NEW ASPECTS OF THE CHEMISTRY OF 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINE

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UDC 547.892

Under basic catalysis conditions the reaction of 4- and 4'-substituted chalcones with o-phenylenediamine leads to 2,3-dihydro-2,4-diaryl-1H-1,5-benzodiazepines; β-amino adducts, the ability of which to undergo intramolecular condensation increases as the basicity of the catalyst is increased, are formed as intermediates. A different pathway for the process (the formation of an azomethine) is observed in the reaction with cinnamaldehyde. It is concluded that conformational factors play a primary role in the direction of the reaction.

The chemistry of 2,3-dihydro-1H-1,5-benzodiazepine is reflected satisfactorily in a previous review [1]; nevertheless, some problems concerning the synthesis of aromatic derivatives need to be reexamined. Thus, in the first communication [2, 3] regarding the reaction of o-phenylenediamine with chalcone and benzalacetone it is asserted that the reactivity of the C=O group in the molecules of these ketones is substantially lower than that of the conjugated C=O bond, as a consequence of which β amination takes place exclusively. However, dihydrodiazepines were obtained in [4] by the reaction of pyridine analogs of chalcone with o-phenylenediamine, although it is known that the pyridine ring displays appreciable electron-acceptor properties and decreases the reactivity of the C=O group substantially, particularly in the case of 1-phenyl-3-(2-pyridyl)propen-3-one. The possibility of the synthesis of dihydrobenzodiazepine on the basis of chalcone itself was demonstrated recently in [5, 6].

In an attempt to arrive at a deeper understanding of the reasons for the contradictions discussed above we studied the reaction of o-phenylenediamine with 4- and 4'-substituted chalcones. In the principal experiment we reproduced the reaction conditions that we described in [6]: the catalyst was N,N-dimethylbenzylamine, the solvent was methanol or n-butanol, the reflux time was 7-25 h, and the yield increased appreciably when excess o-phenylenediamine was present. In all cases, regardless of the electronic character of the substituent in the chalcone, we isolated exclusively cyclization products, viz., 2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepines (I-XI, Table 1), and a certain amount of the starting chalcone was recovered, but β-aminated adducts of the XII type were not observed. It should be noted that diazepine I was obtained in 36% yield even without heating when the same solution was maintained at room temperature for 2 days.

The $\nu_{C=O}$ (chalcone) and ν_{NH_2} (diamine) bands vanish in the IR spectra of I-XI, and characteristic vibrations at 1600-1617 (C=N), 3337-3371 (NH), and 3030-3077 cm^{-1} (CH) are observed. It should be noted here that the interpretation of the IR spectra of dihydrobenzodiazepines in [4], viz., 1570 (NH) and 1515 cm^{-1} (C=N), is erroneous. A broad singlet of an N–H group and a typical ABX system of the –CH–CH_2– fragment of the dihydrodiazepine ring are observed distinctly in the PMR spectra. The UV spectra and the results of elementary analysis are in agreement with the proposed structures of I-XI. All of the substances are colored (from yellow to red), and this may serve as a qualitative analytical sign of their classification as dihydrodiazepines (the products of β amination are colorless [2]).

In a series of experiments we reproduced the conditions for the reaction of o-phenylenediamine with chalcone that are described in [2]: the catalyst was piperidine, and the reflux time in alcohol was 5 h. As in [5], only dihydrodiazepines I were isolated as the reaction products in most of the experiments; however, in some cases we were able to isolate addition product XII, which was described in [2], in low yield; the IR spectrum of XII –

A. M. Gorkii Kharkov State University, Kharkov 310077. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 697-700, May, 1980. Original article submitted June 17, 1979.

