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Chemistry of 1,3-Dioxepins. XII.[#] 4,7-Dihydro-5-nitro-1,3-dioxepins in the Diels-Alder Reaction with 4-Methyloxazole*

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4,7-Dihydro-5-nitro-1,3-dioxepins **4** prepared by dehydrohalogenation of *vic*-chloronitro-dioxepanes **2** and/or dehydrohalogenation-demercuration of *vic*-chloromercurynitro-dioxepanes **3** represent reactive dienophiles in the Diels-Alder cycloaddition with 4-methyloxazole (**5**), giving pyridoxine (**8**) intermediates 1,5-dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridines **6** in poor yields. The side products of this reaction were 4,7-dihydro-4-hydroxyimino-6-nitro-1,3-dioxepins **7**, the structure of which was confirmed by parallel synthesis, *i.e.* by nitrosation of **4** with ethyl nitrite. The order of reactivity in the series of 5-substituted-4,7-dihydro-1,3-dioxepins, calculated by AM1 semiempirical method, is predicted to be 5-nitro- > 5-unsubstituted- > 5-cyano- > 5-chloro-4,7-dihydro-1,3-dioxepin, and it is in agreement with experimental data.

INTRODUCTION

Diels-Alder reactions of carefully selected oxazole with complementary selection of an olefinic dienophile provide an appropriate route for the syn-

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[#] Part XI, Ref. 1.

* Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.

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thesis of pyridoxine (vitamin B_6, **8**).[1–5] Cycloadditions of 4-methyloxazole as diene are performed

- in the presence of hydrogen acceptor (oxidizing agent), or
- by choosing at the double bond with electron-withdrawing and/or good leaving group substituted olefin,

which provide aromatization of fragmentated cycloadduct.[5–9]

In our investigations in the same field,[10] we have synthesized *cis*-2-halo-1,4-dimethoxy-2-butene,[11] 5-halo-,[11,12] 5-nitro-,[13] 5-alkoxy-[12] and 5-dialkylamino-[12] substituted-4,7-dihydro-1,3-dioxepins. While the halogen substituted dimethoxybutenes and dihydrodioxepins led to pyridoxine,[11] the 5-alkoxy- and 5-dialkylamino-4,7-dihydro-1,3-dioxepins were unstable and even at room temperature underwent, like analogous dihydrofurans,[14] allyl- vinyl-ether isomerization, furnishing the corresponding 6,7-dihydro- derivatives.[12]

Now, we would like to describe our results of pyridoxine synthesis from 4,7-dihydro-5-nitro-1,3-dioxepins **4** as dienophiles.

RESULTS AND DISSCUSION

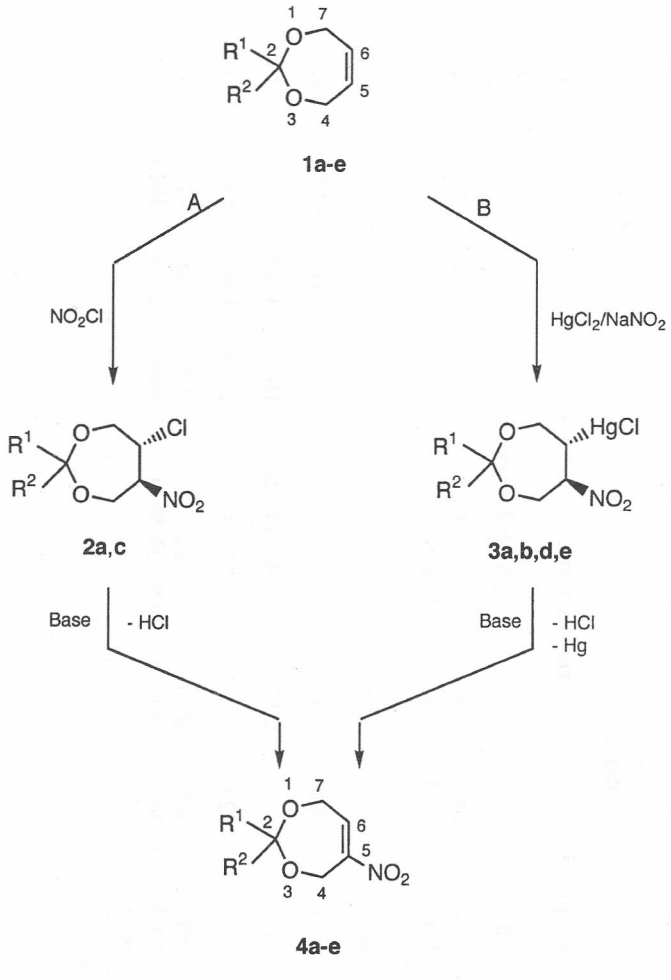
Synthesis of 4,7-Dihydro-5-nitro-1,3-dioxepins 4

In our first attempt, the nitrodioxepins **4** were prepared by addition of nitryl chloride to 4,7-dihydro-1,3-dioxepins **1,** followed by dehydrochlorination of the intermediate *vic*-chloronitro adducts **2** (Scheme 1). The key point of that synthesis, the addition of nitryl chloride to **1**, was unselective and characterized by poor yields of **2.**[13] We therefore directed our attention to the nitromercuration/demercuration procedure of the starting dioxepins **1**, which appeared to be a suitable method for preparing nitro-dioxepins, *i.e.* 4,7-dihydro-2,2-dimethyl-5-nitro-1,3-dioxepin (**4e**)[15] and 4,7-dihydro-2-methyl-5-nitro-1,3-dioxepin (**4b**).[16,17]

Thus, in our somewhat modified procedure, the 4,7-dihydro-1,3-dioxepin (**1a**) was nitromercurated with mercury(II) chloride and sodium nitrite (mol ratio 1 : 1 : 2) in water at room temperature for 24 hours. The crude nitromercurial **3a** (68.7%) was separated, suspended in methylene chloride and demercurated by sodium hydroxide solution (c = 2.5 mol L^{-1}) under vigorous stirring at room temperature for 90 minutes. After separation of the formed metallic mercury and evaporation of the washed and dried methylene chloride layer, the crude, TLC pure nitrodioxepine **4a** (69.5%), identical to the authentic sample,[13] was obtained.

In this manner, nitromercurials **3d** and **3e**, as well as nitrodioxepins **4d** and **4e**, were also prepared (Scheme 1, Table I).

