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NITRATION OF 7- AND 8-METHYL-4-R-1H-2,3-DIHYDRO-1,5-BENZODIAZEPIN-2-ONES

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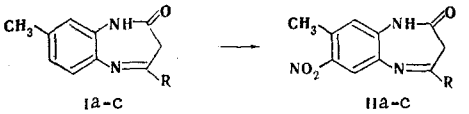
4-R-8-Methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones are nitrated in the 7 position, whereas their 7-methyl analogs are nitrated in the 1, 8, or 9 position. The nitration of 4,8-dimethyldihydrobenzodiazepinone proceeds as primary substitution at the N_1 atom of the amide group. The resulting N_1-nitroamide undergoes prototropic rearrangement to the 9-nitro isomer in strongly acidic media.

In the nitration of 1,5-benzodiazepin-2-ones the nitro group enters the 7 position, i.e., the para position relative to the amide grouping [1, 2]. In the present research we established that the introduction of a CH_3 group in the 8 position does not change the orientation (although one might have expected the formation of the 9-nitro isomer). The corresponding 7-nitro compounds (IIa-c) are formed in 78-93% yields from 4-substituted 8-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (Ia-c) by nitration with potassium nitrate in concentrated sulfuric acid.



Ia-c IIa-c

I, II a R=CH_3; b R=C_6H_5; c R=$C_6H_4OCH_3$-*p*

The PMR spectrum of IIa contains two singlets of the 6-H and 9-H aromatic protons (7.56 and 8.57 ppm), and the observed shift of 0.77 ppm of the singlet of the methyl group of the benzene ring as compared with the signal in the spectrum of the starting benzodiazepinone Ia is in agreement with the usual shift under the in-

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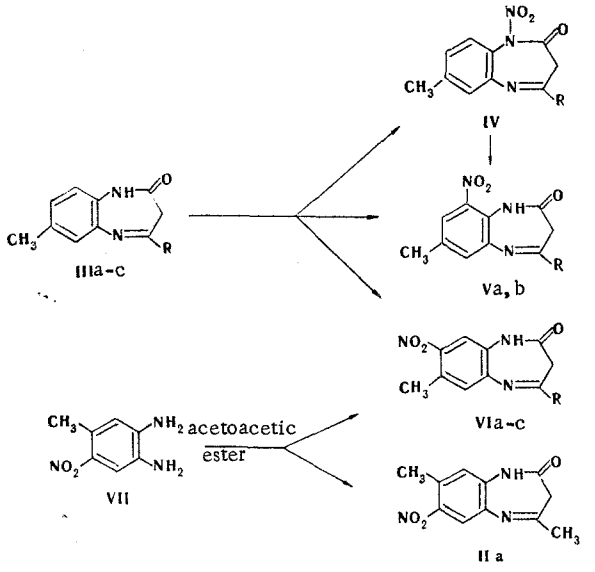
fluence of an adjacent nitro group. An ion peak with m/e 203 (2.5% of the maximum peak), which is formed as a result of the elmination of an NO molecule that is characteristic for aromatic nitro compounds, is observed in the mass spectrum of Ia in addition to a rather intense (26%) molecular ion peak. In addition, the molecular ion may undergo fragmentation with the splitting out of an OH radical (2%) (this process provides evidence that the nitro and methyl groups are in adjacent positions [4]) or ketene and an OH group split out to give a maximum ion in the spectrum (m/e 174). Splitting out of ketene has often been noted for such structures [5]. A similar mass spectrum was also obtained for IIb.

The position of the nitro group in IIb, c was confirmed by acid hydrolysis to diamine VII. The UV spectra of these compounds [maxima at 275-285 nm (log ε 4.30-4.40)] are similar to the UV spectra of the model 7-nitrodiazepinones [2].

In the nitration of 4,7-dimethyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IIIa), in which the 7 position is blocked by a methyl group, we isolated three mononitro compounds (IV, Va, and VIa) in 33.6, 26.5, and 5.7% yields, respectively.