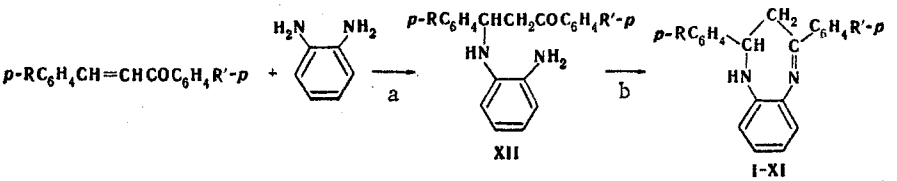
0009-3122/80/1605-0547$07.50

TABLE 1. Dihydrobenzodiazepines I-XI

Compound	R	R′	mp, °C	IR spectrum, cm⁻¹ NH	IR spectrum, cm⁻¹ C=N	λmax, nm (ε · 10⁻³), in ethanol	N found, %	Empirical formula	N calc., %	Yield, %
I	H	H	129—129,5	3362	1608	256 (24,6); 367 (6,2)	9,4	$C_{21}H_{18}N_2$	9,4	85
II	OCH_3	H	146—147	3347	1604	274 (20,2); 362 (8,1)	8,5	$C_{22}H_{20}N_2O$	8,5	54
III	Br	H	142	3371	1617	255 (25,5); 370 (6,25)	7,4	$C_{21}H_{17}BrN_2$	7,4	63
IV	NO_2	H	189—189,5	3374	1615	264 (27,2); 364 (5,6)	12,2	$C_{21}H_{17}N_3O_2$	12,2	77
V	H	CH_3	127	3353	1607	267 (25,5); 364 (6,9)	9,0	$C_{22}H_{20}N_2$	9,0	57
VI	H	OCH_3	139—140	3354	1601	274 (20,6); 360 (8,5)	8,5	$C_{22}H_{20}N_2O$	8,5	46
VII	H	Ph	179—180	3356	1602	287 (28,0); 374 (9,1)	7,5	$C_{27}H_{22}N_2$	7,5	45
VIII	H	Br	142—143	3346	1609	267 (26,3); 376 (6,9)	7,4	$C_{21}H_{17}BrN_2$	7,4	77
IX	H	Cl	129—130	3351	1608	263 (24,7); 377 (6,6)	8,4	$C_{21}H_{17}ClN_2$	8,4	60
X	H	NO_2	104—105	3349	1600	298 (23,8); 420 (6,8)	12,3	$C_{21}H_{17}N_3O_2$	12,2	76
XI	H	—*	136—137	3337	1601	300 (28,6); 392 (10,2)	8,6	$C_{23}H_{20}N_2$	8,6	50

*The C_6H_4R' group in XI was replaced by a $CH{=}CH{-}C_6H_5$ group.

1673 (C=O), 3324 and 3412 cm^{-1} (NH_2) — unambiguously confirms its structure. When adduct XII is subjected to further refluxing in methanol, it is converted completely to dihydrodiazepine I, thereby confirming the formation of the dihydrodiazepines through a step involving β amination when piperidine is used.



The failure of attempts to isolate a β-amino adduct when we used a more basic tertiary amine may be a consequence either of significant acceleration of step b or a change in the sequence of the condensation and β-addition steps. Monitoring of the course of the reaction by means of IR spectroscopy (primarily from the $\nu_{C=O}$, ν_{NH_2}, and γ_{C-H}^{trans} frequencies of the starting compounds and the $\nu_{C=N}$ and ν_{N-H} frequencies of the reaction products) did not give an unambiguous answer to this question but did show that the percentage of dihydrodiazepine I in solution is quite high even after 5 h. The reaction of o-toluidine (pK_a 4.57, as compared with pK_a 4.47 for o-phenylenediamine at 20°C [7]) with chalcone, which leads only to a β adduct, may serve as indirect evidence that the basicity of the catalyst most likely has a substantial effect on the rate of step b and does not change the sequence of the steps.

