ESTABLISHMENT OF THE CONFIGURATION OF 2,3,4,4a,9,9a-HEXAHYDRO-INDENO[2,1-b]-1,4-OXAZINES ACCORDING TO ^1H AND ^{13}C NMR DATA

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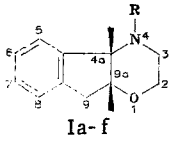
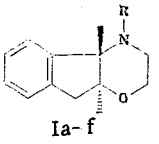
It was shown by a study of the ^1H and ^{13}C spectra of derivatives of 2,3,4,4a,9,9a-hexahydroindeno[2,1-b]-1,4-oxazines that the investigated compounds are mixtures of cis- and trans-isomers. On the basis of a comparison of the chemical shifts of ^{13}C in indanoxazines and stereoisomers of decalin, as well as the values of the spin–spin interaction constants of indanoxazines and indanopiperidine (J_{4a9a}), it was concluded that the cis-isomer predominates in the mixture of isomers.

In the synthesis of 2,3,4,4a,9,9a-hexahydroindeno [2,1-b]-1,4-oxazines(Ia-f) by cyclization of aminoindandiones in 70% H_2SO_4 it was found that the reaction proceeds nonstereospecifically [1]. On the basis of the data of thin-layer chromatography, IR and mass spectra it was suggested that the compounds isolated exist in the form of a mixture of cis- and trans-isomers.



Ia-f

cis-Isomer



Ia-f

trans-isomer

a R=H; b R=CH_3; c R=C_2H_5; d R=$CH(CH_3)_2$; e R=n-C_4H_9; f R=cyclohexyl

A confirmation of these data and an establishment of the ratio of the isomers in the mixture were performed in this work by NMR spectroscopy.*

In the ^{13}C spectrum of the unsubstituted compound Ia in the region of the signals of the saturated carbon atoms, a double set of signals of substantially different intensity is observed (Fig. 1). Such a nature of the spectrum corresponds to the data on the fact that the compound is not individual but represents a mixture of cis- and trans-isomers. Considering the influence of the electronegativity of the neighboring atoms on the chemical shift of the sp^3-hybridized carbon atom, the ^{13}C spectrum of compound Ia in a system of incomplete suppression of spin–spin interaction with protons permits the signals of the carbon atoms to be assigned in each of the isomers. The doublet signals at 77.9 and 60.8 ppm in the predominant isomer were assigned to $C_{(9a)}$ and $C_{(4a)}$, respectively, in agreement with the electronegativities of the neighboring heteroatoms. By analogy, the signals of the carbon atoms of the methylene groups – triplets at δ 66.5, 40.7, and 37.8 ppm – were assigned to $C_{(2)}$, $C_{(3)}$, and $C_{(9)}$ of this isomer. The assignment of the last two signals, close in chemical shifts, is confirmed by the correlated dependence of the chemical shifts of $C_{(3)}$ and $C_{(4a)}$ on the substituent at the nitrogen atom in the entire series of compounds under consideration. The substantially less intense signals of the atoms $C_{(9)}$, $C_{(3)}$, $C_{(2)}$, $C_{(4a)}$ and $C_{(9a)}$ of the

*The ^{13}C and ^1H NMR spectra were recorded on a Varian XL-100A spectrometer with working frequency 25.2 MHz for ^{13}C and 100 MHz for ^1H.

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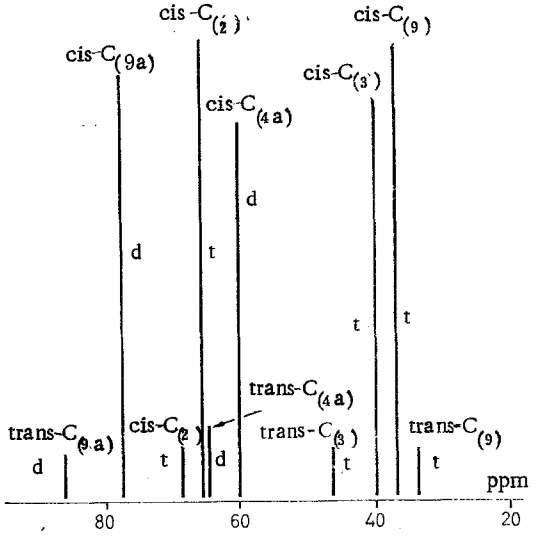

Fig. 1. ^{13}C NMR spectrum (with complete suppression of spin–spin interaction with protons) of compound I in $CDCl_3$.

second isomer are arranged in the same sequence in the spectrum of compound Ia (Fig. 1, Table 1).

An analogous type of spectrum in the region of the signals of the saturated carbon atoms corresponding to a mixture of cis- and trans-isomers was also observed for N-substituted derivatives Id-f (Table 1). As can be seen from Table 1, the difference of the chemical shifts of the same carbon atoms in cis- and trans-isomers Ia, d-f reaches 7 ppm; moreover, the signals of the carbon atoms of the bond, common to the indene and morpholine nuclei ($C_{(4a)}$ and $C_{(9a)}$) in the predominant isomer are responsible for the strong-field shift. A difference of the chemical shifts of the carbons of the bond between rings, of the same order of magnitude, is observed in the spectra of cis- and trans-isomers of decalin and decahydroquinoline [2]; moreover, in a stronger field the signals of the carbon atoms of the cis-isomer are noted. On this basis it can be assumed that in the investigated mixtures of isomers of indenoxazines, the cis-isomer predominates. We should mention that the strong-field shift of most of the carbon atoms of the cis-isomers in Ia, d-f in comparison with the trans-isomers can be explained by steric hindrance of the cis-isomers [3].

