NITRATION OF 8-SUBSTITUTED 2,3-DIHYDRO-1H-1,5-BENZODIAZEPIN-2-ONES

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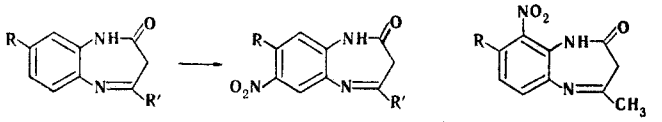
The nitration of a number of 8-R-4-R'-2,3-dihydro-1H-1,5-benzodiazepin-2-ones with substituents in the diazepin (4-R = CH_3, C_6H_5, and $C_6H_4OCH_3$-p) and benzene (8-R = Cl, Br) rings takes place in the 7 position. The presence in the benzene ring of a strong electron-donor substituent (methoxy group), by determining the direction of electrophilic substitution in the ortho position with respect to it, leads to the formation of 7- and 9-nitro isomers in a ratio of 4:3.

It has been shown [1] that the presence of a methyl group in the 7 or 8 position of dihydro-1,5-benzodiazepin-2-ones has a significant effect on the orientation during electrophilic substitution. In this connection, we studied the nitration of dihydro-1,5-benzodiazepinones (I) containing various substituents in the benzene (in the 8 position) and heterocyclic rings of the molecule.

One nitro group is incorporated in the benzene ring in the reaction of potassium nitrate in concentrated sulfuric acid with 8-chloro-4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (Ia), and 7-nitro-8-chloro-4-methyldihydrobenzodiazepin-2-one (IIa) is formed in 92% yield:

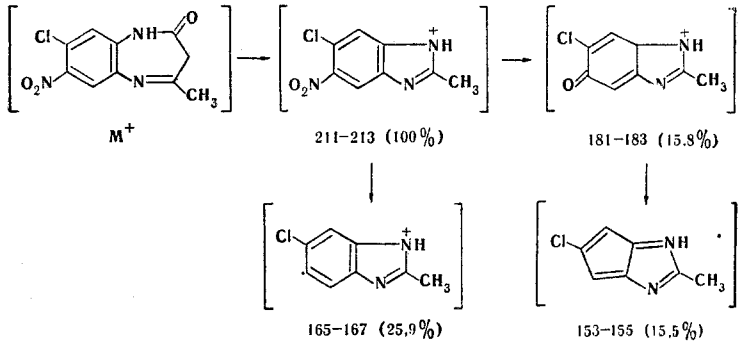


I a-g II a-g III

I, II a R=Cl, R'=CH_3; b R=Br, R'=CH_3; c R=Cl, R'=C_6H_5; d R=Br, R'=C_6H_5; e R=Cl, R'=$C_6H_4OCH_3$-p, f R=Br, R'=$C_6H_4OCH_3$-p; I g II g III R=OCH_3

The change in the UV spectrum on passing from starting Ia to nitration product IIa is significant; a maximum at 270 nm, which is characteristic for 7-nitrodihydro-1,5-benzodiazepin-2-ones, appears in the spectrum of IIa, and the decrease in its intensity in acidic media that is typical for model 7-nitro isomers [1, 2] is observed.

The PMR spectrum in the aromatic region contains two singlets of 6-H and 9-H protons (7.70 and 8.43 ppm); this is in agreement with their para orientation. The maximum peak in the mass spectrum of IIa is the peak of $[M - CH_2CO]^+$, ions, the subsequent fragmentation of which corresponds to the detachment of nitro and nitroso groups from the fragment ion (211-213).*



M^+ 211-213 (100%) 181-183 (15.8%) 165-167 (25,9%) 153-155 (15,5%)

*Here and subsequently, the m/e values are presented for the ion peaks.