The spectrum of minor component VIa contains the intense absorption at 230 nm that is characteristic for the 8-nitro isomer. The same compound is the principal product of the reaction of 4-methyl-5-nitro-o-phenylenediamine (VII) with acetoacetic ester in refluxing xylene; this provides a basis for the assignment of the 4,7-dimethyl-8-nitro-2,3-dihydro-1H-1,5-benzodiazepin-2-one structure (VIa) to it.

The PMR spectrum of Va contains two doublets of meta-coupling protons ($J_{6,8} \simeq 2$ Hz), which indicates that the nitro group is in the 9 position. The NH band in the IR spectrum is observed in the form of a broad peak at 3260 cm^{-1} due to an intramolecular hydrogen bond between o-oriented nitro and acetamido groups.



III, V, VI a R = CH_3; b R = C_6H_5; c R = $C_6H_4OCH_3$-*p*

The IR spectrum of the third compound (IV) does not contain appreciable absorption in the NH region, but its isomerization to the 9-nitro isomer (Va) is observed when it is dissolved in 50% sulfuric acid; this is in agreement with the Bamberger rearrangement for N-nitroanilines [6, 7] and makes it possible to assign the 1-nitro-4,7-dimethyl-1H-2,3-dihydro-1,5-benzodiazepin-2-one structure to it. When the nitration of IIIa is monitored by thin-layer chromatography (TLC), IV and traces of Va are detected in the reaction mixture in the first minutes, but the amount of isomer Va increases appreciably with time. Isomer VIa is formed slowly and can be detected only toward the end of the reaction.

Thus in the case of 7-substituted benzodiazepin-2-one we were able to observe primary substitution at the nitrogen atom of the amide group, during which the resulting N-nitroamide IV undergoes prototropic rearrangement to 9-nitro isomer Va. Steric factors (the effect of the CH_3 group) retard C nitration in the 8 position.

In the nitration of 4-phenyl-7-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IIIb), in which conjugation between the benzene rings promotes delocalization of the positive charge in the transition state, we were unable

to detect (by TLC) compounds of the IV type, but isomers Vb and VIb are formed in almost equal amounts. Replacement of the phenyl group by a p-methoxyphenyl group has an even stronger effect on the isomer ratio, and only 8-nitro-4-(p-methoxyphenyl)-7-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VIc) was isolated in the nitration of IIIc.

The mass spectrometric fragmentation data are also in agreement with the structures of Va, b and VIa, b. Thus in the case of ortho orientation of the nitro and methyl groups in VIa, b the maximum peaks are the peaks of ions corresponding to splitting out of a ketene molecule and a hydroxyl group from the molecular ion. In the case of 9-nitro derivatives Va, b the maximum peak becomes the peak of $(M - CH_2CO)^+$ ions, which subsequently undergo fragmentation with the elimination of a nitro group.

m/e VALUES AND RELATIVE INTENSITIES (IN PERCENT RELATIVE TO THE MAXIMUM PEAK) OF THE ION PEAKS IN THE MASS SPECTRA OF IIa,b, Va,b, and VIb

IIa 233 (23,0), 216 (2,0), 203 (1,3), 191 (24,2), 175 (7,3), 174 (100), 147 (6,1), 146 (24,2), 145 (12,1), 144 (7,6), 133 (4,7), 119 (9,8), 105 (12,1), 104 (6,2), 103 (3,3), 91 (4,6), 92 (4,4), 78 (4,8), 77 (18,5), 76 (4,6)

IIb 295 (77,9), 278 (4,6), 265 (2,7), 254 (3,4), 253 (13,9), 237 (13,3), 236 (100), 223 (3,6), 209 (3,6), 206 (7,2), 181 (3,9), 105 (8,1), 104 (32,6), 103 (24,4), 91 (32,6), 177 (58,1), 76 (6,9)

Va 233 (22,0), 192 (10,0), 191 (100), 161 (2,1), 146 (8,4), 145 (54,0), 144 (5,6), 143 (3,6), 118 (6,0), 104 (6,0), 103 (4,0), 92 (3,2), 91 (3,2), 90 (3,2), 78 (4,0), 76 (6,8), 133 (6,8)

