BROMO DERIVATIVES OF 4-PHENYL-2,3-DIHYDRO-1H-1,5-BENZODIAZEPIN-2-ONE

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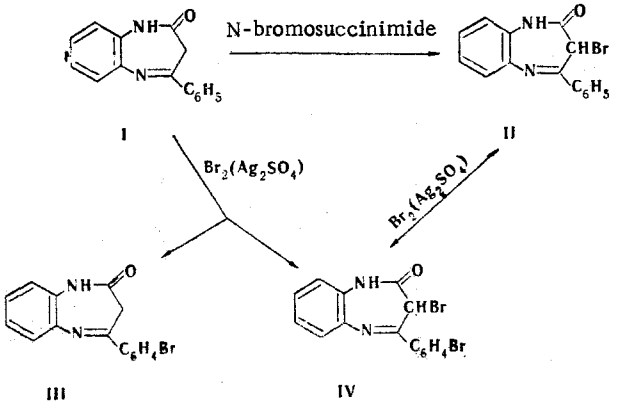
Monobromo and dibromo derivatives were synthesized by bromination of 4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one with bromine under various conditions and with N-bromosuccinimide in CCl_4. 7-Bromo- and 8-bromo-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones were obtained by condensation of 4-bromo-o-phenylenediamine with benzoylacetic ester in refluxing xylene. The UV and PMR spectra of the products are discussed.

It has been observed [1] that the bromination of 4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one proceeds primarily at the methyl group in the 4 position. The bromination of 4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (I) is of special interest for the establishment of the effect of the phenyl group on the orientation of electrophilic substitution.

It has been reported [2] that this diazepinone is brominated in the 3 position by molecular bromine (on the basis of IR spectral data), and it was assumed that the reaction proceeds by addition of two bromine atoms to the double bond with subsequent splitting out of hydrogen halide.

We have investigated the bromination of dihydrobenzodiazepinone I with various brominating agents. Bromination with an equimolar amount of N-bromosuccinimide (NBS) in carbon tetrachloride leads to the formation of 3-bromo-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (II).



Excess reagent does not lead to the formation of new substances, but the yield of bromo derivative II increases appreciably in the presence of benzoyl peroxide.

Bands of stretching vibrations of free and associated NH groups at 3180-3400 cm^{-1} and absorption bands of amide and C=N groups at 1675 and 1610 cm^{-1}, respectively, are observed in the IR spectrum of II.

Since a structure with a double bond between the 3 and 4 carbon atoms was previously [2] assumed *a priori* for diazepinone I, we compared the PMR spectra of I and II in deuterodimethyl sulfoxide. Signals of methylene (3.43 ppm), aromatic (7.18-8.17 ppm), and imino (10.65 ppm) protons are observed in the spectrum of I. The character of the spectrum and the ratio of the integral intensities (9:2:1) confirm a 2,3-dihydro-1H-1,5-benzodiazepin-2-one structure

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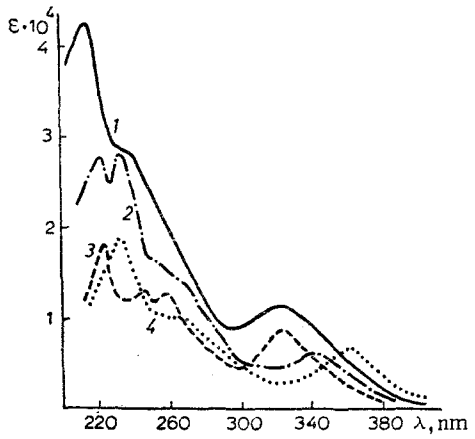


Fig. 1. UV spectra: 1) 4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one; 2) 3-bromo-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one; 3) 4-(p-bromophenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one; 4) 3-bromo-4-(p-bromophenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one.

rather than a 2,5-dihydro-structure [2]. Diazepinone II, the PMR spectrum of which contains, in addition to a multiplet of aromatic protons (7.23-8.16 ppm) and NH protons (11.25 ppm), a singlet of a methylidyne proton at 6.05 ppm, the paramagnetic shift of which is explained by the effect of the adjacent phenyl ring and the bromine atom, also has an identical structure.

