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SPATIAL STRUCTURE OF 3-ACYL-2-METHYLINDOLE OXIMES

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UDC 547.753'288.4:541.634:543.422

It has been established on the basis of the results of ^{1}H and ^{13}C NMR, UV, and IR spectroscopy that 3-acyl-2-methylindole oximes each exist in the form of a mixture of two isomers with a predominance of syn-s-trans form. The proportion of the anti form rises (to 25-35%) with an increase in the volume of the alkyl radical in the oxime grouping.

It has been shown previously that oximes of 2-unsubstituted 3-acylindoles exist mainly in the syn-s-trans form [1]. The aim of the present investigation was to determine the influence of a methyl group in position 2 of the indole nucleus on the spatial structure of the oximes.

The introduction of a methyl group also substantially changes the spectral properties of the 3-acylindole oximes. Thus, in the UV spectra of the 3-acyl-2-methylindole oximes two absorption bands are observed, at 225-231 and 280-283 nm, while in the spectra of the 2-unsubstituted oximes three absorption maxima appear, at 222-226, 257-259, and 283-290 nm. The disappearance of one of the absorption bands on the introduction of a methyl group into position 2 of the indole nucleus is apparently due to a disturbance of the coplanarity of the system and of the conjugation of the indole nucleus with the oxime grouping caused by steric hindrance between the methyl group and the radical in the oxime grouping.

The IR spectra of the oximes are unsuitable for answering the question of structure, since the bands of the C═N stretching vibrations in them lie in the 1610-1640 cm^{-1} region (Table 1) while the same band for unconjugated oximes is located at about 1640 cm^{-1} [2].

The PMR spectra of the 3-acyl-2-methylindole oximes show double sets of the signals of the protons of the methyl group in position 2, of the alkyl groups of the oxime residue, and of the hydroxy group (Table 2), which indicates the existence of two forms, due either to s-cis-trans or to syn-anti isomerism. A donor methyl group in position 2 changes the polarization and, consequently, the anisotropy of the C═N bond of the oxime grouping and causes a regular upfield shift of the signal of the 4-H proton as compared with 2-unsubstituted 3-acylindole oximes (Δδ 0.40-0.55 ppm). In spite of this, the signal of the 4-H proton remains in a weaker field than that for indole itself, which permits the assumption of the retention of the s-trans conformation and the ascription of the presence of two forms to syn-anti isomerism.

M. V. Lomonosov Moscow State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 65-68, January, 1984. Original article submitted July 19, 1983.

0009-3122/84/2001-0055$08.50

TABLE 1. 3-Acyl-2-methylindole Oximes (Ia-j)

Compound	R^1	R^2	mp, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, C=N, cm^{-1}	Found, %		Empirical formula	Calc, %		Yield, %
						C	H		C	H	
Ia	H	H	208—209	228 (4,38), 273 (4,00)	1615	70,6	6,7	$C_{11}H_{12}N_2O$	70,2	6,4	90
Ib	CH_3	H	248—249	231 (4,24), 284 (3,93)	1640, 1620 (tr.)	71,3	6,9	$C_{12}H_{14}N_2O$	71,3	6,9	69
Ic	H	CH_3	133—134	227 (4,38), 275 (4,00)	1620	71,6	7,1	$C_{12}H_{14}N_2O$	71,3	6,9	59
Id	CH_3	CH_3	223—224	229 (4,27), 283 (3,95)	1640 (tr.)	72,4	7,5	$C_{13}H_{16}N_2O$	72,2	7,4	78
Ie	H	C_2H_5	131—132	226 (4,40), 275 (3,98)	1617	71,9	7,6	$C_{13}H_{16}N_2O$	72,2	7,4	69
If	H	C_3H_7	170—171	226 (4,42), 275 (4,00)	1615	72,8	7,9	$C_{14}H_{18}N_2O$	73,0	7,8	58
Ig	H	*iso*-C_3H_7	111—112	226 (4,27), 275 (3,98)	1615	73,2	7,6	$C_{14}H_{18}N_2O$	73,0	7,8	68
Ih	CH_3	*iso*-C_3H_7	183—185	226 (4,45), 280 (3,99)	1630, 1610 (tr.)	73,5	8,4	$C_{15}H_{20}N_2O$	73,8	8,2	84
Ii	H	C_6H_5	155—156	226 (4,31), 277 (3,98)	1630, 1590 (tr.)	77,3	6,1	$C_{17}H_{16}N_2O$	77,3	6,1	80
Ij	CH_3	C_6H_5	186—187	226 (4,52), 283 (4,02)	1635, 1618 (tr.)	77,4	6,8	$C_{18}H_{18}N_2O$	77,7	6,5	78