While the yields of **3d** and **4d** were relatively high, the overall yield of **4e** (4.4%) was significantly poorer than that cited (67%).[15] The lower yield



a) $R^1 = R^2 = H$;
b) $R^1 = H$, $R^2 = Me$
c) $R^1 = H$, $R^2 = i\text{-}Pr$;
d) $R^1 = H$, $R^2 =$ 
e) $R^1 = R^2 = Me$

Scheme 1

in demercuration step (**3e** to **4e**) could be explained by demercuration time exceeding the cited 5 minutes.[15] But, the low yield of nitomercurial **3e** (only 13%) turned our attention to the nitromercuration step, since the concentration of the nitromercuration reagent and reaction time have a decisive influence in the nitromercuration step for some olefins.[18] Therefore, the nitromercuration of **1e** was continued by varying the mol ratio of the reactants

TABLE I

Synthesis and physical data of all known nitrodioxepins **4**

	1		Method	Mole ratio	Time/h	**3**	Nitrodioxepin **4**						Ref.
	R^1	R2	see Sch. 2	**1e** : $HgCl_2$: $NaNO_2$		Yield/% **1**→**3**	Yield/% **3**→**4**	Yield/% **1**→**4**	m.p./°C (b.p./°C/Pa)	IR ν/cm^{-1} C=C	NO_2		
a	H	H	A	–	–	–		19.5	48–49	1670	1520	1330	13
			B	1 : 1 : 2	24	68.7	69.5	47.7					
b	H	Me	B	ND	ND	ND	ND	ND	ND	ND	ND	ND	16,17
c	H	*i*-Pr	A	–	–	–	–	20.7	(90–94/133.3)	1675	1520	1335	13
d	H	Z*	B	1 : 1 : 2	24	82.8	62.9	52.1	113–114	1680	1525	1345	1
e	Me	Me	B	1 : 1 : 2	30	ND	ND	67.0	ND	ND	ND	ND	15
			B	1 : 1 : 2	24	13.0	34.0	4.4	(80–85/93.3)	1680	1520	1340	
			B	1 : 2 : 8	3	52.0	33.1	17.2					

* Z = 4,7-Dihydro-1,3-dioxepin-2-yl-; ND = No data.

and reaction time, following the demercuration step to **4e** withouth isolation of **3e**. The obtained results showed that the optimum time for nitromercuration of **1e** was 3 hours, and that the used mol ratios of reactants **1e** : $HgCl_2$: $NaNO_2$ = 1 : 1–4 : 2–8 made no great difference in the overall yield of **4e** (3–25%).

Thus, at the mol ratio of **1e** : $HgCl_2$: $NaNO_2$ = 1 : 2 : 8 and nitromercuration time of 3 hours, the nitromercurial **3e** was isolated in 52% yield. In this case, the overall yield of **4e** was 17.2% (Table I).

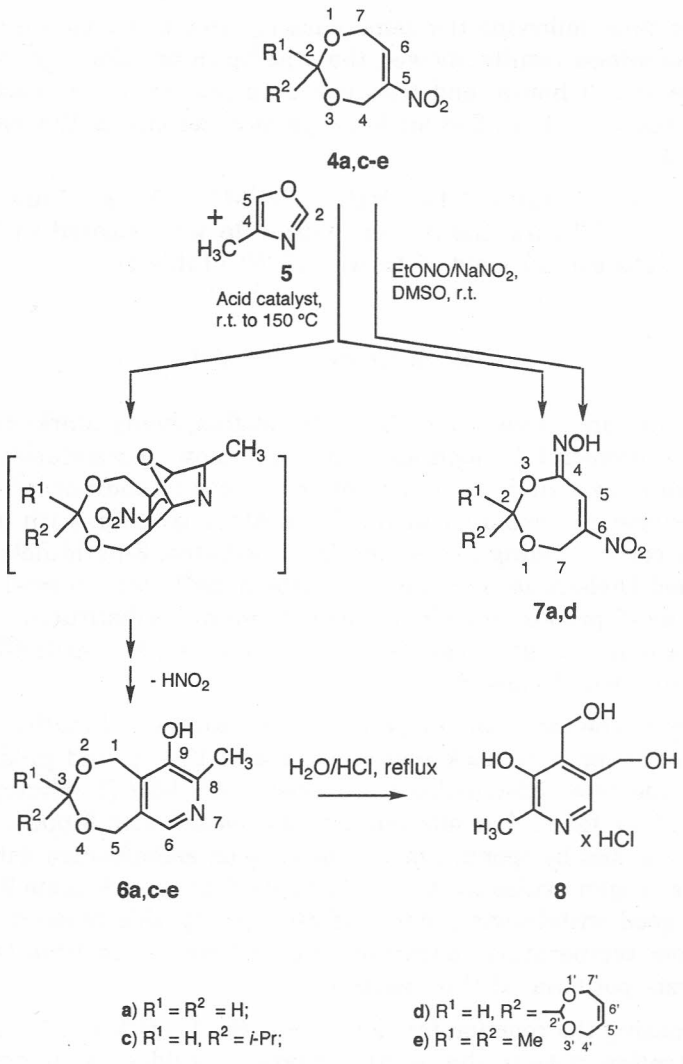
Diels-Alder Reaction of 4

Despite an early recognition that nitro olefins, being markedly electron deficient, are powerful dienophiles[19] and well known possibilities of removing the nitro moiety under eliminative or reductive conditions,[20] they have not been extensively explored in the Diels-Alder reaction with oxazoles to prepare the corresponding pyridoxine intermediates, 3-pyridinols. The only so far studied Diels-Alder reactions of nitroethene[21] and 1-nitro-1-propene[22] with 4-methyl-5-propoxyoxazole furnished mainly substituted 3-nitropyrroles, and only in the latter case a small amount of 2,5-dimethyl-3-hydroxy-4-nitropyridine was formed.[22]

Contrary to the fact that the [4 + 2]-cycloaddition of 4-methyloxazole (**5**) with dihydrodioxepin **1a** took place only above 150 °C and produced pyridoxine intermediate, 1,5-dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino-[5,6-*c*] pyridine **6a**,[6a] we found that nitrodioxepin **4a** reacted with **5** under mild reaction conditions, and by spontaneous aromatization accompanied with elimination of the nitrogen oxides led to dioxepinopyridinol **6a** (Scheme 2, Table II). Due to the good withdrawing ability of nitro group, this reaction took place even at room temperature, naturally, over a long period time (4 months). Acid catalysts potentiated this reaction.

