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SYNTHESIS OF N-ACYL-4-METHYL-7(8)-NITRO-2,3,4,5-TETRAHYDRO-1H-1,5-BENZODIAZEPIN-2-ONES AND THEIR SPECTRAL PROPERTIES

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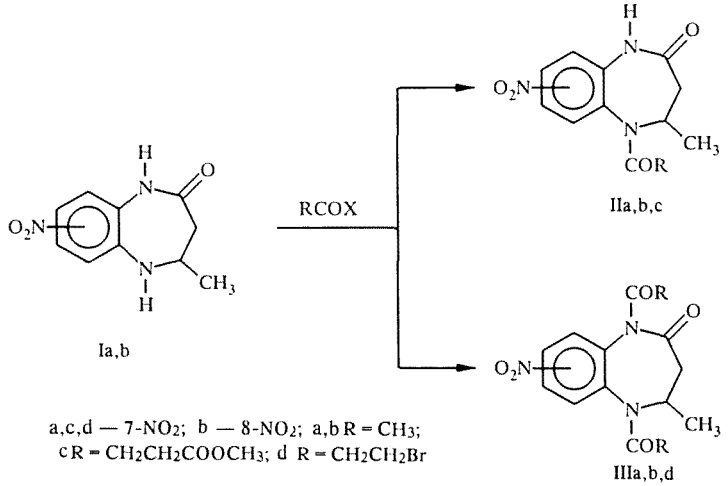
The conditions were studied of mono- and diacylation of 7(8)-nitro-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones. It was found that under mild conditions (lower temperatures, weak acylating agents), the 7-nitro isomers are acylated only at the 5-position; increase in the temperature or treatment with an active acylating agent gives the 1,5-diacyl derivatives. Under mild conditions the 8-nitro isomer is not acylated, while under more rigorous conditions a mixture of mono- and diacylated products is formed.

We have recently shown that the alkylation of isomeric 7(8)-nitro-substituted 2,3,4,5-tetrahydro-1H-1,5-benzodiazepinones proceeds qualitatively differently from that of compounds unsubstituted in the benzene ring [1]. For the latter it was also known that the acylation in chloroform proceeds in most cases only at the more nucleophilic nitrogen atom in the 5-position [2, 3], giving compounds with high anti-inflammatory activity. This prompted us to study the direction of the acylation reaction of isomeric 7(8)-nitro substituted compounds Ia and Ib.

It was found that the direction of the reaction and the extent of the acylation process are substantially influenced by the reactivity of the acylating agent, the solvent, the reaction temperature and the position of the nitro group in the benzene ring. Both 7-(Ia) and 8-nitro-(Ib) substituted benzodiazepinones did not react with acetic anhydride in boiling THF even for 72 h (A). At the same time, boiling in an excess of the same acylating agent (B) led to bisacylation of compound Ia*, but only to a mixture of 5-acetyl- (IIb) and 1,5-diacetyl substituted (IIIb) derivatives in the case of compound Ib (Scheme 1, Table 1).



a,c,d — 7-NO_2; b — 8-NO_2; a,b R = CH_3; c R = $CH_2CH_2COOCH_3$; d R = CH_2CH_2Br

*Traces of the monoacetylated derivative were identified only on a chromatographic level.

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TABLE 1. Influence of Reaction Conditions on the Yield of Acylation Products of Compounds Ia, d

