BROMINATION OF 4-(p-METHOXYPHENYL)-2,3-DIHYDRO-1H-1,5-BENZODIAZEPIN-2-ONE

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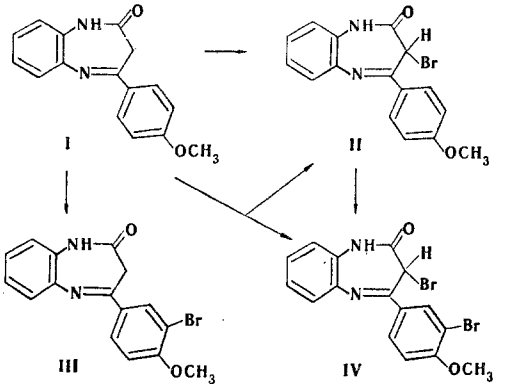
Mono- and dibromo derivatives were obtained in the bromination of 4-(p-methoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one in media with different acidities with N-bromosuccinimide in carbon tetrachloride. The UV, PMR, and mass spectra of the compounds obtained are discussed.

It has been previously shown [1] that the bromination of 4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one takes place at the methylene group, i.e., in the 3 position. We studied the halogenation of 4-(p-methoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one (I) with various halogenating agents. The introduction of a substituent increases the electron density on the C_8 atom and may facilitate incorporation of bromine in both the ring and in the ortho position relative to the methoxy group. It was found that bromination with an equimolar amount of N-bromosuccinimide (NBS) or an excess of NBS in carbon tetrachloride, including also in the presence of benzoyl peroxide, gives, as in the case of unsubstituted diazepinone, 3-bromo-4-(p-methoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one (II).

The IR spectrum of II contains high-intensity absorption bands of an NH bond at 3080-3200 cm^{-1} and of C=N and amide bonds at 1610 and 1675 cm^{-1}; this is characteristic for such systems [2]. The signals of the methyl (4.11 ppm), methylidyne (6.25 ppm), and aromatic (7.20-8.20 ppm) protons in the PMR spectrum confirm the assigned structure.



The UV spectrum of diazepinone I (Fig. 1, curve 1) contains four intense absorption maxima at 213, 240, 264, and 320 nm. A comparison with the previously described [3] spectrum of 4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one provides a basis for the assumption that the appearance of an additional absorption maximum at 264 nm is due to the presence of a methoxy group. The introduction of a bromine atom in the 3 position of II (Fig. 1, curve 2) results in the disappearance of the two absorption maxima at 240 and 264 nm, and a hypsochromic shift and a hyperchromic effect of the bands at 220 and 310 nm are observed.

The mass spectrum of II contains a molecular-ion peak* [M^+] at 344-346. In contrast to 3-unsubstituted benzodiazepin-2-ones, the molecular ion undergoes fragmentation in two directions, viz., with successive splitting out of CHBrCO and CH_3 groups, which confirms the

*Here and subsequently, the m/e values are given for the ion peaks, and the relative intensities are presented in parentheses.

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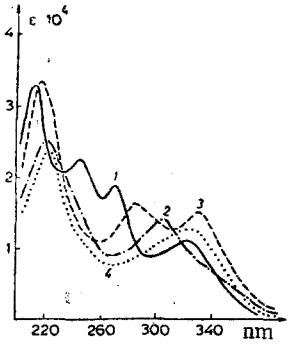
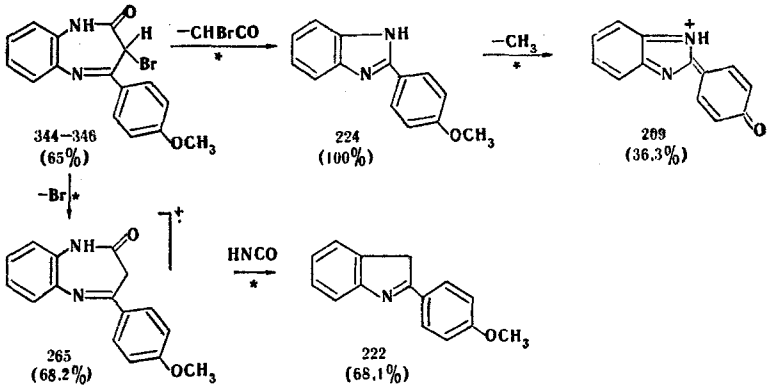