By increasing the reaction temperature to 90 °C (reflux of **5**) or more and the concentration of **4a** in the reaction mixture, besides **6a**, accompanied by undefined oligomeric material, 4,7-dihydro-4-hydroxyimino-6-nitro-1,3-dioxepin (**7a**), as the representative of the new class of functionalized dioxepins, was additionally isolated (Scheme 2, Table II).

Unfortunately, all the studied **4** gave the corresponding dioxepinopyridinols **6** in poor yields (Table II). Thus, **4c** gave only 4.1% of isopropyl derivative **6c**. But, if instead of **4c** the chloronitroderivative **2c** was boiled under the same reaction conditions, the **6c** (20.0%) and pyridoxine base (13.3%) were isolated, *i.e.* the whole reaction yield was 33.3%. This finding points to the instability of nitrodioxepins **4** under the studied conditions. On the other hand, decomposition of **4** can be prevented by its *in situ* trapping with 4-methyloxazole.



Scheme 2

Nitro-bis(4,7-dihydro-1,3-dioxepine) **4d** furnished only the mono adduct **6d**,[1] the structure of which was confirmed by the single crystal X-ray diffraction analysis (Figure 1).[23] This suggests, that only the double bond, activated by nitro group, reacted with diene, while the second, unsubstituted double bond of **4d**, was inactive under the given reaction conditions. This conclusion was supported by the formation of both mono-**6d** and bis-adducts under stronger reaction conditions (15 hours at 150 °C) in the Diels-Alder reaction of bis-dioxepine **1d** with 4-methyl-5-oxazolecarbonitrile.[1]

TABLE II

Diels-Alder reaction of nitrodioxepins **4** with 4-methyloxazole (**5**)

	4			Mol ratio	React. cond.	Catalyst[a]	Yield / %	
	R^1	R^2	mol × 10^{-3}	**5/4**	temp. / time		**6**	**7**
				8.7	r.t. / 133 d	T/H	17.6	–
				8.7	refl. / 4.5 h	–	6.5	7.9
				10.5	refl. / 6.0 h	P	13.2	13.7
a	H	H	1.38	8.7	refl. / 7.5 h	T/H	11.8	13.7
				8.7	refl. / 12 h	P/H	16.0	17.1
				8.7	refl. / 12 h	C	tr[b]	–
				4.4	130 °C / 30 min	T/H	10.6	13.3
				4.4	150 °C / 15 min	T/H	17.0	22.9
a	H	H	6.90	8.7	refl. / 7.5 h	P/H	12.2	14.1
c	H	*i*–Pr	6.90	15.0	refl. / 10 h	P/H	4.1	–
d	H	Z[c]	6.90	21.0	refl. / 4 h	P/H	30.3	34.8
e	Me	Me	6.90	8.7	refl. / 11 h	P/H	2.4	–

[a] T = *p*-Toluenesulfonic acid, H = hydrochinone, P = perchloric acid, C = calcium oxide;
[b] tr = traces;
[c] Z = 4,7-dihydro-1,3-dioxepin-2-yl-.

In all the performed experiments, 6-nitro-4-oxime **7a** was formed in a practically equimolar ratio to the obtained dioxepinopyridinol **6a**. The only exception was the procedure performed at room temperature when only **6a** was isolated (Table II). From this finding, it can be concluded that **7a** is formed by nitrosation of **4a** by nitrogen oxides, liberated in the course of the reaction. It is interesting that **7a** precipitated from the reaction mixture, and it was only possible to recrystallize it from 4-methyloxazole. ^{1}H-NMR spectrum of such a sample, dried under the reduced pressure (2.0 kPa) at room temperature, showed that the precipitate contained almost equimolar quantities of **7a** and 4-methyloxazole. 4-Methyloxazole free **7a** was obtained by drying of the crude sample under reduced pressure of 67–133 Pa and temperature of 50 °C. Unfortunately, it was not possible to prepare a good quality single crystal for the X-ray structure analysis and, at the moment, it could be proposed that **7a**, due to the great acidity of oximino group, forms the salt with 4-methyloxazole, like 2-hydroxyimino-3-methyl-5-nitro-3-thiolen-1,1-dioxide.[24]

In contrast, the nitrooxime **7d** could be easily recrystallized from ethyl acetate. All attempts to isolate nitrooximes **7c** and **7e** were unsuccessful, in spite of finding the low intensity TLC spots of similar characteristics, like **7a** or **7d**. Structures of the obtained nitrooximes **7** were elucidated by spectroscopic methods and in both cases confirmed by parallel synthesis, *i.e.* by nitrosation of the corresponding **4** with ethyl nitrite in DMSO (*ii*, Scheme 2).

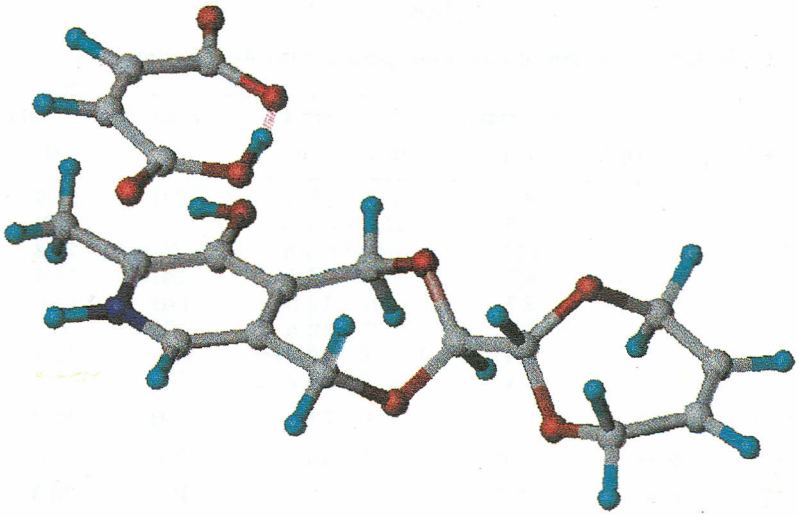


Figure 1. Molecular structure of maleic acid salt of **6d**.[23]

All synthesized dioxepinopyridinols **6** represent known pyridoxine intermediates in which they can be easily hydrolyzed by hydrochloric acid.