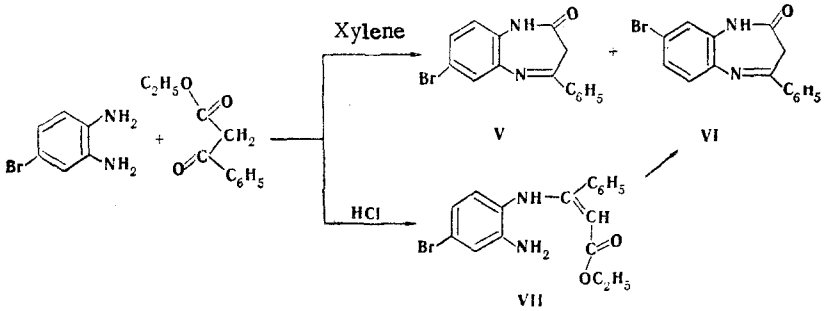
The UV spectrum of diazepinone I contains an intense absorption maximum at 218 nm and a low-intensity absorption maximum at 322 nm; this is characteristic for systems of this type [3]. The introduction of a bromine atom in the diazepine portion of the molecule leads to splitting of the absorption maxima at 222 and 232 nm and an appreciable bathochromic shift (18 nm) of the long-wave band, which is accompanied by a hypsochromic effect.

When diazepinone II is heated with sulfuric acid, it undergoes recyclization [4] to benzimidazolone and phenacyl bromide.

The bromination of I with molecular bromine in media with different acidities (in acetic and sulfuric acids and in mixtures of these acids) also leads to bromo derivative II. Thus for the protonated and unprotonated form of the I molecule the direction of electrophilic substitution in bromination, in contrast to nitration, is determined to a considerable extent by the character of the substituent in the 4 position.

If bromination is carried out with gaseous bromine in the presence of silver sulfate by the method in [5], two substances – monobromo derivative (III) and a dibromo derivative (IV) – can be isolated. It is known [6] that the nitration of 4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one leads to the formation of a 7-nitro derivative; this was the basis for the assumption of a similar orientation of bromine incorporation in our case.

In this connection, we accomplished the synthesis of 7-bromo- (V) and 8-bromo-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (VI). The indicated isomers were obtained in boiling xylene from 4-bromo-o-phenylenediamine and benzoylacetic ester.



We were able for the first time to separate the mixture of isomers (formed in a ratio of 4:1) by preparative chromatography. The same mixture [7] of isomers from 4-bromo-o-phenylenediamine and benzoylacetic ester was previously assumed to be an individual substance. Benzodiazepinone VI was also synthesized by cyclization of ethyl-3-(4-bromo-2-aminoanilino)cinnamate (VII) in the presence of sodium ethoxide.

The IR spectra of diazepinones V and VI are similar to one another and to the spectrum

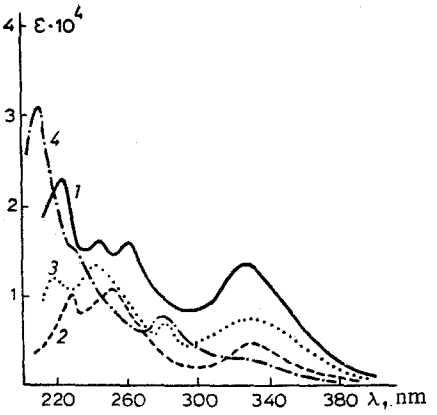


Fig. 2. UV spectra: of 7-bromo-2,3-dihydro-1H-1,5-benzodiazepin-2-one (2, 3) and 8-bromo-2,3-dihydro-1H-1,5-benzodiazepin-2-one (1, 4): 1) and 2) in ethanol; 3) and 4) in acidic ethanol (pH 1.15).