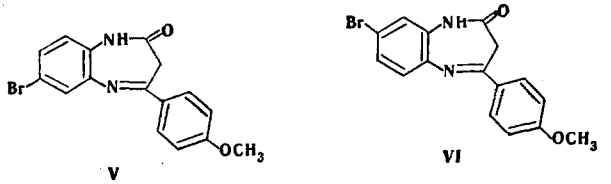
Fig. 1. UV spectra of 2,3-dihydro-1H-1,5-benzodiazepin-2-ones (in ethanol): 1) I; 2) II; 3) III; 4) IV.

presence of a bromine atom in the 3 position, and with splitting out of a bromine atom and an HNCO molecule. These fragmentation pathways are confirmed by metastable transitions.



The bromination of diazepinone I with gaseous bromine in the presence of silver sulfate gives monobromide III, the UV spectrum of which contains three absorption maxima at 220, 286, and 330 nm. The presence of three absorption maxima that differ with respect to their bathochromic shifts and hyperchromic effects as compared with the spectrum of I provides a basis for the assumption that bromine does not enter the 3 position. This assumption is confirmed by the presence in the PMR spectrum of signals of methylene protons at 3.55 ppm.

In acidic media the N_5 atom is protonated [4], and this creates the conditions for a coordinated orientation of the acetamide and protonated azomethine groups. In this connection, one might have assumed incorporation of bromine in the 7 position or the ring of the substituent activated by a methoxy group. In order to confirm or exclude this possibility we synthesized 7-bromo-4-(p-methoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one from 4-bromo-o-phenylenediamine and p-methoxybenzoylacetic ester [5]. When the reaction mixture is heated in xylene, a mixture of isomeric 7- and 8-bromodihydrobenzodiazepinones is formed in a ratio of 1:3. This mixture was separated by column chromatography on silica gel. However, V and VI differ from III with respect to their melting points, R_f values, and UV and IR spectra. This provides a basis for the assumption that bromine attacks the phenyl ring of the substituent. The hydrolytic cleavage of III in sulfuric acid by the method in [6] to give 3-bromo-4-methoxyacetophenone also constitutes evidence in favor of this conclusion.



V VI

The mass spectrum of III contains an intense molecular-ion peak (M^+) at 344-346 (92%). The principal pathways of fragmentation of the molecular ion are the characteristic (for 1,5-benzodiazepin-2-ones) splitting out of ketene molecules and the formation of a fragment

TABLE 1. Bromo Derivatives of 4-(p-Methoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-ones

Compound	mp, °C (from ethanol)	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	Br	N		C	H	Br	N	
II	215—216	55,7	3,7	23,1	8,2	$C_{16}H_{13}BrN_2O_2$	55,6	3,8	23,3	8,1	78
III	250—252	55,6	3,8	23,2	8,1	$C_{16}H_{13}BrN_2O_2$	55,6	3,8	23,2	8,1	79
IV	205—206	45,3	2,7	37,8	6,5	$C_{16}H_{12}Br_2N_2O_2$	45,3	2,8	37,7	6,6	67
V	231—232	55,6	3,7	23,1	8,1	$C_{16}H_{13}BrN_2O_2$	55,6	3,8	23,2	8,1	20
VI	220—221	55,7	3,7	23,2	8,2	$C_{16}H_{13}BrN_2O_2$	55,6	3,8	23,2	8,1	62

ion at 302-304 (100%), the peaks of which are the maximum peaks in the spectrum. In contrast to nitration [3], the phenyl ring of the substituent rather than the heteroring consequently undergoes electrophilic attack in strongly acidic media in the presence of a catalyst that facilitates the formation of a bromine cation.

