CRITERIA FOR ESTABLISHMENT OF THREE-DIMENSIONAL STRUCTURES OF DIELS–ALDER ADDUCTS IN THE ISOINDOLE SERIES. 2.* REACTION OF 1,2-DISUBSTITUTED ISOINDOLES WITH MALEINIMIDE DERIVATIVES

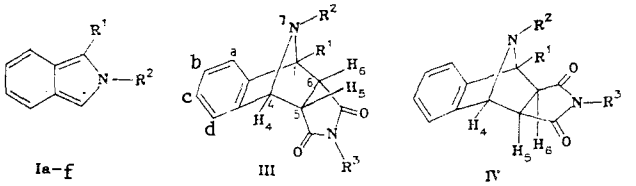
V. A. Kovtunenko, Z. V. Voitenko,
T. T. Kucherenko, A. V. Turov,
A. K. Tyltin, and F. S. Babichev

UDC 547.759.4:535.422.25:
541.634'124

The Diels–Alder reaction of a series of 1,2-disubstituted isoindoles with maleinimide derivatives under conditions of kinetic and thermodynamic control was investigated. Criteria for the establishment of the three-dimensional structures of the adducts obtained were found. The possibility of supra-antara cycloaddition and the formation of 1:2 adducts was demonstrated.

Reinterpretation of the role of pericyclic bonding is characteristic for the present stage in investigations of the Diels–Alder reaction that deal with the study of its mechanism. Some computational and experimental data of recent years compel one to ponder over the question as to whether the classical supra-surface process with a concerted synchronous mechanism is the rule for the Diels–Alder reaction or an elegant exception. For example, the kinetic investigations of Dewar demonstrate an unsymmetrical transition state in the reaction of furan derivatives with maleic anhydride [2]. According to data obtained by the same author on the basis of calculations by the MINDO/3 and MNDO methods, any synchronous processes with the participation of more than one bond have energies of activation that are too high for them to be actually realized [3].

For us the question of the synchronicity of cycloaddition did not arise until we had to deal with symmetrically substituted isoindoles such as N-methylisoindole (Ia) and N-arylisoindoles Ib. Addition with cis fusion of the rings, which leads to endo (III) and exo (IV) adducts, is characteristic for these compounds. We have previously worked out criteria for the determination of such substances (R^1 = H) [1].



Ia R^1=H, R^2=Me; b R^1=H, R^2=Ar; c R^1=Me, R^2=Ar; d R^1=NMe_2, R^2=Ar; e R^1=SEt, R^2=Me, Ar; f R^1=Ph, R^2=Me

However, if a nonsynchronous Diels–Alder reaction is, in principle, possible, the degree of this "nonsynchronicity" may also be different. On the one hand, this means that the formation of supra-supra adducts III and IV is not sufficient evidence for a synchronous one-

*See [1] for Communication 1.

T. G. Shevchenko Kiev State University, Kiev 252017. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 190-202, February, 1990. Original article submitted May 19, 1988.

TABLE 1. Theoretical Constants of Spin-Spin Coupling of the 4-H, 5-H, and 6-H Protons in Cyclic Systems III-VI

Structure	Angle (°) $H_{(4)}$—C—C—$H_{(5)}$*	$J_{4,5}$, Hz		Angle (°) $H_{(5)}$—C—C—$H_{(6)}$*	J_{56}, Hz	
		[8]	[9]		[8]	[9]
III	38	4,9	6,2	0	8,2	10
	42	4,4	5,5	—	—	—
IV	80	−0,02	0,3	0	8,2	10
	85	−0,2	0,1	—	—	—
V	98	−0,3	0,2	158	7,9	13,7
	102	0,1	0,4	162	8,3	14,4
VI	65	1,4	1,8	158	7,9	13,7
	70	0,8	1,2	162	8,3	14,4

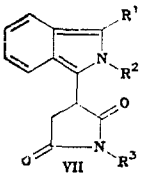
*The boundary values of the angles for each of the configurations were determined by means of plastic models of the Dreiding type (R. J. M. Exports Ltd., UK).

step reaction mechanism; on the other hand, an entire spectrum of mechanisms with different degrees of pericyclic bonding up to the absence of the latter, i.e., a reaction with a two-step mechanism, is possible. However, when we are dealing with a two-step mechanism, the closing of the intermediate particle (a zwitterion or a biradical [4, 5]) to form a Diels—Alder adduct cannot obey the Woodward—Hoffmann rules, and either a supra-supra or a supra-antara process may take place with equal probability. As the next more complex stage in the investigations we considered a study of unsymmetrically substituted isoindoles, since, from the point of view of formal logic, an unsymmetrical transition state is more likely in such diene systems, and one might expect a lower degree of "synchronicity" and, in the limiting case, expect to obtain supra-antara adducts V and VI.

It should be noted that the question of the configuration of the Diels—Alder adducts from unsymmetrically substituted (in the 1 and 3 positions) isoindoles had not been studied prior to our investigations. The reason for this lies in two interrelated factors: on the one hand, few such isoindoles were known [6], and, on the other hand, there was no method for the determination of the configuration of complex structures of this sort.

In the present research we investigated the Diels—Alder reaction of 2-aryl-1-methyl- (Ic), 2-aryl-1-dimethylamino- (Id), 2-R-1-ethylthio- (Ie), and 2-methyl-1-phenylisoindole (If) with maleinimides II under conditions of kinetic and thermodynamic control (method A and method B, respectively).

