New Epoxyisoindolines by Intramolecular Diels-Alder Reactions of Some Methyl-substituted Allylaryl-2-furfurylamines

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Received February 24. 1997
Revised May 6, 1997

N-Alkenyl-*N*-(5-substituted-2-furfuryl)-*N*-*p*-toluidines **1-10** have been selected to study the intramolecular Diels-Alder reaction of furans. New epoxyisoindolines **11-20** were prepared and fully characterised.

J. Heterocyclic Chem., **34**, 1315 (1997).

Building blocks of many natural and other bioactive compounds often are polycyclic, condensed and sometimes bridged systems. Synthesis of such units could be effectively performed by using a pathway that includes the intramolecular Diels-Alder reaction. The synthetic and theoretical aspects of this reaction are well documented [1]. In the reaction two rings are formed with generally high, predictable regio- and stereoselectivity. If the dienic and the dienophilic components are a part of cyclic system and/or have cyclic substituents, a complex polycyclic system could be formed in a single step [2].

More than three decades ago Wasserman and Doumaux observed an intramolecular Diels-Alder reaction involving furan ring [3]. Moreover Hahn discovered shortly afterwards that even simple furans underwent extraordinarily facile intramolecular Diels-Alder reactions [4a]. After the early report on the reaction on tertiary allylarylfurfuryl amines from our laboratory in early sixties [4], interest in the intramolecular Diels-Alder reaction of furans [5] increased exponentially. The dienic reactivity of furan was exploited in the syntheses of biologically active compounds, as well as other complex carbo- and heterocyclic molecules [1g,2]. The success of an intramolecular Diels-Alder reaction with furan as diene is found to be highly dependable upon substituents on the furan ring and the structure of the tethering unit. Among these the bond lengths, bond angles and nonbonding interactions which are not disfavoured are of prime importance [6]. The proposal that steric, rather than electronic factors, dictate the likelihood of furan intramolecular [4+2] cycloaddition is supported by a number of examples [7]. The intramolecular Diels-Alder reactions with three member tethering carbon bridge between dienic and dienophilic part of the molecule proceed mostly through the *trans*-addition yielding *exo*-adducts [6,8] but sometimes the mixture of *endo*- and *exo*-products was found [9]. The methyl substitution of dienophilic part of the molecule or enlargement of tethering bridge generally slow down or prevent the cycloaddition [7,8b]. With tertiary allylfurfuryl amines [4,10] and quaternary ammonium salts [11] the reactivity is in favour of cycloaddition. With amide groups as a part of tethering unit [12,13] the cycloaddition is possible when substituents or some polar effects are bringing diene and dienophile in favourable conformation.

As far as our research is concerned, we found that steric and electronic effects of substituents at dienic, furane moiety were crucial in explaining the influence on the rate of cycloaddition [10,14]. On the basis of so far studied examples with *N*-allyl group as dienophile an electronically "neutral" type [15] of Diels-Alder reaction was supposed [10b]. Substituents in *N*-aryl group were of no significant influence, but a remarkable drop in the rate of the reaction in case where double bond was included in a ring system (*N*-cyclohexenyl derivative) [14] was found. Since we are interested in the intramolecular Diels-Alder reaction of furans as the synthetic utility for nitrogen containing polycyclic (i.e. heterocyclic) compounds [16], we found necessary to complete our present knowledge of the substituent effects to the intramolecular Diels-Alder reaction of tertiary allylarylfurfurylamines by a systematic study of effects caused by the substituents directly connected with the dienophilic, *N*-alkenyl, double bond. Starting with sterically crowded allylarylfurfurylamines, some questions about the steric effects in competition with electronic influence on the rate of the reaction and the geometry of adducts could be solved.

The present paper deals with the influence of terminal methyl groups in alkenyl moiety to the reaction rate and the outcome of the intramolecular Diels-Alder reaction of

selected *N*-alkenyl-*N*-[2-(5-substituted)furfuryl]-*N*-*p*-toluidines **1-10**.

New epoxyisoindolines **11**, **13** and **15-20** (Scheme 1, Table 1) have been prepared by heating of the anhydrous benzene solution of tertiary amines **1-10**.

Scheme 1

1-10 **11, 13, 15-20**

The starting tertiary amines *i.e.* *N-trans*-2-butenyl- and *N*-2-isopentenyl-*N*-[2-(5-substituted)furfuryl]-*p*-toluidines **1-10** were synthesised according to reported procedure [17].

The structures of the epoxyisoindolines were elucidated by spectroscopic (Tables 2-6) and X-ray crystallographic determination (Figure 6).

The intramolecular Diels-Alder reactions of these sterically hindered tertiary amines were studied in benzene solutions at various temperatures and the results were compared with those of *N*-allyl- [10] and *N*-2-cyclohexenyl- [14] analogues (Figures 1-3).

