PROPERTIES OF 1,4,5-BENZOTRIAZOCINES

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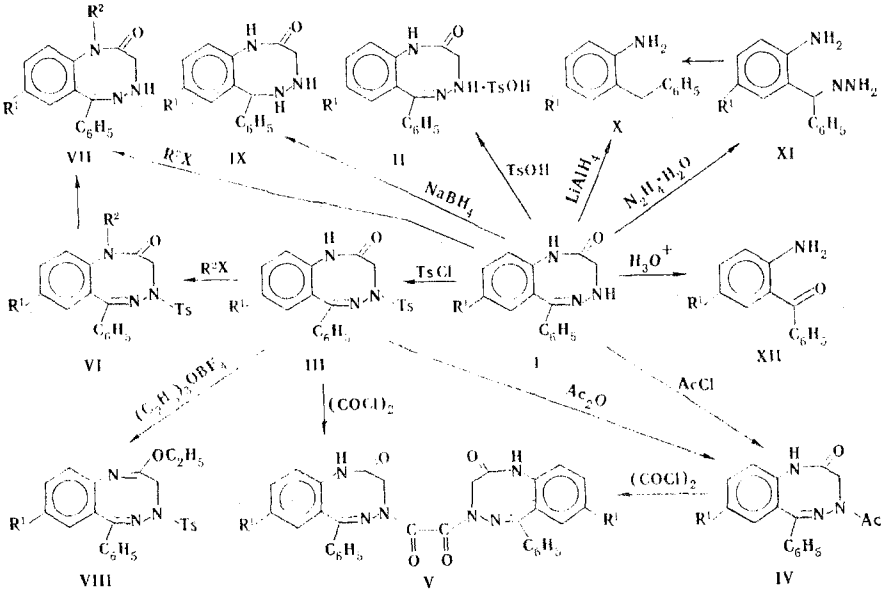
The chemical transformations of 1,2,3,4-tetrahydro-1,4,5-benzotriazocin-2-ones that involve the heteroring, viz., alkylation, acylation, reduction, solvolysis, etc., were studied. Data from the IR, PMR, and mass spectra of the synthesized compounds are presented. The ionization constants of a number of 1,4,5-benzotriazocin-2-ones were determined.

Virtually no study has been devoted to the chemical properties of 1,4,5-benzotriazocines. In the present research we examined some of the chemical transformations of 1,2,3,4-tetrahydro-1,4,5-benzotriazocin-2-ones Ia-d [1] that, on the one hand, serve to characterize their reactivities and, on the other, open up possibilities for the synthesis of new compounds of both the class under consideration and other classes. Reactions were carried out in order to ascertain the character of the nucleophilic and basic behavior of 1,4,5-benzotriazocines I due to the presence of three nitrogen atoms (amide, imine, and amine) and a carbonyl oxygen atom (see the scheme presented below).

It seemed of interest to evaluate the basicities of benzotriazocines and to determine their place in this respect among related heterocycles, viz., 1,2-dihydro-3H-1,4-benzodiazepin-2-ones, quinazolin-2-ones, etc. The relative half-neutralization potentials in potentiometric titration in a nonaqueous medium served as a measure of the basicities. The data obtained are presented in Table 1. 1,4,5-Benzotriazocin-2-ones behave like monacidic bases under the given conditions. A salt of this substance with a base:acid ratio of 1:1 was obtained by refluxing a solution of Ia and p-toluenesulfonic acid in toluene.

In conformity with the general assumptions regarding electronic effects the basicities of benzotriazocines increase on passing from compounds with electron-acceptor substituents (R^1 = Br, Cl) to the 8-unsubstituted compound and then to the 8-methyl derivative. The ioni-



I-V, VIII-XII R^1 = Br

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TABLE 1. Basicities of 1,2,3,4-Tetrahydro-1,4,5-benzotriazocin-2-ones

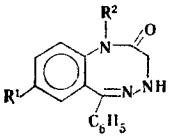
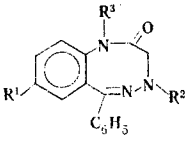
	Compound	R^1	R^2	pK	$-E_{1/2}$, mV
	Ia	Br	H	1,8	225
	Ib	Cl	H	2,0	219
	Ic	H	H	2,6	184
	Id	CH_3	H	2,7	187
	VIIa	Br	CH_3	1,8	224
	VIIb	Cl	CH_3	1,8	225