Proceeding from what we have stated above, for these dienes in general one might have expected four types of Diels—Alder adducts III-VI. One also could not disregard the possibility of the formation of Michael adduct VII, which is easily distinguished from Diels—Alder adducts from the long-wave absorption band in the UV spectrum [6, 7], since an isoindole chromophore is retained in it. However, as one might have supposed, the PMR spectra will give the most useful information regarding the conformation of the adducts. A theoretical analysis of structures III-VI carried out by means of models of the Dreiding type made it possible to link the values of dihedral angles $H_{(4)}$—C—C—$H_{(5)}$ and $H_{(5)}$—C—C—$H_{(6)}$ with the expected spin-spin coupling constants (SSCC) calculated from the Karplus [8] and Williamson—Johnson [9] formulas (Table 1).



VII

On the basis of these data an endo structure (IIIa-IIIm, Table 2) can be assigned to the adducts of isoindoles Ic, Ie, and If, obtained under conditions of kinetic control, since the corresponding SSCC J_{45} = 4.0-5.9 Hz and J_{56} = 7.6-8.4 Hz constitute unequivocal evidence for this. As one should have expected [1], of the bridge protons the doublet of the 4-H pro-

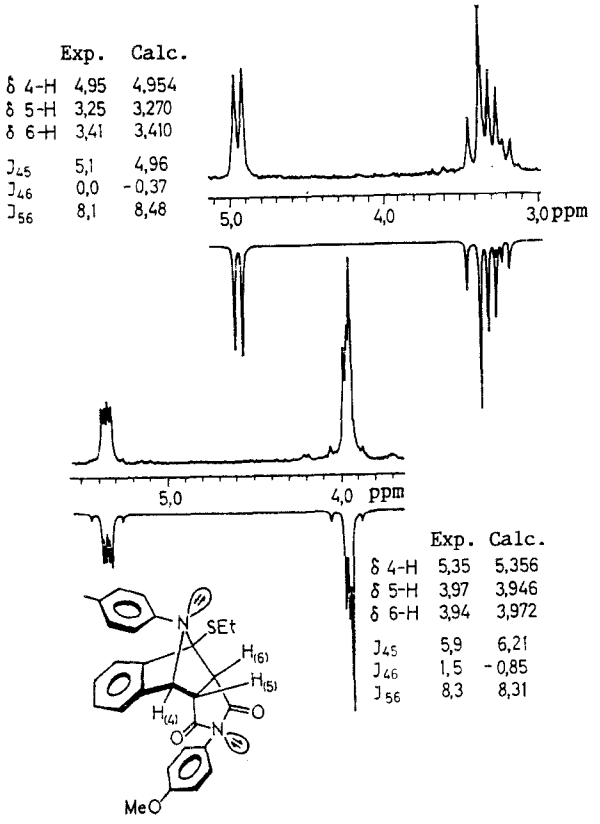


Fig. 1. Section of the PMR spectrum of the adduct of 2-phenyl-1-ethylthioisoindole with N-anisylmaleinimide recorded in C_6D_6 (top) and $CDCl_3$. The spectrum calculated by means of the PANIC iteration program is presented below each experimental spectrum.

ton shows up at weakest field at 4.70-5.35 ppm (Table 2). The substituent in the 1 position of the starting isoindole has virtually no effect on the position of the signal of this proton. Thus, the difference in the 4-H chemical shifts in $CDCl_3$ ranges from 0.08 to 0.1 ppm for IIIa and IIIj, IIIg and IIIk, and IIIc and IIIh. At the same time, a dependence on the nature of substituent R^2 is observed. If R^2 = Ar, the 4-H signal shows up at weaker field by 0.3-0.5 ppm than in the case of adducts that have a methyl substituent attached to the $N_{(7)}$ atom (compare IIIa and IIIk, IIId and IIIℓ, and IIIg and IIIi).

The 5-H and 6-H protons of endo adducts IIIa-IIIm absorb at 3.09-4.18 ppm. The fact of the inversion of the regions of absorption of the 5-H and 6-H protons is interesting (for example, compare IIIa and IIIj). This can be explained by the positive inductive effect of the methyl group attached to the bridge carbon atom, which increases the shielding of the 6-H proton but does not affect the 5-H proton. The use of N-arylmaleinimides as the dienophile leads to a weak-field shift of the 5-H and 6-H signals as compared with the adducts of NH-maleinimide. The difference between the 5-H and 6-H chemical shifts decreases on introduction of an electron-acceptor substituent into the 1 position (R^1 = Ph, S–C_2H_5) (Table 2). Thus, the effects of remote groups may also influence the regions of absorption of these protons (compare IIIg and IIIh-j and IIIk, m and IIIℓ).

It should be noted that for many endo adducts (IIIg-IIIm) the solvent has a very marked effect on the general form of the PMR spectrum. The experimental and calculated (by means of the PANIC iteration program) patterns of spin-spin coupling of the 4-H, 5-H, and 6-H protons for the IIIj adduct are shown in Fig. 1. It is apparent from this figure that in $CDCl_3$ the 5-H and 6-H protons show up in the form of multiplets of higher orders; however, replacement of the solvent by deuterobenzene simplifies the pattern of spin-spin splitting to first order. In view of the complexity of the spectra and the possibility of inversions of the regions of absorption of the signals the chemical shifts and SSCC of the 5-H and 6-H protons for such compounds were refined by means of double-resonance experiments. In Fig. 2 we show