Theoretical Calculation

The AM1 semiempirical method has proven to be very useful in determining the reactivity of dienes in the Diels-Alder reactions with different dienophiles.[25] To obtain a more accurate scale of reactivity of dioxepins, we calculated the transition state structures for unsubstituted (A), 5-electron withdrawing group substituted (5-cyano-B and 5-nitro-C) and electron donating group substituted (5-chloro-D) 4,7-dihydro-1,3-dioxepin in addition to 4-methyloxazole (Figure 2).

There are 8 transition state structures for the reaction of 4-methyloxazole as diene and 4,7-dihydro-1,3-dioxepin as dienophile in respect of dioxepin conformation and possibility of stereoisomers (*endo* & *exo*) formation. Among these candidates, one, with the lowest calculated $\Delta_f H$, characterized as *endo* isomer with the chair conformation of dioxepin pattern, was chosen as a possible transition state structure (Figure 2, A). In the cases of 5-cyano-, 5-nitro- and 5-chloro-derivatives of 4,7-dihydro-1,3-dioxepin, the same transition structures were also the most stable, and the substituent in position 5 of dioxepin ring was in each case located at the same site as the oxazole nitrogen atom (Figure 2, B, C and D). Thermodynamic parameters of the studied Diels-Alder reaction, including the corresponding activation energies, are presented in Table III.

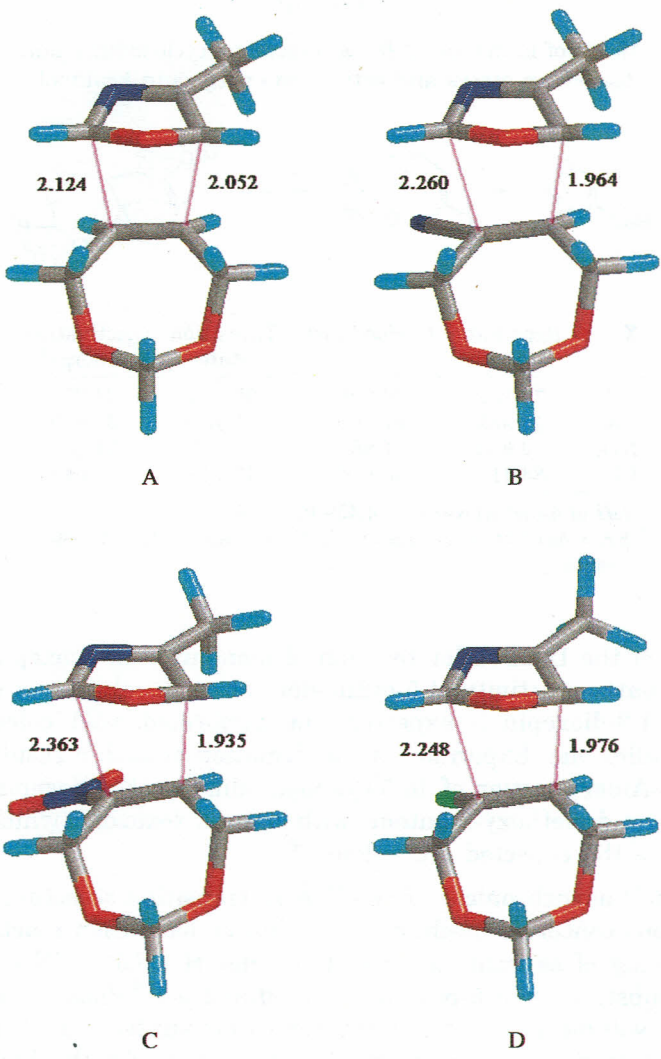
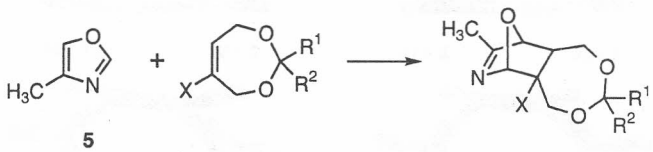


Figure 2. Transition state structures for [4+2]-cycloaddition of 5-substituted-4,7-dihydro-1,3-dioxepins (unsubstituted-A, 5-cyano-B, 5-nitro-C & 5-chloro-D) to 4-methyloxazole.

All the studied dioxepins show a comparatively high activation energy barrier. The order of reactivity in such kinetically controlled reactions is predicted to be 5-nitro- > 5-unsubstituted > 5-cyano- > 5-chloro-4,7-dihydro-1,3--dioxepin. The activation energy difference between 5-nitro- and unsubstituted 4,7-dihydro-1,3-dioxepin of 3.21 kcal/mol is in agreement with our experimental data and confirms the exclusive formation of monoadduct **6d**

TABLE III

Heats of formation ($\Delta_f H$) for reactants, cycloadducts and transition states and activation energies in kcal/mol[a]



5

X	Reactant	Cycloadduct	Transition state	Activation energy[b]
–H	–77.152	–80.306	–38.421	34.271
–CN	–44.965	–41.564	– 4.877	35.629
$-NO_2$	–72.665	–71.862	–37.145	31.061
–Cl	–84.117	–80.876	–42.146	37.512

[a] $\Delta_f H$ of 4-methyloxazole = 4,459 kcal/mol;
[b] EA = $\Delta_f H$ (transition state) – [$\Delta_f H$ (reactant) + $\Delta_f H$ (4-methyloxazole)].

in the case of the Diels-Alder reaction of mononitro-bis-dioxepin **4d**.[1,23] Although a greater reactivity of 5-cyano-derivative in relation to unubstiuted 4,7-dihydro-1,3-dioxepin is expected, the performed AM1 calculation predicted a smaller one. Experimental confirmation of such a result was found in the Diels-Alder reaction of, to 5-cyano-4,7-dihydro-1,3-dioxepin very close, 2-cyano-*cis*-1,4-dimethoxy-2-butene with 4-methyloxazole, which furnished only traces of the expected cycloadduct.[9]

Very small asynchronicity of 0.072 Å in transition structure A points to a synchronous concerted mechanism for that cycloaddition reaction. The observed growing of asynchronicity in the order H < Cl < CN < NO_2 by exchange of substituent in 5-position of 4,7-dihydro-1,3-dioxepin is in concordance with volume growing of each particular substituent. Therefore, we assume that steric repulsion might be responsible for the high (0.428 Å) asynchronicity of the transition structure C. Consequently, this indicates an asynchronous concerted cycloaddition of 5-nitro-4,7-dihydro-1,3-dioxepins to 4-methyloxazole.

