SPECIFICITY IN THE FORMATION OF A SEVEN-MEMBERED RING IN THE SYNTHESIS OF DIHYDRO-1,5-BENZODIAZEPINONES FROM AROMATIC DIAMINES

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UDC 547.785.5'892:543.422.25.4.6

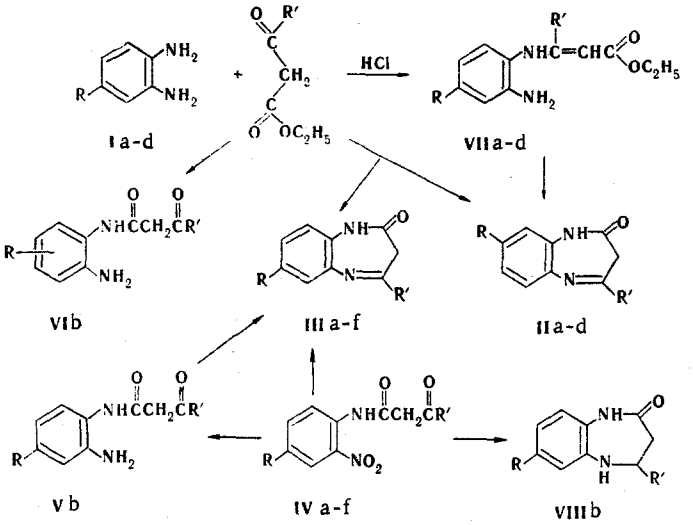
It is shown that a mixture of 7- and 8-substituted 2,3-dihydro-1,5-benzodiazepinones is formed in the reaction of unsymmetrical aromatic diamines (4-chloro-, 4-methyl-, and 4-methoxy-o-phenylenediamines) with acetoacetic and benzoylacetic esters under severe conditions. The corresponding anilide of benzoylacetic acid, the cyclization of which again leads to a mixture of isomeric dehydrobenzodiazepinones, can be isolated (in the case of benzoylacetic ester) when the concentrations of the reacting substances and the reaction time are decreased; this makes it possible to assume amidation of the β-keto acids as one of the steps in the high-temperature synthesis of dihydrobenzodiazepinones. The quantitative ratio of the isomers formed in the reaction was determined by UV spectroscopy. The UV, IR, and PMR spectral data are presented.

The problem concerning the products of the reaction of unsystematical aromatic diamines with β-keto esters has been discussed repeatedly in the literature. In a number of studies it has been shown that the more electrophilic carbonyl carbon atom reacts with the most basic nitrogen atom under relatively mild conditions to give the corresponding arylaminocrotonate, cyclization of which leads to a dihydro-1,5-benzodiazepin-2-one [1, 2]. The reaction proceeds in a more complex manner under severe conditions, and 1-isopropenylbenzimidazol-2-ones [3, 4] and 2-methylbenzimidazolones [5] can be isolated along with dihydrobenzodiazepinones. In addition, the available data indicate that the dihydro-1,5-benzodiazepinones also have different structures. In some cases the structure corresponds to the reaction of the carbonyl group [6, 7], while in others it corresponds to reaction of the carbethoxy group [4, 8, 9] of the β-keto ester with the more basic amino group. Examples in which both isomeric dihydrobenzodiazepinones have been isolated have been described [10, 11]. We therefore felt it was necessary to investigate this reaction in detail to correctly evaluate the structure of the dihydro-1,5-benzodiazepinone obtained under the conditions of the high-temperature synthesis (see scheme on next page).

The 7-chloro-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one structure was previously assigned [8] to the substance (mp 206°C) isolated in the reaction of 4-chloro-o-phenylenediamine (Ib) with benzoylacetic ester in refluxing xylene. However, we were able to demonstrate that this compound is a mixture of two substances with only slightly different R_f values, which we were able to separate by chromatography on aluminum oxide. The IR spectra of both compounds contain bands of stretching vibrations of an amide C=O group (1670-1680 cm^{-1}), and the UV spectra contain absorption maxima at 245 and 320 nm, which are characteristic for the azomethine grouping [12]. All of this indicates dihydrobenzodiazepine structures IIb and IIIb.