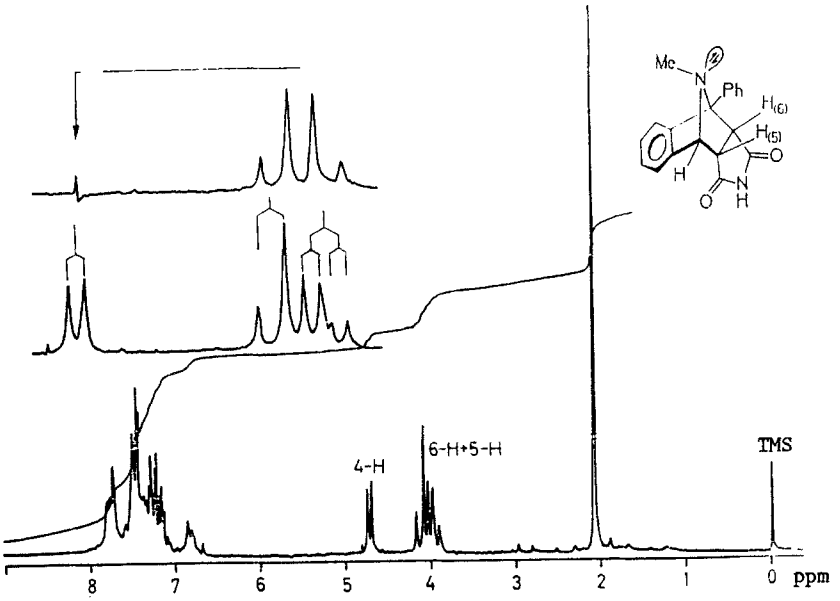


Fig. 2

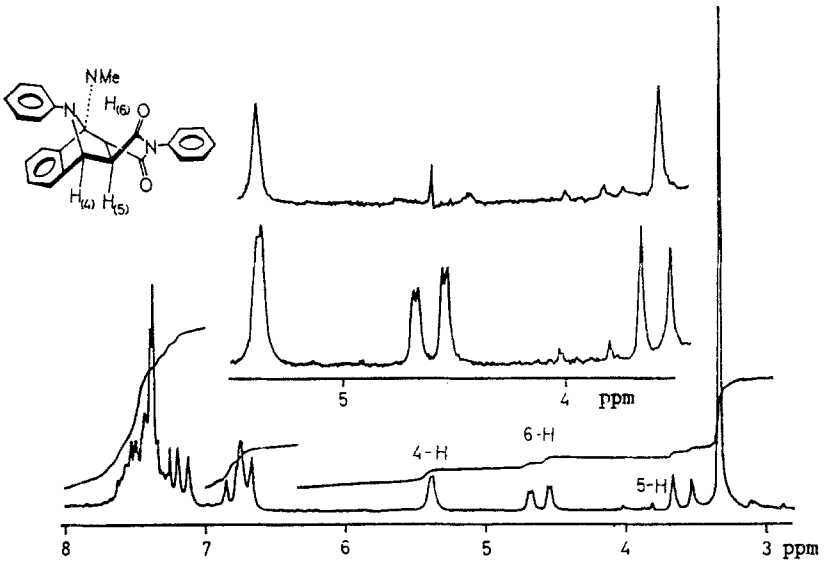


Fig. 3

Fig. 2. Summary PMR spectrum of the adduct of 1-phenyl-2-methylisoindole with maleinimide in $CDCl_3$.

Fig. 3. PMR spectrum of the adduct of 1-dimethylamino-2-phenylisoindole with N-phenylmaleinimide in $CDCl_3$.

how the 5-H (doublet of doublets) and 6-H (doublet) signals in the multiplet of 5-H and 6-H protons can be correctly assigned.

Previously in the PMR spectra of endo adducts of N-methyl- [1] and N-arylisoindoles [10] we observed constants of long-range spin-spin coupling between the 1-H and 5-H and 4-H and 6-H protons. A long-range $^3J_{46}$ constant is not always manifested in the spectra of adducts of unsymmetrically substituted isoindoles IIIa-m. In Table 2 and in Fig. 1 it is shown that for some adducts a long-range constant ($^3J_{15}$ = 1.8 Hz) can be recorded in deuterochloroform, while this coupling cannot be detected in other solvents.

An interesting peculiarity of the PMR spectra of IIIg-j (see Table 2) is the possibility of the observance in a number of solvents of diastereotopic character of the protons of the

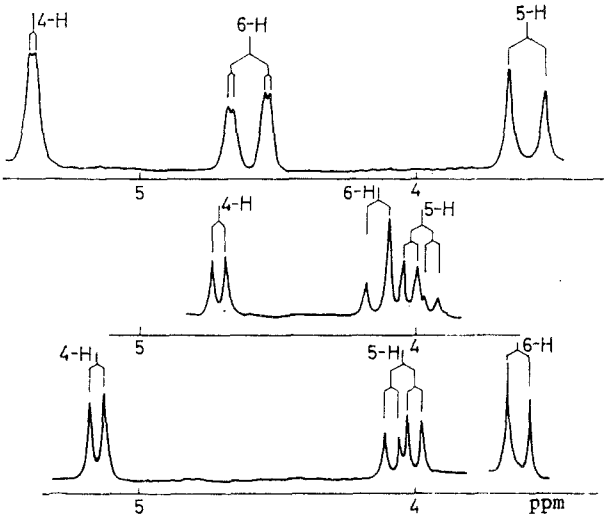


Fig. 4. Inversion of the absorption regions of the 5-H and 6-H protons on passing from adducts of 1-methyl-2-(p-anisyl)-isoindole (lower spectrum) to adducts of 1-phenyl-2-methyl-isoindole (middle spectrum) and then to adducts of 1-dimethylamino-2-phenylisoindole (upper spectrum) with maleinimide derivatives (N-phenylmaleinimide in the first and third cases and unsubstituted maleinimide in the second case).

methylene group of the S–CH_2–Me fragment. In the spectrum of adduct IIIi in $CDCl_3$ this signal is the superimposition of two quartets. When the solvent is replaced by C_6D_6 or CD_3CN, the methylene group is manifested as a pure quartet, in view of the fact that the form of the signal in such cases depends on the rate of internal rotation and the character of the equilibria that exist in the molecule.

An analysis of the PMR spectra of the endo adducts with R^2 = Ar makes it possible to note a pronounced diamagnetic shift of the resonance absorption of the α-H protons and the protons of the methoxy groups (γ position) (see Table 3) as compared with the values usually observed for them. This is associated with the effect of the o-phenylene grouping situated in an almost coplanar orientation with respect to R^2. We have previously described a similar effect in a series of endo adducts of symmetrically substituted isoindoles [3, 10].