TABLE 2. PMR Spectra of the 3-Acyl-2-methylindole Oximes

Compound	N—CH_3	2-CH_3		4-H	Protons of the CH_2R^2 radical		OH		NH
		syn	anti		syn	anti	syn	anti	
Ia	—	2,43	—	7,68	2,25 (s, CH_3)		9,68		10,02
Ib*	3,67	2,48	2,28	7,62	2,22 (s, CH_3)	2,16 (s, CH_3)	10,71	10,32	—
Ic	—	2,40	2,27	7,58	2,80 (q, CH_2); 1,05 (t, CH_3)	2,56 (q, CH_2); 0,93 (t, CH_3)	9,63	9,42	10,01
Id*	3,67	2,46	2,30	7,70	2,80 (q, CH_2); 1,07 (t, CH_3)	2,63 (q, CH_2); 0,98 (t, CH_3)	10,63	10,27	—
Ie	—	2,39	2,27	7,60	2,80 (t CH_2); 1,46 (m CH_2); 0,84 (t, CH_3)	2,54 (t, CH_2); 0,79 (t, CH_3)	9,64	9,38	10,01
If	—	2,40	2,28	7,60	2,83 (t, CH_2); 1,40 (m CH_2CH_2); 0,86 (t, CH_3)		9,72	9,56	10,04
Ig	—	2,37	2,27	7,82	2,79 (d, CH_2); 1,13 (d, CH_3)	2,47 (d, CH_2); 1,26 (d, CH_3)	9,99	9,65	10,60
Ih*	3,70	2,50	2,37	7,77	2,83 (d, CH_2); 0,8 (d, CH_3)		10,43	10,67	—
Ii*	—	2,33	2,20	7,73	4,20 (s, CH_2)		10,90	11,20	
Ij*	3,60 3,55†	2,35	2,17	7,73	4,40 (s, CH_2)	4,17 (s, CH_2)	10,85	11,27	—

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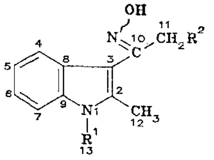
*The spectra of compounds (Ia, c, and e-g) were taken in acetone-d_6, and those of (Ib, d, and h-j) in DMSO-d_6.

†Signals of the protons of the N—CH_3 group in the anti form.

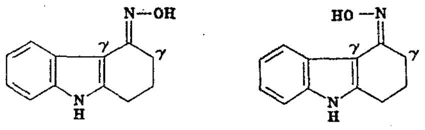
TABLE 3. ^{13}C NMR Spectra of the 3-Acyl-2-methylindole Oximes

Compound		C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13
Ia		134,24	109,10	119,50	119,80	120,90	110,89	126,65	135,02	151,23	13,41	14,91	—
Ib	syn	134,03	107,84	—	—	—	110,22	126,60	134,56	156,00	21,30	13,04	—
	anti	—	103,60	—	—	—	109,85	126,10	—	—	28,30	13,00	—
Id	syn	136,02	108,94	118,99	119,70	120,80	109,50	126,53	136,48	156,14	21,86	11,51	29,61
	anti	135,64	106,23	118,80	119,26	120,44	109,42	125,87	136,70	153,68	28,54	12,03	29,54
If	syn	134,25	108,83	119,06	120,38	121,44	111,53	127,22	135,17	155,23	27,98	13,50	—
	anti	134,05	106,16	118,65	120,04	121,06	111,09	126,88	135,39	152,71	34,26	13,18	—
Ik	syn	137,17	111,53	122,55	122,37	120,71	111,50	125,68	141,95	153,84	23,57	23,13	—
	anti	137,32	108,17	123,44	122,45	121,66	112,07	126,01	142,09	153,89	38,82	23,77	—

The question of the type of isomerism of the 3-acyl-2-methylindole oximes was answered definitely with the aid of ^{13}C NMR spectra (Table 3). The doubling of the signals of practically all the carbon atoms in the spectra also indicates the existence of two isomeric forms. If the existence of two forms were actually due to syn-anti isomerism, the so-called γ-effect, which is connected with the influence of the substituent (in our case, the hydroxyl group) in the γ-position with respect to the carbon atom under consideration (C-3 and C-11), on its chemical shift should appear [3].



Ia-j



Ik

s-trans-syn

s-trans-anti

This effect appears all the more strongly the greater is the number of protons on the carbon atom under consideration and the closer, spatially, is the γ-substituent. In actual fact, for the C-11 atom of 1,2-dimethyl-3-propionylindole oxime (Id), two signals were observed, one of them (28.54 ppm) being close to the signal of this carbon atom in the spectrum of the ketone (29.41 ppm), and the other, stronger, signal being shifted upfield (21.63 ppm), which is due to the γ-effect of the OH group in the syn position ($\Delta\delta_{C-11}$ 6.9 ppm). For the C-3 carbon atom, likewise, two signals are seen (105.95 and 108.76 ppm), the intensities of which have, as was to be expected for syn-anti isomerism, the opposite distribution, i.e., the more intense signal is located in the weaker field. In accordance with theoretical ideas, the γ-effect for this quaternary carbon atom is substantially less than for C-11 ($\Delta\delta_{C-3}$ 2.8 ppm).