Table 1

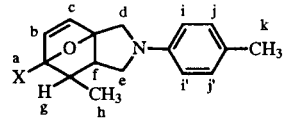
Preparation of New Epoxyisoindolines

X	R	R'	R"	Tertiary amine [17]	Reaction conditions [a] °C	Hours	Epoxy -isoindoline	Yield (%)	mp (°C)
H	H	CH_3	H	**1**	80	120	**11**	46	136-138
H	H	CH_3	CH_3	**2**	80	240	**12**	-	-
CH_3	H	CH_3	H	**3**	80	120	**13**	35	134-135
CH_3	H	CH_3	CH_3	**4**	80	240	**14**	-	-
I	H	CH_3	H	**5**	80	48	**15**	95	187-188
I	H	CH_3	CH_3	**6**	80	240	**16**	90	180-182
OCH_3	H	CH_3	H	**7**	70	72	**17** [b]	79 [c,d]	-
OCH_3	H	CH_3	CH_3	**8**	80	240	**18**	51	163-165
NO_2	H	CH_3	H	**9**	40	72	**19**	94	176-178
NO_2	H	CH_3	CH_3	**10**	50	72	**20**	83	173-175

[a] Benzene solution. [b] Formation of **17** indicated by ^1H nmr spectra of crude product. [c] The yield evaluated from the intensity of *p*-tolyl methyl group. [d] After chromatographic purification of crude **17** only the aromatized compound, that is *N*-*p*-tolyl-4-methyl-5-methoxyisoindoline (87%) and *N*-*p*-tolyl-7a-hydroxy-4-methyl-5-oxotetrahydroisoindoline [18] (7.5%) were isolated.

Table 2

^1H nmr Spectra [a] of *N*-*p*-Tolyl-4-methyl-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline and 5-Substituted Derivatives

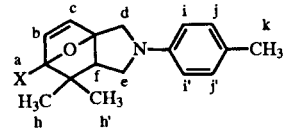


Compound	b	c	d		e		f	g	i, i'	j, j'	k	h	a
11	6.50	6.34	3.85	3.29	3.77	2.95	1.72	2.34	6.46	7.01	2.23	0.88	4.86
X = H	d, 1H	dd, 1H	d, 1H	d, 1H	t, 1H	t, 1H	dt, 1H	m, 1H	d, 2H	d, 2H	s, 3H	d, 3H	dd, 1H
	J = 5.6	J = 5.6 J"=1.5	J = 11.4	J = 11.4	J = 8.8	J = 8.8	J = 8.8 J'=2.9		J = 8.5	J = 8.5		J = 7.0	J = 4.4 J"=1.5
13	6.50	6.19	3.81	3.47	3.77	3.00	2.03-1.78		6.46	7.02	2.23	0.89	1.56
X = CH_3	d, 1H	d, 1H	d, 1H	d,1H	t, 1H	t, 1H	m [b], 2H		d, 2H	d, 2H	s, 3H	d, 3H	s, 3H
	J = 5.6	J = 5.6	J = 11.1	J = 11.1	J = 8.8	J = 8.8			J = 8.5	J = 8.5		J = 7.0	
15	6.44	6.47	3.94	3.57	3.85	3.10	2.02	2.54	6.47	7.04	2.25	1.00	
X=I	d, 1H	d, 1H	d, 1H	d, 1H	t, 1H	t, 1H	dt, 1H	dq, 1H	d, 2H	d, 2H	s, 3H	d, 3H	
	J = 5.6	J = 5.6	J = 11.7	J = 11.7	J = 8.8	J = 8.8	J = 8.8 J'=2.9	J = 7.3 J'=2.9	J = 8.5	J = 8.5		J = 7.3	
19	6.78	6.69	3.93	3.62	3.90	3.14	2.06	2.56	6.49	7.04	2.25	1.15	
X = NO_2	d, 1H	d, 1H	d, 1H	d, 1H	t, 1H	t, 1H	dt, 1H	dq, 1H	d, 2H	d, 2H	s, 3H	d, 3H	
	J = 5.6	J = 5.6	J = 12.0	J = 12.0	J = 8.8	J = 8.8	J = 8.8 J'=2.9	J = 7.3 J'=2.9	J = 8.5	J = 8.5		J = 7.3	

[a] (deuteriochloroform) δ in ppm, J in Hz. [b] The coupling constants H_e, H_f, H_g, and H_h at J = 8.8 i J'=7.0 i J"=2.9 Hz.

Table 3

^{1}H NMR Spectra [a] of *N*-*p*-Tolyl-4,4-dimethyl-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline and 5-Substituted Derivatives