The conclusion of a cis-configuration of the predominating isomer of indenoxazines is also confirmed by the ^1H spectra of mixtures of isomers Ib-f. It is known that the spin–spin interaction constants of the vicinal protons, oriented in the cis- or trans-positions relative to one another, differ appreciably; moreover, for six-membered rings $J_{cis} < J_{trans}$ [4]. Thus, for example, for cis- and trans-3-methyl-9-phenylindenopiperidine [5, 6], the steric structure of which is close to the structure of indenoxazines, the values of J_{4a9a}^{cis} and J_{4a9a}^{trans} are equal to 6 and 11 Hz, respectively.

In the spectra of compounds Ib-f the signals of the protons in the positions 2, 3, 4a, and 9 of the two isomers are observed in the region of 2.0-3.9 ppm in the form of overlapping multiplets. The signal of the proton in the 9a-position is separate from this group (4.20-4.40 ppm). However, the determination of J_{4a9a} according to its splitting (octet in spectrum Ib and quartet in Ic-f) is not unambiguous. When tris-(dipivaloylmethanato)europium is added to a solution (in C_6D_5Br) of compounds Ib-f, all signals are shifted in the weak-field direction; moreover, with increasing C_p/C_s in the spectra a doublet of the proton in the 4a-position is distinguished. The value of J_{4a9a} for all the investigated compounds is equal to 5 Hz, which permits this doublet to be assigned to the proton of the cis-isomer. The doublet of the proton 4a-H of the trans-isomer cannot be distinguished in the spectrum. Evidently this is due to the low content of this isomer in the mixture of isomers. Actually, according to the ^1H spectrum of compound Ib ($CDCl_3$ + $Eu(dpm)_3$), in which the signals of the N–CH_3 groups are distinguished in both isomers, it was found that the content of the trans-isomer does not exceed 10%.

TABLE 1. Chemical Shifts of ^{13}C (ppm) in 2,3,4,4a,9,9a-Hexahydroindeno[2,1-b]-1,4-oxazines*

R	$C_{(2)}$		$C_{(3)}$		$C_{(4a)}$		$C_{(9a)}$		$C_{(9)}$	
	cis	trans	cis	trans	cis	trans	cis	trans	cis	trans
H	66,5	68,5	40,7	45,9	60,8	65,5	77,9	84,4	37,8	34,2
p-C_4H_9	63,3	67,9	47,6	54,2	66,6	71,3	76,8	83,7	36,3	34,9
$CH(CH_3)_2$	64,7	68,8	43,1	44,5	63,0	64,7	77,8	84,7	35,9	34,8
Cyclohexyl	64,7	68,6	43,5	46,3	62,7	63,7	77,5	84,5	36,3	34,5

*Solutions in $CDCl_3$, internal standard TMS.

Thus, indenoxazines of type I, isolated during the synthesis described earlier [1], represent a mixture of cis- and trans-isomers with substantial predominance of the former.

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2-[HYDROXY(DIALKYL)METHYL]-4-ARYL-6,6-DISUBSTITUTED 4,5-DIHYDRO-6H-1,3,4-OXADIAZINONES-5

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The reactions of arylhydrazides of dialkylglycolic acids with chlorides of α-halocarboxylic acids, followed by cyclization, yielded 2-[hydroxy(dialkyl)methyl]-4-aryl-6,6-disubstituted 4,5-dihydro-6H,1,3,4-oxadiazinones-5.

It is known that halides of α-halocarboxylic acids react with amides, forming 4(5H)-oxazolines [1], while with hydrazides they give derivatives of 4,5-dihydro-6H-1,3,4-oxadiazinone-5 [2]. It is interesting to study arylhydrazides of dialkylglycolic acids, which have a more complex acid residue, in this reaction. However, experiments showed that the formation of a seven-membered ring with attack at the hydroxy group is not observed, and the reaction proceeds analogously to the conversion of the phenylhydrazide of acetic acid [2] with the formation of 2-[hydroxy(dialkyl)methyl]-4-aryl-6,6-disubstituted 4,5-dihydro-6H-1,3,4-oxadiazinone-5 (IVa-m). Such a course of the reaction is explained by the negative inductive effect of the carbonyl groups, as well as by the preferential formation of a six-membered ring:

In the acid chloride IIa the mobility of the α-chlorine atom is so great that the intermediate acyl derivative cannot be isolated, and substances IVa-k are formed immediately when compounds Ia-k and IIa are boiled in benzene. Compounds IVl and IVm are formed from the corresponding acyl derivatives IIIb, when they are boiled in anhydrous acetone with potassium carbonate [2]. The synthesized compounds are presented in Table 1. They are colorless crystalline substances (with the exception of IVl), insoluble in water, readily soluble in alcohol,

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