Method	Ratio of starting materials		Time of reaction, h	Solvent	T,°C	Yield, %	
						II	III
A	Ia : Ac_2O	1 : 1	72	TGF	65	—	—*2
A	Ib : Ac_2O	1 : 1	72	TGF	65	—	—*2
B	Ia : Ac_2O	1 : 10	5	Ac_2O	140	—*3	65 (IIIb)
B	Ib : Ac_2O	1 : 15	8	Ac_2O	140	32 (IIb)	32 (IIIb)
C	Ia : Ac_2O	1 : 4,5	8	Pyridine	115	—*3	70 (IIIb)
C	Ia : $(-CH_2-CO)_2O$	1 : 4,5	20	Pyridine	115	—	—*3
C	Ia : AcCl : Py	1 : 1 : 11	24	Dioxane	20	54 (IIa)*2	—
C	Ia : AcCl : Py	1 : 1 : 11	8	Dioxane	40	35 (IIa)	39 (IIIa)
D	Ia : $MeO_2C(CH_2)_2COCl$: Py	1,5 :1,5 :1,5	6	Dioxane	110	54 (IIc)	—
D	Ib : AcCl : Py	1 : 1 : 11	8	Dioxane	80	35 (IIb)	28 (IIId)
E	Ia : AcCl	1 : 2	16	$CHCl_3$	61	58 (IIa)	23 (IIIa)
E	Ia : $Br(CH_2)_2COCl$	1 : 4	16	$CHCl_3$	61	—	81 (IIId)
F	Ia : AcCl : AcONa	1 : 2 : 2	3	AcOH	118	62 (IIa)	—
F	Ib : AcCl : AcONa	1 : 2 : 2	3	AcOH	118	—	—*2
F	Ia : $MeO_2C(CH_2)_2COCl$: AcONa	1 : 2 : 2	3	AcOH	118	38 (IIa)	—

*The yields are given for chromatographically pure compounds after recrystallization.

2*The starting Ia or Ib were isolated.

*3The presence of IIa has been established in the raw product.

*4Based on the compounds which entered the reaction.

The acetylation of isomer Ia with acetyl chloride in a dioxane solution in the presence of pyridine (D), even at room temperature, leads to the 5-monoacetyl derivative IIa, but with increase in the temperature to 40°C a mixture of compounds IIa and IIIa is formed. A similar mixture of mono- and diacetylated derivatives IIb and IIIb is formed under these conditions from isomer Ib. Replacement of pyridine by sodium acetate even on increasing the temperature (boiling acetic acid, F) does not lead to the acylation of the 8-nitro derivative, while its 7-nitro isomer is smoothly monoacetylated under these conditions into the 5-position. We should note that the acylation of isomer Ia under these conditions by the acid chloride of a monomethyl ester of succinic acid instead of the expected compound IIc gives only the N-acetylated product IIa, which is probably due to the formation of a mixed anhydride in the reaction mixture. On using method B, compounds Ia does not react with succinic anhydride, although it smoothly forms a bisacetylation product in the reaction with acetic anhydride. The more reactive acid chloride of a monomethyl ester of succinic acid reacts with compound Ia only at the 5-position (D), but boiling of the same isomer Ia in chloroform (E) with β-bromopropionyl chloride at once causes the formation of a bisacyl derivative IIId, although the reaction under similar conditions with acetyl chloride leads to a mixture of mono- IIa and bis- IIIa acetylated compounds.

Thus, the introduction of a nitro group into the 7-position of the benzene ring of the benzodiazepinone molecule promotes the acylation reactions at the amide nitrogen atom in the presence of fairly strong basic agents (pyridine, acetic anhydride). However, in the molecule of the 8-nitro isomer Ib the reactivity of both the nitrogen atoms becomes equalized, probably due to the increase in the acidity of NH group at the 5-position, and a pure mono- or bisacylation product cannot be obtained.

The structure of all the compounds obtained was confirmed by the analysis of their spectral data.

In the UV spectra of the monoacyl 7-nitro substituted compounds (Table 2) a long wave absorption band (the electron transfer band) is observed in the 305 nm region, which is characteristic for p-nitroacetanilide [4, 6], but underwent a small (by 10 nm) hypsochromic shift due to the acetylalkylaniline fragment present in the m-position.

