2,4-DIARYL-2,3-DIHYDROBENZO[b][1,4]THIAZEPINES

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2,4-Diaryl-2,3-dihydrobenzo[b][1,4]thiazepines are obtained in a single stage from chalcones and ortho-aminothiophenol in the presence of triethylamine. The nature of the electronic transitions in their UV absorption spectra is discussed with the use of quantum-chemical methods. It was shown that the seven-membered ring does not invert in the range of temperatures between −80 and +140°C and is in the boat form. The main initial event in the fragmentation of the molecules of the obtained compounds under electron impact is the formation of benzothiazole-containing radical-ions. In an acidic medium 2,4-diphenyl-2,3-dihydrobenzo[b][1,4]thiazepine is hydrolyzed to 3-(2-aminophenylthio)-1,3-diphenyl-1-propanone, and in its reaction with 2,4-dinitrophenylhydrazine chalcone hydrazone and o-aminothiophenol are formed.

There are several reports in the literature on the synthesis of 2,4-diaryl-2,3-dihydrobenzo[b][1,4]thiazepines [1-5]. Thus, it was shown [1, 2] that with o-aminothiophenol under the conditions of base catalysis (piperidine) chalcones form the products from β-addition, i.e., 3-(2-aminophenylthio)-1,3-diaryl-1-propanones, which undergo cyclization to the desired benzothiazepines under the influence of catalytic amounts of acid. The possibility of the direct formation of a seven-membered ring under the conditions of base catalysis with the presence of electron-withdrawing substituents (Br, NO_2) or ortho substituents in the aromatic rings of the chalcones was indicated in [3, 4], and this was attributed to change both in the electron density at β-carbon atom and in the relative cyclization rate. Individual diaryldihydrobenzothiazepines were obtained in the reactions of o-aminothiophenol hydrochloride with chalcones [5].

In the present work we set out to develop a general method for the single-stage synthesis of 2,4-diaryl-2,3-dihydrobenzo[b][1,4]thiazepines (I-VII) and to study their spectral characteristics and stability in acidic media and also their conformational structures. The synthesis of (I-VII) was realized by our previously developed method [6] for the production of derivatives of 2,3-dihydrobenzo[b][1,4]diazepine. The main difference from the methods proposed in [3, 4] was the use of triethylamine instead of piperidine as catalyst. Both in the reaction of chalcones with o-phenylenediamine [6] and in the present case substitution of the secondary amine by a tertiary amine made it possible to obtain compounds (I-VII) (Table 1) in a single stage with good yields.

It is curious that the basicity of triethylamine is even somewhat lower than that of piperidine (pK_α 10.65 and 11.22 respectively [7]), and from this standpoint the acceleration of the condensation process is obscure. The observed changes are probably due to a difference in the mechanism of catalysis, namely, the fact that the catalytic effect of tertiary amines is determined by the presence of hydroxide ions in their solutions whereas for the remaining amines an immonium derivative is formed in the course of the catalytic cycle, and their activity correlates directly with the basicity [8].

The PMR spectra of (I-VII) were measured in deuterochloroform at room temperature (Table 1), and the spectrum of (I) was measured in the range of temperatures between −80 and +140°C. A resonance septet and a quartet for a three-spin system, belonging to the protons of the CH_2—CH group, show up early in the spectra. The fact that the form of the signals in the spectrum of (I) does not change over the whole investigated range of temperatures indicates with great probability the absence of inversion in the seven-membered ring of this molecule.

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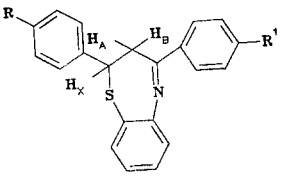
TABLE 1. The Physicochemical Characterics of the Dihydrobenzothiazepines