The position of the substituents in IIb and IIIb was proved by comparison with samples with authentic structures. 8-Chloro-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IIb) is formed from ethyl 3-(2-amino-4-chloroanilino)cinnamate (VIIb) by heating in sodium ethoxide. Ester VIIb was obtained by the action of benzolacetic ester on 4-chloro-o-phenylenediamine in the presence of catalytic amounts of hydrochloric acid. We obtained the isomeric 7-chloro-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IIIb) through a step involving the formation of the o-nitro-p-chloroanilide (IVb) of benzoylacetic acid and subsequent reduc-

Dnepropetrovsk State University, Dnepropetrovsk 320625. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 834-838, June, 1977. Original article submitted September 1, 1976.



I—IV a R=H, R′=C_6H_5; I—VIII b R=Cl, R′=C_6H_5; I—IV, VII c R=CH_3, R′=C_6H_5; d R=OCH_3, R′=CH_3; III—IV e R=CH_2, R′=CH_3; f R=Cl, R′=CH_3

tive cyclization over Raney nickel. The possibility of the formation of a tetrahydrobenzodiazepinone under reductive cyclization conditions is indicated in the patent literature [13]. We actually isolated 7-chloro-4-phenyl-1H-2,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (VIIIb) and benzoylacetic acid o-amino-p-chloranilide (Vb) along with IIIb by column chromatography of the reaction mixture. There is no doubt about the structure of Vb, since heating it in xylene gives pure IIIb, as confirmed by the melting points, the R_f values, and the VU spectra.

When we changed the conditions of the high-temperature reaction between Ib and benzoylacetic ester (by decreasing the concentrations of the reactants and the reaction time), in addition to the isomeric dihydrobenzodiazepinones IIb and IIIb, we were able to isolate a substance with an IR spectrum that contains two intense bands at 1726 and 1685 cm^{-1}, which correspond to two carbonyl groups in the benzoylacetanilide derivatives [14]; this constitutes evidence that IVb is an anilide of benzoylacetic acid. At the same time, cyclization of the latter in xylene, which gives a mixture of dihydrobenzodiazepinones IIb and IIIb, provides a basis for the assumption that one of the steps in the high-temperature synthesis involves the formation of products of amidation of the β-keto acids.

Isomeric dehydrobenzodiazepinones IIb and IIIb can be distinguished from their UV spectra if the intensities of the maxima at 245 and 320 nm, which are sensitive to the position of the substituent in the benzene ring, are selected as the criterion. It is apparent from the data in Table 1 that the short-wave maximum is more intense in the spectrum of the 7 isomer (IIIb), whereas the long-wave maximum is more intense in the spectrum of the 8 isomer (IIb). At the same time, the product of the reaction of Ib with benzoylacetic ester has maximum intensities that lie within the regions whose extreme points are bounded by the

