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STEREOCHEMISTRY OF THE [3+2] CYCLOADDITION OF ACRYLONITRILE TO THE N-OXIDE OF 5-METHYL-4,5-DIHYDRO-3H-SPIRO[BENZ-2-AZEPINE-3,1'-CYCLOHEXANE]

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The [3+2] cycloaddition of acrylonitrile to the N-oxide of 5-methyl-4,5-dihydro-3H-spiro[benz-2-azepine-3,1'-cyclohexane] under conditions of both kinetic and thermodynamic control proceeds without regioselectivity or stereoselectivity with the formation of eight isomeric 1-cyano- and 2-cyano-7-methyl-1,2,4,6,7,11b-hexahydro-5H-spiro[isoxazolidino[3,2-a]benz-2-azepine-5,1'-cyclohexanes], six of which were isolated in an individual state. Their structure and stereochemistry were established by ^{1}H NMR.

Keywords: alkenes, benz-2-azepines, spiro compounds, cyclic nitrones, [3+2] cycloaddition.

The [3+2] cycloaddition reaction is the most studied area of the chemistry of nitrones [1-3]. Interest in this reaction is caused by the ease of fission of the N–O bond in the resulting isoxazolines and isoxazolidines, which is used for constructing complex organic molecules. As a rule intermolecular cycloaddition occurs with a high degree of regioselectivity and the composition of the cycloaddition adducts, depending on the reaction conditions, may be determined both by kinetic and thermodynamic control. The stereochemistry of [3+2] cycloaddition to a cyclic nitrone has been studied little [4-6] but nitrones of the benz-2-azepine series have not been studied at all. The regio- and stereoselectivity of cycloaddition to cyclic nitrones depends on the conditions of carrying out the reaction, the size of the electron density at the double bond of the dipolarophile, the steric effects of substituents, and also the effect of the secondary interaction of the limiting orbital of the nitrone nitrogen atom with the orbitals of the substituents of the dipolarophile [4,7]. Thus the cycloaddition of alkenes to a cyclic nitrone formed *in situ* from hydroxylamines in the presence of palladium catalyst proceeds with 100% regio- and stereoselectivity [8]. Depending on the structure of the alkene, cycloaddition to 3-(ethoxycarbonyl)-2-oxo-3,4-dihydro-β-carboline proceeds with full or high regio- and stereoselectivity. Due to steric hindrance only *trans* addition of the alkene occurs relative to the ethoxycarbonyl group in position 3 [7].

We have studied the cycloaddition of acrylonitrile to the N-oxide of 5-methyl-4,5-dihydro-3H-spiro[benz-2-azepine-3,1'-cyclohexane] (1) [9]. The reaction was carried out for preparative purposes in toluene with a threefold excess of acrylonitrile at 105°C (24 h), and to determine the ratio of products at various stages of the reaction in benzene-D_6 with a 10% excess of acrylonitrile at 20°C in an NMR spectrometer sample tube (7 days).