Adducts of 2-aryl-1-dimethylaminoisoindoles Id with maleinimide derivatives IIa-e were also obtained under conditions of kinetic control. The spectrum of the adduct of 1-dimethylamino-2-phenylisoindole with N-phenylmaleinimide is presented in Fig. 3. The pattern of spin-spin splitting of the bridge protons (in the direction of a decrease in the chemical shifts: doublet, doublet, doublets, doublet) resembles the pattern for endo structures. However, $^2J_{56}$ = 13.5 Hz, which indicates unambiguously the transoid fusion of the rings, since such a large SSCC is possible only for supra-antara compounds V and VI (see Table 1). This conclusion is also valid for other adducts of 2-aryl-1-dimethylaminoisoindoles (see Table 2, lines 10-15). It is further logical to assume that the choice between structures V and VI can be made on the basis of the vicinal constant of spin-spin coupling between the 4-H and 5-H protons (Table 1). For all of the adducts of 1-aryl-2-dimethylaminoisoindole except one (Table 2, line 14) one observes additional splitting of the signals of the bridge protons with SSCC 1.8 Hz. If this is the $^2J_{45}$ vicinal constant, the investigated adducts have the VI structure. We have shown that this hypothesis can be verified by means of the Overhauser nuclear effect (ONE). Additional irradiation at the resonance frequency of the 4-H proton under the assumption of the VI structure should lead to the development of a signal at 4.5 ppm in the differential spectrum. In fact, in this case an increase in the intensity of the strong-field doublet at 3.6 ppm was observed. It turns out that the central (in the analyzed region) doublet of doublets belongs to the 6-H proton and not to the 5-H proton and that the corresponding constant of 1.8 Hz reflects long-range coupling of the 4-H and 6-H protons (i.e., it is not the vicinal constant). This fact was also similarly established for other compounds (Table 2, lines 10-12 and 15). However, the vicinal $^2J_{45}$ constant is equal to zero in all cases, on the basis of which the affiliation of the adducts of 1-aryl-2-dimethylaminoisoindoles with maleinimides with the supra-antara series (V) (Table 1) is demonstrated unequivocally.

TABLE 2. Chemical Shifts and SSCC of the 4-H, 5-H, and 6-H Protons of the Diels–Alder Adducts from Unsymmetrical Isoindoles

Line	Compound	R^1	R^2	R^3	Solvent	δ			Δ 4-H—5-H	Δδ 5-H—6-H	J_{45}	J_{56}	J_{46}
						4-H	5-H	6-H					
1	IIIa	Me	Phenyl	p-Anisyl	$CDCl_3$	d 5,23	d.d 4,04	3,61	1,19	0,43	5,5	8,2	—
2	IIIb	Me	p-Tolyl	Phenyl	$CDCl_3$	d 5,19	d.d 4,04	3,61	1,15	0,43	5,5	8,3	—
3	IIIc	Me	p-Anisyl	Phenyl	$CDCl_3$	d 5,15	d.d 4,04	3,61	1,11	0,40	5,5	8,4	—
4	IIId	Me	*	H	$(CD_3)_2SO$	d 5,06	d.d 3,79	3,43	1,27	0,36	5,5	8,1	—
5	IIIe	Me	p-Phenethyl	H	$CDCl_3$	d 5,00	d.d 3,83	3,42	1,17	0,41	5,4	8,3	—
6	IIIf	Me	**	H	$CDCl_3$	d 5,10	d.d 3,81	3,44	1,29	0,37	5,5	8,3	—
7	IVa	Me	Phenyl	p-Anisyl	$CDCl_3$	s 5,18	d 3,10	2,87	2,08	0,23	—	6,8	—
8	IVb	Me	p-Anisyl	p-Anisyl	$CDCl_3$	s 5,10	d 3,07	2,84	2,03	0,23	—	6,9	—
9	IVc	Me	p-Tolyl	Phenyl	$CDCl_3$	s 5,15	d 3,10	2,87	2,05	0,23	—	6,9	—
10	Va	NMe_2	p-Anisyl	H	$CDCl_3$	s 5,08	d 3,40	4,46	1,68	−1,06	—	13,6	1,8
11	Vb	NMe_2	p-Anisyl	Phenyl	$CDCl_3$	s 5,25	d 3,60	4,53	1,65	−0,93	—	13,5	1,8
12	Vc	NMe_2	p-Anisyl	***	$CDCl_3$	s 5,10	d 3,61	4,55	1,49	−0,94	—	13,1	1,8
13	Vd	NMe_2	Phenyl	Phenyl	$CDCl_3$	s 5,39	d 3,60	4,62	1,79	−1,02	—	13,5	1,8
14	Ve	NMe_2	p-Anisyl	p-Anisyl	$CDCl_3$	s 5,25	d 3,56	4,51	1,69	−0,95	—	13,2	—
15	Vf	NMe_2	p-Anisyl	p-Tolyl	$CDCl_3$	s 5,28	d 3,58	4,51	1,70	−0,93	—	13,3	1,8
16	IIIg	S—Et	Me	p-Anisyl	$CDCl_3$	d 4,73	d.d 3,93	3,66	0,80	0,27	5,1	8,1	—
					C_6D_6	d 4,19	d.d 3,23	3,09	0,96	0,14	4,9	8,2	—
17	IIIh	S—Et	p-Anisyl	Phenyl	$CDCl_3$	d 5,23	d.d 3,94	4,03	1,29	−0,09	4,4	8,1	—
					C_6D_6	d 4,86	d.d 3,25	3,45	1,61	−0,20	5,0	8,4	—
					CD_3CN	d 5,23	d.d 3,99	3,92	1,24	0,07	5,3	8,2	—
18	IIIi	S—Et	p-Tolyl	p-Anisyl	$CDCl_3$	d 5,29	d.d 3,93	4,02	1,36	−0,09	4,0	8,1	1,8
					C_6D_6	d 4,95	d.d 3,32	3,46	1,63	−0,14	4,8	8,4	—
					CD_3CN	d 5,29	d.d 3,96	3,91	1,33	0,05	5,0	8,4	—
19	IIIj	S—Et	Phenyl	p-Anisyl	$CDCl_3$	d 5,34	d.d 3,93	4,01	1,41	−0,08	4,4	8,1	1,8
					C_6D_6	d 4,95	d.d 3,25	3,41	1,70	−0,16	5,1	8,1	—
					CD_3CN	d 5,35	d.d 3,98	3,93	1,37	0,05	4,9	8,4	—
20	IIIk		Me	p-Anisyl	$CDCl_3$	d 4,85	d.d 4,21	4,17	0,64	0,04	5,9	7,6	1,5
21	IIIℓ		Me	H	$CDCl_3$	d 4,70	d.d 3,96	4,12	0,74	−0,16	4,8	8,0	—
22	IIIm		Me	p-Tolyl	$CDCl_3$	d 4,86	d.d 4,18	4,13	0,68	0,05	4,0	7,8	1,5

