CONDENSED IMIDAZO-1,2,4-AZINES.

8.* SYNTHESIS OF 5H-3,4-DIHYDROIMIDAZO[1,2-b]-1,2,4-TRIAZEPINE DERIVATIVES

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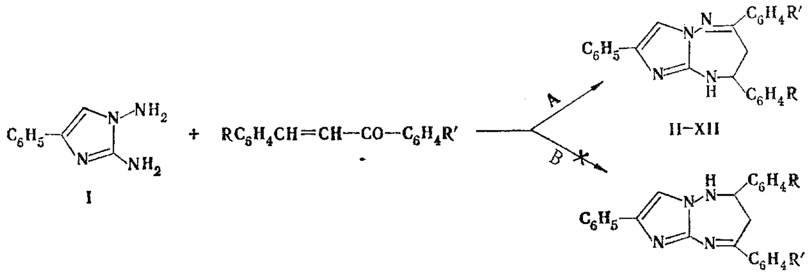
2,4,7-Triaryl-5H-3,4-dihydroimidazo[1,2-b]-1,2,4-triazepines were obtained on the basis of 4-phenyl-1,2-diaminoimidazole and chalcones. Their IR, UV, PMR, and mass spectra are discussed. It is shown that the more basic 1-NH_2 group of the starting diamine participates in the formation of the azomethine bond of the seven-membered heteroring. The seven-membered ring has a "quasi-boat" form in which the 2- and 4-aromatic substituents occupy equatorial positions.

We have previously [2] worked out the conditions for the synthesis of 2,4-diaryl-1H-2,3-dihydro-1,5-benzodiazepines on the basis of o-phenylenediamine and chalcones; the reaction was catalyzed by tertiary alkylamines in alcohol. We used this method in the present research for the synthesis of the previously undescribed 2,4,7-triaryl-5H-3,4-dihydroimidazo[1,2-b]-1,2,4-triazepines (II-XII, Table 1). 1,2-Diamino-4-phenylimidazole (I) and chalcones were subjected to the reaction; the yields of the desired products II-XII averaged 15-20% lower than in the case of the reaction of chalcones with o-phenylenediamine [2], probably because of the decreased reactivity of starting diamine I.

The formation of dihydroimidazotriazepine derivatives II-XII is confirmed by the results of elementary analysis and data from the UV, IR, PMR, and mass spectra. Thus the presence in the UV spectra of two to three absorption bands, of which the longest-wave band lies at 340-400 nm and is of low intensity (Table 1), is characteristic for chromophore systems of the N-arylene—N=C-aryl type [3]. Bands of stretching vibrations of NH and C=N groups (Table 1) and of alicyclic C—H bonds (2900-3150 cm^{-1}) are observed in the IR spectra. Multiplets of the $CH—CH_2$ fragment of the seven-membered heteroring show up distinctly in the PMR spectra, and the mass spectra contain peaks of molecular ions, the m/z values of which correspond to the molecular masses of the desired compounds.

The nonequivalence of the amino groups in starting diamine I is responsible for two probable pathways for its reaction with chalcones:



In addition, chromatographic and spectral monitoring confirms the individuality of II-XII, and the mutually consistent spectral characteristics make it possible to assign them to a single series of isomers.

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*See [1] for communication 7.

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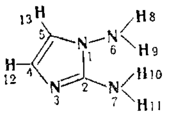
TABLE 1. 2-(p-R'-Phenyl)-4-(R-phenyl)-7-phenyl-5H-3,4-dihydroimidazo[1,2-b]-1,2,4-triazepines