A mixture of mono- (II) and dibromide (IV) in a ratio of 1:5 is formed if diazepine I is brominated with excess molecular bromine in a mixture of sulfuric and acetic acids. The UV spectrum (Fig. 1, curve 4) of IV contains two absorption maxima at 224 and 320 nm; this confirms incorporation of the bromine atom in the 3 position and also in the phenyl ring. The hydrolysis of IV gives a 3-bromo-4-(p-methoxyphenyl) ketone and benzimidazolone. Compound IV was also obtained by bromination of monobromide II in sulfuric acid in the presence of silver sulfate. This set of data makes it possible to assign the 3-bromo-4-(3-bromo-4-methoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one structure to IV.

The intense peaks in its mass spectrum are the molecular ion peak (M^+) at 422-426 and the peak of the fragment ion at 302-304, which is formed by splitting out of a bromo ketene molecule from the molecular ion. In addition, the molecular ion undergoes fragmentation with splitting out of a bromine atom and an HNCO molecule; this is characteristic for the fragmentation of compounds with substituents in the 3 position.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrophotometer. The electronic spectra of solutions of the compounds in ethanol were obtained with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in trifluoroacetic acid were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the internal standard. The mass spectra were obtained with an MKh-1303 spectrometer with a system for volatilization immediately in the vicinity of the ionization region at an ionizing voltage of 50 eV, an emission current of 150 mA, and an ionization-chamber temperature of 150°C. The course of the reactions and the purity of the individual compounds were monitored by thin-layer chromatography (TLC) on Silufol plates in a benzene—ethyl acetate system (7:3). The characteristics of the synthesized bromides are presented in Table 1.

3-Bromo-4-(p-methoxyphenyl)-2,3-dihydro-1H-1,5-Benzodiazepin-2-one (II). A mixture of 1.26 g (0.005 mole) of diazepinone I and 0.89 g (0.005 mole) of N-bromosuccinimide (NBS) in 40 ml of CCl_4 was refluxed for 2 h, after which the precipitated succinimide was removed by filtration. The crystals that precipitated after a certain time were separated and recrystallized from ethanol. Mass spectrum: 346 (59.0), 345 (13.6), 344 (71.5), 267 (32.9), 266 (25.0), 265 (68.1), 264 (3.6), 238 (2.77), 237 (12.5), 236 (7.0), 235 (2.92), 225 (34.0), 224 (100), 223 (17.7), 222 (68.1), 221 (9.3), 210 (7.74), 209 (36.3), 208 (3.9), 207 (4.8), 205 (5.9), 195 (8.7), 194 (37.4), 193 (23.8), 192 (9.7), 182 (5.8), 181 (26.1), 180 (5.5), 179 (5.0), 168 (8.7), 167 (6.5), 166 (5.7), 146 (6.2), 134 (6.1), 133 (10.6), 129 (7.1), 128 (3.5), 119 (3.6), 118 (7.7), 117 (14.6), 112 (8.0), 111 (6.4), 104 (8.1), 103 (17.0), 102 (10.3), 92 (6.1), 91 (7.7), 90 (14.7), 89 (36.2), 78 (10.2), 77 (19.3), 76 (13.6), 75 (9.2).

4-(3-Bromo-4-methoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one (III). A 0.0016-mole sample of bromine was added to a mixture of 0.001 mole of diazepinone I in 10 ml of concentrated H_2SO_4 and 0.178 g of silver sulfate, and the mixture was stirred vigorously for 5 h. It was then poured over ice, and the resulting precipitate was separated and recrystallized from ethanol. Mass spectrum: 346 (86.0), 344 (92.0), 304 (100), 302 (94.0), 289 (38.0), 287 (45.5), 265 (12.6), 260 (7.4), 258 (8.2), 224 (18.6), 211 (5.2), 209 (9.7), 208 (32.0), 195 (5.2), 194 (11.9), 193 (29.8), 192 (14.1), 191 (5.2), 159 (5.9), 153 (6.71), 152 (16.4), 151 (13.4), 134 (11.9), 133 (13.4), 132 (15.6), 131 (9.7), 129 (7.4), 118 (7.4), 117

(11.1), 106 (7.7), 105 (17.9), 104 (26.1), 103 (24.6), 102 (22.3), 101 (6.7), 98 (8.2), 97 (6.7), 92 (11.1), 91 (14.1), 90 (42.5), 89 (58.2), 88 (10.4), 87 (5.2), 79 (6.7), 78 (40.2), 77 (50.7), 76 (23.1), 75 (15.6).