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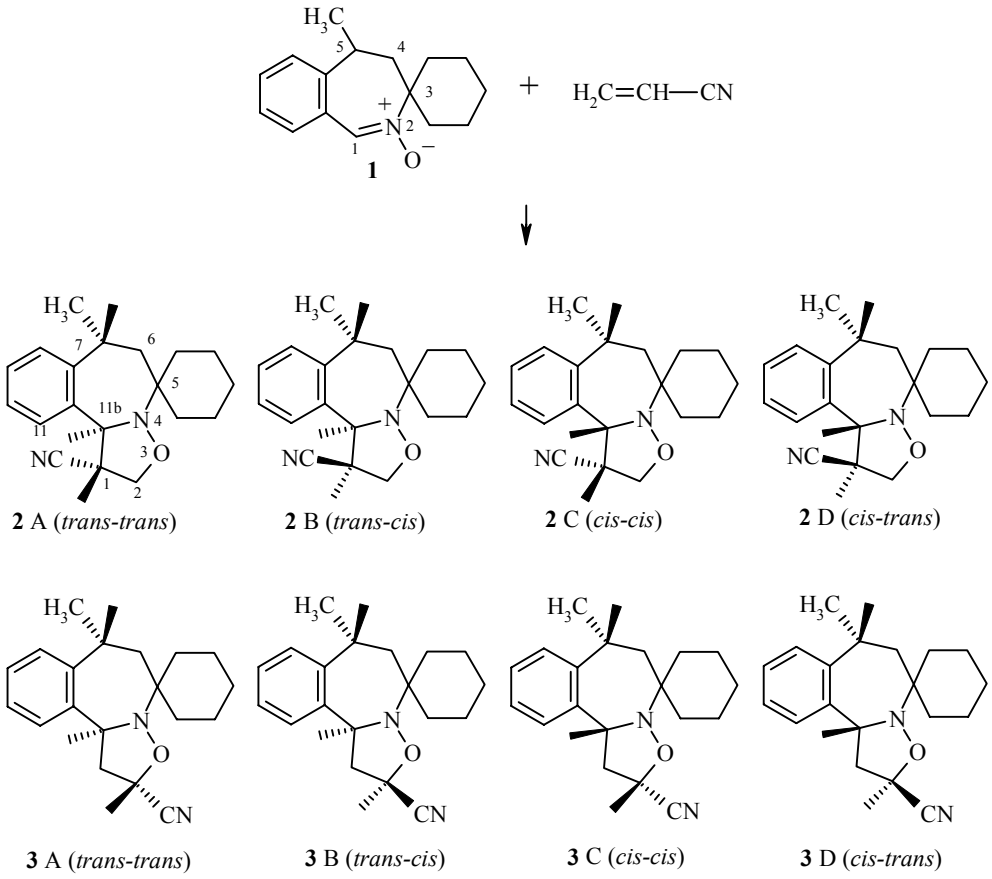
Depending on the orientation of acrylonitrile in the cycloaddition process two regioisomers may be formed. These are 1-cyano- and 2-cyano-7-methyl-1,2,4,6,7,11b-hexahydro-5H-spiro[isoxazolidino[3,2-*a*]benz-2-azepine-5,1'-cyclohexanes] (**2** and **3** respectively). Four geometric isomers are possible for each regioisomer, since acrylonitrile can add both at the *cis* and *trans* position relative to the 5-CH_3 of compound **1** and cycloaddition takes place both through *exo* and *endo* transition states. The cycloaddition adduct may therefore be in the form of eight isomers **2A-D** and **3A-D** the configuration of which may be characterized by the mutual arrangement of the hydrogen atoms 7-H, 11b-H, and 1-H (in the **2A-D** series), or 2-H (in the **3A-D** series).

The 5-CH_3 group occupies a pseudoequatorial orientation in nitrone **1**.



The reaction mixture obtained on carrying out the synthesis in toluene was subjected to chromatographic separation. The **2A-D**, **3A**, and **3C** isomers were isolated in an individual state in this way but the **3B** and **3D** isomers were obtained as a mixture with a main component content of 60-70%. The compositions of the reaction mixtures are given in Table 1.

The content of isomers **2A-D** and **3A-D** in the reaction mixtures was determined from the integrated intensities of signals in the ^{1}H NMR spectra in the 2.3-4.9 ppm region. The parameters of the characteristic signals in the ^{1}H NMR spectra of the isomers of **2** and **3** are given in Table 2. The structures of all the isomers of **2** and **3** were established by ^{1}H and ^{13}C NMR spectra using homonuclear (^{1}H–^{1}H) and heteronuclear (^{1}H–^{13}C) correlation spectroscopy and also by measuring nuclear Overhauser proton-proton effects (the establishment of the stereochemistry of the isomers of **2** and **3** is reported in a separate publication).

TABLE 1. Composition of Reaction Mixtures, Type of Transition State, and Direction of Attack of Acrylonitrile on Cycloaddition to Compound **1**

Compound	Content in reaction mixtures, %*		Type of transition state	Direction of attack of acrylonitrile relative to 7-CH_3	Relative positions of 7-H, 11b-H, 1-H (**2**) and 2-H (**3**)
	at 20°C*[2]	at 105°C*[3]			
2A	16	34	*exo*	*trans*	*trans-trans*
2B	15	6	*endo*	*trans*	*trans-cis*
2C	5	2	*endo*	*cis*	*cis-cis*
2D	17	25	*exo*	*cis*	*cis-trans*
3A	16	7	*exo*	*trans*	*trans-trans*
3B	3	7	*endo*	*trans*	*trans-cis*
3C	17	7	*exo*	*cis*	*cis-cis*
3D	11	12	*endo*	*cis*	*cis-trans*