of I. The UV spectra of the isomers differ substantially which makes it possible to use them for identification. The spectrum of 7-isomer V differs from the spectrum of monobromo derivative II only with respect to the appreciable hypsochromic effect. However, the participation of bromine in the conjugated system of the chromophore leads to splitting of the second band and to an appreciable bathochromic effect in the case of V 8-isomer (see Fig. 1). In acidic media (pH 1.15) protonation of the azomethine fragment leads to a decrease in the intensity of the long-wave band and to the appearance of a weak absorption band at ∿ 280 nm. In addition, disappearance of one absorption maximum is observed in the spectrum of 8-isomer VI in the short-wave region; this does not occur in the case of 7-isomer V (Fig. 2). The V, VI, and III bromo derivatives with the $C_{15}H_{11}BrN_2O$ composition were found to be different substances. A singlet of methylene protons at 3.55 ppm is observed in the PMR spectrum of III; this constitutes evidence for substitution of the hydrogen atom in the phenyl ring, whereas the formation of p-bromoacetophenone by acid cleavage of III confirms incorporation of bromine in the para position of the phenyl group. In the presence of a catalyst that facilitates the development of a bromine cation III and IV are formed in 85 and 13% yields, respectively. Diazepine IV was obtained in low yield (20%) by bromination of III, while the same reaction with 3-bromo derivative II gives IV in 98% yield. When silver sulfate is absent, II is not brominated under the investigated conditions. The PMR spectrum of dibromodiazepinone IV (in trifluoroacetic acid) contains a 3-H singlet (5.94 ppm) and a multiplet of aromatic protons (6.94-7.81 ppm). p-Bromophenacyl bromide was isolated when IV was heated with sulfuric acid, and this confirms the IV structure.

The UV spectra of diazepinones III and IV differ. The spectrum of III is more similar to the spectrum of 8-bromo derivative V and also has four absorption maxima, since in this case bromine is included in the conjugated system. The incorporation of another bromine atom in this molecule in the 3 position leads to disappearance of one of the absorption maxima and a bathochromic shift.

Bromination of dihydrobenzodiazepinone I in the presence of silver sulfate consequently proceeds primarily in the phenyl ring, and the presence of bromine in the 3 position appreciably facilitates attack in the para position of this group. Protonation of the seven-membered heteroring evidently deactivates the benzene ring of the dihydrobenzodiazepinone molecule markedly, lowers the electron density on 7-C, and thereby facilitates the incorporation of bromine in the side chain.

Thus the orientations of incorporation of a substituent were found to be different in nitration and bromination; this is probably explained by the different spatial requirements of the reagents in nitration and bromination [5].

EXPERIMENTAL

The IR spectra of KBr pellets of I-VI were recorded with a UR-20 spectrometer at 400-3700 cm^{-1}. The UV spectra of ethanol solutions of the compounds were obtained with a Specord UV-vis spectrophotometer. The PMR spectra of solutions of the compounds in trifluoroacetic acid and deuterodimethyl sulfoxide were obtained with a Tesla B-487B spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The course of the reactions and the purity of the compounds obtained were monitored by thin-layer chromatography (TLC) on Silufol plates in a benzene–ethyl acetate system (7:3). Isomers V and VI were separated with a chromatographic column in the same solvent system with an automatic fraction collector. The physical

TABLE 1. Bromo Derivatives of 4-Phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one

Compound	mp, °C	Found, %				Empirical formula	Calc., %			
		C	H	Br	N		C	H	Br	N
II	188	57,2	3,5	25,5	8,8	$C_{15}H_{11}BrN_2O$	57,1	3,5	25,4	8,9
III	210—211	57,2	3,5	25,4	8,9	$C_{15}H_{11}BrN_2O$	57,1	3,5	25,4	8,9
IV	207—208	45,8	2,5	40,6	7,0	$C_{15}H_{10}Br_2N_2O$	45,7	2,5	40,6	7,1
V	240—241	57,1	3,5	—	—	$C_{15}H_{11}BrN_2O$	57,1	3,5	—	—
VI	215—216	57,1	3,5	—	—	$C_{15}H_{11}BrN_2O$	57,1	3,5	—	—

constants of the compounds are presented in Table 1.

3-Bromo-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (II). A) A mixture of 2.3 g (0.01 mole) of 4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (I), obtained by the method in [8], 40 ml of carbon tetrachloride, and 1.93 g (0.01 mole) of N-bromosuccinimide (NBS) was refluxed for 6 h, after which the precipitated succinimide was removed by filtration, and the filtrate was cooled. The yellow crystals that formed after a short time were removed by filtration and recrystallized from ethanol. The yield was 1.8 g (55%).