Compound	R	R'*	mp, °C	ν_{N-H}	$\nu_{C=N}$	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	Reflux time, h	R_f	N found, %	Empirical formula	N calc, %	Yield, %
II	H	H	223—224	3440	1640	280 (23,4); 352 (7,8)	10	0,36	15,40	$C_{24}H_{20}N_4$	15,38	66
III	H	CH_3	218—219	3443	1635	283 (13,5); 347 (5,2)	9	0,35	14,78	$C_{25}H_{22}N_4$	14,81	56
IV	H	OCH_3	210—211	3429	1641	288 (28,9); 343 (12,3)	16	0,21	14,22	$C_{25}H_{22}N_4O$	14,21	25
V	H	Cl	229—230	3443	1636	284 (28,5); 361 (6,8)	5	0,42	14,02	$C_{24}H_{19}ClN_4$	14,05	53
VI	H	Br	230—231	3451	1651	284 (21,7); 361 (6,4)	8	0,38	12,63	$C_{24}H_{19}BrN_4$	12,64	64
VII	H	NO_2	249—250	3387	1647	299 (17,5); 403 (5,7)	3	0,39	17,09	$C_{24}H_{19}N_5O_2$	17,11	62
VIII	H	a	191—192	3465	1640	280 (18,1); 300 (20,3); 367 (11,0)	8	0,31	15,12	$C_{22}H_{18}N_4S$	15,14	48
IX	H	b	189—190	3423	1651	302 (37,0); 311 (38,5); 370 (13,3)	14	0,29	14,37	$C_{26}H_{22}N_4$	14,36	54
X	2-OH	H	251—252	3373	1627	279 (18,6); 345 (6,4)	5	0,20	14,71	$C_{24}H_{20}N_4O$	14,74	73
XI	4-OCH_3	H	179—180	3432	1628	279 (28,7); 349 (10,0)	18	0,25	14,20	$C_{25}H_{22}N_4O$	14,21	28
XII	4-Cl	H	222—223	3425	1639	279 (28,8); 351 (10,5)	9	0,38	14,04	$C_{24}H_{19}ClN_4$	14,05	50

*2-Thienyl (a) and styryl (b) groups were also used in place of p-R'-phenyl groups.

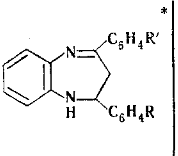
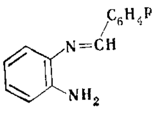
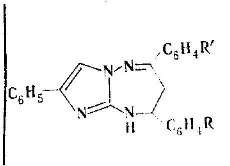
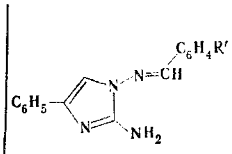
TABLE 2. Distribution of the Effective Charges in 1,2-Diaminoimidazole

Numbering of the atoms	Atoms and effective charges					
	N_1	0,064	N_6	−0,255	H_{11}	0,137
	C_2	0,253	N_7	−0,234	H_{12}	−0,080
	N_3	−0,266	H_8	0,082	H_{13}	0,072
	C_4	0,121	H_9	0,068		
E_{tot} = −72,296	C_5	−0,088	H_{10}	0,126		

The choice between pathways A and B can be made on the basis of the following data. It is known [4] that the basicity of the amine is an important factor that affects the rate of azomethine condensation and the position of the equilibrium in neutral and weakly basic media. The fact that the amino group in the 1 position of diaminoimidazole I has hydrazine character makes it possible to assume that it has higher reactivity in condensation reactions with carbonyl compounds as compared with the 2-amino group, which has the properties of a typical aromatic amine. Calculations by the CNDO/2 (complete neglect of differential overlap) method (the effective charges on the atoms of this molecule are presented in Table 2) actually predict greater nucleophilicity for the 1-amino group, and this makes it possible to regard pathway A as the preferable route in the investigated reaction.