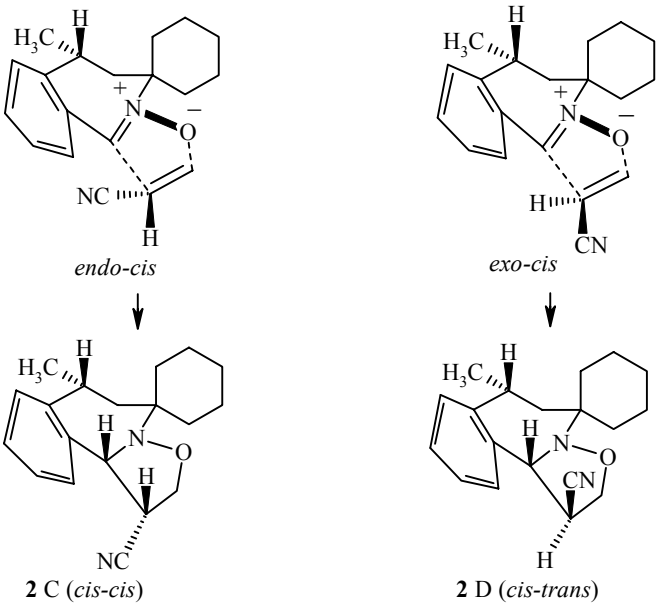
* Determined from ^{1}H NMR spectra.
*[2] After 7 days storage in the ^{1}H NMR spectrometer tube at 20°C, ratio **2**/**3** was about 1:1.
*[3] After 24 h refluxing in toluene, ratio **2**/**3** was about 1:2.

As is seen from the data of Table 1, under conditions of kinetic control (20°C) the cycloaddition reaction does not proceed regio- or stereoselectively. The ratio of the regioisomers **2**/**3** is about 1 : 1. All the stereoisomers except for **2C** and **3B** are formed in similar yield. The transition state for compounds **2C** and **3B** is probably sterically hindered. At 20°C the extent of conversion of **1** into **2** and **3** after 30 min was 9%. After 7 days the reaction has practically finished, conversion was 93%. The ratio of isomers in the reaction mixture was practically unchanged throughout. At 105°C cycloaddition became regiodirected. Regioisomer **2** predominated in the reaction mixture (ratio **2/3** was about 2 : 1), corresponding to the polarization of the double bond in acrylonitrile. Stereoselectivity also grew for isomer **2**. All the features mentioned may be explained satisfactorily by the concepts of the reversibility of cycloaddition and kinetic and thermodynamic control [2, 10]. The content of stereoisomers **2A-D** and **3A-D** in the reaction mixtures is determined both by the direction of approach of acrylonitrile to the nitrone fragment of compound **1** (*cis* and *trans* addition relative to the 5-CH_3 group), and also by the type of transition state (*exo* or *endo*). At 20°C *cis* and *trans* addition of acrylonitrile proceeds with equal probability [ratio of adducts of *cis* and *trans* addition Σ(**2C, 2D, 3C, 3D**)/Σ(**2A, 2B, 3A, 3B**) is about 1 : 1], at 105°C *trans* addition is preferred somewhat (ratio is about 1:1.2). However for each of the regioisomers **2** and **3** it is possible to note the feature of the direction of addition of acrylonitrile to nitrone **1**, caused probably by steric factors. On forming regioisomer **2** both at 20°C and at 105°C *trans* addition of acrylonitrile is preferred [at 20°C Σ(**2C, 2D**)/Σ(**2A, 2B**) is about 1:1.3, at 105°C about 1:1.5]. On forming regioisomer **3** *cis* addition is preferred (at 20 and 105°C *cis/trans* is about 1.4:1).

As already mentioned acrylonitrile may add to nitrone **1** by two diastereo-selective routes, through the *endo* and *exo* transition states. In the case of the cycloaddition of conjugated alkenes to cyclic nitrones under conditions of kinetic control, adducts of *exo* addition usually predominate [4, 7, 11]. The *endo* and *exo* transition states for the addition of acrylonitrile on forming regioisomer **2** for example are shown in the scheme.