TABLE 1. 2,3-Dihydro-1H-1,5-benzodiazepin-2-ones

Compound	R	R′	mp, °C	R_f*	Found, %		Empirical formula	Calc., %		UV spectra, λ_{max}, ($\varepsilon \cdot 10^{-3}$)	Yield, %
					C	H		C	H		
IIa	H	C_6H_5	210	0.26	75,9	4.9	$C_{15}H_{12}N_2O$	76,3	5,1	240 (22.7), 310 (9,7)	87
IIb	Cl	C_6H_5	217	0.58	66.2	3,9	$C_{15}H_{11}ClN_2O$	66,5	4,1	242 (22,9), 320 (9,9)	85
IIIb	Cl	C_6H_5	230	0,50	66,7	4,3	$C_{15}H_{11}ClN_2O$	66,5	4,1	245 (28,6), 320 (8,0)	65
IIc	CH_3	C_6H_5	213	0,29	76,5	5,2	$C_{16}H_{14}N_2O$	76,8	5,6	245 (20,7), 320 (10,2)	81
IIIc	CH_3	C_6H_5	225	0.25	76.7	5,3	$C_{16}H_{14}N_2O$	76,8	5,6	245 (24,1), 320 (8,55)	60
IId	OCH_3	CH_3	185	0,19	64.5	5.8	$C_{11}H_{12}N_2O_2$	64.7	5,9	217 (34,1)	82
IIId	OCH_3	CH_3	127	0.22	64,4	5,4	$C_{11}H_{12}N_2O_2$	64,7	5,9	215 (31,4), 238 (15,6)	56
IIIe	CH_3	CH_3	184	0.40	70,0	6,1	$C_{11}H_{12}N_2O$	70,2	6,4	213 (35,9), 230 † (18,9)	38
IIIf	Cl	CH_3	183	0,35	57,2	4,1	$C_{10}H_9N_2O$	57,6	4,3	214 (34,8), 235 (18,75) †	32

*Thin-layer chromatography on activity II Al_2O_3, elution with hexane saturated with alcohol.

†Shoulder.

TABLE 2. Ethyl Arylaminocrotonates and Cinnamates

Compound	R	R′	mp, °C	Found, % C	Found, % H	Empirical formula	Calc., % C	Calc., % H	PMR spectral data,* δ, ppm	Yield, %
VIIa	H	C_6H_5	136	72,2	6.2	$C_{17}H_{18}N_2O_2$	72,4	6,4	t 1,30 (CH_3), q 4,13 (CH_2), s 5,0 (CH), s 3,63 (NH_2)	70
VIIb	Cl	C_6H_5	158	64,1	5,1	$C_{17}H_{17}ClN_2O_2$	64,5	5,4	t 1,23 (CH_3), q 4,13 (CH_2), s 4,95 (CH), s 3,76 (NH_2)	83
VIIc	CH_3	C_6H_5	165	72,9	6.6	$C_{18}H_{20}N_2O_2$	72,9	6,8	t 1,25 (CH_3), q 4,21 (CH_2), s 5,06 (CH), s 3,81 (NH_2), s 2,11 (CH_3—Ar)	54
VIId	OCH_3	CH_3	86	57,4	8,0	$C_{13}H_{18}N_2O_3$	57,5	8,0	t 1,20 (CH_3), q 4,07 (CH_2), s 4,57 (CH), s 3,74 (NH_2), s 3,60 (CH_3O)	84

*The solvent was chloroform.

TABLE 3. Benzoylacetic and Acetoacetic Acid Arylamides

Compound	R	R′	mp, °C	Reaction time, h	Found, % C	Found, % H	Empirical formula	Calc., % C	Calc., % H	UV spectra, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	Yield, %
IVb	Cl	C_6H_5	122	18	56,8	3,7	$C_{15}H_{11}ClN_2O_4$	56,5	3,5	240 (18,9), 256 (17,9)	36
IVc	CH_3	C_6H_5	142	5	64,4	4,7	$C_{16}H_{14}N_2O_4$	64,6	4,7	231 (14,4), 245 (18,6)	51
IVd	OCH_3	CH_3	81	4	51,3	4,0	$C_{11}H_{12}N_2O_5$	51,7	4,3	235 (15,8)	38
IVe	CH_3	CH_3	105	7	55,0	5,1	$C_{11}H_{12}N_2O_4$	55,9	5,1	232 (15,1)	41
IVf	Cl	CH_3	87	18	46,5	3,7	$C_{10}H_9ClN_2O_4$	46,8	3,5	236 (17,0)	41

intensities of the maxima of isomers IIb and IIIb. This makes it possible to make a quantitative evaluation of the isomer ratios by the method in [15] (Table 4).