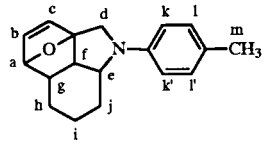


Compounds	b	c	d		e		f	i,i'	j,j'	k	h	h'	a
16	6.65	6.29	3.91	3.45	3.59	3.11	2.13	6.51	7.00	2.25	1.03	1.32	
X = I	d, 1H	d, 1H	d, 1H	d, 1H	t, 1H	t, 1H	t, 1H	d, 2H	d, 2H	s, 3H	s, 3H	s, 3H	
	J = 5.6	J = 5.6	J = 11.7	J = 11.7	J = 9.1	J = 9.1	J = 9.1	J = 8.5	J = 8.5				
18	6.54	6.37	3.79	3.45	3.53	3.12	2.04	6.50	7.03	2.24	0.97	1.14	3.78
X = OCH_3	d, 1H	d, 1H	d, 1H	d, 1H	t, 1H	t, 1H	t, 1H	d, 2H	d, 2H	s, 3H	s, 3H	s, 3H	s, 3H
	J = 5.6	J = 5.6	J = 11.4	J = 11.4	J = 9.1	J = 9.1	J = 9.1	J = 8.5	J = 8.5				
20	6.75	6.67	3.93	3.61	3.68	3.17	2.15	6.51	7.05	2.25	1.17	1.22	
X = NO_2	d, 1H	d, 1H	d, 1H	d,1H	t, 1H	t, 1H	t, 1H	d, 2H	d, 2H	s, 3H	s, 3H	s, 3H	
	J = 5.6	J = 5.6	J = 12.0	J = 12.0	J = 9.1	J = 9.1	J = 9.1	J = 8.5	J = 8.5				

[a] (deuteriochloroform) δ in ppm, J in Hz.

Table 4

^{1}H NMR spectra [a] of *N*-*p*-Tolyl-3a,4,5,7a-tetrahydro-5,7a-epoxy-3,4-propanoisoindoline [b]

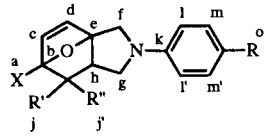


Compound	b	c	d	e, f, g, h, i, j	k, k'	l, l'	m	a
	6.46	6.37	3.70	2.14-1.11	6.54	7.04	2.25	4.65
- [b]	d, 1H	dd, 1H	s, 2H	m, 9H	d, 2H	d, 2H	s, 3H	d, 1H
	J=6.2	J=6.2	J=1.5		J=8.5	J=8.5		J=1.5

[a] (deuteriochloroform) δ in ppm, J in Hz; [b] Prepared earlier [14].

Table 5

^{13}C NMR Spectra [a] of *N*-Aryl-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindolines and Substituted Derivatives

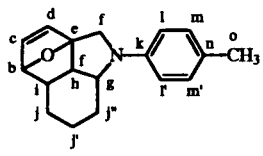


Compound	X	k	c	d	m,m'	n	l,l'	e	b	f	g	h	i	o	j	j'	a
11 [b]	H	145.4 (s)	134.5 (d)	135.8 (d)	129.4 (d)	126.7 (s)	111.6 (d)	96.1 (s)	83.5 (d)	52.7 (t)	50.2 (t)	50.6 (d)	39.3 (d)	20.0 (q)	16.5 (q)		
13 [b]	CH_3	145.4 (s)	137.9 (d)	136.2 (d)	129.4 (d)	124.7 (s)	111.6 (d)	94.6 (s)	90.6 (s)	52.9 (t)	50.4 (t)	53.6 (d)	45.5 (d)	20.1 (q)	16.4 (q)		17.4 (q)
15 [b,c]	I	145.1 (s)	141.6 (d)	135.8 (d)	129.5 (d)	125.3 (s)	111.8 (d)	95.4 (s)	72.7 (s)	52.5 (t)	50.1 (t)	52.9 (d)	52.0 (d)	20.1 (q)	16.2 (q)		
16 [d]	I	144.3 (s)	140.8 (d)	135.8 (d)	129.7 (d)	126.0 (s)	112.4 (d)	94.6 (s)	65.9 (s)	51.2 (t)	49.1 (t)	54.2 (d)	52.1 (s)	20.3 (q)	24.6 (q)	26.1 (q)	
18 [d]	OCH_3	146.0 (s)	137.2 (d)	135.1 (d)	129.6 (d)	125.3 (s)	112.2 (d)	78.9 (s)	117.1 (s)	51.5 (t)	48.9 (t)	54.6 (d)	41.8 (s)	20.3 (q)	21.3 (q)	26.4 (q)	56.6 (q)
19 [b]	NO_2	144.9 (s)	138.2 (d)	131.8 (d)	129.6 (d)	125.8 (s)	111.9 (d)	94.4 (s)	115.1 (s)	52.4 (t)	50.1 (t)	53.9 (d)	45.3 (d)	20.2 (q)	15.9 (q)		
20 [d]	NO_2	145.8 (s)	137.4 (d)	134.0 (d)	129.8 (d)	126.2 (s)	112.4 (d)	94.0 (s)	117.0 (s)	50.9 (t)	48.7 (t)	54.9 (d)	45.5 (s)	20.3 (q)	20.5 (q)	26.0 (q)	
- [e]	H	147.5 (s)	136.9 (d)	134.7 (d)	129.0 (d)	115.8 (d)	111.6 (d)	95.1 (s)	80.1 (d)	52.8 (t)	49.7 (t)	42.1 (d)	30.9 (t)				
- [f]	CH_3	147.5 (s)	140.1 (d)	135.2 (d)	129.0 (d)	115.8 (d)	111.6 (d)	94.9 (s)	88.1 (s)	52.0 (t)	50.0 (t)	45.4 (d)	37.6 (t)				19.1 (q)

[a] (deuteriochloroform) δ in ppm. [b] R, R ' = CH_3, R" = H; [c] Signals of **h** and **i** interchangeable. [d] R, R', R" = CH_3. [e] R, R', R" = H (*N*-phenyl derivative, prepared earlier [4]. [f] R, R', R" =H (*N*-phenyl derivative, prepared earlier) [10a].