TABLE 2. ^{1}H NMR Spectra of Isomers **2A-D** and **3A-D** in C_6D_6

Compound	Chemical shift, δ, ppm (multiplicity)						Coupling constant, *J*, Hz					
	1A-H	1B-H	2A-H	2B-H	7-H	11b-H	1, 1	1, 2A or 2, 1A	1, 2B or 2, 1B	1A, 11b	1B, 11b	2, 2
2A	2.67 (ddd)		3.52 (dd)	3.33 (t)	3.32 (m)	4.64 (d)	—	5.2	8.2	7.2		8.2
2B	2.87 (dt)		3.71 (dd)	3.32 (dd)	3.74 (m)	4.21 (d)	—	3.6	7.2	7.2		8.4
2C	2.78 (dt)		3.71 (dd)	3.29 (dd)	2.79 (m)	4.11 (d)	—	3.6	6.0	6.0		8.0
2D	3.24 (ddd)		3.66 (dd)	3.48 (dd)	2.65 (m)	4.65 (d)	—	4.8	6.4	6.8		8.0
3A	2.34 (ddd)	~1.87 (br. m)	3.88 (dd)		3.34 (m)	4.58 (t)	12.8	2.0	8.2	8.4	8.4	—
3B	2.24 (ddd)	2.20 (ddd)	3.88 (dd)		3.51 (m)	4.11 (t)	12.2	8.4	5.6	8.4	8.4	—
3C	2.62 (ddd)	1.80 (ddd)	3.95 (dd)		2.83 (m)	4.11 (dd)	12.8	4.4	7.6	7.0	8.8	—
3D	2.52 (ddd)	1.86 (ddd)	4.05 (dd)		2.77 (m)	4.52 (dd)	12.2	7.6	1.6	11.2	5.2	—



Analysis of the *endo/exo* selectivity for our case shows that at 20°C cycloaddition also occurs predominantly through the *exo* transition state. For regioisomer **2** the ratio of Σ(**2A, 2D**)/Σ(**2B, 2C**) is about 1.6:1, for regioisomer **3** *exo/endo* is about 2.3:1. At 105°C on forming the stereoisomers of compound **2** the fraction of *exo* adducts grew to 7.9:1. When forming isomers **3** *endo* addition begins to predominate (*exo/endo* is about 1:1.4), which is probably caused by the secondary orbital interaction of the boundary orbitals of the nitrone nitrogen atom and the acrylonitrile nitrile group carbon atom [12]. On *trans* addition of acrylonitrile to regioisomer **3** the ratio of *exo* and *endo* adducts (**3A**/**3B**) changes from 4.9:1 at 20°C to 1:1 at 105°C, and on *cis* addition (**3C**/**3D**) from 1.5:1 to 1:1.7 respectively. The rules noted for regio- and stereoselectivity for the cycloaddition of acrylonitrile to nitrone **1** are satisfactorily explained by steric and secondary orbital interactions and also by the reversibility of the cycloaddition reaction.

Study of the mass spectrometric behavior under electron bombardment of the regioisomers **2A-D** and **3A,3C** (Table 3) isolated in a pure state showed that in the mass spectra of all the compounds a molecular peak was observed with *m/z* 296 corresponding to their empirical formula. Peaks with *m/z* 226 and 253 had the greatest intensity in the spectra. The formation of fragment ions with *m/z* 281, 267, and 253 is linked with decomposition of the cyclohexane ring (fissions 1-3) and ejection respectively of methyl, ethyl, and propyl radicals.

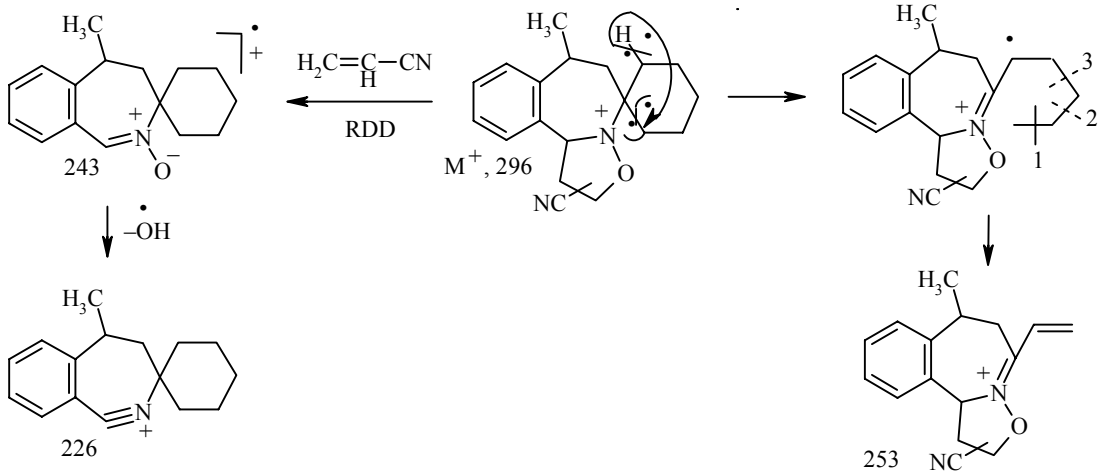


TABLE 3. Intensity (I_{rel}, %) of the Main Fragment Ions in the Electron Bombardment Mass Spectra of Cyano-substituted Spiro[isoxazolo[3,2-*a*]-5H-benz-2-azepine-5,1'-cyclohexanes] **2** and **3**