The formation of a mixture of isomeric dihydrobenzodiazepin-2-ones (IIa-f and IIIa-f) was established in all cases in the analogous condensation of other 4-R-o-phenylenediamines (where R = CH_3, Cl, and OCH_3) and β-keto esters (acetoacetic and benzoylacetic) in xylene. The isomer ratio in the mixture, which was obtained by analysis of the UV spectra of the reaction product and the corresponding 7- and 8-substituted dihydrobenzodiazepinones, is presented in Table 4. Genuinely pure samples of IIa-f and IIIa-f were synthesized in accordance with the above scheme. Data confirming the structures of the intermediates and the physical constants and yields of the compounds are presented in Tables 2 and 3.

Compounds IIa-d and IIIb-f were characterized as dihydrobenzodiazepinones by means of their PMR and UV spectra. The PMR spectra of IIId-f in trifluoroacetic acid contain signals of methylene (3.8-3.7 ppm) and methyl (2.8-3.0 ppm) protons, and aromatic ring protons appear in the form of a multiplet at 7.0-7.5 ppm. Absorption bands at 240-245 and 310-320 nm corresponding to the dihydrobenzodiazepine structure are present in the UV spectra of IIb, c and IIIa-c.

The authors thank Professor A. N. Kost for his advice and assistance in carrying out this research.

EXPERIMENTAL

The IR spectra of the KBr pellets of the compounds were recorded with a UP-20 spectrometer. The PMR spectra of chloroform and trifluoroacetic acid solutions of the compounds were obtained with a Varian T-60 spectrometer with hexamethyldisiloxane as the external standard. The electronic spectra were measured with an SF-16 spectrophotometer. The percentage composition of the mixture of isomers obtained in the high-temperature synthesis was determined spectrophotometrically. Alcohol was used as the solvent to record the UV spectra of compounds containing a phenyl group in the seven-membered ring, and hydrochloric acid solutions with pH 0 were used to record the UV spectra of the 4-methyldihydro-1,5-benzodiazepinones.

Compounds IIe, f were synthesized by the methods in [4, 2], and their purity was confirmed by TLC data.

Ethyl 3-(2-Amino-4-R-anilino)cinnamate and Crotonates (VIIa-d). These compounds were synthesized by the method in [2]. The reaction time for the preparation of VIIA-c was in-

TABLE 4. Ratios of Isomeric Dihydrobenzodiazepinones

Starting compounds		Ratio of isomers III to II in percent in the product of condensation of 4-R-o-phenylenediamine with acetoacetic ester
4-R-o-phenylenediamine	β-keto ester	
R=Cl	benzoyl(aceto)acetic ester	54 : 46
$R=CH_3$	Acetoacetic ester	63 : 37
$R=CH_3$	Benzoylacetic ester	54 : 46
R=Cl	Acetoacetic ester	63 : 37
$R=OCH_3$	The same	72 : 28

creased to 10 days. The products were purified by recrystallization from ether–hexane (see Table 2).

Acetoacetic and Benzoylacetic Acid Anilides (IVb-f). A solution of the appropriate 2-nitro-4-R-aniline (0.02 mole) in 500 ml of xylene was added dropwise to a refluxing solution of 0.1 mole of benzoyl- or acetoacetic ester in 40 ml of xylene; the xylene was removed constantly by distillation during the addition at such a rate that the volume of the reaction mixture was 60-70 ml. At the end of the reaction, the solution was cooled, and the precipitate was removed by filtration, washed with ether, and crystallized from propyl alcohol. The reaction times, yields, and physical constants of the products are indicated in Table 3.

Condensation of Unsymmetrical o-Phenylenediamines with β-Keto Esters in Xylene. A) The condensation with acetoacetic ester was carried out as described in [4], and the condensation with benzoylacetic ester was carried out as described in [8]. The resulting mixture of benzodiazepinones IIb and IIIb was separated preparatively on aluminum oxide, whereas II and IIIc-f were identified from their R_f values and UV spectra. The characteristics of the substances and the isomer ratios are presented in Table 4.