TABLE 2. 1,2,3,4-Tetrahydro-1,4,5-benzotriazocin-2-ones



Compound	R^1	R^2	R^3	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
					C	H	N		C	H	N	
III	Br	Ts	H	274	54,6	3,7	8,6	$C_{22}H_{18}BrN_3O_3S$	54,5	3,7	8,7	68
IVa	Br	CH_3CO	H	204	54,8	3,7	11,2	$C_{17}H_{14}BrN_3O_2$	54,8	3,8	11,3	89
IVb	Br	C_6H_5CO	H	284	61,0	3,8	9,8	$C_{22}H_{16}BrN_3O_2$	60,8	3,7	9,7	93
IVc	Br	C_5H_5NCO	H	234	57,6	3,3	12,9	$C_{21}H_{15}BrN_4O_2$	57,9	3,4	12,9	79
IVd	Br	$TsNHCH_2CO$	H	311	53,8	4,0	10,5	$C_{24}H_{21}BrN_4O_4S$	53,2	3,8	10,3	88
IVe	Br	$CF_3CONHCH_2CO$	H	268	47,8	2,7	11,3	$C_{19}H_{14}BrF_3N_4O_3$	47,2	2,9	11,2	86
IVf	Br	$CF_3CONH(CH_2)_3CO$	H	282	49,5	3,9	11,0	$C_{21}H_{18}BrF_3N_4O_3$	49,3	3,5	10,9	74
VIa	Br	CH_3	Ts	249	55,7	4,1	8,5	$C_{23}H_{20}BrN_3O_3S$	55,4	4,0	8,4	89
VIb	Cl	CH_3	Ts	248	60,8	4,5	9,3	$C_{23}H_{20}ClN_3O_3S$	60,9	4,4	9,3	87
VIIa	Br	CH_3	H	218	55,8	4,3	12,4	$C_{16}H_{14}BrN_3O$	55,8	4,1	12,2	93
VIIb	Cl	CH_3	H	207	64,2	4,8	14,0	$C_{16}H_{14}ClN_3O$	64,1	4,7	14,0	89
VIIc	Br	$CH_2C_6H_5$	H	187	62,8	4,3	10,0	$C_{22}H_{18}BrN_3O$	62,5	4,2	9,8	94
VIId	Br	$(CH_2)_2N(C_2H_5)_2$	H	137	58,7	5,8	12,9	$C_{21}H_{25}BrN_4O$	58,4	5,8	12,7	73
VIIe	Br	$CH_2CO_2C_2H_5$	H	89	55,0	4,4	10,1	$C_{19}H_{19}BrN_3O_3$	54,8	4,3	10,1	93

zation constants of Ia-d and VIIa,b were found from the relative half-neutralization potentials. With respect to their basicities, benzotriazocines occupy an intermediate position between the stronger quinazolin-2-one bases and the slightly basic 1,4-benzodiazepin-2-ones [2].

The protonation center in benzotriazocines can be determined on the basis of data from the UV spectra in neutral and acidic media. The UV spectra of Ia-d in ethanol contain absorption maxima at 204-206 and 235-240 nm, while the second absorption maximum vanishes in acidic media. Protonation of the amino nitrogen atom in the 4 position disrupts the conjugation chain and leads to disappearance of the long-wave band in the spectrum. If the proton had added to the imino nitrogen atom, the conjugation chain would not have been interrupted, and only a bathochromic shift would have been observed [3].

Using the different nucleophilicities of the heteroatoms in the triazocine ring we were able to carry out the selective alkylation of the most "acidic" amide nitrogen atom (Table 2). The formation of 1-substituted derivative VIIa from Ia was confirmed by synthesis of the former from 4-tosylbenzotriazocine (VIa).

The presence of a secondary amino group in benzotriazocine Ia makes it possible to introduce acyl residues in the 4 position of the heteroring (Table 2); these acyl groups can be replaced by transacylation. Glyoxal derivative V was obtained in this way.

The heteroring can be converted to lactim form VIII by the action of triethyloxonium tetrafluoroborate.