This conclusion is in good agreement with the data in [5, 6], according to which I reacts with aldehydes to give azomethines exclusively at the 1-amino group. The structures of these azomethines were confirmed by alternative synthesis and do not raise any doubts. This fact made it possible to obtain a direct spectral confirmation of the structure of II-XII, which is based on the fact that the principal chromophore systems of azomethines synthesized by condensation of diamine I with p-R'-benzaldehydes and of the compounds obtained via reaction A (with identical R' substituents) differ only with respect to their conformational

TABLE 3. Electronic Absorption Spectra of Compounds with Related π Systems

	λ_{max}, nm (in ethanol)					
R′	* 		compound		compound	
H	367, 256	367, 244	II	352, 280	XIII	352, 277
Br	376, 267	375, 277	VI	361, 286	XIV	361, 284
NO_2	420, 298	416, 287	VII	403, 306	XV	403, 299

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*Data taken from [2].

labilities. It has been shown [3] that the inclusion of the $HN{-}C_6H_4{-}N{=}C{-}C_6H_4R'$ chromophore system in a seven-membered ring has virtually no effect on the energies of the long-wave transitions, and it was noted that the λ_{max} values of the long-wave absorption bands in the spectra of molecules that contain this chromophore are most sensitive to the introduction of electron-acceptor R′ groups. The spectral characteristics of derivatives of o-phenylenediamine (Table 3), the symmetry of the molecules of which excludes nonequivalence of the amino groups, illustrate this well.

The indicated principles determined the selection of monoazomethines XIII-XV (Table 3), which were obtained by condensation of benzaldehyde and its p-Br and p-NO_2 derivatives with 4-phenyl-1,2-diaminoimidazole (I). The melting points of XIII-XV are in agreement with the literature data [5, 6]. A doublet ν_{NH_2} band (~3340, 3430 cm^{-1}) and a $\nu_{C=H}$ band (1610-1640 cm^{-1}) are observed in the IR spectra of these compounds. The electronic absorption spectra of azomethines XIII-XV are in complete agreement with the spectra of the corresponding dihydroimidazotriazepine derivatives (II, VI, and VII; Table 3); in our opinion, this unambiguously confirms that the investigated reaction proceeds via pathway A.

The data presented in Table 3 also constitute evidence that the long-wave absorption band of II, VI, and VII is shifted hyposochromically as confirmed with the analogous band of the corresponding dihydrobenzodiazepine derivatives. The reaction constant ($\rho = 9.0 \pm 0.2$), the correlation coefficient ($r = 0.997$), which was calculated from the equation $\Delta\nu hc/2.3KT = \rho\sigma$, where $\Delta\nu = 1/\lambda_H - 1/\lambda_{R'}$ ($1/\lambda_H$ is the frequency of the long-wave absorption band of II, and $1/\lambda_{R'}$ is the analogous frequency of III-VII), and the σ constants of the R′ substituents show that the electronic conductivity in the π system of dihydroimidazotriazepine is higher than in the π system of dihydrobenzodiazepine ($\rho = 8.6 \pm 0.1$ [2]). A possible reason for this contradiction is the weakened interaction of the N—H group with the imidazole ring as a consequence of deformation of the bond angles, which also explains the high ν_{NH} values in the IR spectra of II-XII (Table 1; ν_{NH} 3337-3371 cm^{-1} in the series of benzo analogs [2]).