Bromination of 4-(p-Methoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one. A) A solution of 0.01 mole of bromine in 5 ml of acetic acid was added dropwise in the course of 1 h to a solution of 0.756 g (0.003 mole) of diazepinone I in 15 ml of concentrated H_2SO_4, after which the mixture was stirred for another 4 h. It was then poured over ice, and the precipitate was removed by filtration.

B) A solution of 0.01 mole of bromine in 5 ml of acetic acid was added dropwise to a solution of 0.756 g (0.003 mole) of diazepinone I in 20 ml of acetic acid, and the precipitate was separated, washed, and dried. The mixture obtained in experiments A and B was separated preparatively with a column filled with silica gel to give bromides II and IV in a ratio of 1:5.

3-Bromo-4-(3-bromo-4-methoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IV). A 0.0004-mole sample of bromine was added with stirring to a mixture of 0.12 g (0.0003 mole) of diazepinone II, 0.05 g of silver sulfate in 5 ml of sulfuric acid. After 6-7 h, the mixture was poured over ice, and the precipitate was separated. The filtrate was neutralized to pH 6 with potassium hydroxide solution, and the precipitated crystals were recrystallized from ethanol. Compound IV did not depress the melting point of the compound that was isolated preparatively in methods A and B, and the compounds had identical IR spectra. Mass spectrum: 426 (44.6), 425 (21.5), 424 (82.3), 423 (11.5), 422 (38.0), 381 (8.9), 379 (6.8), 346 (96.6), 345 (59.9), 344 (22.8), 343 (49.4), 317 (5.3), 316 (3.5), 315 (6.1), 314 (4.5), 305 (12.9), 304 (79.8), 303 (20.2), 302 (100), 301 (8.9), 300 (32.9), 289 (15.2), 288 (4.6), 287 (17.7), 286 (3.9), 274 (15.2), 273 (11.7), 272 (16.4), 271 (10.1), 265 (6.1), 264 (5.5), 261 (9.2), 259 (10.0), 236 (5.7), 224 (9.5), 223 (5.3), 222 (5.5), 221 (10.3), 212 (7.1), 210 (6.6), 193 (11.4), 192 (12.6), 180 (7.4), 179 (8.5), 139 (35.5), 134 (5.5), 133 (7.98), 132 (26.6), 118 (5.5), 117 (25.3), 104 (6.0), 103 (19.4), 102 (12.6), 101 (5.7), 91 (5.3), 90 (15.2), 89 (48.1), 88 (7.3), 78 (7.3), 77 (26.6), 76 (25.2), 75 (16.4).

Condensation of 4-Bromo-o-phenylenediamine with p-Methoxybenzoylacetic Ester. A solution of 0.004 mole of p-methoxybenzoylacetic ester in 5 ml of xylene was added dropwise to a refluxing solution of 0.001 mole of 4-bromo-o-phenylenediamine in 25 ml of xylene, and the mixture was refluxed for 1 h. It was then cooled, and the resulting crystals were removed by filtration. The mixture of V and VI was separated with a column filled with silica gel in a benzene—ethyl acetate system (7:3).

Hydrolysis of 4-(3-Bromo-4-methoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one. A 0.001-mole sample of diazepinone III was refluxed in 3 ml of 2 N sulfuric acid for 2 h, after which the precipitate was removed by filtration and recrystallized from petroleum ether to give 3-bromo-4-methoxyacetophenone with mp 85°C (mp 84-85°C [7]).

Hydrolysis of 3-Bromo-4-(3-bromo-4-methoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepin-2-one. This reaction was carried out similarly. Workup gave 2,3-dibromo-4'-methoxyacetophenone [sic] with mp 112°C (mp 112°C [7]).

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