In the reduction of the benzotriazocines either the axomethine bond is saturated to give cyclic hydrazine derivative IX (with sodium borohydride as the reducing agent) or the heteroring is completely disrupted (with lithium aluminum hydride as the reducing agent) to give diphenylmethane derivative X, which was obtained by alternative synthesis from the corresponding hydrazone XI [4].

The benzotriazocines are readily hydrolyzed in aqueous alcohol solutions of mineral acids to 2-aminobenzophenones XII. Hydrazone XI is formed in the hydrazinolysis of Ia; here, as in hydrolysis, the amide bond is cleaved — hydrazine hydrate acts as a deacylating agent — and transhydrazonation takes place simultaneously: The alkylhydrazine residue is replaced by a hydrazine residue.

EXPERIMENTAL

The mass spectra were obtained with a Varian MAT 112 spectrometer. The IR spectra of solutions in chloroform and KBr pellets were recorded with an IKS-29 spectrometer. The PMR spectra of solutions in d_6-DMSO were recorded with a Tesla BS-467C spectrometer (60 MHz). The purity of the compounds was monitored by means of thin-layer chromatography (TLC) on Silufol plates; iodine vapors and UV irradiation were used to develop the chromatograms, and acetone—hexane—chloroform (2:2:1) and chloroform—benzene—ether (1:1:1) systems were used as the eluents.

The half-neutralization potentials were determined by means of an LPM-60M pH meter at 25°C and constant concentrations of the substances; the equivalence points were determined by a differential method. The measuring electrode was an ÉSL-411-05 glass electrode, and the reference electrode was a silver chloride electrode with a saturated KCl solution.

8-Bromo-6-phenyl-1,2,3,4-tetrahydro-1,4,5-benzotriazocin-2-one Tosylate (II). A solution of 1 g (3 mmole) of Ia [1] in 80 ml of toluene was refluxed with 0.6 g (3.5 mmole) of p-toluenesulfonic acid for 1 h, after which it was cooled, and the precipitate was washed with benzene to give 1 g (71%) of tosylate II with mp 259°C (dec.). Found: C 52.4; H 3.8; N 8.3; S 6.7%. $C_{22}H_{20}BrN_3O_4S$. Calculated: C 52.6; H 4.0; N 8.4; S 6.4%.

4-Acetyl-8-bromo-6-phenyl-1,2,3,4-tetrahydro-1,4,5-benzotriazocin-2-one (IVa). A) A 2.4-g (0.03 mole) sample of acetyl chloride was added to a solution of 5 g (0.015 mole) of Ia in 200 ml of chloroform, and the mixture was refluxed for 2 h. It was then cooled and evaporated *in vacuo*, and the residue was recrystallized from ethanol to give 5 g (89%) of IVa with mp 204°C. IR spectrum: 3320 (N—H), 1680 (C=O), and 1620 cm^{-1} (C=N). PMR spectrum: 2.7 (s, 3H), 3.8-4.2 (q, 2H), and 6.7-8.0 ppm (m, 9H). Mass spectrum, m/z: 373, 371, 345, 343, 330, 328, 302, and 300. Compounds III and IVb-f were similarly obtained by acylation of benzotriazocine Ia with tosyl chloride, benzoyl, nicotinyl [5], tosylaminoacetyl [6], trifluoroacetamidoacetyl [7], and trifluoroacetyl-γ-aminobutyryl [7] chlorides.

B) A 1-g (2.1 mmole) sample of III was dissolved in 30 ml of acetic anhydride, and the solution was refluxed for 3 h and evaporated *in vacuo*. Recrystallization of the residue from ethanol gave 0.5 g (65%) of IVa.

1,2-Bis(8-bromo-6-phenyl-1,2,3,4-tetrahydro-1,4,5-benzotriazocin-2-on-4-yl)glyoxal (V). A 1-g (2 mmole) sample of III was refluxed in 5 ml of oxalyl chloride for 2 h, after which it was evaporated *in vacuo*, and the residue was treated with ethanol. Recrystallization of the solid material from ethyl acetate—benzene gave 0.3 g (47%) of V with mp 224°C (dec.). IR spectrum: 3300 (N—H), 3000-3090 (C—H_{arom}), 1675 (C=O), and 1610 cm^{-1} (C=N). Found: C 54.0; H 3.3; N 11.8%. $C_{32}H_{22}Br_2N_6O_4$. Calculated: C 53.8; H 3.1; N 11.8%.