In conclusion, we here present the experimental evidence and theoretical support of the great reactivity of 4,7-dihydro-5-nitro-1,3-dioxepins **4** as dienophiles in the Diels-Alder synthesis of pyridoxine from 4-methyloxazole (**5**) as diene.

Relatively low, although not optimized yields of dioxepinopyridinol intermediates **6** are a consequence of other reactions, especially the nitrosation of **4**, which seem to be the dominant processes under these conditions.

EXPERIMENTAL

Chemistry. General Information

Melting points were determined using a Fischer-Johns apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer from KBr pelleted sample or as film. ^{1}H-(300 and 90 MHz) and ^{13}C-(75 and 25 MHz) NMR spectra were recorded by a Varian XL-GEMINI 300 and Jeol FX 90Q spectrometers, with TMS as internal standard; the values of chemical shifts (δ) are given in ppm and coupling constants (J) in Hz; DMSO-d_6 was used as solvent unless otherwise stated. Mass spectra were recorded on a Shimadzu GC-MS QP- 1000A instrument, operating at 70 eV. TLC was performed using Merck Kieselgel 60 F_{254} silica plates and the components were visualized using UV light (UV 254 nm), iodine vapor and spraying with diazotized sulfanilamide (red spots) or by 2,6-dichloroquinone-4-chloroimide (blue spots). Compounds were purified by column chromatography using a Merck Kieselgel 60 (0.063–0.200 mm, 70–230 mesh), and were homogeneous by TLC. Solvents *p.a.* grade were used without further purification. All chemicals used were commercially available and were supplied by Merck. 4,7-Dihydro-1,3-dioxepins (**1a**[26], **1c**[26], **1d**[1], **1e**[27]), chloromercurynitro-dioxepane (**3d**),[1] nitrodioxepins **4c**,[13] and **4d**[1] and 4-methyloxazole (**5**)[28] were prepared according to reported procedures. Hydroquinone was used as antioxidant and *p*-toluenesulfonic and perchloric acid as catalysts. The yields were not optimized.

5-Chloromercury-6-nitro-1,3-dioxepane ***(3a)***

To the solution of mercury(II) chloride (54.4 g, 0.199 mol) and sodium nitrite (27.6 g, 0.399 mol) in 600 mL water, dioxepin **1a** (20.0 g, 0.199 mol) was added in small portions for 1 hour. The mixture was stirred at room temperature for 24 hours and the formed precipitate was filtered, washed with water and dried under vacuo at room temperature to give nitromercurial **3a** (52.4 g, 68.6%, m.p. 260 °C decompn.). IR (KBr) ν_{max}/cm^{-1}: 2980m, 2950vs, 2890vs, 2870vs, 2790m, 1515vs, 1450s, 1375s, 1350s, 1315m, 1270s, 1230s, 1160s, 1130s, 1100vs, 1000s, 970s, 910m, 880w, 810s and 720w.

2,2-Dimethyl-5-chloromercury-6-nitro-1,3-dioxepane ***(3e)***

To the solution of mercury(II) chloride (4.3 g, 0.016 mol) and sodium nitrite (4.4 g, 0.064 mol) in 75 mL water, dioxepin **1e** (1.0 g, 0.008 mol) was added in small portions for 1 hour. The mixture was stirred at room temperature for 3 hours and the formed precipitate was filtered, washed with water and dried under vacuo at room temperature to give nitromercurial **3e** (1.6 g, 52%, m.p. 260 °C decompn.). IR (KBr) ν_{max}/cm^{-1}: 2980w, 2940m, 2885s, 2780w, 1520vs, 1445s, 1380vs, 1350vs, 1320s, 1270vs, 1235s, 1165s, 1130s, 1105–1075vs, 980vs, 910s, 875s, 860m, 810vs and 715s.

4,7-Dihydro-5-nitro-1,3-dioxepin ***(4a)***

To the suspension of crude nitromercurial **3a** (26.2 g, 0.068 mol) in 270 mL of dichloromethane, the aqueous sodium hydroxide solution (27.3 mL, c = 2.5 mol L^{-1}) was added dropwise under vigorous stirring at room temperature for 1 hour. The reaction mixture was stirred at the same temperature for further 30 minutes. After

addition of diatomaceous earth (4.0 g) the precipitated elementary mercury was filtered. The dichloromethane layer was washed with water, dried over anhydrous sodium sulfate and concentrated, furnishing the crude **4a** (6.7 g, 69.5%) as viscous oil. After recrystallization from petroleum ether, the sample showed m.p. 48–49 °C (m.p.[13] 48–49 °C). IR (KBr) ν_{max}/cm^{-1}: 3060vw, 2950–2830m, 1520s, 1440w, 1330s, 1240s, 1130s, 1100s, 1025w, 930s, 830m, 780m and 695m; ^{1}H-NMR ($CDCl_3$) δ: 7.29 (t, 1H, J = 3.8, H-C6), 4.89 (s, 2H, H-C2), 4.80-4.74 (m, 2H, H-C4), 4.50–4.41 (m, 2H, m, H-C7); ^{13}C-NMR ($CDCl_3$) δ: 150.77 (C5), 136.95 (C6), 95.88 (C2), 63.14 (C4), 62.97 (C7).

Its spectra were identical to the spectra of an authentic sample.[13]

4,7-Dihydro-2,2-dimethyl-5-nitro-1,3-dioxepin ***(4e)***

From Isolated Nitromercurial ***3e***

To the suspension of crude nitromercurial **3e** (1.5 g, 0.004 mol) in 16 mL of dichloromethane the aqueous sodium hydroxide solution (1.5 mL, c = 2.5 mol L^{-1}) was added dropwise under vigorous stirring at room temperature for 1 hour. The reaction mixture was stirred at the same temperature for further 30 minutes. After addition of diatomaceous earth (1.0 g), the precipitated elementary mercury was filtered. The dichloromethane layer was washed with water, dried over anhydrous sodium sulfate and concentrated furnishing the crude **4e** (0.43 g, 33.1%) as viscous oil. After distillation under reduced pressure the sample showed b.p. 80–85 °C/93.33 Pa. IR (film) ν_{max}/cm^{-1}: 3070w, 2990s, 2940s, 2850m, 1680m, 1520vs, 1445s, 1380vs, 1340vs, 1275s, 1220vs, 1160vs, 1100vs, 1045m, 1025m, 1000s, 980w, 875s, 835s, 785s and 730m; ^{1}H-NMR ($CDCl_3$) δ: 7.21 (t, 1H, J = 3.9, H-C6), 4.76–4.70 (m, 2H, H-C4), 4.47–4.38 (m, 2H, m, H-C7), 1.45 (s, 6H, CH_3); ^{13}C-NMR ($CDCl_3$) δ: 150.49 (C5), 136.58 (C6), 102.78 (C2), 58.37 (C4 & C7), 23.35 (CH_3-C2).