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TABLE 1. Mass Spectra of Nitro-8-R-2,3-dihydro-1H-1,5-benzodiazepinones (IIa,g and III)

Compound	m/e (intensity in percent of the maximum ion peak)
IIa	255 (2,0), 253 (26,0), 213 (29,3), 211 (100), 183 (5,7), 181 (16,6), 167 (8,3), 165 (26,7), 155 (3,5), 153 (12,0), 138 (5,6), 129 (3,3), 124 (8,2), 112 (3,0), 111 (2,8), 103 (2,6), 102 (4,7), 99 (3,6), 98 (3,3), 97 (14,5), 85 (3,3), 81 (3,0), 77 (3,2), 76 (10,6), 73 (4,9)
IIg	250 (12,0), 249 (100), 207 (88,0), 192 (3,4), 173 (16,0), 162 (4,4), 161 (7,6), 160 (40,0), 159 (4,4), 149 (7,7), 147 (8,3), 135 (7,6), 134 (16,0), 133 (20,0), 132 (10,6), 131 (64,0), 130 (15,2), 119 (5,4), 118 (6,1), 108 (4,8), 105 (13,6), 104 (13,6), 103 (5,4), 92 (11,4), 91 (8,3)
III	249 (19,2), 208 (7,8), 207 (100), 192 (3,4), 177 (1,0), 176 (5,4), 161 (3,7), 160 (24,4), 147 (5,9), 134 (6,3), 133 (11,3), 132 (5,9), 131 (48,7), 130 (2,5), 105 (5,1), 104 (10,0), 93 (7,3), 92 (4,4), 90 (8,8), 77 (10,3)

The 7-nitro isomer (IIb) is the principal product of nitration of 8-bromo-1,5-benzodiazepin-2-one (Ib). Similar (to IIa) characteristics of the changes in the UV spectrum as the solvent is replaced (alcohol replaced by acid) and a PMR spectrum (Table 2) that is typical for 7,8-disubstituted benzodiazepinones are observed for it.

It might have been assumed that the introduction of a phenyl group or an even more active p-methoxyphenyl group in the 4 position would lead to a change in the orientation during nitration. However, the nitration of 4-phenyl-8-chloro(bromo)- (Ic,d) and 4-(p-methoxyphenyl)benzodiazepin-2-ones (Ie,f) leads only to the 7-nitro derivatives (IIc-f). Thus the acid hydrolysis of 7-nitro-8-chloro-4-phenyl (or p-methyoxyphenyl)benzodiazepin-2-one (Ic,e) gives 4-chloro-5-nitro-o-phenylenediamine (IV), and the absence in the UV spectrum of the absorption at 230-240 nm that is characteristic for 8-nitro isomers [2] indicates that the nitro group is in the 7 position in IIc-f.

The behavior of 8-methoxy-4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (Ig) proved to be exceptional, since a mixture of isomers with nitro groups in the 7 and 9 positions was obtained as a result of nitration. The presence in the IR spectrum of a single broad NH band at 3275 nm, which corresponds to the absorption of an NH group tied up by an intramolecular hydrogen bond with the nitro group [3], indicates that the nitro group in III is in the 9 position. The PMR spectrum contains two doublets of an AB system at 7.77 and 7.18 ppm ($J_{6,7} \simeq 9$ Hz). The small inflection at 230 nm ($\varepsilon = 16{,}000$) in the UV spectrum was assigned to the absorption of an o-nitroacetamide fragment.

In the case of the second isomer IIg the PMR spectrum in the aromatic region contains two singlets of 6-H and 9-H protons (7.00 and 8.22 ppm). The observed shift of the signal of the 6-H proton ($\Delta\delta = 0.74$ ppm) when a nitro group is incorporated in the 7 position is in agreement with the usual shift of the proton signal under the influence of a nitro group in the ortho position [4].

The most intense peaks in the mass spectra of IIg and III are the molecular ion peaks and the peaks of ions formed by detachment of a ketene molecule (207) from the molecular ions. The latter can undergo fragmentation with the elimination of NO (177) and NO_2 (161) molecules and with detachment of an HNO_2 molecule, thereby indicating that the nitro and methoxy groups in IIg and III are adjacent [5]. The subsequent fragmentation proceeds with detachment of CH_2O, CHO, CH_3, and CO particles and involves the condensed benzene ring (Table 1).

EXPERIMENTAL

The UV spectra of solutions of the compounds in alcohol and 70% sulfuric acid were recorded with an SF-16 spectrophotometer. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in trifluoroacetic acid were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the external standard. The mass spectra were obtained with an MKh-1303 mass spectrometer at an ionizing-electron energy of 50 eV, an emission current of 150 mA, and a temperature of 70-150°C.