TABLE 2. Properties of Compounds IIa-c and IIIa, b, d

Compound	MP, °C	UV spectra, λ_{max} (log ε)	IR spectra, cm^{-1}				PMR spectra (δ, ppm, multiplicity)						
			ν_{CO}	ν_{NH}	ν_{NO_2}		4-CH_3	4-CH	1-NH	5-CH_3CO	1-CH_3CO	6-H	9-H
					s	*as*							
IIa	218...220	221 (4,8) 305 (4,9)	1635, 1690	3255	1310, 1340	1520	1,11d	5,01 m	9,85	1,6 s	–	8,35d*2	7,29d*2
IIb	235...236	244 (4,6) 287 (4,2)	1650, 1685	3180	1315, 1347	1525	1,06d	5,06 m	9,98	1,6s	–	7,55d*3	7,86d*3
IIc	173...175	223 (4,7) 305 (4,9)	1650, 1695 1730	3255	1310, 1340	1520	1,21d	5,35 m	9,11	2,58 m*	–	8,35d*2	7,30d*2
IIIa	184...186	218 (4,7) 279 (4,0)	1660, 1696 1725	–	1350	1530	1,11d	5,23 m	–	1,8c	2,62 s	8,03d*2	7,48 d
IIIb	174...176	213 (4,7) 279 (4,1)	1665, 1725	–	1350	1530	1,06d	5,20 m	–	1,75 s	2,60 s	7,50*3	8,20*3
IIIc	162...166	209 (4,7) 278 (4,0)	1665, 1715 1725	–	1340	1530	1,11d	5,18 m	–	2,46m ($COCH_2$-)	3,44m (CH_2Br)	8,20*2	7,63*2

*Signals of CO-CH_2-CH_2-$COOCH_3$; δ_{COCH3} = 3.55.

*2$J_{6.8}$ = 2.5, $J_{9.8}$ = 8.5 Hz.

*3$J_{6.7}$ = 8.5, $J_{9.7}$ = 2.5 Hz.

TABLE 3. Mass Spectra of Compounds IIa,b , IIIa

Compound	m/z (relative intensity, %)
IIa	263(62), 221(72), 219(27), 206(75), 204(22), 178(31), 177(75), 164(100), 132(32), 118(33), 69(70)
IIb	263(33), 221(27), 219(33), 206(47), 178(34), 177(85), 164(100), 132(28), 131(19), 118(38), 69(66)
IIIa	305(22), 263(80), 221(67), 219(33), 206(62), 204(40), 179(72), 178(28), 177(46), 164(66), 69(100)

TABLE 4. Peak Intensity of Characteristic Ions in the Mass Spectra of Compounds IIa,b and IIIa (% Σ_{50})

Compound	W_M[II]	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	Φ_8	Φ_9	Φ_{10}
IIa	8,1	8,9	3,3	0,3	0,9	9,0	9,3	2,4	12,1	2,5	8,2
IIb	3,0	2,2	2,7	0,3	0,6	6,2	3,9	1,4	8,3	1,8	5,5
IIIa	6,2*	5,1	2,4	0,4	5,2	3,0	4,4	2,9	4,8	1,7	6,8

*I_M^{II}; W_M^{III} = 1.9.

In the UV spectrum of the 8-nitro isomer IIb this absorption band is shifted into the shorter wave region at 286 nm, the magnitude of which is close to the arithmetic mean between the values of λ_{max} for m-nitroacetanilide (250 ml) and p-nitro-N-alkyl-acetanilide (320 nm) [4]. Introduction of two acyl residues into the molecules of the isomers Ia, b (compounds IIIa, b, d) leads to practically indistinguishable UV spectra of the compounds.