Anal. calcd. for $C_7H_{11}NO_4$ (M_r = 173.16): C 48.55, H 6.40, N 8.09%; found: C 48.73, H 6.61, N 8.06%.

From ***1e*** *without Isolation of Nitromercurial* ***3e***

To the solution of mercury(II) chloride (2.2 g, 0.008 mol – 8.6 g, 0.032 mol) and sodium nitrite (0.55 g, 0.008 mol – 4.4 g, 0.064 mol) in 75 mL water, dioxepin **1e** (1.0 g, 0.008 mol) was added in small portions for 1 hour. The mixture was stirred at room temperature for 1–16 hours. After addition of methylene chloride (50 mL), the aqueous sodium hydroxide solution (15 mL, c = 2.5 mol L^{-1}) was added dropwise under vigorous stirring at room temperature for 1 hour. The reaction mixture was stirred at the same temperature for further 30 minutes. After addition of diatomaceous earth (5.0 g), the precipitated elementary mercury was filtered. The dichloromethane layer was washed with water, dried over anhydrous sodium sulfate and concentrated, furnishing the crude **4e** (3.1–24.7%) as viscous oil (Table I), the IR spectra of which were identical to the spectrum of an authentic sample prepared as above.

General Procedure for the Diels-Alder Reaction of 4,7-Dihydro-5-nitro-1,3-dioxepins ***4*** *with 4-Methyloxazole* ***(5)***

A mixture of nitrodioxepin **4** (1.378×10^{-3} or 6.9×10^{-3} mol), 4-methyloxazole (4.4 to 21 molar excess to **4**) and a catalytic amount of acid catalyst was allowed to

stay at 25 °C, refluxed, or heated in a sealed tube at 150 °C for a defined period of time (133 days to 15 minutes). The excess of 4-methyloxazole was removed by distillation under reduced pressure, and purification of the residue by silica-gel chromatography with ethyl acetate–acetone (1 : 1) as eluent furnished, besides the starting nitrodioxepin **4**, accompanied by some other unindentified products, first nitrooxime **7**, and second, the dioxepinopiridinole **6**.

*Reaction of Nitrodioxepin **4a** with 4-Methyloxazole. Preparation of 1,5-Dihydro--9-hydroxy-8-methyl-3*H*-[1,3]dioxepino[5,6-c]pyridine (**6a**) and 4,7-dihydro-4-hydroxyimino-6-nitro-1,3-dioxepin (**7a**)*

According to the general procedure a mixture of nitrodioxepine **4a** (0.200 g, 1.378×10^{-3} mol), 4-methyloxazole (0.500 g, 6.0×10^{-3} mol) and catalytic amounts of *p*-toluenesulfonic acid and hydroquinone was heated in sealed tube at 150 °C for 15 minutes. After the workup of the reaction mixture according to the general procedure, the crude resinous **7a** was obtained first. After addition of 4-methyloxazole (2 mL), it crystallized as **7a** × **5** (1 : 1) adduct (80 mg, m.p. 160–175 °C. ^{1}H-NMR δ: 11,68 (s, 1H, OH of **7a**), 8.21 (s, 1H, H-C2 of **5**), 7.77 (m, 1H, H-C5 of **5**), 7.33 (t, 1H, J = 1.6, H-C5 of **7a**), 5.36 (s, 2H, H-C2 of **7a**), 4.97 (d, 2H, J = 1.6, H-C7 of **7a**), 2.10 (d, 3H, J = 0.9, CH_3 of **5**).

The 4-methyloxazole free **7a** (55 mg, 22.9%, m.p. 170–175 °C) was obtained after the drying of the adduct under reduced pressure (67 to 133 Pa) at 50 °C for 5 hours. After recrystallization from 4-methyloxazole and drying under reduced pressure of 67 to 133 Pa at 50 °C for 5 hours, the **7a** sample showed m.p. 175–177 °C. IR (KBr) ν_{max}/cm^{-1}: 3460vs, 3440vs, 3085m, 3055m, 2920w, 1665m, 1660s, 1525s, 1430m, 1385m, 1355s, 1340s, 1325vs, 1305s, 1185s, 1135s, 1045vs, 1010s, 970s, 930m, 900m and 800m; ^{1}H-NMR (acetone-d_6) δ: 10.86 (s,1H, OH), 7.51 (t, 1H, J = 1.8, H-C5), 5.52 (s, 2H, H-C2), 5.17 (d, 2H, J = 1.8 Hz, H-C7); ^{13}C-NMR (DMSO-d_6) δ, 150.54 (C4), 148.59 (C6), 124.71 (C5), 92.80 (C2), 68.48 (C7); MS *m/z* (relative intensity, %): 174, M^+ (29.6), 130 (100.0), 114 (17.8), 100 (25.3), 98 (30.5), 69 (43.5), 68 (48.2), 67 (99.4), 55 (57.9), 53 (34.0), 52 (44.9).

Anal. calcd. for $C_5H_6N_2O_5$ (M_r = 174.11): C 34.49, H 3.47, N 16.09%; found: C 34.57, H 3.59, N 16.17%.

Continuing the workup procedure, the crude TLC pure compound **6a** (42.7 mg, 17.0%), m.p. 171–175 °C was obtained. After recrystallization from ethyl acetate the sample showed m.p. 181–183 °C (lit.:[29] m.p. 175–176 °C; lit.:[30] m.p. 178–179 °C). IR (KBr) ν_{max}/cm^{-1}: 3300–2000 broad absorption with max. at 2920 and 2870, 1590w, 1475w, 1430s, 1410s, 1335s, 1280m, 1250m, 1225s, 1135s, 1090m, 1060s, 1000m, 975m, 950w, 870m, 835w and 700m; ^{1}H-NMR (DMSO-d_6) δ: 8.95 (s, 1H, OH), 7.81 (s, 1H, H-C6), 4.97 (s, 2H, H-C1), 4.91 (s, 2H, H-C5), 4.78 (s, 2H, H-C3), 2.37 (s, 3H, CH_3-C8); ^{13}C-NMR δ: 147.15, 146.31, 137.96, 133.99 & 133.56 (C-pyridine ring), 97.70 (C3), 67.72 (C1), 64.83 (C5), 19.54 (CH_3-C8).