Table 6

^{13}C NMR Spectra [a] of *N*-*p*-Tolyl-3a,4,5,7a-tetrahydro-5,7a-epoxy-3,4-propanoisoindoline [b]



Compound	k	c	d	m	n	l	e	b	f	g	h	i	o	j	j'	j''
-[b]	144.5 (s)	137.0 (d)	135.4 (d)	129.5 (d)	124.2 (s)	111.4 (d)	95.4 (s)	87.0 (d)	49.0 (t)	56.9 (d)	44.0 (d)	35.8 (d)	20.0 (q)	27.2 (t)	21.1 (t)	28.8 (t)

[a] (deuteriochloroform) δ in ppm. [b] Prepared earlier [14].

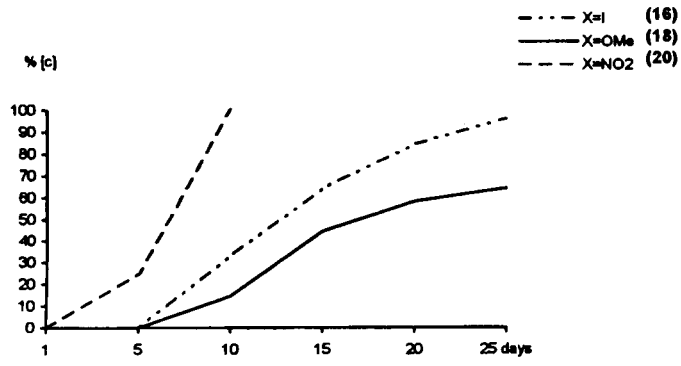


Figure 1. Progress curves [a] of the intramolecular Diels-Alder reaction of selected *N*-2-isopentenyl-*N*-(5-substituted-2-furfuryl)-*p*-toluidines [b].

[a] Reaction temperature: 25° (1-5), 60° (6-10) and 80° (11-25 days). [b] For compound **2** (X = H) and **4** (X = Me) there was no reaction during the measured period. [c] Conversion.

As expected, the presence of one or two terminal methyl groups at the dienophilic part of the molecule reduced the intramolecular Diels-Alder reaction of furans profoundly. The effect may be explained by unfavourable steric interactions within the transition state. These interactions are present

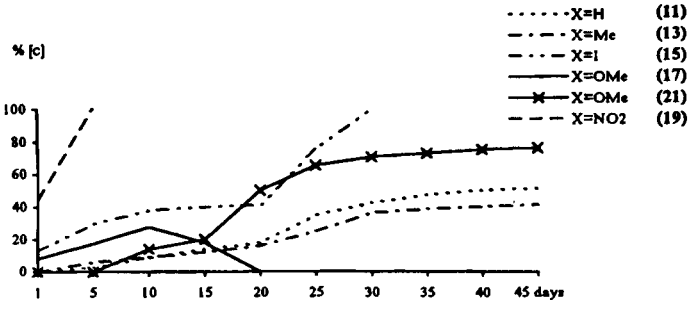


Figure 2. Progress curves [a] of the intramolecular Diels-Alder reaction of *N*-*trans*-2-butenyl-*N*-(5-substituted-2-furfuryl)-*p*-toluidines [b].

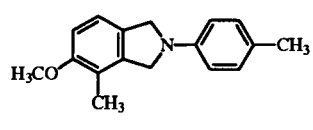
[a] Reaction temperature: 45° (1-19) and 70° (20-45 days). [b] After 5 days at 45° beside epoxyisoindoline **17**, the aromatized product **21** (18] appeared with a concomitant drop in the quantity of **17** being obviously the intermediate. After 20 days only **21** was detected. [c] Conversion.

regardless to the type of substitution on the dienic part of tertiary amine (Figures 4 and 5). The intramolecular Diels-Alder reactions of 2-isopentenyl derivatives were absent during 5 days at room temperature if H (**2**), CH_3 (**4**), I (**6**) or OCH_3 (**8**) groups were present at position 5 of furan diene (Figure 1). The exception was the 5-nitro derivative **10** which with a moderate rate yielded after 5 days about 25% of corresponding epoxyisoindoline **20**.

The essential unreactivity of 2-isopentenyl derivatives (two terminal methyl groups at the dienophilic part of the molecule) was found for unsubstituted **2** and 5-methyl-substituted **4** tertiary furfurylamine even at elevated temperature (80° for 25 days). On the other hand I (**6**), OCH_3 (**8**) and NO_2 (**10**) derivatives were at elevated temperature quite reactive yielding at 60° after 5 additional days 30%, 20% and 100% of cycloadduct, respectively. After additional 15 days at 80° I (**6**) and OCH_3 (**8**) derivatives yielded 96% and 65% of the adduct, respectively.

The effect of one terminal methyl group in 2-butenyl derivatives was not so dramatic, but very similar influence of 5-furan substituent has been observed (Figure 2).