Compound	R	R'	m. p. °C*	UV spectrum λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	PMR spectrum, δ, ppm, J, Hz						θ_{AX}	θ_{BX}	Yield, %
					H_A	H_B	H_X	J_{AB}	J_{AX}	J_{BX}			
I	H	H	114—115	259 (16,9), 335 (3,7)†	3,04	3,27	4,96	12,74	4,62	12,53	55	167	70
II	H	OCH_3	124—125	258 (19,7), 328 (4,0)	3,06	3,30	4,90	12,85	4,49	12,35	58	165	67
III	H	Cl	132	261 (18,9), 340 (4,1)	3,03	3,21	4,94	13,15	4,89	12,31	53	166	67
IV	H	Br	136	262 (23,3), 341 (4,8)	2,98	3,23	4,91	12,75	4,99	12,40	45	167	73
V	OCH_3	H	127—128	258 (20,1), 334 (3,8)	2,99	3,28	5,01	12,60	4,68	12,70	55	170	65
VI	Cl	H	128	257 (23,0), 334 (4,4)	2,98	3,24	4,92	12,67	4,66	12,62	55	169	72
VII	Br	H	131	256 (22,7), 335 (4,5)	3,02	3,29	5,00	12,69	4,71	12,75	55	171	59
VIII†	—	—	129—130	256 (24,6), 367 (6,2)	2,90	3,08	4,99	13,60	3,50	8,85	48	168	85

*The melting points of (I-VI) agree with published data [3, 4].
†2,4-Diphenyl-2,3-dihydrobenzo[b][1,4]diazepine.

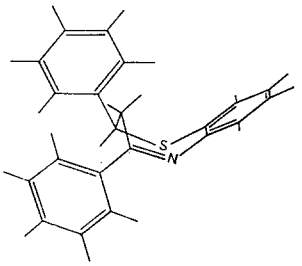


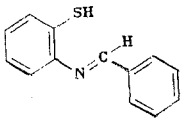
Fig. 1. The Dreiding model of the molecule of 2,4-diphenyl-2,3-dihydrobenzo[b]-[1,4]thiazepine (I).

In order to determine the dihedral angles in the CH—CH_2 fragment (θ_{AX} and θ_{BX}, Table 1) we used the Karplus equation [9]. The correctness of its use is confirmed by the fact that the difference $\Delta\theta = \theta_{BX} - \theta_{AX}$ in all cases close to 120°, i.e., to the projection angle which must be expected in the heterocycle if the standard bond angles are preserved. It should be noted that in the case of (VIII) more real values of $\Delta\theta$ were obtained with the use of the Karplus equation from [10], which takes account of the electronegativity of the neighboring groups. The results obtained during the analysis of a Dreiding model agree well with the calculated values of the dihedral angles; its projections, taken in two mutually perpendicular planes, make it possible to estimate the coordinates and dihedral angles of the molecule.* Here it follows from the model that the seven-membered ring of the molecule of (I) exists in a rigid boat form, for which the equatorial arrangement of the 2-phenyl group (Fig. 1) is more favorable for steric reasons. This orientation of the 2-phenyl radical is also confirmed by the magnitude of the vicinal constant J_{BX} in the CH—CH_2 fragment (Table 1), which is typical of spin—spin coupling between axial protons.

The electronic absorption spectra of (I-VII) are characterized by the presence of two absorption bands in the region of 257-341 nm (Table 1). The more long-wave band has undergone a hypsochromic shift (by 32-37 nm) compared with the analogous band in the UV spectra

*The projections were recorded with the kind assistance of M. Yu. Kornilov, to whom the authors express their gratitude.

TABLE 2. Data from Calculation of o-Mercaptobenzylideneaniline



Electronic transition	Band in UV spectrum	Calculated		Experimental		Localization of transition, %				Charge transfer e			
		E, eV	f	E, eV	f	S	Φ_A	C=N	Φ_B	S	Φ_A	C=N	Φ_B
0→1	1	3,71	0,09	3,78	0,03	16,7	32,6	44,3	6,4	0,33	0,10	0,39	0,04
0→2		4,25	0,007			6,7	51,5	18,5	23,3	0,12	0,22	−0,29	−0,05
0→3		4,51	0,01			0	4,3	11,8	83,9	0	−0,01	−0,12	0,13
0→4	2	4,81	0,22	4,91	0,4	20,7	11,7	20,1	47,5	0,41	−0,13	−0,24	−0,04
0→5		5,48	0,06			0	30,5	26,3	43,2	0	0,19	−0,42	0,23

