THE CONFIGURATION OF ESTERS OF β-(INDOL-3-YL)-α-NITROACRYLIC ACID

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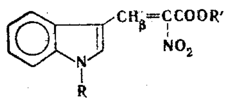
UDC 541.634: 547.757

It has been shown by PMR spectroscopy that for the methyl and benzyl esters of β-(indol-3-yl)-α-nitroacrylic acid and their N-acetylated derivatives the isomers with the cis arrangement of the nitro group and the indole nucleus are the more stable.

Esters of β-(indol-3-yl)-α-nitroacrylic acid (I and II), the synthesis of which has been described previously [1] can exist in the form of cis and trans isomers.



I a $R=H$, $R'=CH_3$;
b $R=COCH_3$, $R'=CH_3$
II a $R=H$, $R'=CH_2C_6H_5$;
b $R=COCH_3$, $R'=CH_2C_6H_5$

It has been found that in the PMR spectra of compounds (Ia) and (IIa) there is a double set of signals corresponding to the two geometric isomers in relative proportions of 3 : 2. In the aromatic region, in addition to the complex multiplets due to the protons of the benzene ring, there are two singlets from the β-H and 2-H protons, one of which is considerably broadened. After the addition of CD_3OD, this signal becomes considerably narrower. On this basis, the broadened signal was ascribed to the proton at C_2, interacting with N_1H, and the other one to the proton at C_β. However, even after the elimination of the influence of NH, the signal of the 2-H proton proved to be wider than that of the β-H. This broadening is apparently due to interaction with the protons of the benzene ring or to the influence of quadrupole relaxation of the N atom. In the spectrum it is possible to observe the long-range SSCC of the 2-H and β-H protons (J = 0.6 Hz).

The isomers (Ia) and (IIa) could not be separated by crystallization or by chromatography on various adsorbents. When a benzene solution of the mixture (Ia) or (IIa) with a ratio of the isomers of 3 : 2 was irradiated with a quartz–mercury lamp for 1 h, the partial conversion of the more stable isomer into the other one took place, and the relative proportion of the isomers became 1 : 1.

When a solution of compound (Ia) was heated to 65°C [solvent $(CD_3)_2CO$], a fusion of the analogous signals of the two isomeric forms was observed. Such a low temperature of coalescence indicates a low barrier to rotation around the C=C double bond.

For compounds (Ib) and (IIb), acetylated at the nitrogen atom, it was possible to isolate one of the isomers in the pure form in each case. The second isomers of (Ib) and (IIb) were isolated by preparative chromatography on plates coated with silica gel (Ib, R_f 0.69, 0.61*; IIb, R_f 0.57, 0.46); however, they very rapidly isomerized and in the PMR spectra they already appeared in the form of a mixture of isomers. When the spectra of (Ib) and (IIb) in $(CD_3)_2CO$ were recorded at 60°C, it was possible to observe the partial transformation of the more stable into the less stable isomers. Equilibrium was achieved after about 20 min. In the region of aromatic signals, in addition to the multiplets from the protons of the benzene ring, two singlets were observed due to the 2-H and β-H protons (J = 0.6-0.8 Hz), while for both the isomers

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* For (Ib) the eluent was benzene–ether (4 : 1), and for (IIb) it was benzene.

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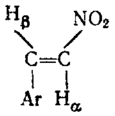
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 86-89, January, 1974. Original article submitted January 2, 1973.

TABLE 1. Calculated and Experimental Values of the Chemical Shifts of the α-H and β-H Protons in (III) (ppm)

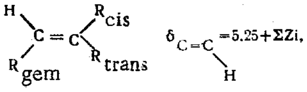
Calculation	Experiment*	$\Delta\delta=\delta_{calc}-\delta_{exp}$
	IIIa δα-H 7,73 δβ-H 8,27	$\Delta\delta_{\alpha\text{-}H}$ —0,12 $\Delta\delta_{\beta\text{-}H}$—0,17
δα-H 7,61 δβ-H 8,10	IIIb δα-H 7,74 δβ-H 8,15	$\Delta\delta_{\alpha\text{-}H}$—0,13 $\Delta\delta_{\beta\text{-}H}$—0,05

*Solvent – $CDCl_3$.

one of the singlets was somewhat broadened. As in the case of the N-unsubstituted derivatives, the broadened singlet was ascribed to the proton at C_2.

Attention is attracted by the considerable difference in the values of the chemical shifts of the β-H protons for each pair of isomers: 0.55 ppm (Ia), 0.45 ppm (Ib), 0.51 ppm (IIa), and 0.45 ppm (IIb), the β-H signals in the stable isomers being located in the stronger field. This can be used to determine the configuration of compounds of this series.

Pascual et al. [2, 3] have proposed a scheme of calculating chemical shifts of protons of substituted olefins which additively takes into account the influence of the substituents present in the gem, cis, and trans positions relative to the proton being determined.