It should be noted that with 5-OCH_3 group (**7**) a spontaneous aromatization of primarily formed epoxyisoindoline **17** takes place so after 10 days at 45° substantial drop of the epoxyisoindoline yield was registered (Figure 2). After heating at 70° the corresponding isoindoline derivative, *i.e.* *N*-*p*-tolyl-4-methyl-5-methoxyisoindoline (**21**) was found [18]. From the crude product traces of *N*-*p*-tolyl-7a-hydroxy-4-methyl-5-oxotetrahydroisoindoline (**22**) were also found [18].



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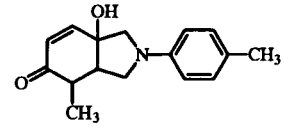

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The relative reactivity of 5-unsubstituted derivatives is illustrated in Figure 3. The cycloaddition at room temperature can be detected only with *N*-allyl derivative **A** [10].

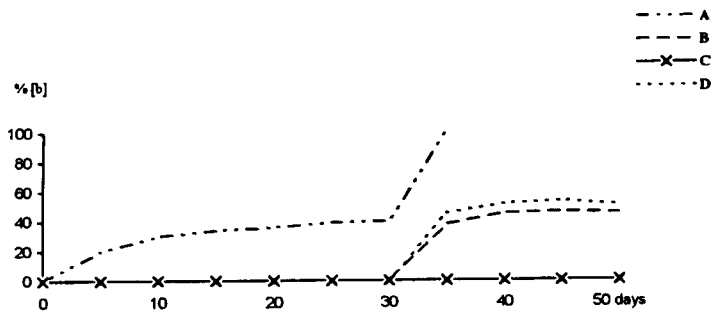


Figure 3. Progress curves [a] of the intramolecular Diels-Alder reaction of *N*-allyl-, *N*-cyclohexenyl, *N-trans*-2-butenyl- and *N*-2-isopentenyl-derivatives of *N*-2-furfuryl-*N*-*p*-toluidine.

A: R = R' = R" = H; **B**: R = R" = H, R' = CH_3 (**1**); **C**: R = H; R '= R" = CH_3 (**2**); **D**: R' = H, R = R" = -$(CH_2)_3$-.

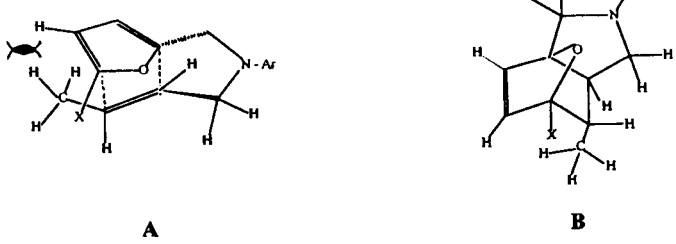
[a] Reaction temperature: 25° (1-30) and 80° (31-50 days). [b] Conversion.

The 2-cyclohexenyl derivative [14] **D** (Figure 3), as well as the 2-butenyl derivative **1**, **B** (Figure 3) and the 2-isopentenyl derivative **2**, **C** (Figure 3) were fully unreactive during 30 days. After the temperature has been raised to 80°, **D** and **B** after 5 days yielded roughly 50% of adduct each. The *N*-2-isopentenyl derivative **2**, **C** (Figure 3) was completely recovered even after 60 days at 80°. The results could be rationalised by the steric effects in the transition state of the intramolecular Diels-Alder reaction that dominates over the present electronic effects of either electron-donors or electron-acceptors at furanic diene, keeping up our previous supposition about the "neutral" type of the Diels-Alder reaction [10b].

The conformational analysis by ^1H nmr technique (Tables 2-4) and the X-ray structural analysis (Figure 6) of obtained epoxyisoindolines undoubtedly pointed out the *trans*-addition and formation of *exo*-products. This conclusion is in a full agreement with several published examples [1h,13,19].

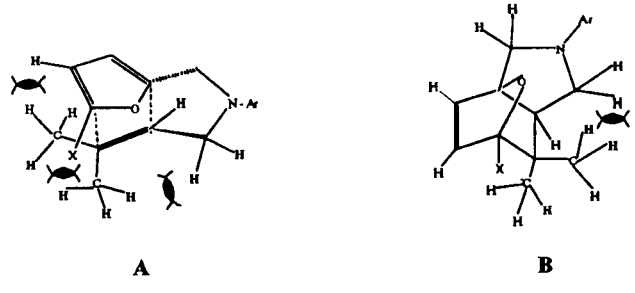
In order to start [4+2] cycloaddition the reactive centres at dienic and dienophilic part of the molecule should be properly oriented. In the transition state preceding *exo*-adduct in *N-trans*-2-butenyl tertiary amine **A** (Figure 4) there is an extensive nonbonding interaction within the terminal group of dienophile and the furanic C-4 hydrogen, opposing the intramolecular Diels-Alder reaction with a tendency of methyl group to be *endo* oriented.

