. The synchronous addi-

tion of pyrrolidine to trans-chalcone has been discussed only in [9], but it remains unclear to what degree this is general in character. It is also known [10] that 4-dimethylamino- and 4-nitrochalcones do not react with secondary amines; this fact correlates well with the data that we obtained.

EXPERIMENTAL

The IR spectra of KBr pellets (1 mg of the substance in 100 mg of KBr) were measured with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with an XL-100 spectrometer (100 MHz) with tetramethylsilane as the internal standard. The UV spectra of solutions of the compounds in ethanol [$(2\text{-}4)\cdot10^{-5}$ mole/liter] were measured with a Specord UV-vis spectrophotometer. The individuality of the compounds obtained was monitored by TLC on Silufol plates (elution with chloroform).

The calculation of the electronic characteristics of the excited states of o-aminocinnamalacetone and its 4-methoxy derivative (they can be regarded as models of the conjugated chain of styryldiazepines) was carried out by the MO LCAO self-consistent-field (SCF) configuration interaction (CI) method in the Pariser–Parr–Pople (PPP) variant with the standard set of parameters [11], and an estimate of the contribution of the fragment to the overall molecular excitation was given for each electron transition with the aid of the quantitative criteria of localized character [12].

2-Phenyl-4-(p-methoxystyryl)-2,3-dihydro-1,5-benzodiazepine (II). A mixture of 2.64 g (0.01 mole) of 1-phenyl-5-(4-anisyl)pentadien-3-one and 1.08 g (0.01 mole) of PDA in 30-40 ml of methanol and 5 ml of triethylamine was refluxed for 7-8 h, during which the solution became intensely red. The mixture was cooled to precipitate II, an additional amount of which was obtained after evaporation of part of the solvent (~50% by volume). The overall weight of II, with mp 138-139°C, was 2.3 g (93%). Compounds IX-XII, as well as mixtures of IV and VII and V and VIII, were similarly obtained.

2-Phenyl-4-(p-nitrostyryl)-2,3-dihydro-1H-1,5-benzodiazepine (VI). A mixture of 5.56 g (0.02 mole) of 1-phenyl-5-(4-nitrophenyl)pentadien-3-one and 2.16 g (0.02 mole) of PDA in 60 ml of methanol and 40 ml of triethylamine was refluxed for 8-10 h, after which the solvent was evaporated with a rotary evaporator to give an oily residue, which was crystallized twice from benzene–hexane (3:1) to give 3.1 g (42%) of a product with mp 154-154.5°C. Compound XIII was similarly obtained.

2-(p-Chlorophenyl)-4-styryl-2,3-dihydro-1H-1,5-benzodiazepine (VII). A mixture of 2.89 g (0.01 mole) of 1-phenyl-5-(4-chlorophenyl)pentadien-3-one and 1.08 g (0.01 mole) of PDA was dissolved by gentle heating in 45 ml of ethanol, 2-3 ml of triethylamine was added, and the mixture was allowed to stand at room temperature for 3-4 days, as a result of which 2.6 g (72%) of a yellow precipitate with mp 146°C (from methanol) formed. Compound VIII was similarly obtained.

4-Methyl-2-phenyl-2,3-dihydro-1H-1,5-benzodiazepine (XIV). A 14.6-g (0.1 mole) sample of benzalacetone and 10.8 g (0.1 mole) of PDA were dissolved by heating in 40 ml of triethylamine, and the mixture was allowed to stand overnight. The resulting prismatic crystals of regular form were crystallized from chloroform–ether (3:1) to give 15.3 g (65%) of a product with mp 109-111°C.

Condensation of XIV with Aromatic Aldehydes. A) A 2.36-g (0.01 mole) sample of XIV and 1.49 g (0.01 mole) of p-dimethylaminobenzaldehyde were dissolved in 15 ml of triethylamine, 2 ml of a 20% solution of sodium methoxide was added, and the mixture was refluxed for 1 h. The solvent was removed by distillation, and the residue was dissolved in chloroform and chromatographed with a column filled with silica gel. The first fraction contained unchanged benzaldehyde, the second fraction contained dihydrodiazepine III, and the third fraction contained starting dihydrodiazepine XIV. Recrystallization from methanol gave 0.95 g (25%) of III with mp 142-143°C.

Method A was used to carry out the condensation of XIV with p-OCH_3-, p-Cl-, p-Br-, and p-NO_2-benzaldehydes.

B) A 0.7-g (0.003 mole) sample of XIV was dissolved in 45 ml of ethyl ether, and a stream of dry HCl was passed through the solution for 30 min. The resulting yellow precipitated salt was separated from the ether and dissolved in 5 ml of pyridine containing 0.45 g (0.003 mole) of p-dimethylaminobenzaldehyde. The resulting solution was heated at

100°C for 1 h, after which it was cooled to precipitate the salt of III. It was removed by filtration, dissolved in methanol, and hydrolyzed with concentrated ammonium hydroxide, as a result of which a yellow precipitate of free base III [0.13 g (35%)], with mp 142-143°C (from methanol), was obtained.

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CONDENSED IMIDAZO-1,2,4-AZINES.

4.* SYNTHESIS OF 1,4-DIHYDROIMIDAZO[1,5-c]-1,2,4-TRIAZINE DERIVATIVES

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The reaction of 2-methyl-4(5)-nitro- and 2-methyl-4(5)-nitro-5(4)-bromoimidazoles with α-halo ketones was investigated, during which a number of 1-acylmethyl-substituted 2-methyl-4-nitro- and 2-methyl-4-nitro-5-bromoimidazoles were obtained. 1,4-Dihydro derivatives of imidazo[1,5-c]-1,2,4-triazine were synthesized by reaction of the latter with hydrazine and its monosubstituted derivatives. The structures of the 1-acylmethyl-substituted 2-methyl-4-nitro-5-bromoimidazoles and 1,4-dihydro derivatives of imidazo[1,5-c]-1,2,4-triazine were confirmed by their IR, PMR, and mass spectra.

We have previously reported [4] that imidazo[1,2-b]-1,2,4-triazine derivatives luminesce intensely in the UV and blue-violet regions both in the solid state and in solutions. In this connection, it seemed of interest to synthesize other isomeric imidazo-1,2,4-triazines and investigate their luminescence and biological properties.

Prior to our brief communications [3, 5, 6], the heterocyclic 1H-imidazo[1,5-c]-1,2,4-triazine system and its derivatives had not been described. In order to obtain 1-acylmethyl-substituted 2-methyl-4-nitro-5-bromoimidazoles, which are intermediates for the synthesis of derivatives of the two-ring system indicated above, we studied the reaction of 2-methyl-4(5)-nitro- (V) and 2-methyl-4(5)-nitro-5(4)-bromoimidazoles (VI) with α-halo ketones. It

*See [1-3] for Communications 1-3, respectively.

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