Characteristic multiplets (a quartet and an octet) of the protons of the $CH{-}CH_2$ fragment and a broad signal of an NH group are observed in the PMR spectra of II and IX (the low solubilities of most of the investigated imidazotriazepines hinder these studies). The chemical shifts and the spin-spin coupling constants (SSCC) of the protons of the $CH{-}CH_2$ group calculated in the variant of the ABC system have the following values for II and IX, respectively: $\delta_A = 3.07$ and 2.86 ppm, $\delta_B = 3.27$ and 3.16 ppm, $\delta_C = 4.76$ and 4.71 ppm, $J_{AB} = 16.6$ and 16.4 Hz, $J_{AC} = 2.23$ and 2.38 Hz, and $J_{BC} = 7.17$ and 7.32 Hz; the δ_{NH} values were 4.92 and 4.71 ppm. The vicinal J_{AB} and J_{AC} constants differed substantially from those in the spectrum of 2,4-diphenyl-1H-2,3-dihydro-1,5-benzodiazepine ($J_{AC} = 3.50$ Hz, $J_{BC} = 8.85$ Hz). This fact undoubtedly reflects the conformational rearrangement of the seven-membered heteroring that is observed when the size of the annelated ring changes. The Karplus [7] dihedral θ_{AC} and θ_{BC} angles of the $CH{-}CH_2$ fragment of II and IX were ~100 and 135°, respectively. The Dreiding model constructed for the II molecule is in agreement with these calculations and confirms the sufficient rigidity of the structure of the seven-membered heteroring. It also follows from an analysis of the model that the seven-membered ring has a "quasi-boat" form (a tendency to form an envelope structure is displayed) with maximum deviation of the imidazole ring from the plane of the methylene group. An equatorial orientation of the 2- and 4-phenyl groups is characteristic for II, and this is responsible for their mutual trans orientation.

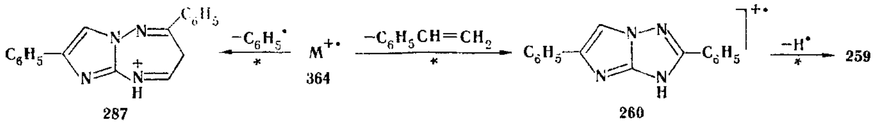
TABLE 4. Mass Spectra of II, V, IX, and XII

Compound	m/z values (relative intensities of the peaks, %)[a]
II	**364 (100)**, 287 (26), 286 (6), 261 (11), 260 (39), 259 (9), 247 (7), 246 (12), 218 (8), 205 (6), 191 (8), 189 (7), 184 (14), 158 (9), 157 (21), 143 (10), 130 (13), 129 (9), 117 (19), 116 (11), 115 (23), 105 (8), 104 (39), 103 (22), 102 (7), 90 (8), 89 (6), 78 (29), 77 (42), 76 (7), 55 (9), 52 (9), 50 (9)
V	**400 (33)**, **398 (100)**, 323 (7), 322 (6), 296 (8), 295 (9), 294 (22), 293 (10), 260 (12), 247 (8), 246 (11), 218 (6), 205 (6), 204 (8), 191 (7), 189 (7), 184 (12), 157 (18), 151 (7), 143 (9), 142 (10), 137 (6), 130 (11), 129 (9), 117 (11), 115 (20), 111 (11), 105 (6), 104 (24), 103 (15), 102 (12), 90 (7), 89 (6), 78 (12), 77 (16), 57 (6), 55 (8), 51 (7)
IX	**390 (100)**, 314 (7), 313 (22), 299 (8), 287 (7), 286 (18), 285 (11), 260 (13), 259 (6), 247 (11), 246 (16), 219 (9), 205 (9), 204 (11), 191 (9), 184 (18), 183 (7), 157 (13), 155 (44), 144 (11), 143 (22), 142 (13), 141 (13), 131 (9), 130 (22), 129 (24), 128 (18), 117 (18), 116 (18), 115 (36), 104 (44), 103 (53), 102 (16), 91 (11), 90 (11), 83 (10), 78 (16), 77 (46), 55 (10), 51 (11)
XII	**400 (33)**, **398 (100)**, 294 (12), 288 (7), 287 (27), 281 (7), 280 (8), 273 (7), 261 (7), 260 (38), 259 (21), 246 (12), 217 (7), 204 (10), 191 (10), 189 (10), 184 (13), 158 (12), 157 (21), 156 (21), 151 (12), 143 (12), 142 (13), 140 (6), 138 (7), 130 (14), 129 (13), 117 (14), 116 (13), 115 (26), 105 (11), 104 (55), 103 (33), 97 (7), 95 (7), 89 (12), 85 (19), 83 (26), 81 (10), 78 (50), 77 (60), 76 (11), 73 (11), 71 (12), 69 (19), 60 (14), 57 (24), 56 (12), 55 (31), 54 (7), 52 (17), 51 (27), 50 (17)

[a] The ion peaks with intensities >5% are presented. The mass numbers of the molecular ions are given in boldface type.