Analogous interaction within the product **B** is not so prominent. The unfavourable interaction of two terminal methyl groups of 2-isopentenyl derivatives (Figure 5) is even more prominent. Namely, because of the presence of *cis*-methyl group in this derivative some additional nonbonding interactions with the furan 5-substituent and with the methylene group next to the nitrogen could be anticipated. Within the *exo*-cycloadduct **B** (Figure 5) interaction of the *endo*-methyl group originated from *trans*-methyl in **A** (Figure 5) and furanic C-4 hydrogen ceased. Also this is true for the *exo*-methyl group **B** (Figure 5) originated from the *cis*-methyl group in **A** (Figure 5) and furanic C-5 substituent, but potentially very unfavourable interaction of the *exo*-methyl group and a tetrahydropyrrol hydrogen appeared. These unfavourable nonbonding interactions could account for the much lower reactivity of the tertiary *N*-2-isopentenyl furfurylamines.



A **B**

Figure 4.



A **B**

Figure 5.

It should be noted that this type of steric hindrance would be avoided by *cis*-addition leading to *endo*-products, but in this case another very unfavourable nonbonding interaction of C-3 furan hydrogen and methylenic group in the dienophile should appear even with examples without the terminal methyl groups. Such a conclusion is supported by previously reported similar examples of the intramolecular Diels-Alder reaction [1h].

The results of the present studies support our proposal of an electronically neutral concerted reaction [10b]. The very profound influence of the 5-nitro substituent is in full agreement with the anticipated lowering of the energy of diene frontier orbitals [20].

As a final proof of the structure and stereochemistry of cycloaddition X-ray crystallographic studies of four epoxyisoindolines **11**, **15**, **19** and **20** were performed showing *exo*-epoxyisoindoline structure (Figure 6) [21].

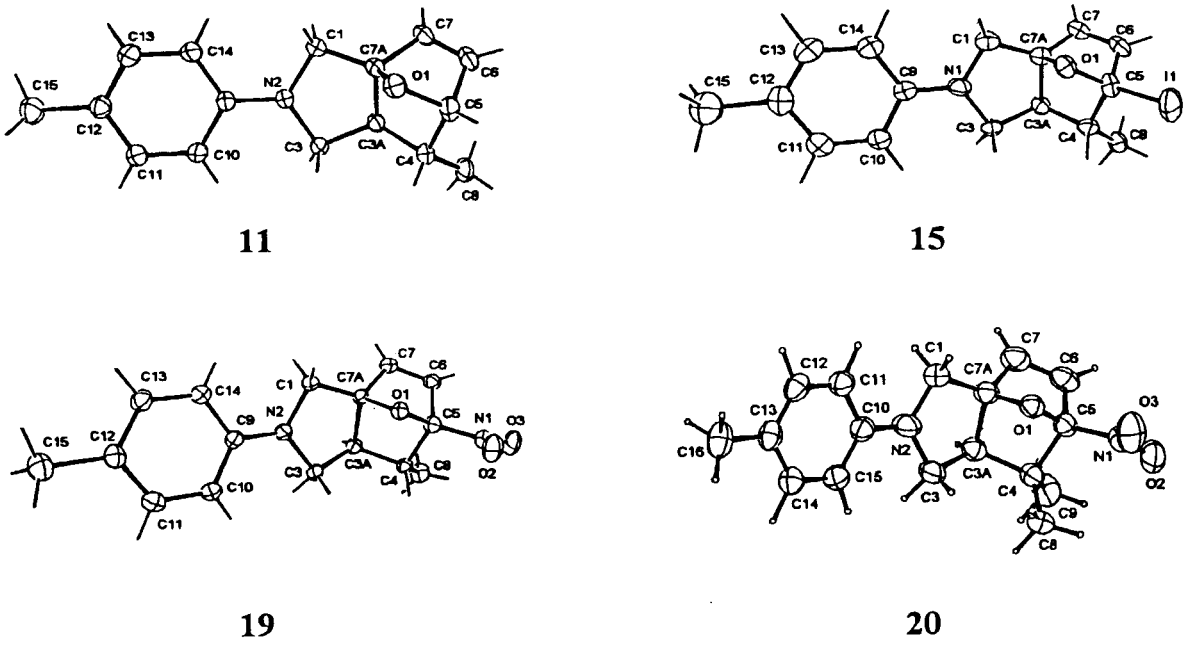


Figure 6. Perspective view and atom labelling of the X-ray structures of selected epoxyisoindolines.

EXPERIMENTAL

All melting points were determined on an Original Kofler Mikroheiztisch apparatus (Reichert, Wien) and are not corrected. Infrared spectra were obtained for samples in potassium bromide pellets on a Perkin-Elmer Model 297 instrument. The ^1H and ^{13}C nmr spectra were recorded on a Jeol FX 90 Q spectrometer. Mass spectra were run by a Varian MAT CH-7 spectrometer at 70 eV by direct insertion probe. X-Ray structure analyses were run on an automatic difractometer PHILIPS PW 1100 and were solved by the direct method with the SHELX86 program 22. Silica gel (0.063-0.2 mesh, "Kemika") and neutral aluminium oxide (Brockmann Grade I, "Kemika") were used for chromatographic purification. "Merck" DC Alufolien (Kieselgel 60 F_{254}, 0.2 mm and Aluminiumoxid 60 F_{254} neutral, 0.2 mm) were used for R_f determinations. All tertiary amines were prepared by alkylation of *N*-(5-substituted-2-furfuryl)-*p*-toluidine with a slight excess of the appropriate alkenyl bromide [17].