Vb 295 (35,1), 254 (14,4), 253 (100), 236 (2,0), 223 (1,8), 208 (5,3), 207 (32,9), 206 (3,5), 205 (3,5), 196 (3,5), 195 (4,8), 192 (5,3), 105 (15,8), 104 (13,1), 103 (22,4), 102 (6,6), 91 (6,1), 78 (6,6), 77 (55,2), 76 (6,1)

VIb 295 (73,8), 254 (3,6), 253 (21,4), 237 (11,9), 236 (100), 223 (5,8), 209 (4,0), 208 (19,5), 207 (13,1), 149 (4,8), 105 (7,1), 104 (19,0), 103 (11,9), 77 (3,6)

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of alcohol solutions of the compounds were recorded with an SF-16 spectrophotometer. The PMR spectra of trifluoroacetic acid solutions of the compounds were obtained with a Varian T-60 spectrometer with hexamethyldisiloxane as the external standard. The mass spectra were obtained with an MKh-1303 mass spectrometer.

7-Nitro-8-methyl-4-R-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (IIa-c). A mixture of 1.01 g (10 mmole) of potassium nitrate and 7 ml of concentrated sulfuric acid was added dropwise at −14°C to a solution of 10 mmole of Ia-c in 10 ml of concentrated sulfuric acid, and the mixture was stirred at 0 to 10°C for 2 h. It was then poured into water, and the aqueous mixture was cooled and neutralized to pH 2 with potassium hydroxide solution. The resulting precipitate was removed by filtration and crystallized from DMF. The yields of IIa-c are presented in Table 1.

Nitration of 4,7-Dimethyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one. A mixture of 0.61 g (6 mmole) of potassium nitrate and 4 ml of concentrated sulfuric acid was added dropwise at −14°C to a solution of 1.1 g (6 mmole) of IIIa in 8 ml of concentrated sulfuric acid, and the mixture was stirred for 30 min as the temperature was gradually raised to 0°. It was then poured into ice water, and the aqueous mixture was neutralized with thorough cooling to pH 7 with potassium hydroxide solution and extracted with chloroform. The chloroform was removed from the extract in vacuo, and the residue was subjected to chromatography with aluminum oxide. Elution with chloroform gave the following products (successively): Va (0.47 g), IV (0.37), and VI (0.08 g). PMR spectrum of 9-nitro isomer Va (in CF_3COOH): 2.55 (s, CH_3); 3.01 (s, CH_3); 3.75 (s, CH_2); 7.8 and 8.27 ppm (d, 6H and 8H, $J_{6,8} \simeq 2$ Hz).

Rearrangement of 1-Nitro-4,7-dimethyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one. A 0.11 g (0.5 mmole) sample of IV was sprinkled into 20 ml of 50% sulfuric acid cooled to 15°C, during which the mixture warmed up to 25°C. The resulting solution was stirred with thorough cooling for 5 min as it was neutralized to pH 7 with alkali solution. The resulting red crystals were removed by filtration, dried, and crystallized to give 0.09 g (82%) of Va, which was identical to the product isolated from the mixture of products of nitration of IIIa.

Condensation of 4-Methyl-5-nitro-o-phenylenediamine with Acetoacetic Ester in Xylene. A solution of 0.4 g (3 mmole) of acetoacetic ester in 10 ml of xylene was added dropwise to a refluxing solution of 0.5 g (3