B) The reaction was carried out as in experiment A, but catalytic amounts of benzoyl peroxide were added. The yield was 2.4 g (76%).

C) A solution of 2.3 g (0.015 mole) of bromine in 5 ml of acetic acid was added to a solution of 2.3 g (0.01 mole) of dihydrobenzodiazepinone I in 20 ml of H_2SO_4, and the mixture was stirred at room temperature for 6 h. It was then poured over ice, and the precipitated crystals were separated and recrystallized from ethanol. The yield was 2.68 g (85%).

D) A solution of 1.6 g (0.01 mole) of bromine in 5 ml of acetic acid was added with stirring to a solution of 2.3 g (0.01 mole) of diazepinone I in 25 ml of acetic acid, and the precipitate was separated and recrystallized from ethanol. The yield was 1.9 g (69%).

4-(p-Bromophenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one (III). Gaseous bromine was blown with vigorous stirring into a mixture of 1 g (0.005 mole) of diazepinone I in 15 ml of sulfuric acid and 0.85 g of silver sulfate, after which stirring was continued for 6-7 h. The mixture was then poured over ice, and the precipitate was removed by filtration and recrystallized from ethanol to give 0.25 g (12.7%) of IV. The filtrate was neutralized to pH 7 with KOH solution, and the precipitated crystals were removed by filtration and recrystallized from ethanol–water (2:1). The yield of III was 1.34 g (85.5%).

3-Bromo-4-(p-bromophenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IV). A total of 1.8 g (0.0113 mole) of gaseous bromine was added to a solution of 0.8 g (0.0025 mole) of II in 10 ml of sulfuric acid and 0.425 g of silver sulfate, and the mixture was stirred for 6 h. It was then poured over ice, and the precipitate was separated and recrystallized from ethanol to give 0.975 g (98%) of IV.

Ethyl 3-(2-Amino-5-bromophenylamino)cinnamate (VII). A 2.88-g (0.015 mole) sample of benzoylacetic ester and one drop of concentrated HCl were added to 1.87 g (0.01 mole) of 4-bromo-o-phenylenediamine, and the mixture was stirred at room temperature and allowed to stand for 5 days. It was then washed with ethanol, and the precipitate was separated and recrystallized from ethanol to give 2.3 g (63.3%) of a product with mp 171-172°C. Found, %: C 56.4; H 4.7; H 7.8. $C_{17}H_{17}BrN_2O_2$. Calculated, %: C 56.5; H 4.7; N 7.7.

8-Bromo-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VI). A 3.6-g (0.01 mole) sample of ester VII was added to a solution of sodium ethoxide (from 0.28 g of sodium and 10 ml of absolute ethanol), and the mixture was refluxed for 1.5 h. The alcohol was removed, and the residue was poured into 50 ml of water. The aqueous mixture was neutralized to pH 6 with acetic acid, and the precipitated crystals were removed by filtration and recrystallized from ethanol. The yield was 3 g (83%).

7- (V) and 8-Bromo-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (VI). A mixture of 1.4 g (0.008 mole) of 4-bromo-o-phenylenediamine, 1,45 g (0.009 mole) of benzoylacetic ester, and 65 ml of xylene was refluxed with a Dean–Stark adapter for 2 h, after which it was cooled,

and the precipitated crystals were removed by filtration. The mixture of 7- and 8-bromo isomers was separated by preparative chromatography on silica gel in a benzene–ethyl acetate system (7:3). Benzodiazepinone V had R_f 0.53 and mp 240-241°C. Benzodiazepinone VI had R_f 0.68 and mp 215-216°C.

Hydrolysis of 3-Bromo-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one. A 0.15-g (0.0005 mole) sample of diazepinone II was refluxed in 5 ml of 2 N H_2SO_4 for 5 h, and the precipitate was removed by filtration and washed with ether. The ether was removed by distillation to give phenacyl bromide with mp 51°C.

Hydrolysis of 3-Bromo-4-(p-bromophenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one. This reaction was carried out as in the preceding experiment. Workup gave p-bromoacetophenone with mp 109°C.

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