N-p-Tolyl-4-methyl-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline (**11**).

A solution of **1** [17] (1.20 g, 5 mmoles) in dry benzene (50 ml) was heated at 80° for 120 hours. Benzene was evaporated at diminished pressure. The residual solid was purified on a silica gel column. Elution of the column with petroleum ether/chloroform 5:2 followed by petroleum ether/ether 10:1 gave colourless crystalline **11** (0.55 g, 46%); R_f 0.25 (silica gel-petroleum ether/ether 10:1), mp 136-138°; ir (potassium bromide): 3060 (w), 2960 (m), 2910 (m), 2840 (m), 1615 (s), 1520 (s), 1460 (s), 1360 (s), 1170 (s), 1090 (m), 1070 (m), 975 (s), 900 (s), 860 (s), 810 (s), 790 (s) and 720 (s) cm^{-1}; ms: m/z (relative intensity) 241 (78, M^+), 198 (6), 187 (6), 186 (10), 170 (5), 158 (19), 144 (8), 133 (5), 119 (14), 118 (25), 105 (16), 105 (16), 91 (42), 81 (100), 65 (46), 55 (17) and 53 (23); ^1H nmr: Table 2; ^{13}C nmr: Table 5.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.99; H, 8.18; N, 5.64.

N-p-Tolyl-4,5-dimethyl-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline (**13**).

A solution of **3** [17] (1.28 g, 5 mmoles) in dry benzene (60 ml) was heated at 80° for 120 hours. After benzene evaporation, the residual solid was purified on a silica gel column. On elution with petroleum ether/chloroform 5:2 and with petroleum ether/ether 5:1, colourless crystals of **13** (0.45 g, 35%) were obtained. R_f 0.31 (silica gel-petroleum ether/ether 5:1), mp 134-135°; ir (potassium bromide): 3080 (w), 2980 (m), 2900 (m), 2860 (m), 1620 (s), 1560 (m), 1520 (s), 1470 (s), 1370 (s), 1170 (s), 1035 (m), 965 (m), 900 (m), 860 (s), 800 (s), 790 (s) and 710 (s); ms: m/z (relative intensity) 255 (29, M^+), 161 (24), 95 (100), 91 (18), 77 (21), 65 (32), 55 (29) and 43 (10); ^1H nmr: Table 2; ^{13}C nmr: Table 5.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.83; H, 8.24; N, 5.34.

N-p-Tolyl-5-iodo-4-methyl-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline (**15**).

This compound was prepared by refluxing a dry benzene solution of **5** [17] (1.84 g, 5 mmoles) for 48 hours. Benzene was evaporated to yield the crude product that was chromatographed on a silica gel column with petroleum ether/chloroform 5:2 and with petroleum ether/ether 10:1. On evaporation of the solvents, colourless crystals of **15** (1.80 g, 95%) were obtained. The purity has been proven by tlc on silica gel; R_f 0.36 (petroleum ether-ether 5:1), mp 187-188°;

ir (potassium bromide): 3080 (w), 2920 (m), 2980 (m), 2860 (m), 1620 (s), 1560 (m), 1520 (s), 1470 (m), 1360 (s), 1190 (m), 1175 (m), 1080 (s), 990 (s), 950 (s), 930 (s) 850 (w), 820 (s), 800 (s) and 715 (m) cm^{-1}; ms: m/z (relative intensity) 367 (87, M^+), 207 (100) and 91 (48); ^1H nmr: Table 2; ^{13}C nmr: Table 5.

Anal. Calcd. for $C_{16}H_{18}INO$: C, 52.33; H, 4.94; N, 3.81. Found: C, 52.51; H, 4.67; N, 3.71.

N-p-Tolyl-4,4-dimethyl-5-iodo-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline (**16**).

This compound was obtained by heating a dry benzene solution of **6** [17] (1.90 g, 5 mmoles) at 80° for 240 hours. Benzene was evaporated and the residual solid chromatographed on a silica gel column with petroleum ether/chloroform 5:2 and petroleum ether/ether 10:1 as eluents. On evaporation of solvents colourless crystals of **16** (1.70 g, 90%) were separated. The purity was proven by tlc. R_f 0.35 (silica gel-petroleum ether/ether 5:1), mp 180-182; ir (potassium bromide): 2990 (m), 2860 (m), 2840 (m), 1620 (m), 1570 (w), 1520 (s), 1460 (s), 1380 (s), 1060 (m), 990 (m), 970 (s), 850 (w), 800 (s) and 700 (m) cm^{-1}; ms: m/z (relative intensity) 381 (8, M^+), 380 (41), 335 (24), 333 (22), 207 (63), 187 (100), 169 (35), 159 (37), 149 (44), 91 (39), 71 (59) and 69 (61); ^1H nmr: Table 3; ^{13}C nmr: Table 5.

Anal. Calcd. for $C_{17}H_{20}INO$: C, 53.56; H, 5.29; N, 3.67. Found: C, 53.71; H, 5.15; N, 3.53.

N-p-Tolyl-4,4-dimethyl-5-methoxy-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline (**18**).