A significant increase in the δ_{NH} values as compared with 2,4-diaryl-1H-2,3-dihydro-1,5-benzodiazepines (δ_{NH} 3.6-3.8 ppm) is observed in the PMR spectra of II and IX; this is most likely due to the anisotropic effect of the unshared electron pair of the N_3 atom of the imidazole ring.

The mass spectra of II, V, IX, and XII were recorded (Table 4). One peculiarity that they have in common is the high intensity of the molecular-ion peak. The principal fragmentations of the molecular ion are presented in the case of the mass spectrum of II:



The detachment of precisely a 4-phenyl radical from the $M^{+\bullet}$ ion is confirmed by the fact that a C_6H_4Cl fragment is eliminated when a chlorine atom is introduced into this ring (XII). The ejection of a styrene molecule leads to a formation of an ion with m/z 260, which probably has the structure of the pseudomolecular ion of diphenylimidazotriazole.

EXPERIMENTAL

The electronic absorption spectra of solutions of II-XII in ethanol [(2-5)$\cdot 10^{-5}$ mole/liter] were recorded with a Specord UV-vis spectrophotometer. The IR spectra of KBr pellets were recorded with a Specord IR-75 spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$ were obtained with a Varian XL-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with a Varian MAT CH-6 spectrometer with direct introduction of the samples into the ion source; the ionization chamber temperature was 180°C, the ionizing voltage was 70 eV, the emission current was 100 μA, and the samples were heated to 70-100°C.† The individuality of all the compounds was verified by TLC on Silufol UV-254 plates by elution with methanol—chloroform (1:3).

2,4,7-Triphenyl-5H-3,4-dihydroimidazo[1, 2-b]-1,2,4-triazepine (II). A solution of 1 g (5.7 mmole) of 1,2-diamino-4-phenylimidazole, 1.2 g (5.7 mmole) of chalcone, and 0.1 ml of triethylamine in 25 ml of methanol was refluxed for 10 h, after which it was cooled, and the yellow precipitate was removed by filtration and crystallized from benzene—methanol (1:2) to give 1.08 g (66%) of II with mp 223-224°C.

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*Metastable transitions.

†We thank B. M. Zolotarev for his assistance in measuring the mass spectra.

Compounds III-XII were synthesized similarly; only the reflux times of the solutions were varied (Table 1).

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NUCLEOPHILIC ACYLATION OF BENZIMIDAZOLE

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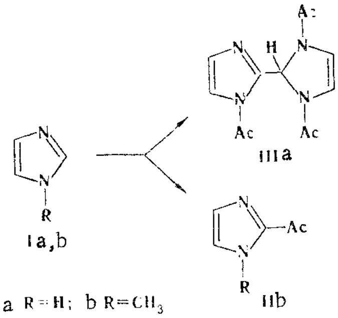
Conditions that make it possible to realize the direct $C_{(2)}$ acylation of benzimidazole and some of its derivatives were found. It is shown that bis products, which are converted to 2-acylbenzimidazoles upon heating to 140-200°C with acyl halides in the presence of triethylamine, are formed in attempts to carry out $C_{(2)}$ acylation.

The nucleophilic acylation of azoles was recently reported [1-4]. In particular, it was shown that an imidazole alkylated at the NH group (Ib) gives 2-acyl derivatives (IIb) smoothly and in good yields upon reaction with carboxylic acid halides in the presence of triethylamine in polar aprotic solvents.



This method was found to be sensitive to the structure of the starting heterocycle, and attempts to extend it to NH unsubstituted imidazole (Ia) and benzimidazole (IVa) lead to the formation of bis products IIIa and Va-e rather than to 2-acyl derivatives [4].

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