TABLE 3. The Mass Spectra of Compounds (I, III, IV)*

Compound	m/z values (intensity of ion peaks, % of maximum)
I	315 (4), 290 (8), 275 (8), 256 (5), 248 (20), 235 (5), 234 (8), 211 (100), 210 (21), 209 (24), 139 (8), 110 (8), 109 (38), 108 (5), 82 (13), 77 (10), 65 (17), 63 (29)
III	351 (5), 349 (14), 249 (5), 248 (15), 247 (97), 246 (45), 245 (100), 244 (13), 218 (5), 211 (5), 210 (22), 139 (5), 110 (5), 109 (15), 108 (4), 82 (18), 77 (12), 65 (6), 63 (5)
IV	351 (4), 349 (10), 213 (16), 212 (43), 211 (100), 210 (27), 209 (10), 139 (5), 109 (9), 108 (3), 82 (12), 77 (16), 65 (5), 63 (6)

*The peaks of ions with m/z > 60 and with intensity ⩾ 5%, and also those mentioned in the discussion are given.

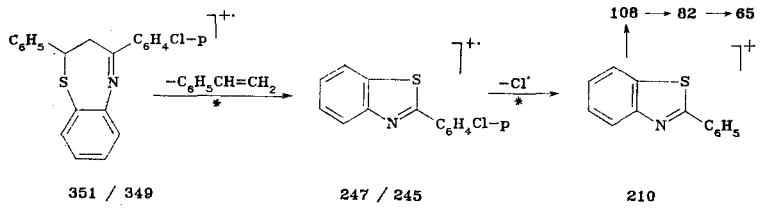
of dihydrobenzodiazepines [6], e.g., compounds (I) and (VIII) in Table 1. This effect is probably due both to difference in the electronegativities of the sulfur and nitrogen atoms and to a partial change in the geometry of the heterocycle.

The UV spectra of a series of derivatives of dihydrobenzodiazepine were presented earlier in [3], but a detailed discussion of the spectra was not given. For the interpretation of the nature of the electronic transitions we therefore undertook a calculation for a model compound (o-mercaptobenzylideneaniline) by the LCAO-MO SCF CI method in the PPP version with the usual set of parameters [11]. In this case, however, significant discrepancy was observed between the calculated and experimental data. Therefore, in order to take account of the acoplanarity of the calculated fragment we varied the values of the resonance integrals for the C–S, C=N and C–N= bonds. The best agreement between the calculated results and the UV spectrum of compound (I) was obtained with $\beta_{CS} = -1.0$ eV and $\beta_{C=N} = \beta_{C-N=} = -2.5$ eV (Table 2).

From the calculated data it follows that a one-electron transition 0 → 1, mostly localized in the S–C_6H_4–N=C– fragment, is responsible for the long-wave absorption band. The transition is accompanied by substantial transfer of electron density from the mercapto group to the conjugated chain. Therefore, the same relationships appear in the spectra of the dihydrobenzothiazepines (I-VII) as in the series of dihydrobenzodiazepines [6, 12]; electron-donating substituents R^1 lead to a hypsochromic shift of the long-wave band, and electron-withdrawing substituents lead to a bathochromic shift.

The calculation predicts the existence of low-intensity electronic transitions 0 → 2 and 0 → 3, significantly localized at the aromatic nuclei of the conjugated system in the molecule of (I) (overlapped by stronger bands in the measured spectra). The second experimentally observed band corresponds to the 0 → 4 transition, also accompanied by a significant transfer of charge (0.41 e) from the sulfur atom to the diazepines (I, III, IV) (Table 3) are characterized by comparatively low intensity for the molecular ion peaks. A common process is the loss of the $RC_6H_4CH{=}CH_2$ fragment by the $M^{+\cdot}$ ion, which is confirmed by metastable ions. The subsequent fragmentation corresponds fully to the processes described for 2-arylbenzothiazoles [13], and this makes it possible to propose the following scheme

of dissociation [for the case of compound (III)]:



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By varying the substituents R and R^1 it is easy to show that the formation of the benzothiazolium radical-ions is always accompanied by the removal of styrene containing the substituent R from the $M^{+\cdot}$ ion.