This compound was obtained by refluxing of the benzene solution of **8** [17] (1.43 g, 5 mmoles) for 240 hours. On evaporation of the benzene, a crude product separated. The solid was purified on a neutral aluminium oxide column with petroleum ether/chloroform 5:2 followed by petroleum ether/ether 10:1. Colourless crystals of **18** (0.73 g, 51%), mp 163-165° were obtained; R_f 0.31 (alumina-petroleum ether/ether 5:1); ir (potassium bromide): 2990 (m), 2910 (s), 2860 (m), 1620 (m), 1520 (s), 1460 (m), 1385 (m), 1350 (m), 1160 (m), 1070 (s), 990 (s), 860 (s), 810 (s) and 700 (s) cm^{-1}; ms: m/z (relative intensity) 285 (10, M^+), 175 (4), 121 (2), 119 (2), 112 (6), 111 (100), 107 (5), 91 (5), 83 (5), 79 (5), 69 (6) and 41 (3); ^1H nmr: Table 2; ^{13}C nmr: Table 5.

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.94; H, 8.06; N, 5.11.

N-p-Tolyl-4-methyl-5-nitro-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline (**19**).

The solution of **9** (1.43 g, 5 mmoles) in dried benzene (50 ml) was heated at 40° for 72 hours. The residual solid was chromatographed on a neutral aluminium oxide column with petroleum ether/chloroform 5:2 followed by petroleum ether/ether 10:1 as eluents. Light yellow crystalline **19** (1.34 g, 94%) was obtained. R_f 0.17 (alumina-petroleum ether/ether 5:1); ir (potassium bromide): 3100 (w), 2980 (m), 2900 (m), 2850 (s), 1625 (m), 1560 (s), 1525 (s), 1480 (m), 1360 (s), 1160 (m), 1130 (m), 960 (m), 860 (m), 800 (s), 720 (s) and 700 (m) cm^{-1}; ms: m/z (relative intensity) 286 (100, M^+), 271 (10), 245 (5), 232 (18), 160 (12), 157 (13), 118 (31), 117 (18), 105 (16), 91 (51), 65 (20) and 55 (35); ^1H nmr: Table 2; ^{13}C nmr: Table 5.

Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.31; H, 6.27; N, 9.56.

N-p-Tolyl-4,4-dimethyl-5-nitro-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline (**20**).

This compound was obtained by heating of the dry benzene solution of **10** [17] (1.80 g, 5 mmoles) at 50° for 72 hours. The crude product was purified by column chromatography on neutral aluminium oxide with petroleum ether/chloroform 5:2 followed by petroleum ether/ether 10:1. Yellow crystals of **20** (1.50 g, 83%) have mp 173-175°; R_f 0.15 (alumina-petroleum ether/ether 5:1; ir (potassium bromide): 2980 (m), 2910 (s), 2860 (m) 1620 (m), 1560 (s), 1520 (s)m 1470 (m), 1365 (m), 1350 (m), 1140 (m), 880 (s), 830 (m), 810 (s) and 710 (s) cm^{-1}; ms: m/z (relative intensity) 300 (100, M^+), 186 (21), 157 (17), 106 (25), 91 (38), 69 (75), 43 (52) and 41 (21); ^1H nmr: Table 3. ^{13}C nmr: Table 5.

Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.10; H, 6.79; N, 9.19.

N-p-Tolyl-3a,4,5,7a-tetrahydro-5,7a-epoxy-3,4-propanoisoindoline (**14**).

This compound was prepared according to the reported procedure [14], yield: 30%, mp 94-95° (lit [14] mp 94-95°); R_f 0.41 (silica gel-petroleum ether/ether 5:1); ir (potassium bromide): 3000 (s), 2940 (s), 2860 (s), 1620 (s), 1565 (m), 1520 (s), 1460 (s), 1360 (s), 1330 (s), 1190 (m), 1165 (m), 1090 (m), 1070 (m), 990 (m), 800 (s), 750 (s) and 690 (s) cm^{-1}; ms: m/z (relative intensity) 267 (40, M^+), 239 (25), 187 (13), 186 (17), 158 (11), 149 (11), 115 (16), 98 (9), 91 (17), 83 (15), 81 (100), 57 (17) and 55 (13); ^1H nmr: Table 4; ^{13}C nmr: Table 6.

The Rate of Intramolecular Diels-Alder Reaction of Tertiary Amines **1-10**.

The experiments were carried out in nmr tubes. The deuteriobenzene solutions of tertiary amine **1-10** [17] were heated at the temperature stated in Figures 1 and 2 and the progress of the reaction followed mostly by the relative intensity of a distinct and well-separated methyl-singlet (*N-p*-tolyl-substituent) of a tertiary amine (δ 2.18-2.29 ppm) [17] and for the corresponding 5-methyl singlet of the isomeric epoxyisoindolines (δ 2.23-2.26 ppm) (Tables 2 and 3).

Acknowledgements.

We are grateful to the Ministry of Science and Technology of the Republic of Croatia for the support of this research by the grant (Code No. 1.07.039). The authors thank the staff of the analytical laboratory of Institute "Rugjer Bošković" for microanalyses and the laboratories for nmr and mass spectroscopy for nmr and mass spectra.

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