7-Nitro-4-R'-8-R-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (IIa-f). A nitrating mixture composed of 2.02 g (0.02 mole) of potassium nitrate and 15 ml of concentrated H_2SO_4 was added

TABLE 2. Nitro Derivatives of 4-Methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones

Compound	8-R	mp, °C (crystallization solvent)	Found, % C	Found, % H	Empirical formula	Calc., % C	Calc., % H	UV spectra, λ max (ε · 10⁻³) in alcohol	UV spectra, λ max (ε · 10⁻³) 50% H_2SO_4	PMR spectrum, δ, ppm	Yield, %
IIa	Cl	248 (DMF)	47,3	2,9	$C_{10}H_8ClN_3O_3$	47,3	3,2	270 (17,7), 300 (8,8)*	196 (18,2), 260 (11,5), 300 (4,9)	3,07 (s CH_3) 4,07 (s CH_2) 7,70 (s 6-H) 8,43 (s 9-H)	92
IIb	Br	248 (DMF)	39,9	2,9	$C_{10}H_8BrN_3O_3$	40,3	2,8	270 (13,4), 300 (7,3)*	202 (13,2), 265 (13,5)	3,08 (s CH_3) 4,05 (s CH_2) 7,68 (s 6-H) 8,41 (s 9-H)	62
IIg	OCH_3	258 (DMF)	52,9	4,8	$C_{11}H_{11}N_3O_4$	53,0	4,4	218 (28,5), 265 (16,8), 310 (6,5)	212 (18,2), 265 (9,1)	3,00 (s CH_3) 3,97 (s CH_2) 4,03 (s CH_3O) 7,00 (s 9-H) 8,22 (s 6-H)	40
III	OCH_3	195 (alcohol)	53,3	4,4	$C_{11}H_{11}N_3O_4$	53,0	4,4	214 (43,7), 276 (8,9)	204 (30,6), 230 (16,0), 290 (8,9)	2,83 (s CH_3) 3,84 (s CH_2) 3,92 (s CH_3O) 7,18 (d 7-H) 7,77 (d 9-H)	34

*Shoulder.

TABLE 3. 7-Nitro-4-R'-2,3-dihydro-1H-1,5-benzodiazepin-2-ones

Compound	R	R'	mp, (from DMF)	Found, % C	Found, % H	Empirical formula	Calc., % C	Calc., % H	UV spectra, λmax (ε·10⁻³) in alcohol	UV spectra, λmax (ε·10⁻³) in .70H_2SO_4	Yield, %
IIc	Cl	C_6H_5	265	56,9	3,0	$C_{15}H_{10}ClN_3O_3$	57,1	3,2	263 (24,9) 320 (12,1)*	205 (18,1) 335 (19,6)	82
IId	Br	C_6H_5	267	49,8	3,1	$C_{15}H_{10}BrN_3O_3$	50,0	2,8	273 (22,3) 320 (12,1)*	208 (19,2) 335 (19,5)	70
IIe	Cl	$C_6H_4OCH_3$	272	55,8	3,9	$C_{16}H_{12}ClN_3O_4$	55,6	3,5	240 (22,1)* 260 (19,1) 275 (15,7) 330 (15,8)	217 (14,2) 365 (20,8)	96
IIf	Br	$C_6H_4OCH_3$	277	49,5	3,5	$C_{16}H_{12}BrN_3O_4$	49,0	4,0	240 (20,5)* 260 (18,9) 274 (18,6) 330 (15,8)	216 (14,3) 369 (21,0)	60

*Shoulder.

dropwise at −15°C to a solution of 0.02 mole of the 4-R'-8-R-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (Ia-f) in 20 ml of concentrated H_2SO_4, and the mixture was stirred for 2 h while the temperature was gradually raised to 10°C. It was then poured into water, and the aqueous mixture was cooled and treated with KOH to pH 2. The physical constants and yields of nitro compounds IIa-f are given in Tables 2 and 3.