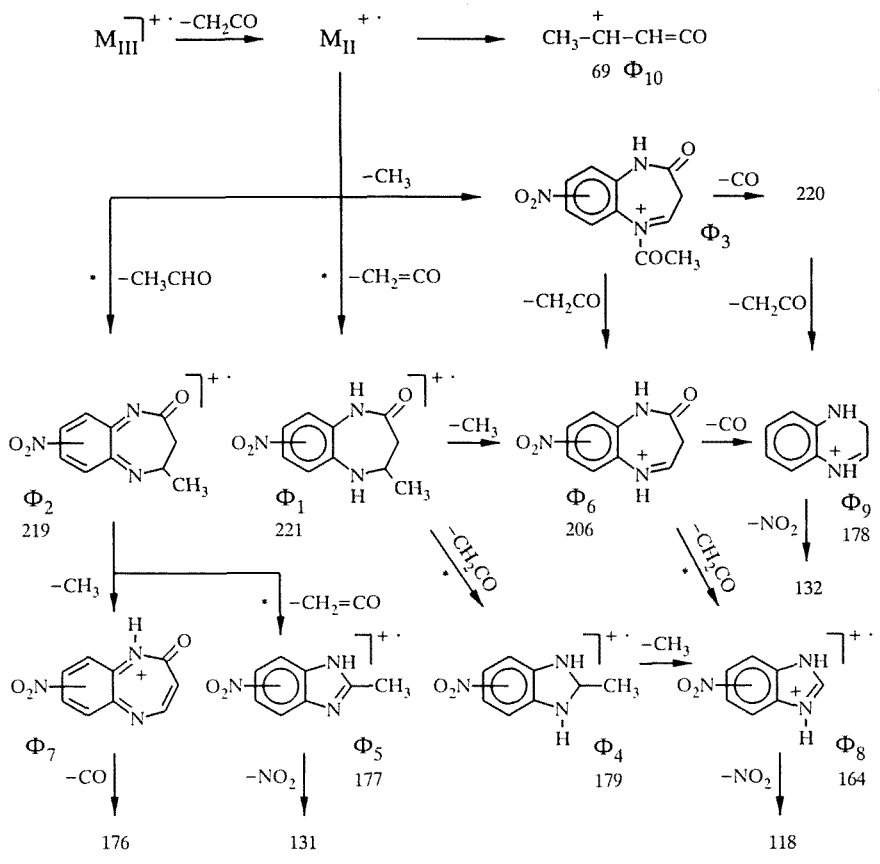
In the IR spectra of monoacylated compounds IIa-c (Table 2) two absorption bands are observed of the stretching vibrations of the lactam (1635-1650) and acetyl (1685-1690) carbonyl groups, while the vibration spectra of the diacetylated compounds, three "carbonyl absorption bands" are present (1660-1665, 1695 and 1725 cm^{-1}), the last of which corresponds to the stretching vibrations of the 1-acetyl fragment. The differences between the IR spectra of 7- and 8-nitro isomeric compounds are insignificant and are manifested in a 5 cm^{-1} decrease in the vibration frequency of the carbonyl group at the 5-position and a similar increase in the frequency of the "lactam carbonyl" in the spectra of the 8-nitro substituted compound IIb.

For the PMR spectra of the synthesized compounds (Table 2) a weak-field shift of the signal of a proton at $C_{(4)}$ is characteristic (by 1.2-1.5 ppm in comparison with Ia, b, [3]), and smaller ($\sim$0.4-0.6 ppm) weak-field shifts of the 6-H and 9-H proton signals in the spectra of the diacylated compounds IIIa, b, d. A similar influence of the carbonyl fragment of the acetylamino group on the CS of the proton in the peri-position was observed in the PMR spectra of N-acetyltetrahydroquinolines and was explained by the anisotropy of the carbonyl in the case of the S-Z conformation (the carbonyl group is directed in the direction of the aromatic ring) [7]. Relatively weak-field shifts of the 6-H proton signal and a strong shift in the direction of large values of δ of the 4-H proton signal leads us to assume a preferential S-E conformation of the acetyl fragment.

In the mass spectra of compounds IIa, b and III (Table 3), relatively intense peaks are observed of the molecular ions, whereby the fragmentation of the latter begins with the elimination of one (IIa, b) or successively two (IIIa) molecules of keten. The this formed pseudomolecular ion Φ_1 (scheme 2, Table 4) further loses the methyl group (Φ_3) and a molecule of keten (Φ_4) in variable sequence, which leads to fragment Φ_8 probably having a structure of a protonated nitrobenzoimidazolium [8]. Only at this stage a loss of a nitro or nitroso groups is observed (ions with m/z 132, 131, 118), which is characteristic for the aromatic and heteroaromatic nitro compounds [10]. Together with this main direction of the decomposition of ion $M_{II}^{+\cdot}$, its fragmentation takes place by a previously not described path, due to the transfer of a hydrogen atom from the $N_{(1)}$ atom to the acetyl fragment*, elimination of the acetaldehyde molecule and formation of ion Φ_2 The latter further loses either the methyl group or a molecule of keten (ions Φ_7 and Φ_5, respectively), after which the splitting off of the nitro group also follows. lastly, in the mass spectra of all the acylated compounds, as in the case of N-alkyltetrahydrobenzodiazepinone [1], an intense peak

*Confirmed by the analysis of the mass spectrum of a 1-N-deuterated compound IIa.

of ion Φ_{10} (m/z 69) is observed, which is formed, as confirmed by the analysis of the metastable ions, directly from the M_{II}+ ion according to the keten type dissociation of acetylanilines [11] with splitting off of a seven-membered ring and transfer of one hydrogen atom, most probably, to the $N_{(1)}$ atom. We should note that the ions shown in Scheme 1 and in Table 4, comprising 40-60% of the sum of all ions, indicate a high selectivity of the fragmentation process.