Compound	Ions, *m/z*											
	296 M^+	281	267	253	243	226	211	201	185	184	170	169
2A	28	14	9	68	11	100	19	10	16	—	—	52
2B	15	4	4	16	14	100	13	11	13	—	35	—
2C	14	2	4	22	16	100	13	10	—	12	—	10
2D	42	13	28	100	11	75	17	10	—	13	—	18
3A	13	20	7	82	13	85	12	14	—	15	10	—
3C	37	11	16	100	15	73	12	12	—	15	10	—

TABLE 4. Characteristics of the Spiro[isoxazolidinobenz-2-azepine-5,1'-cyclohexanes] **2A-D** and **3A,3C** Isolated in a Pure State

Compound	Found, % / Calculated, %			mp, °C (hexane)	IR spectrum, ν_{CN} (cm^{-1})	R_f *[3]	Yield, % *[4]
	C	H	N				
2A	76.82 / 77.00	7.85 / 7.70	9.46 / 9.46	104.0-106.5	2244	0.60	7.7
2B	76.90 / 77.00	7.50 / 7.70	9.32 / 9.46	133.0-133.5	2246	0.28	8.9
2C	77.21 / 77.00	7.43 / 7.70	9.58 / 9.46	126.0-127.0	2256	0.26	6.1
2D	— / 77.00	— / 7.70	— / 9.46	*[2]	2248	0.25	>1.0
3A	76.80 / 77.00	7.81 / 7.70	9.42 / 9.46	105.5-106.5	2248	0.43	7.2
3C	76.71 / 77.00	7.71 / 7.70	9.68 / 9.46	128.0-129.0	2245	0.36	7.4

* The empirical formula of all the compounds synthesized is $C_{19}H_{24}N_2O$.
*[2] Due to the low yield this compound was characterized by IR and ^{1}H NMR spectroscopy and mass spectrometry.
*[3] Ethyl acetate–hexane, 1:4.
*[4] Yield of pure isomers after chromatographic separation.

The high intensity of the ion with *m/z* 253 is caused by the formation of a relatively stable conjugated system [13]. The second direction of fragmentation of the M^+ ions is linked with elimination of a molecule of acrylonitrile as a result of a retrodiene decomposition (RDD). The resulting ion of the initial nitrone with *m/z* 243 splits off an $HO^{\cdot}$ radical giving a fragment ion with *m/z* 226. The characteristic fragment ions mentioned above confirm the structure of compounds **2** and **3**, however they do not make it possible to make any proposals for their stereochemistry.

EXPERIMENTAL

The IR spectra were recorded on a UR 20 instrument in KBr tablets. The mass spectra were measured on a Varian MAT 112 instrument with direct injection of samples into the ion source at an ionizing potential of 70 eV. The ^{1}H NMR spectra of approximately 7% solutions of isomers **2A-D, 3A, 3C** and mixtures of **3B** and

3D, and also the reaction mixtures in C_6D_6 were recorded at 20°C on a UNITY plus 400 spectrometer with an operating frequency of 400 MHz. Chemical shifts were measured relative to the signal of the residual protons of the solvent ($C_6\underline{H}D_5$ 7.15 ppm). Neutral aluminum oxide of zero activity on the Brockmann scale was used for column chromatography, Silufol UV 254 plates were used for TLC, visualization was with iodine vapor.

1-Cyano- and 2-Cyano-7-methyl-1,2,4,6,7,11b-hexahydro-5H-spiro[isoxazolidino[3,2-*a*]benz-2-azepine-5,1'-cyclohexanes] (2A-D and 3A-D). A solution of nitrone **1** (1.70 g, 7.00 mmol) and acrylonitrile (1.12 g, 21 mmol) in toluene (30 ml) was refluxed for 24 h. The toluene and the remainder of the acrylonitrile were removed in vacuum. The glassy mass obtained was chromatographed on a column of aluminum oxide (60 × 1.5 cm), eluent was ethyl acetate–hexane 1:50. The overall yield of all the fractions isolated was 85% (Table 4).

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