Nitration of 4-Methyl-8-methoxy-2,3-dihydro-1H-1,5-benzodiazepin-2-one. A 4.08-g (0.02 mole) sample of Ig in 20 ml of concentrated H_2SO_4 was similarly nitrated with a mixture of 2.04 g (0.02 mole) of potassium nitrate in 15 ml of concentrated H_2SO_4. Workup gave 3.7 g of a mixture, from which 9-nitro-8-methoxy-4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (III) (1.7 g) was extracted with hot chloroform. The insoluble residue (2 g) was 7-nitro-8-methoxy-4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IIg).

4-Chloro-5-nitro-o-phenylenediamine (IV). A 5-mmole sample of 7-nitro-8-chloro-4-R'-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IIa,c,e) was heated for 24 h in 2.5 ml of methanol and 2.5 ml of 5.5 N hydrochloric acid, after which the mixture was evaporated to 2 ml, and the concentrate was made alkaline to pH 8 with concentrated ammonium hydroxide. The resulting precipitate was removed by filtration to give IV, with mp 200-201°C (from water, in 60-75% yield). The product was identical to the substance obtained by hydrolysis of Ia,c,e with respect to its IR spectrum and its failure to depress the melting point of an authentic sample. Found: Cl 18.4%. $C_6H_6ClN_3O_2$. Calculated: Cl 18.0%.

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CONDENSATION OF 4-AMINO-3-HYDRAZINO-1,2,4-TRIAZOLINE-5-THIONE WITH α- and β-DICARBONYL COMPOUNDS

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sym-Triazolo[3,4-b][1,2,4,5]tetraazepines were obtained by condensation of 4-amino-3-hydrazino-1,2,4-triazoline-5-thione with α-dicarbonyl compounds, and 1-[4-amino-1,2,4-triazol-3-yl]-3,5-dialkylpyrazoles were obtained by condensation of the same thione with β-dicarbonyl compounds.

In the present research we investigated the reaction of 4-amino-3-hydrazino-1,2,4-triazoline-5-thione (I) with α- and β-dicarbonyl compounds. This thione contains three vicinal functional groups, and this makes it possible to obtain unusual heterocyclic compounds from it. Thus sym-triazolo[3,4-b]tetraazepines (II, III) were obtained when I was heated with α-dicarbonyl compounds (benzil and phenylglyoxal) in acidic media. It is interesting to note that only monohydrazones are formed in the reaction of 4-amino-3-hydrazino-1,2,4-triazole (which differs from I with respect to the absence of a thioamide group) with benzil and diacetyl in acidic media [1].

The reaction of hydrazine I with α-dicarbonyl compounds was investigated in the case of acetylacetone and some unsymmetrical polyfluorinated β-diketones [2]. The ability of β-diketones to undergo keto–enol tautomerism made it possible to expect the formation of condensed triazolotriazepines or compounds with a triazolopyrazole structure (IV) and, considering the data on the condensation of I with α-dicarbonyl compounds, compounds of the II type in the case of condensation with I.

Monotypic IV-IX, the individuality and purity of which were confirmed by thin-layer chromatography (TLC), were obtained in the condensation of I with β-diketones in alcohol containing hydrochloric acid. Their structures were studied in the case of IV. This compound reacts with p-nitrobenzaldehyde to give azomethine X, which makes it possible to exclude structures of the II type from consideration. The presence of a free amino group in IV was also confirmed by the fact that its methylthio derivative (XI) is readily deaminated to give XII. In addition, IV undergoes condensation with such difunctional compounds as α-chloropropionitrile and ω-bromoacetophenone to give s-triazolothiadiazepine XIII and sym-triazolothiadiazine XIV, respectively. The IR spectra of IV-IX contain absorption bands at 1600, 3220, and 3305 cm^{-1}, which are characteristic for the amino group and can be ascribed to deformation vibrations and symmetrical and asymmetrical stretching vibrations, respectively [3]. One absorption band is observed in the UV spectra of each of these compounds.

The selection of structure IV was made on the basis of the mass spectra of II, IV, VI, and VIII. The steric hindrance in structure IV makes the system deviate from the coplanar state, and this is responsible for cleavage of the interannular bond and the recording of peaks of ions corresponding in mass to one (IV) or both (VI and VIII) hetaryl fragments in

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