The 1-substituted 1,2,3,4-tetrahydro-1,4,5-benzotriazocin-2-ones (VI, VII) were obtained by a known method [1].

8-Bromo-4-tosyl-6-phenyl-2-ethoxy-3,4-dihydro-1,4,5-benzotriazocine (VIII). A solution of 1 g (2 mmole) of III in 30 ml of methylene chloride was added to a solution of 2 g (10.5 mmole) of triethyloxonium tetrafluoroborate in 20 ml of methylene chloride, and the mixture was stirred at room temperature for 7 h and allowed to stand overnight. A 10-ml sample of a saturated solution of sodium carbonate was added with stirring to the reaction mixture, and the organic layer was separated, washed with water (three 100-ml portions), and evaporated *in vacuo*. The residue was treated with ether to give 0.8 g (83%) of VIII with mp 173°C. IR spectrum: 3000-3080 (C—H_{arom}), 1620 (C=N), 1320 (S—O), 1250 (C—O), and 1150 cm^{-1} (S—O). Mass spectrum, m/z: 513, 511, 468, 466, 358, and 356. Found: C 56.4; H 4.7; N 8.3%. $C_{24}H_{22}BrN_3O_3S$. Calculated: C 56.3; H 4.3, N 8.2%.

8-Bromo-6-phenyl-1,2,3,4,5,6-hexahydro-1,4,5-benzotriazocin-2-one (IX). A 1-g (3 mmole) sample of Ia was dissolved in 50 ml of tetrahydrofuran (THF), and the solution was heated with stirring with 0.4 g (10.5 mmole) of sodium borohydride for 4 h. It was then cooled, treated with 30 ml of water and 30 ml of 0.5 N HCl, and extracted with chloroform (three 50-

ml portions). The extract was evaporated *in vacuo* to give 0.8 g (80%) of IX with mp 202°C. IR spectrum: 3290, 3180 (N–H); 3000-3090 (C–H_{arom}); 1620 cm^{-1} (C=N). Mass spectrum, m/z: 333, 331, 305, 303, 290, and 288. Found: C 54.4; H 4.3; N 12.7%. $C_{15}H_{14}BrN_3O$. Calculated: C 54.2; H 4.2; N 12.7%.

2-Benzyl-4-bromoaniline (X). A) A solution of 0.5 g (1.5 mmole) of Ia in 40 ml of THF was added to a suspension of 0.2 g (5.3 mmole) of lithium aluminum hydride in 20 ml of THF, and the mixture was stirred at room temperature for 4 h. Water (200 ml) was then added with stirring and cooling, and the aqueous mixture was extracted with chloroform (three 20-ml portions). The extract was evaporated *in vacuo*, and the residue was chromatographed on silica gel in a chloroform–benzene–hexane system (1:1:1) to give 0.25 g (63%) of a product with mp 67°C. Found: C 59.9; H 4.8; N 5.1%. $C_{13}H_{12}Br$. Calculated: C 59.5; H 4.6; N 5.3%.

B) A 1-g (3.4 mmole) sample of XI and 0.4 g (10 mmole) of sodium hydroxide were heated in 15 ml of diethylene glycol at 150°C for 1 h, after which the mixture was cooled and treated with 50 ml of chloroform and 500 ml of water. The organic layer was separated, washed with water (three 200-ml portions), and evaporated *in vacuo*. The residue was chromatographed on silica gel in a chloroform–benzene–hexane system (1:1:1) to give 0.5 g (59%) of product.

2-Amino-5-bromobenzophenone Hydrazone (XI). A 10-ml sample of 99% hydrazine hydrate was added to 0.5 g (1.5 mmole) of Ia, and the mixture was heated to the boiling point and poured into 200 ml of water. The precipitate was removed by suction filtration and washed with water to give 0.4 g (91%) of XI with mp 161°C [4].

2-Amino-5-bromobenzophenone (XII). A 0.5-g (1.5 mmole) sample of Ia was dissolved at 80°C in a mixture of 10 ml of ethanol and 10 ml of concentrated HCl, and the mixture was poured into water to give 0.37 g (90%) of XII with mp 109°C [8].

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