B) A solution of 0.01 mole of benzoylacetic ester in 20 ml of xylene was added dropwise to a refluxing solution of 0.01 mole of 4-chloro-o-phenylenediamine in 100 ml of xylene, and the mixture was refluxed for 10 min. It was then cooled, and the resulting precipitate was removed by filtration. The mixture of products (1.1 g) was chromatographed with a column filled with Al_2O_3 [elution with chloroform and chloroform–alcohol (1:1)] to give a mixture of IIb and IIIb in 18% yield and a mixture (VIb) of o-amino-p-chloro- and o-amino-m-chloroanilides of benzoylacetic acid in 14% yield. The latter mixture could not be separated into individual substances and had mp 171-175°. Found: C 62.8; H 4.2%. $C_{15}H_{13}ClN_2O_2$. Calculated: C 62.4; H 4.5%.

A mixture [0.2 g (74%)] of 7- and 8-chlorobenzodiazepin-2-ones, with mp 201-206° (from alcohol), was formed when a solution of 0.28 g (0.001 mole) of mixture VIb in 5 ml of xylene was refluxed for 1 h. This mixture was identical to the mixture obtained by method A.

4-R'-8-R-2,3-Dihydro-1H-1,5-benzodiazepin-2-ones (IIa-d). These compounds were synthesized from esters VIIa-d by the method in [2]; the characteristics of the substances are presented in Table 1. Compounds IIa-c were crystallized from alcohol, and IId was crystallized from toluene. No melting-point depression was observed for a mixture of IIb with a sample of IIb isolated preparatively by method A; the two samples also had identical IR spectra.

4-R'-7-R-2,3-Dihydro-1H-1,5-benzodiazepin-2-ones (IIIb-f). Compounds IVb-f (5 mmole) were hydrogenated in 15 ml of absolute alcohol over Raney nickel. After the calculated amount of hydrogen had been absorbed, the catalyst was removed by filtration, the solvent was removed by vacuum distillation, and the residue was chromatographed with a column filled with aluminum oxide (elution with chloroform). Compounds IIId-f were eluted with the first fraction and were crystallized from toluene. In the synthesis of IIIa-f, the precipitate was removed by filtration and washed on the filter with three 50-ml portions of chloroform. The chloroform was removed, and the residue was crystallized from alcohol. Compound IIIb had the same IR spectrum and melting point as IIIb isolated preparatively by method A.

Benzoylacetic Acid o-Amino-p-chloroanilide (Vb). Compound IVb was hydrogenated as described above. At the end of the reaction, the catalyst was washed with 30 ml of hot alcohol, the solvent was removed from the alcohol filtrate, and the residue was chromatographed with a column filled with Al_2O_3 [with successive elution with chloroform and chloroform–alcohol systems (20:1; 1:1)] to give 7-chloro-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-

one in 65% yield, 7-chloro-4-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one in 5% yield [mp 161°, from benzene. Found: C 66.1; H 5.0%. $C_{15}H_{13}ClN_2O$. Calculated: C 66.0; H 4.8%. IR spectrum: 1665 cm^{-1} (CO). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 230 (40.6); and 260 nm (7.4)] and benzoylacetic acid o-amino-p-chloroanilide in 12% yield (mp 185°. Found: C 62.4; H 4.2%. $C_{15}H_{13}ClN_2O_2$. Calculated: C 62.4; H 4.5%).

Cyclization of Benzoylacetic Acid o-Amino-p-chloroanilide. A 0.28-g (1 mmole) sample of Vb was heated in 5 ml of xylene for 1 h, after which the mixture was cooled, and the resulting precipitate was removed by filtration and dried to give 0.19 g (70%) of a product with mp 229° (from alcohol). The product had the same IR spectrum as IIIb isolated preparatively by method A and did not depress its melting point.

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