Cinnamaldehyde behaves quite peculiarly in the reaction with o-phenylenediamine. The formation of orange crystals, which correspond to the condensation product, viz., azomethine XIII, is observed at room temperature at the instant solutions of the starting components in methanol are mixed [2]. If these crystals are allowed to stand in solution or the reaction is carried out at a temperature above 40°C, an oil, which solidifies with difficulty when the solvent is removed and was identified as a low-melting polymer, is formed. The reason that the primary act in the case of cinnamaldehyde is condensation should, in our opinion, be sought primarily in the stereochemistry of the carbonyl compounds. It is known [8] that α,β-unsaturated aldehydes exist in solution exclusively in the s-trans form. The replacement of the hydrogen atom of the formyl group by a bulky group is accompanied by the development of s-cis conformers; the percentage of this form increases as the size of the group increases [9] (for example, for chalcone in CCl_4 the ratio of the s-cis:s-trans populations is 1:4 [10]). The stereochemical factor undoubtedly determines the certain shielded character of the C=O group in the ketones. Saturation of the vinyl group during the formation of the β adduct increases the conformational freedom of the carbonyl group markedly and favors intramolecular condensation step b.

The electronic absorption spectra of I-XI in ethanol and isooctane were recorded; most of the spectra are characterized by the presence of two sufficiently resolved absorption bands. An analysis of the UV spectra of dihydrodiazepines I-XI confirms that the low-

intensity long-wave absorption (360-420 nm)* in the spectra of various molecular systems with a common —N—C_6H_4—N=C—Ar chromophoric group, is due to transfer of electron density from the nitrogen atom of the N—H group to the azomethine group, as evidenced by the distinctly expressed effect of the substituent in the 4 position: electron-acceptor groups (VIII-X), as well as groups that lengthen the conjugation chain (VII, XI), give rise to bathochromic shifts of the long-wave band, which is illustrated by the correlation

$$\left(\frac{1}{\lambda_H}-\frac{1}{\lambda_R}\right)\frac{hc}{2.3KT}=\rho\sigma,$$

where $1/\lambda_H$ is the frequency of the absorption band of I, $1/\lambda_R$ is the frequency of the absorption band of V-X, ρ = 8.59 (±0.12), and r = 0.998.

Calculations show localization of the π—π^* electron transition responsible for the second clearly expressed band (227-298 nm) on the N—C_6H_4—N=C fragment [11]. However, as seen from Table 1, the absorption maxima of this band vary substantially in different compounds. It is most probable that this is due to superimposition of the bands of electron transitions with close energies. The certain hypsochromic shift of the long-wave absorption that is observed in isooctane solutions as compared with alcohol solutions confirms the π character of the electron transition.

EXPERIMENTAL

The electronic absorption spectra were recorded with a Specord spectrophotometer. The IR spectra were obtained with a UR-20 spectrometer. The PMR spectra were recorded with a Varian XL-100 spectrometer with tetramethylsilane as the internal standard.

The individuality of all of the compounds was verified by chromatography on Silufol plates.

2,3-Dihydro-2-phenyl-4-(4-bromophenyl)-1H-1,5-benzodiazepine (VIII). A 2.5-g (0.01 mole) sample of 4-bromochalcone and 1.62 g (0.015 mole) of o-phenylenediamine were dissolved by refluxing in 40 ml of methanol; 2.5 ml of N,N-dimethylbenzylamine was added, and the mixture was refluxed for 7 h. Yellow crystals of VIII, with mp 142-143°C (from methanol), were obtained after evaporation of two thirds of the volume of solvent and cooling.

Compounds I-III, V, IX, and XI were similarly synthesized.

The following method was used in the case of the slightly soluble 4- and 4'-nitro- and 4'-phenylchalcones.

2,3-Dihydro-2-phenyl-4-(4-diphenylyl)-1H-1,5-benzodiazepine (VII). A 3.73-g (0.01 mole) sample of 4-phenylchalcone and 1.62 g (0.015 mole) of o-phenylenediamine were dissolved in 80 ml of sec-butyl alcohol, 2.5 ml of N,N-dimethylbenzylamine was added, and the mixture was refluxed for 25 h. The starting chalcone precipitated when the mixture was cooled. Evaporation of the filtrate yielded a mixture of chalcone and VII, which were separated by fractional crystallization. The yield of product with mp 179-180°C was 45%.