*3,4-Methylenedioxyphenyl.
**3,4-Dimethoxyphenyl.
***p-Nitrophenyl.

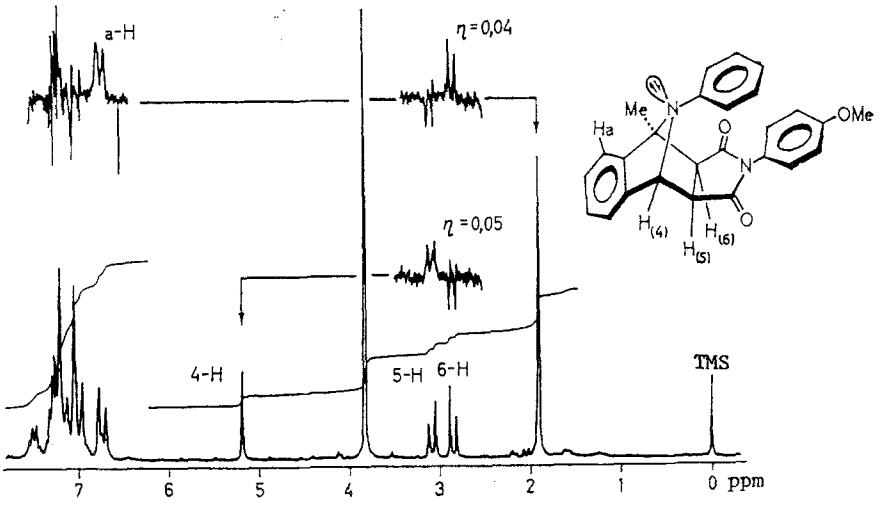


Fig. 5. Summary PMR spectrum of the adduct of 1-methyl-2-phenylisoindole with N-anisylmaleinimide. The intensification of the 5-H, 6-H, and a-H signals as a result of the Overhauser nuclear effect is shown above the spectrum.

The 5-H proton of Va-f absorbs at stronger field than the 6-H proton, as was characteristic for some adducts of the endo series with acceptor substituents in the 1 position. However, in contrast to the latter, the supra-antara adducts have a greater difference between the absorption frequencies of these protons (see Table 2). Models of the Dreiding type show that the 5-H proton in the V structure may experience the shielding effect of two aromatic rings – both the isoindole and arylmaleinimide fragments.

By analyzing the data in Table 2 as a whole one can construct the pattern of the gradual drawing together of the signals of the bridge 5-H and 6-H protons on passing from adducts IIIa-f to IIIg-j and of their drawing apart on passing to Va-f in the reverse order (Fig. 4).

It is important to note that the formation of supra-antara adducts Va-f indicates unequivocally a nonsynchronous mechanism of cycloaddition in isoindole series Id, because a synchronous thermal supra-antara process is forbidden according to the Woodward–Hoffmann rules.

From the material set forth above it should be concluded that isoindoles Ic, e, f investigated in this research, like symmetrically substituted dienes Ia, b [3, 10], give endo adducts with various maleinimides under conditions of kinetic control. 2-Aryl-1-dimethylaminoisoindoles, which form supra-antara adducts under the same conditions, constitute an exception.

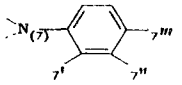
Under conditions of thermodynamic control (method B) 2-aryl-1-methylisoindoles are converted to 1:1 adducts, which have higher melting points than the corresponding isomers IIIa-f (Table 3, lines 7-9). An identical spectral pattern of absorption of the protons attached to the bridge carbon atoms – a singlet and two doublets with a constant of 6.8-6.9 Hz (see Table 2, lines 7-9) – the comparison of which with the data in Table 1 makes it possible to assign these substances to exo series IVa-c, is characteristic for them in their PMR spectra. This conclusion is also confirmed by the greater difference in the chemical shifts of the 4-H and 5-H protons as compared with that for IIIa-f, which we previously singled out as one of the criteria for the determination of the configurations of adducts [1]. Proof for the assignment of the 5-H and 6-H doublets was obtained by means of the Overhauser nuclear effect (ONE) (Fig. 5). As a result of irradiation at the frequency of absorption of the 4-H proton in the differential spectrum one observes a 5-H doublet at 3.10 ppm, while the intensities of two signals – 6-H at 2.87 ppm and a-H of the o-phenylene fragment at 6.71 ppm – increase in $\{1\text{-}CH_3\}$ experiments. In the PMR spectrum of IVb the methoxy group in the para position of the phenyl substituent attached to the $N_{(7)}$ atom is manifested at 2.39 ppm (Table 3), which can be explained by diamagnetic shielding of the aryl substituents of the maleinimide residue. This indicates that the orientation of the R^2 substituent in the exo adduct is similar to that shown in Fig. 5.