TABLE 1. Nitro Derivatives of 1,5-benzodiazepin-2-ones

Compound	Positions of the groups		R	mp, °C*	Found, %		Empirical formula	Calc., %		Yield, %
	CH_3	NO_2			C	H		C	H	
IIa	8	7	CH_3	235	56,9	5,0	$C_{11}H_{11}N_3O_3$	56,6	4,7	87
IIb	8	7	C_6H_5	268	65,1	4,4	$C_{16}H_{13}N_3O_3$	65,1	4,4	93
IIc	8	7	$C_6H_4OCH_3$	259	62,9	4,5	$C_{17}H_{15}N_3O_4$	62,8	4,6	78
IV	7	1	CH_3	122	57,0	4,6	$C_{11}H_{11}N_3O_3$	56,7	4,7	26,4
Va	7	9	CH_3	136	56,7	4,8	$C_{11}H_{11}N_3O_3$	56,7	4,7	33,6
Vb	7	9	C_6H_5	223	65,0	4,5	$C_{16}H_{13}N_3O_3$	65,1	4,4	30,3
VIa	7	8	CH_3	218	56,8	4,9	$C_{11}H_{11}O_3N_3$	56,7	4,7	5,7
VIb	7	8	C_6H_5	246	65,4	4,3	$C_{16}H_{13}N_3O_3$	65,1	4,4	24,3
VIc	7	8	$C_6H_4OCH_3$	261	62,7	4,3	$C_{17}H_{15}N_3O_4$	62,8	4,6	77

* Compounds IIa-c were crystallized from DMF, IV was crystallized from ether–hexane, Va,b and VIa were crystallized from alcohol, and VIb,c were crystallized from toluene.

mmole) of VII in 50 ml of xylene, and the mixture was heated for 6 h. It was then cooled, and the precipitate [0.04 g (5.7%)] of isomer IIa was removed by filtration and crystallized from DMF. The product was identical to the sample of IIa isolated in the nitration of benzodiazepinone Ia. The xylene was removed from the filtrate by vacuum distillation, and the residue [0.55 g (78.5%)] was crystallized from alcohol to give VIa. The isolated product was identical with respect to its UV and IR spectra and melting point to the 8-nitrobenzodiazepin-2-one isolated from the mixture of products of nitration of IIIa.

Nitration of 4-phenyl-7-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one. A mixture consisting of 0.6 g (5.6 mmole) of potassium nitrate and 4 ml of concentrated sulfuric acid was added dropwise at −14°C to a solution of 1.4 g (5.6 mmole) of IIIb in 14 ml of concentrated sulfuric acid, and the mixture was stirred at −14 to 0°C for 2 h. It was then poured into water, and the resulting precipitate was removed by filtration, washed with water, dried, and chromatographed with a column filled with aluminum oxide (elution with chloroform) to give 0.5 g (30.3%) of 9-nitro isomer Vb and 0.4 g (24.3%) of the 8-nitro isomer.

8-Nitro-4-(p-methoxyphenyl)-7-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VIc). A 0.72 g (2.8 mmole) sample of benzodiazepinone IIIc in 10 ml of concentrated sulfuric acid was similarly nitrated with a nitrating mixture consisting of 0.28 g (2.8 mmole) of potassium nitrate in 2 ml of concentrated sulfuric acid. The mixture was poured into water, and the precipitate was removed by filtration to give 0.7 g (77%) of VIc.

4-Methyl-5-nitro-o-phenylenediamine (VII). A) A 2-mmole sample of the 8-nitrobenzodiazepin-2-one (VIa-c) was heated in a solution of 10 ml of methanol and 10 ml of 5.5 N hydrochloric acid for 2 h. The mixture was then cooled, neutralized to pH 6-7 with alkali solution, and extracted with ethyl acetate. The solvent was removed from the extract, and the residue was crystallized from water to give a product with mp 145-146°C in 60-93% yield. Found: N 25.0%. $C_7H_9N_3O_2$, Calculated: N 25.2%.

B) A mixture (2 mmole) of the 7-nitrobenzodiazepinone (IIa-c) with 10 ml of 2 N HCl and 10 ml of methanol was refluxed for 5 h, after which the condenser was removed, and the mixture was heated for 30 min to remove the methanol. The solution was then cooled and made alkaline to pH 9-10 with an alkali solution. The resulting precipitate (in 70-81% yield) was removed by filtration to give 4-methyl-5-nitro-o-phenylenediamine with mp 146-147°C (from water).