*The single stage character of the process was confirmed by the presence of a metastable ion.

EXPERIMENTAL

The IR spectra were run on a Specord IR-71 spectrophotometer in KBr tablets. The UV spectra were run in ethanol on a Specord UV-vis spectrophotometer. The PMR spectra were recorded on a Hitachi R-22 spectrometer (90 MHz) using a DMSO-d_6 solution and HMDS as an internal standard. The mass spectra were measured on LKB-2091 and MX 1321A spectrometers with direct introduction of the material into the ionic source at a ionization energy of 70 eV. The differences in the peak intensities in the spectra obtained on different spectrometers did not exceed 10-12% (relative). The course of the reaction and the purity of the compounds were monitored by TLC on Silufol UV-254 plates in a chloroform–ethyl acetate – methanol system, 14:7:1.5. The chromatographaic separation of the compounds was carried out on a column with L40/100μ silica gel. The system was successively washed with solvents with increasing eluotropic capacity, and the fraction was collected, which was eluted by a chloroform–ethyl acetate 1:2 mixture. The mixed samples of compounds obtained by different methods, did not give depression of the melting point.

Acylation of 4-methyl-7(8)-nitro-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones. B. A solution of 4.4 g (20 mmoles) of compound I in 20 ml of (200 mmoles) of acetic anhydride was boiled for 5 h. The mixture was poured onto ice, neutralized with potassium carbonate, extracted with chloroform, the extract was evaporated, and the residue was twice recrystallized from dioxane or chromatographed on a column with SiO_2.

C. A mixture of 4.4 g (20 mmoles) of compound I, 8.5 ml (90 mmoles) of acetic anhydride and 20 ml of dry pyridine was boiled for 8 h, then was poured onto ice, the solution was neutralized with concentrated HCl to pH 6-7 and extracted with chloroform. The extract was washed with sodium carbonate, dried and evaporated.

D. A 0.8 ml portion (10 mmoles) of acetyl chloride in 10 ml of dry dioxane was added with stirring and cooling (0-5°C) to a solution of 2.2 g (10 mmoles) of compound I and 0.9 ml (110 mmoles) of dry pyridine in 200 ml of dry dioxane. The mixture was allowed to stand for 24 h at room temperature, the solvent was evaporated, and the residue was dissolved in chloroform. The solution was washed with a 0.1 N solution of HCl, 5% solution of Na_2CO_3, water, and dried. The solvent was evaporated to dryness and the residue was boiled with 120 ml of ethyl acetate. The insoluble residue was filtered off and dissolved in ethanol. After concentration of the ethyl acetate solution compound II was isolated, while from the ethanolic solution 1.1 g (50%) of the starting compound I was obtained. When the mixture was heated at 40-100°C for 8 h, the chloroformic solution was evaporated and the residue was crystallized from a benzene–ethyl acetate mixture or chromatographed on a column with silica gel, a mixture of compounds II and III was obtained.

E. A solution of 4.4 g (20 mmoles) of compound Ia and 3.3 ml (40 mmoles) of acetyl chloride in 300 ml of dry chloroform was boiled for 16 h. The mixture was cooled, washed with a saturated solution of sodium carbonate, water, and dried. The solvent was evaporated, the residue was recrystallized from an ethyl acetate–dioxane mixture and compounds II and III were obtained.

F. A mixture of 4.4 g (20 mmoles) of compound I, 3.2 ml (40 mmoles) of the corresponding acid chloride and 3.3 g (40 mmoles) of sodium acetate in 80 ml of glacial acetic acid was boiled for 3-5 h. The mixture was poured into 200 ml of cold water, neutralized with sodium carbonate, the precipitate that separated out was filtered off, and recrystallized.

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