TABLE 3. Characteristics and Data from the PMR Spectra of Diels–Alder Adducts from Unsymmetrical Isoindoles

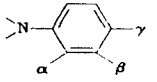
Line	Compound	mp, °C	$N_{(7)}-R^{1*1}$			R^{1*2}			a, b, c. and d protons	Remaining protons	R^1 at $C_{(1)}$	Yield, %
			7′-H	7″-H	7‴-H	α-	β-	γ-				
1	IIIa	154...157	—	—	—	d 3,29 (2H)	—	s 2,27 (3H)	—	m 6,8...7,5 (R+β+ a-d)	s 2,07	87
2	IIIb	134...135	d 6,73 (2H)	d 6,97 (2H)	s 2,22 (3H)	m 6,41 (2H)	—	—	—	m 7,15...7,5 (β+ a-d)	s 2,05	89
3	IIIc	147...149	s 6,72 (4H)		s 3,70 (3H)	m 6,43 (2H)	—	—	—	m 7,1...7,45 (β+γ+ a-d)	s 2,00	87
4	IIId	181...189	d 6,65 d.d 6,21	d 6,40 (1H)	s 5,86 (2H)	—	—	—	m 7,0...7,4 (4H)	—	s 1,84	92
5	IIIe	155...157	s 6,67 (4H)		q 3,89 t 1,33	—	—	—	m 7,05...7,4 (4H)	—	s 1,91	85
6	IIIf	175...177	d 6,66 d 6,21	d 6,44 (1H)	s 3,60 s 3,63	—	—	—	m 7,0...7,4 (4H)	—	s 1,87	93
7	IVa	198...200	—	—	—	d 6,71 (2H)	d 6,94 (2H)	s 3,84 (3H)	—	m 7,0...7,5 (R+ b-d)	s 1,91	83
8	IVb	173...175	s 6,63 (4H)		s 2,39 (3H)	—	—	s 3,67 (3H)	—	m 7,1...7,5 (α+β+ a-d)	s 1,83	85
9	IVc	163...165	—	—	—	d 6,60 (2H)	d 6,90 (2H)	s 2,19 (3H)	—	m 7,15...7,5 (R+ a-d)	s 1,89	89
10	Va	183...184	d.d 6,71 (4H)		s 3,73 (3H)	s 8,74 N–H (1H)		—	m 7,23...7,6 (4H)	—	s 3,30 (6H)	72
11	Vb	155...156	d.d 6,71 (4H)		s 3,74 (3H)	—	—	—	—	m 7,22...7,62 (α–γ+ a-d)	s 3,33 (6H)	63
12	Vc	135...136	d.d 6,73 (4H)		s 3,75 (3H)	d 7,68 (2H)	d 8,31 (2H)	—	m 7,2...7,6 (4H)		s 3,36 (6H)	47
13	Vd	183...184	d 7,16 (2H)	m 6,67...6,86 (3H)		—	—	—	—	m 7,28...7,62 (α–γ+ a-d)	s 3,34 (6H)	78

14	Ve	156...157	d.d 6,71 (4H)		s 3,73 (3H)	d 6,94 (2H)	d 7,26 (2H)	s 3,79 (3H)	m 7,24...7,6 (4H)	—	s 3,31 (6H)	79
15	Vf	254...255	d.d 6,72 (4H)		s 3,73 (3H)	s 6,83 (4H)		s 2,39 (3H)	m 7,15...7,6 (4H)	—	s 3,33 (6H)	64
16	IIIg	150...153	—	s 2,21 (3H)	—	d 6,30 (2H)	d 7,03 (2H)	s 2,26 (3H)	s 7,31 (4H)	—	q 2,78 t 1,36	89
17	IIIh	135...137	d 6,73 (2H)	d 7,09 (2H)	s 3,73 (3H)	m 6,45 (2H)	m 7,2...7,45 (3H)		s 7,36 (4H)	—	q 2,64 t 1,24	87
18	IIIi	164...166	m 7,0...7,3 (4H)		s 2,26 (3H)	d 6,31 (2H)	d 7,05 (2H)	s 2,26 (3H)	s 7,37 (4H)	—	q 2,67 t 1,25	90
19	IIIj	140...142	m 7,1...7,32 (5H)			d 6,32 (2H)	d 7,04 (2H)	s 2,26 (3H)	s 7,36 (4H)	—	q 2,66 t 1,24	91
20	IIIk	141...142	—	s 2,23 (3H)		d 6,32 (2H)	d 7,04 (2H)	s 2,26 (3H)	m 6,90 (1H,H_α) m 7,2...7,4 (3H)		*3	73
21	IIIℓ	145...147	—	s 2,08 (3H)		—	—	—	m 6,83 (1H,H_α) m 7,1...7,35 (3H)		*4	81
22	IIIm	143...145	—	s 2,21 (3H)		d 6,33 (2H)	d 7,05 (2H)	s 2,27 (3H)	m 6,85 (1H,H_α) m 7,2...7,35 (3H)		*5	79
23	VIIIa	205...209	—	s 2,22 (3H)		d 6,35 (2H)	d 7,04 (2H)	s 2,14 (3H)	m 6,76 (1H, H_α) m 7,15...7,35 (3H)		—	48
24	VIIIb	200...203		s 2,21		d 6,34 (2H)	d 7,04 (2H)	s 2,14 (3H)	d.d 6,78 (1H,H_α) m 7,15...7,3 (3H)		—	43

*1



*2



*3 m 7.8-7.9 (2H); m 7.4-7.5 (3H).