Its spectra were identical to the spectra of an authentic sample.[29]

*Reaction of Nitrodioxepin **4c** with 4-Methyloxazole. Preparation of 1,5-Dihydro--9-hydroxy-3-isopropyl-8-methyl-3*H*-[1,3]dioxepino[5,6-c]pyridine (**6c**)*

According to the general procedure, a mixture of nitrodioxepin **4c** (1.29 g, 6.9 × × 10^{-3} mol), 4-methyloxazole (8.60 g, 0.1035 mol) and catalytic amounts of perchloric

acid and hydroquinone was refluxed for 10 hours. After the workup of the reaction mixture according to the general procedure, the crude TLC pure **6c** (63.6 mg, 4.1%) m.p. 159–162 °C was obtained. After recrystallization from ethyl acetate, the sample showed m.p. 163–165 °C (lit.:[29] m.p. 164–164.5 °C; lit.:[30] m.p. 161–163 °C). IR (KBr) ν_{max}/cm^{-1}: 3300–2000 broad absorption with max. at 2970 and 2900, 1605m, 1540m, 1470s, 1450s, 1365vs, 1270vs, 1215vs, 1135vs, 1120vs, 1080s, 1060vs, 945vs, 890vs, 795m, 760m, 700vs and 665s; ^{1}H-NMR δ: 9.0 (br, 1H, OH), 7.82 (s, 1H, H- C6), 5.20 and 4.68 (ABq, 2H, J = 15.2, H-C1), 4.81 and 4.77 (ABq, 2H, J = 14.4, H-C5), 4.57 (d, 1H, J 6.3, H-C3), 2.38 (s, 3H, CH_3-C8), 1.85 (m, 1H, CH_3-C*H*-CH_3), 0.90 (d, 6H, J = 6.7, CH_3-CH-CH_3); ^{13}C-NMR δ: 147.64, 146.98, 138.28, 134.40 & 134.00 (C-pyridine ring), 111.18 (C3), 67.22 (C1), 63.97 (C5), 31.97 (CH_3-*C*H-CH_3), 19.79 (CH_3-C8) 17.69 (CH_3-CH-*C*H_3).

Its spectra were identical to the spectra of an authentic sample.[29]

Reaction of Chloronitrodioxepane ***2c*** *with 4-Methyloxazole. Preparation of 1,5--Dihydro-9-hydroxy-3-isopropyl-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridine (**6c**)*

According to the general procedure, a mixture of chloronitrodioxepane **2c** (1.543 g, 6.9×10^{-3} mol) and 4-methyloxazole (8.60 g, 0.1035 mol) was refluxed for 11 hours. The mixture was neutralized with powdered sodium bicarbonate, and after the workup of the reaction mixture according to the general procedure, the crude TLC pure **6c** (308.0 mg, 20.0%) m.p. 159–161 °C was obtained. After recrystallization from ethyl acetate, the sample showed m.p. 163–165 °C (lit.:[30] m.p. 161–163 °C).

Its spectra were identical to the spectra of an authentic sample as above.

Continuing the workup procedure, the crude TLC pure pyridoxine base (154.0 mg, 13.2 %) m.p. 154–155 °C was obtained. After recrystallization from ethylacetate, the sample showed m.p. 159–160 °C (lit.:[2] m.p. 160 °C; lit.:[31] m.p. 159–160 °C). Its IR spectrum was identical to the spectrum of an authentic sample.[31]

Reaction of Nitrodioxepin ***4d*** *with 4-Methyloxazole. Preparation of 1,5-Dihydro-2--(4,7-dihydro-1,3-dioxepin-2-yl)-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridine (**6d**) and 4,7-Dihydro-2-(4,7-dihydro-1,3-dioxepin-2-yl)-4-hydroxyimino-6-nitro--1,3-dioxepin (**7d**)*

According to the general procedure, a mixture of nitrodioxepine **4d** (1.68 g, $6.9 \times$ $\times 10^{-3}$ mol), 4-methyloxazole (10.40 g, 0.1252 mol) and catalytic amounts of perchloric acid and hydroquinone was refluxed for 4 hours. After the workup of the reaction mixture according to the general procedure, first the crude **7d** (0.655 g, 34.8%) m.p. 200–210 °C was obtained. After recrystallization from ethyl acetate, the sample showed m.p. 211–213 °C.

IR (KBr) ν_{max}/cm^{-1}: 3290s, 3080w, 3005w, 2900w, 2850w, 1665m, 1625w, 1540vs, 1450s, 1430m, 1400m, 1390m, 1375s, 1345vs, 1320vs, 1300s, 1280s, 1270s, 1240s, 1145vs, 1110vs, 1060s, 1010vs, 990s, 970s, 935m, 905s, 820s, 795w, 750s, 735s and 600m; ^{1}H-NMR δ: 11.75 (s, 1H, OH), 7.33 (s, 1H, H-C5), 5.71 (s, 2H, H-C5'&6'), 5.48 (d, 1H, J = 4.2) and 4.82 (d, 1H, J = 4.2) (H-C2&2'), 5.12–4.86 (m, 2H, H-C7), 4.57–4.15 (m, 4H, H-C4'&7'); ^{13}C-NMR δ: 149.86 (C4), 148.78 (C6), 129.23 (C-5'&6'), 125.07 (C5), 99.94 and 99.59 (C2&C2'), 68.16 (C7), 65.74 and 65.29 (C4'&7').

Anal. Calc. for $C_{10}H_{12}N_2O_7$ (M_r = 272.21): C 44.16, H 4.44, N 10.29%; found: C 44.24, H 4.68, N 10.19%.