It is known that the energy barriers of s-cis-trans and of syn-anti isomerisms differ substantially (ΔE 5-10 and 23 kcal/mole, respectively) [4, 5]. As an additional argument in favor of the existence of one or other type of isomerism, it is possible to use an investigation of the temperature dependence of the ^{13}C—{^{1}H} NMR spectra. In spectra taken at temperatures of 25, 140, and 165°C no differences whatever were observed — both the relative intensities of the signals and their positions remained unchanged and, consequently, the energy barrier for the transition of one form of oxime into the other was not reached; it can only be stated that it is greater than 22 kcal/mole, which is evidence in favor of syn-anti isomerism.

In the ^{13}C NMR spectrum of a model compound with a fixed s-trans conformation — the oxime of 1,2,3,4-tetrahydrocarbazol-4-one (Ik) — the signals of two forms likewise appeared, and these can exist only as the result of syn-anti isomerism. As also for the noncyclic 1,2-dimethyl-3-propionylindole oxime (Id), here the γ-effect of the hydroxy group appears clearly, the difference in the chemical shifts for the pairs of signals in the methylene and quaternary carbon atoms being 15.25 and 3.36 ppm, respectively. This fact is also a conformation of the syn-anti isomerism of the 3-acylindole oximes.

The predominant existence of the oximes studied in the syn-s-trans form can be explained by the steric hindrance arising between the hydroxy group of the oxime and the 4-H protons in the anti-s-trans form. A calculation of the coordination of the atoms (made in the planar approximation) for the 3-acetylindole oxime molecule in the anti form shows that the distance from the hydroxy group to a 4-H proton is less than the Van der Waals radii of the groups, i.e., a chemical bond should be formed between them. When the C-9 atom is selected as the origin of coordinates, the coordinates along the y axis for the 4-H and O atoms are 3.199 and 3.958 Å, respectively. For the calculation we used the experimental results on the geometry of the indole molecule and the standard values of the angles and lengths of the C═N, N—O, and O—H bonds [6].

Since the coplanarity of the system in the 3-acyl-2-methylindole oximes, which are additionally sterically hindered in comparison with the 2-unsubstituted oximes, is apparently disturbed, the steric hindrance to the existence of the anti-s-trans form decreases with a departure of the oxime grouping from the plane, which substantially lowers the proportion of anti isomer (according to PMR spectroscopy, it amounts to 25-35% of the total amount of oxime).

EXPERIMENTAL

PMR spectra were taken on T-60 and Varian XL-100/12 instruments in DMSO-d_6 and acetone-d_6 with TMS as internal standard; and ^{13}C NMR spectra were taken at 50°C in DMSO-d_6 on a CFT-20 instrument; UV and IR spectra were recorded on Perkin-Elmer 402 and 577 instruments, respectively. The individuality of the 3-acyl-2-methylindole oximes was checked by TLC on Silufol in the benzene–ethyl acetate (5:1) and benzene–methyl ethyl ketone (20:1) systems, with development of the spots by iodine vapor.

The 3-acyl-2-methylindole oximes (Ia-k) were obtained by a standard procedure [1], and their constants and yields are given in Table 1.

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SYNTHESIS OF O-VINYL ETHERS OF 3-ACYLINDOLE OXIMES AND THEIR HETEROCYCLIZATION TO PYRROLYLINDOLES

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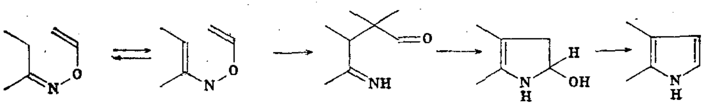
UDC 547.753'759.2'288.4.07:543.422

O-vinyl ether of 3-acylindole oximes have been synthesized and the possibility has been shown of their thermal conversion into pyrrolylindoles, which permits a heterocyclization mechanism including the stage of [3,3]-sigmatropic shift to be suggested.

In 1970, B. A. Trofimov et al. proposed a basically new method for constructing the pyrrole ring – the heterocyclization of ketoximes with acetylene in a superbasic medium [1]. We extended this heterocyclization to 3-acylindole oximes, which enabled the previously unknown 3-(pyrrol-2-yl)indoles to be obtained [2].

The question of the mechanism of the Trofimov reaction cannot be regarded as has been answered hitherto, although the discoverers of the reaction themselves have recently tended towards the opinion that the process takes place through the stage of a [3,3]-sigmatropic shift in O-vinyloximes formed as intermediates [3].



To answer the question of the possibility of such a mechanism in the case of ketoximes of the indole series, we set ourselves the aim of synthesizing O-vinyl ethers of 3-acylindole oximes and investigating the possibility of their conversion into the corresponding pyrrolylindoles. As a prerequisite for this was used the fact that 3-acylindole oximes exist predominantly in the syn configuration [4, 5] which may ensure the six-membered transition state that is necessary for a sigmatropic rearrangement.

The O-vinyl ether of 3-acetyl-1-methylindole oxime (Ia) was obtained from the corresponding oxime and acetylene in the superbasic medium KOH/DMSO at 65-70°C under an acetylene pres-

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M. V. Lomonosov Moscow State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 69-72, January 1984. Original article submitted July 19, 1983.

0009-3122/84/2001-0058$08.50