*4 m 7.8-7.9 (2H); 7.4-7.55 (3H).

*5 7.7-7.83 (2H); m 7.4-7.52 (3H).

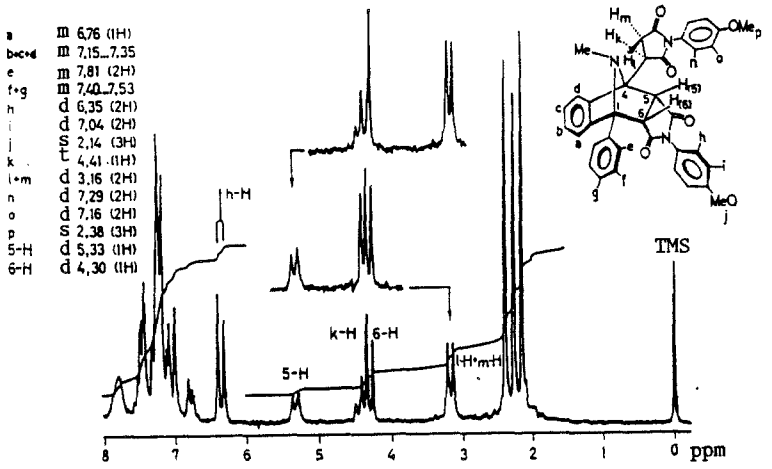


Fig. 6

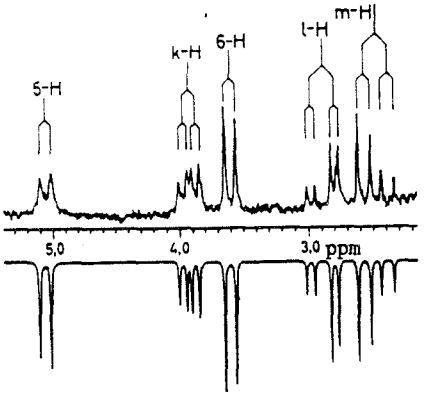


Fig. 7

Fig. 6. Summary spectrum of the adduct (1:2) of 2-methyl-1-phenylisoindole with N-anisylmaleinimide in $CDCl_3$.

Fig. 7. Section of the PMR spectrum of the adduct (1:2) of 2-methyl-1-phenylisoindole with N-anisylmaleinimide in C_6D_6 and the same section modeled by means of the PANIC program. Found: J_{56} = 8.6 Hz. $J_{k\ell}$ = 5.8 Hz, J_{km} = 10.2 Hz, $J_{\ell m}$ = 18.2 Hz.

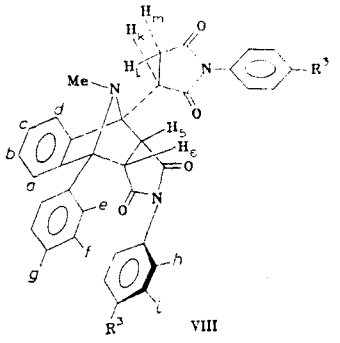
The observation that varying the solvents and the reaction temperature does not affect the three-dimensional structures of the adducts of 2-aryl-1-dimethylaminoisoindoles with maleinimides, although their yields change substantially, is interesting. This indicates the distinctive character of nonsynchronous cycloaddition in the Id series. A retroreaction is characteristic for various systems to various degrees with an increase in the temperature. Adduct Vb, for which the retroreaction occurs in quantitative yields even on recrystallization, is most inclined to undergo this process. In other words, here "thermodynamic control" does not lead to a change in the stereochemistry of the process.

Decomposition with the evolution of ethyl mercaptan is characteristic for the adducts of 1-ethylthio-2-R-isoindoles under the conditions of method B.

2-Methyl-1-phenylisoindole reacts with dienophiles IIc and IId under the same conditions to give unusual adducts VIIIa, b. The summary spectrum of one of them in $CDCl_3$ is presented in Fig. 6. One's attention is drawn to the three singlets of equal intensity at strong field and the extremely unusual pattern of the spin-spin splitting at 3.05-5.5 ppm if one takes into account the ratio of the intensities of the signals (doublet:multiplet:doublet = 1:2:2). Double-resonance experiments made it possible to establish that in this region we have two groups of signals that are not interrelated: a) two doublets at 4.30 and 5.31 ppm; b) triplet at 4.41 ppm and doublet at 3.15 ppm.

The spectra of the same adducts in C_6D_6 are complicated: a doublet of doublets develops in place of the triplet, while the doublet observed at 3.15 ppm is transformed into two doublets, each having an intensity of 1H (Fig. 7). Both spectral patterns were modeled by means of the PANIC program under the assumption that a 1:2 adduct* containing one maleinimide fragment attached via the Michael reaction and another attached via the Diels–Alder reaction is formed. This made it possible to accurately determine the SSCC and explain all of the signals in the PMR spectrum. The three singlets, each having an intensity of 3H, are related to the $N_{(7)}$–Me group and two O–Me groups of the maleinimide residues. The spectral pattern at 3.0-5.5 ppm in $CDCl_3$ is interpreted in the following way: the two doublets are due to the 5-H and 6-H protons, while the triplet and doublet are due to the spin system of the maleinimide residue attached to the $C_{(3)}$ atom via the Michael reaction (the k, ℓ, and m protons; see the formula of VIII).

The spectrum recorded in benzene is interpreted similarly, except that here one can detect the magnetic nonequivalence of the ℓ-H and m-H protons (see Fig. 7). It follows from the values of the J_{56} constant (7 Hz for VIIIa, and 8.8 Hz for VIIIb) that cisoid fusion of the rings occurred. Weak spin-spin coupling through four C–C bonds between the k-H proton (see formula VIII) and the doublet at 5.30 ppm was established by the double-resonance method; we were thereby able to assign the latter signal to the 5-H proton.† The chemical shift of the h-H protons (6.34 ppm) is similar to that in the endo adduct (see Table 3). The diamagnetic shift of these signals is associated with the effect of the magnetically anisotropic o-phenylene grouping with an almost coplanar orientation with respect to the plane of the aryl residue of the maleinimide.