It is interesting to note that structurally similar dihydrobenzodiazepines [14] are also readily transformed by electron impact into the corresponding 2-arylbenzimidazoles. However, their fragmentation is in addition characterized by removal of the aryl radical from position 2 and the formation of quinoxaline ions; analogous processes are not observed for compounds (I, III, IV) on account, probably, of the insufficient stability of the structures which form.

Earlier [15] it was established that dihydrobenzothiazepines readily form salts with mineral acids, are quaternized by methyl iodide, are oxidized at the sulfur atom to sulfodioxides, and are reduced by sodium borohydride to the tetrahydro derivatives. We have shown that when an alcohol solution of compound (I) is boiled with 4-5 drops of concentrated hydrochloric acid, the seven-membered ring opens with the formation of 3-(2-aminophenylthio)-1,3-diphenyl-1-propanone (IX). Together with the data in [1-5] discussed above this result demonstrates the reversible character of the condensation stage in the formation of the thiazepine ring.

Compound (I) reacts slowly with 2,4-dinitrophenylhydrazine (DNPH) hydrochloride, forming a low yield (20%) of chalcone 2,4-dinitrophenylhydrazone and o-aminothiophenol. The reaction of the β adduct of (IX) with DNPH takes place similarly. Therefore, both the behavior of compound (I) in an acidic medium and the experiments with DNPH hydrochloride demonstrate the stability of compound (IX) to elimination of the β-thio group. (In the analogous reactions of dihydrobenzodiazepines it was not possible to record the formation of the corresponding β-amino adducts [16].)

EXPERIMENTAL

The electronic absorption spectra were measured in ethanol with the compounds at concentrations of $2\text{-}3\cdot10^{-5}$ M on a Specord UV-Vis spectrophotometer. The PMR spectra were recorded in deuterochloroform on a Varian XL-100 instrument with TMS as internal standard. The PMR spectra of (I) with temperature variation were obtained on a Jeol FX-100 spectrometer in deuteroacetone (for the range between −80 and +40°C) and naphthalene (80-140°C) at intervals of 20°. The chemical shifts and the spin–spin coupling constants were calculated by the ITRCAL program, and the mean-square deviation was not greater than 0.08%. The mass spectra were obtained on a Varian MAT CH-6 spectrometer with direct injection of the sample into the ion source.

The temperature of the ionization chamber was 180°C, the ionization potential was 70 eV, and the samples were heated at 50-70°C. The individualities of the products were monitored by TLC on Silufol UV-254 plates with chloroform as eluant.

2,4-Diphenyl-2,3-dihydro[b][1,4]thiazepines (I). A solution of 0.5 g (2.4 mmole) of chalcone, 0.3 g (2.4 mmole) of o-aminothiophenol, and 0.5 ml of triethylamine was boiled for 4-5 h. After cooling the precipitate was filtered off and crystallized from methanol. We obtained 0.54 g (70%) of compound (I); mp 115°C. Published data [3]: mp 115°C. Compounds (II-VII) were obtained similarly. The IR spectra of the compounds agreed with published data [3, 4].

3-(2-Aminophenylthio)-1,3-diphenyl-1-propanone (IX). To a solution of 0.2 g (0.6 mmole) of (I) in 10 ml of methanol we added 3-4 drops of concentrated hydrochloric acid. The mixture was boiled for 2 h, one third of the volume of the solvent was evaporated, and the white precipitate was crystallized from benzene. We obtained 0.1 g (47%) of compound (IX); mp 142°C. Published data [2]: mp 142°C.

Reaction of Compound (I) with DNPH. A solution of 0.2 g (0.6 mmole) of (I) in 10 ml of methanol was mixed with 10 ml of a 4% methanol solution of DNPH hydrochloride. The mixture was left at room temperature for 2 days, the precipitated chalcone hydrazone was filtered off (0.05 g 20%), and the product was identified by its melting point of 248°C (published data [17], mp 248°C) and by TLC (R_f 0.56, eluant chloroform). Analysis of the filtrate by TLC also showed the presence of o-aminothiophenol (R_f 0.21, eluant chloroform).

The reaction of the β-adduct of (IX) with DNPH was carried out similarly. The yield of chalcone hydrazone was 30%.

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