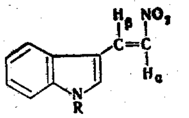


$$\delta_{C=C-H}=5.25+\Sigma Zi,$$

where Zi represents the increments of the substituents for the gem, cis, and trans positions.

We have made use of this scheme to evaluate the chemical shifts of the β-H protons in the two isomeric forms, and on this basis have made an assignment of the configuration in compounds (I) and (II). The values of the increments of the NO_2* and COOR groups were taken from the literature [3, 4]. Since in finding the values of the increments the heteroaromatic systems were not considered, in our calculations the increments for the indole ring were taken as equal to the increments of the aromatic systems [3].

To evaluate the justification for such a change, a calculation was performed on the chemical shifts of the α and β protons in compounds (III) (a, b) the trans configuration of which had been established from the values of the SSCCs of α-H and β-H (J = 13.6 Hz (IIIa) and 13.8 Hz (IIIb)).



III a R=H;
b R=Ac

The calculated and experimental values of the chemical shifts of the α-H and β-H protons in (III) are given in Table 1. It follows from Table 1 that these values for (IIIa and b) are in good agreement and Δδ does not exceed 0.17 ppm [3]. Thus, to take into account the influence of the N-unsubstituted and N-acetylated indole rings it is possible to use the increments for the aromatic ring. The cis isomer was not available to us, but calculation for it gave values of the chemical shifts of 7.18 ppm for the α-H and 7.09 ppm for the β-H. The differences in the values of the calculated chemical shifts for α-H and β-H for the trans and cis isomers are fairly large ($\Delta\delta_{\alpha-H}$ = 0.43, $\Delta\delta_{\beta-H}$ = 1.01 ppm). Hence, when two isomeric forms are present, the possibility arises of determining the configuration of each isomer from the difference in the chemical shifts of the α-H and, in particular, the β-H protons.

This method of calculation was used for compounds (I) and (II). From a comparison of the calculated values of the chemical shifts of β-H for the cis and trans isomers (Table 2) it can be seen that, as was the

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*In the paper of Descotes et al., a printing error has been found for the value of Z_{cis} of the NO_2 group: Z_{cis} = 1.47 ppm (and not 1.67 ppm).

TABLE 2. Calculated and Experimental Values of the Chemical Shifts of the β-H Protons in (I) and (II) (ppm)

Compound		trans* Configuration	cis Configuration	$\Delta\delta_{trans-cis}$
Ia	δ calc	8,55	8,10	0,45
	δ exp	8,52†	7,97	0,55
	$\Delta\delta$ calc-exp	0,03	0,13	—
IIa	δ exp	8,46	7,95	0,51
	$\Delta\delta$ calc-exp	0,09	0,15	—
Ib	δ exp	8,19	7,74	0,45
	$\Delta\delta$ calc-exp	0,36	0,36	—
IIb	δ exp	8,20	7,75	0,45
	$\Delta\delta$ calc-exp	0,35	0,35	—

*The trans isomer is considered to be that in which the indole ring and the NO_2 group are in the trans position with respect to one another. In this case, the universal configurational symbols E and Z are less clear.

†Solvent – $CDCl_3$.

case for the disubstituted derivatives, the trans isomer has the β-H signal in a weaker field than the cis isomer, although the difference $\Delta\delta_{trans-cis}$ for the β-H (0.45 ppm) is somewhat smaller than in the case considered (1.01 ppm). Starting from this, as the signals of the trans isomers in the spectra we took the signals present in the weaker field and under these circumstances the difference $\Delta\delta_{trans-cis}$, as noted above, was in the range from 0.45 to 0.55 ppm for all the pairs of isomers, i.e., extremely close to the calculated figure. The assignment of the isomers of compounds (Ia, Ib, IIa, and IIb) to the cis and trans forms was made on this basis. It follows from this that the most stable isomers proved to be those with the cis arrangement of the nitro groups and the indole rings. It can be seen from Table 2 that the agreement of the calculated and experimental values of the chemical shifts of the of the β-H protons for (Ia) and (IIa) is good. For the N-acetylated derivatives (Ib and IIb) the deviation of the calculated and experimental values is greater than can be accepted. Apparently, the presence of the N-acetyl groups in the indole ring leads to considerable dipole–dipole interactions with the voluminous NO_2 and COOR acceptor groups, which, in its turn, disturbs the additivity of the influence of the substituents. The causes of such deviations in compounds of types (I) and (II) are being made the subject of further investigation.

EXPERIMENTAL

The PMR spectra were taken on a JNM 4H-100 spectrometer with a working frequency of 100 MHz and a C-60-HL spectrometer with a working frequency of 60 MHz. The internal standard was tetramethylsilane.

Compounds (Ia and IIa) were obtained by the method of Babievskii et al. [5], and compounds (Ib) and (IIb) by the method of Vinograd et al. [6].

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