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*In characterizing the UV spectra of I, Nawojski and Nawrocka [5] erroneously cite the band with λ_{max} 252 nm as a long-wave absorption band.

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SYNTHESIS AND PROPERTIES OF 1,2,3-TRIAZOLES THAT CONTAIN A FERROCENYL RING

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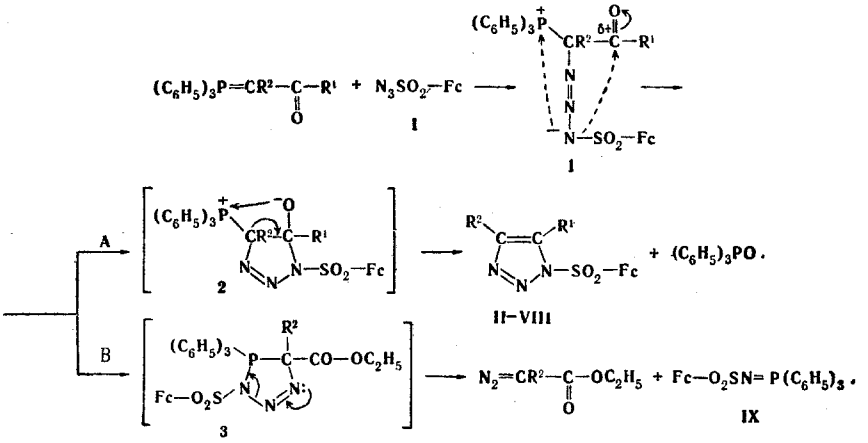
UDC 547.1'3'791.07

Ferrocenesulfonyl azide reacts with a number of aroylmethylenetriphenylphosphinomethylenes in dry methylene chloride to give 1,4,5-trisubstituted 1,2,3-triazoles (61-77% yields), which are readily converted to 4,5-disubstituted 1,2,3-triazoles and ethyl ferrocenesulfonate when they are refluxed in ethanol. The known triphenylphosphazo ferrocenyl sulfone and ethyl diazoacetate are formed in the case of the reaction of ferrocenesulfonyl azide with carbethoxymethylenetriphenylphosphinomethylene. The structures of the synthesized compounds were proved by the results of elementary analysis and IR, UV, and mass spectroscopy.

No information regarding 1,2,3-triazoles that contain a ferrocenyl ring is available in the literature. In developing our research on sulfur-containing derivatives of ferrocene [1, 2] on the one hand, and continuing our investigation of the reactivities of phosphorus ylids [3] on the other, we studied the reaction of ferrocenesulfonyl azide (I) [4] with phosphorus ylids; it is well known [5] that this reaction may lead to various products, depending on the structure of the phosphorus ylid component. Azide I reacts readily in solution in methylene chloride at room temperature with a number of aroyltriphenylmethylenephosphorus ylids [3] to give 1,4,5-trisubstituted 1,2,3-triazoles (II-VIII) and triphenylphosphine oxide. The formation of triazoles II-VIII can be represented by the following scheme [5]:



Fc = $C_5H_5FeC_5H_4$-ferrocenyl

The direction of cyclization in adduct 1 depends on the nature of substituent R^1 in the starting phosphorus ylid. When R^1 = C_6H_5 or p-substituted phenyl groups that have only a slight effect on the electrophilicity of the carbonyl carbon atom, the partial positive charge on which is higher than on the phosphorus atom, the cyclization proceeds

Chernovtsy State University, Chernovtsy 274012. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 701-704, May, 1980. Original article submitted April 16, 1979.

 0009-3122/80/1605-0550$07.50