VIII

In the alternative exo structure the h-H signal is localized at weaker field (no closer than 7.0 ppm). Thus, on the basis of only the preceding investigations it may be asserted that the 1:2 adducts have an endo structure.

Knowing the structure of adducts VIII, it is logical to propose the following sequence of steps in the reaction of 2-methyl-1-phenylisoindole with N-substituted maleinimides: initially, as a result of electrophilic attack in the 3 position, one observes the formation of Michael adduct VII, which undergoes endo cycloaddition in the 1 and 3 positions. Since endo adducts IIIk-m are converted to adducts VIII (with a 1:2 composition) on refluxing in alcohols, it must be assumed that this process takes place through a retroreaction.

Thus, under conditions of thermodynamic control isoindoles Ic give exo adducts, isoindoles Id give "supra-antara" adducts in low yields, and isoindoles Ie give 1:2 adducts.

In general, the criteria for the establishment of the configuration are as follows: a) the pattern of the spin-spin splitting from the bridge protons and the corresponding constants J_{56}, J_{45}, and J_{46}; b) Δ (δ 4-H–δ 5-H) and Δ (δ 5-H–δ 6-H); c) the chemical shift of the α proton of the arylmaleinimide residue attached via the Diels–Alder reaction; d) the ratio of the intensities of the multiplets (in differentiating 1:1 and 1:2 adducts).

EXPERIMENTAL

The melting points were determined with a Boetius apparatus. The PMR spectra were recorded with a WP-100 spectrometer with tetramethylsilane (TMS) as the internal standard.

*The results of elementary analysis of the 1:1 and 1:2 adducts are extremely close to one another.

†This coupling is clearly seen in Fig. 7 in the recording of the PMR spectrum in $CDCl_3$.

Method A. Equimolar amounts of freshly sublimed isoindole Ic, d and N-substituted maleinimide IIa-e were stirred at room temperature in absolute ether (or ethyl acetate), after which the reaction mixture was maintained at the same temperature for several hours. When necessary, the solvent was removed by distillation in vacuo. The precipitated crystals were removed by filtration, and the adduct was purified by crystallization from alcohols (ethanol, isopropyl alcohol) or by column chromatography on silica gel (elution with chloroform).

Method B. A mixture of equimolar amounts of freshly sublimed isoindole and the N-substituted maleinimide was refluxed in isopropyl alcohol. The time required to complete the reaction was determined by means of TLC. The precipitate was removed by filtration and purified by recrystallization from acetonitrile or alcohols (ethanol, isopropyl alcohol).

LITERATURE CITED

1. V. A. Kovtunenko, Z. V. Voitenko, A. K. Tyltin, A. V. Turov, and F. S. Babichev, Ukr. Khim. Zh., 49, 1287 (1983).
2. M. J. S. Dewar and A. V. Pierini, J. Am. Chem. Soc., 106, 203 (1984).
3. M. J. S. Dewar, J. Am. Chem. Soc., 106, 209 (1984).
4. J. Pancir, J. Am. Chem. Soc., 104, 7424 (1982).
5. M. Blain, S. Odiot, G. J. Martin, and J. P. Gouesnard, Tetrahedron, 36, 2663 (1980).
6. F. S. Babichev and V. A. Kovtunenko, The Chemistry of Isoindole [in Russian], Naukova Dumka, Kiev (1983).
7. D. F. Veber and W. Lwowski, J. Am. Chem. Soc., 86, 646 (1964).
8. R. Silverstein, H. Bassler, and T. Morril, Spectrometric Identification of Organic Compounds [Russian translation], Mir, Moscow (1977).
9. N. Bhacca and D. Williams, Application of NMR in Organic Chemistry [Russian translation], Mir, Moscow (1966).
10. V. A. Kovtunenko, T. T. Kucherenko, A. K. Tyltin, Z. V. Voitenko, and F. S. Babichev, Ukr. Khim. Zh., 54, 186 (1988).

STUDY OF THREE-DIMENSIONAL STRUCTURES OF BENZOYLPYRIDINE OXIMES AND THEIR ETHERS BY ^{1}H and ^{13}C NMR SPECTROSCOPY

V. P. Lezina, S. G. Rozenberg, O. M. Glozman, L. A. Zhmurenko, L. M. Meshcheryakova, and V. A. Zagorevskii

UDC 547.824:543.422.25

The ^{1}H and ^{13}C NMR spectra of the E and Z isomers of 2-, 3-, and 4-benzoylpyridine oximes and their ethers were analyzed thoroughly, and the ^{1}H-^{13}C spin-spin coupling constants (SSCC) were determined. It was established that the magnitude of the γ effect for the quaternary carbon atoms in the E and Z isomers depends on the site of substitution in the pyridine ring. It was assumed that the intermolecular hydrogen bond is stronger in the E form than in the Z form. The existence of the Z isomer of 2-benzoylpyridine oxime in deuterochloroform with an intramolecular hydrogen bond was proved.

It is generally known that spatial isomerism in many cases determines the biological activity of molecules, as well as the strength and degree of its selectivity. The determination of the configurations of various oximes by NMR spectroscopy is widely used in organic chemistry. The chemical shifts of certain carbon atoms (the γ effect) and the ^{13}C-^{13}C and ^{15}N-H spin-spin coupling constants (SSCC) are characteristic criteria for the assignment of E and Z isomers (for example, see [1-3]).

Scientific-Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow 125315.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 203-208, February, 1990. Original article submitted July 11, 1988.

0009-3122/90/2602-0172$12.50