The compounds obtained by methods A and B had identical IR spectra, and no melting-point depressions were observed for mixtures of them.

p-Methoxybenzoylacetic Acid 2-Nitro-4-methylanilide. This compound was obtained by heating 2-nitro-4-methylaniline [3.04 g (20 mmole)] with 8.9 g (40 mmole) of p-methoxybenzoylacetic ester in 500 ml of o-xylene with constant removal of xylene by distillation. After 5 h, the volume of the mixture was 30 ml. When it was cooled and worked up, it yielded 2.82 g (86%) of product. Crystallization from propyl alcohol gave a product with mp 141°C. Found: C 62.3; H 4.8%; $C_{17}H_{19}N_2O_5$. Calculated: C 62.2; H 4.9%.

4-(p-Methoxyphenyl)-8-methyl-1H-2,3-dihydro-1,5-benzodiazepin-2-one (Ic). A 1.78 g (15 mmole) sample of 4-methyl-o-phenylenediamine was mixed with 3.35 g (15 mmole) of p-methoyxbenzoylacetic ester, one drop of concentrated hydrochloric acid was added, and the liquid mixture was allowed to stand for 30-45 days, during which it solidified. The solid mass was washed with alcohol to give 3.4 g (81%) of diazepinone Ic with mp 219°C (from toluene). Found: C 72.8; H 5.6%. $C_{17}H_{16}N_2O_2$. Calculated: C 72.8; H 5.7%.

4-(p-Methoxyphenyl)-7-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IIIc). A 1.64 g (5 mmole) sample of VIII was hydrogenated at room temperature and normal pressure in the presence of Raney nickel. The precipitate was removed by filtration and washed on the filter with chloroform. The solvent was removed, and the residual benzodiazepinone IIIc was chromatographed on aluminum oxide (elution with chloroform) to give a product with mp 222°C (from alcohol). The yield was 0.8 g (57%). Found: C 72.6; H 5.4%. $C_{17}H_{19}N_2O_2$. Calculated: C 72.8; H 5.7%.

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ISOTOPIC HYDROGEN EXCHANGE IN 1- AND 2-ARYL-5-METHYLTETRAZOLES

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The rate constants for basic deuterium exchange of the methyl group (k_D) in 2-phenyl-5-methyltetrazole (I) and 1-aryl-5-methyltetrazole (II) and its derivatives with a polar substituent (R) in the phenyl ring were measured. The increased CH acidity of II as compared with I [k_D(II)/k_D(I) ~20] is in agreement with the calculated and experimental values regarding the character of the electron-density distribution in the molecules. The effect of R on the rate of deuterium exchange of the methyl group correlates with the σ° constants (ρ=3.0, r=0.997). The results of measurement of the kinetic isotope effect during deuterium (tritium) exchange in II (k_D/k_T ~1.8) are discussed in connection with the peculiarities of the stepwise reaction mechanism.

Up until recently little was known regarding the reactivities of methyl derivatives of tetrazole. The methyl group in 1-phenyl-5-methyltetrazole does not undergo the condensation with benzaldehyde that is characteristic for compounds with a methyl group attached to a ring azomethine group $(-\underset{\displaystyle CH_3}{\underset{|}{C}}=N-)$, even under

rather severe conditions in the presence of zinc chloride [1]. In our experiments we were unable to obtain a product of condensation of 1-(4-nitrophenyl)-5-methyltetrazole with p-nitrobenzaldehyde either in alcohol in the presence of sodium alkoxide or in acetic anhydride. However, 1-phenyl-5-methyltetrazole reacts with diethyl oxalate to give pyruvic acid derivatives [1]. Quantitative data on the lability of the hydrogen atoms of the methyl group are limited to the results of measurements of the rate of deuterium exchange of 1-phenyl-5-methyltetrazole in an alcohol solution of potassium ethoxide [2]. In the present research we made a comparative study of the effect of structural factors on deuterium exchange in a number of 5-methyltetrazole derivatives (I-VII):

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