Continuing the workup procedure, the crude TLC pure compound **6d** (0.585 g, 30.3%) m.p. 164–165 °C was obtained. After recrystallization from ethyl acetate the sample showed m.p. 176–178 °C (lit.:[1] Y = 27.6%; m.p. 177–179 °C). IR (KBr) ν_{max}/cm^{-1}: 3500–2300 broad, assoc., 1605w, 1450m, 1420m, 1380m, 1330m, 1260s, 1245s, 1210m, 1130vs, 1060m, 1040m, 1000m, 990m, 945s, 900w, 840w, 810w, 750 w and 710w; ^{1}H-NMR δ: 8.99 (br, 1H, OH), 7.81 (s, 1H, H-C6), 5.70 (s, 2H, H-C5',6'), 5.25–4.71 (m, 6H, H-C1,3,5&2'), 4.44 & 4.15 (dd, 4H, J = 15.1, H- C4',7'), 2.36 (s, 3H, CH_3-C8); ^{13}C-NMR δ: 147.29, 146.51, 138.09, 133.64 &133.24 (C5a,6,8,9&9a), 129.57 (C5',6'), 103.50 (C3), 101.96 (C2'), 66.48, 65.69 & 64.28 (C1&4',7'&5), 19.75 (CH_3-C8), MS *m/z* (relative intensity, %): 279, M^+ (4.3), 180 (53.0), 152 (19.0), 151 (14.9), 150 (10.0), 135 (5.8), 134 (23.0), 124 (7.2), 123 (5.5), 122 (9.7), 106 (65.2), 99 (38.7), 79 (7.6), 71 (48.9) and 43 (100.0).

Its spectra were identical to the spectra of an authentic sample.[1]

*Reaction of Nitrodioxepin **4e** with 4-Methyloxazole. Preparation of 1,5-Dihydro--9-hydroxy-3,3,8-trimethyl-3H-[1,3]dioxepino[5,6-c]pyridine (**6e**)*

According to the general procedure a mixture of nitrodioxepine **4e** (1.54 g, 6.9 × × 10^{-3} mol), 4-methyloxazole (5.0 g, 0.060 mol) and catalytic amounts of perchloric acid and hydrochinone was refluxed for 11 hours. After the workup of the reaction mixture according to the general procedure, the crude **6e** (0.035 g, 2.4%) m.p. 169–179 °C was obtained. After recrystallization from ethyl acetate, the sample showed m.p. 182–184 °C (lit.[32] 184–185 °C).

IR (KBr) ν_{max}/cm^{-1}: 3200–2000 broad absorption with max. 2980 and 2930, 1600w, 1450w, 1380m, 1350s, 1275m, 1255m, 1210s, 1085s, 1040m, 1005w and 830m; ^{1}H-MNR δ: 8.82 (s, 1H, OH), 7.75 (s, 1H, H-C6), 4.85 (s, 2H, H-C1), 4.72 (s, 2H, H-C5), 2.37 (s, 3H, CH_3-C8), 1.42 (s, 6H, CH_3-C3); ^{13}C-NMR δ: 147.31, 145.11, 137.59, 133.69 and 133.02 (C-pyridine ring), 102.05 (C3), 60.92 (C1), 59.25 (C5), 23.75 (CH_3-C3), 19.20 (CH_3-C8).

Anal. Calc. for $C_{11}H_{15}NO_3$ (M_r = 209.24): C 63.14, H 7.23, N 6.69%; found: C 63.05, H 7.36, N 6.60%.

Its IR spectrum was identical to the spectrum of an authentic sample.[32]

*General Procedure for the Preparation of Nitrooximes **7** by Nitrosation of Nitrodioxepins **4***

Ethyl nitrite (1.5 mL, 85% GC, 15 mmol) was added dropwise into the solution of nitrodioxepine **4** (1.2 mmol) and sodium nitrite (0.10 g, 1.45 mmol) in dimethyl sulfoxide (6 mL) at room temperature for 15 minutes. The reaction mixture was stirred at the same temperature for another 80 minutes. Water (10 mL) was added, the mixture was extracted with diethyl ether (3 × 10 mL), the collected extracts were washed with water and dried over anhydrous sodium sulfate. After evaporation of diethyl ether *in vacuo*, the residue was purified by column chromatography using ethyl acetate as eluent, furnishing the crude nitrooxime **7**, the sample of which was after recrystallization identical to the sample obtained under the Diels-Alder reaction conditions.

*4,7-Dihydro-4-hydroxyimino-6-nitro-1,3-dioxepin (**7a**)*

According to the general procedure starting from **4a** (175 mg, 1.20 mmol), resinous, TLC pure, **7a** (89 mg, 42.4%) was obtained. After recrystallization from 4-methyloxazole and drying at 67–133 Pa at 50 °C for 5 hours, the **7a** sample showed m.p. 173–176 °C.

Its IR spectrum was identical to the spectrum of an authentic sample prepared as above.

*4,7-Dihydro-2-(4,7-dihydro-1,3-dioxepin-2-yl)-4-hydroxyimino-6-nitro-1,3-dioxepin (**7d**)*

According to the general procedure starting from **4d** (292 mg, 1.20 mmol) crude, TLC pure, **7d** (195 mg, 59.7%), m.p. 205–208 °C was obtained. After recrystallization from ethylacetate the sample showed m.p. 211–213 °C.

Its IR spectrum was identical to the spectrum of an authentic sample prepared as above.

Theoretical Calculation

Diels-Alder reactions were studied by the AM1 semiempirical method implemented in MOPAC 6.[33] Geometry of reactants and cycloadducts was optimized using the internal coordinates and the Eigenvector Following (EF) routine (PRECISE EF HESS = 1 keywords).

The initial guess for the transition state was the reaction path maximum, which was calculated starting with the cycloadduct and by stretching the C-C bond (1.7, 1.9, 2.1, 2.3, 2.5, 2.7, 2.9, 3.1 and 5.0 Å steps). Transition state was also located by the EF routine (TS keyword). Activation energies were estimated by substracting $\Delta_f H$ of reactants from $\Delta_f H$ of transition states (Table II).

All calculations were performed on a DEC Alpha 400/OSF station. Color drawings of transition state structures were done by RasMol.[34]

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SAŽETAK

Kemija 1,3 dioksepina. XII. 4,7-Dihidro-5-nitro-1,3-dioksepini u Diels-Alderovoj reakciji s 4-metiloksazolom

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4,7-Dihidro-5-nitro-1,3-dioksepini **4** pripravljeni dehidrohalogenacijom *vic*-klornitro-dioksepana **2** i/ili dehidrohalogenacijom-demercuracijom *vic*-klormerkurinitro-dioksepana **3** reaktivni su dienofili u Diels-Alderovoj cikloadiciji s 4-metiloksazolom (**5**). Pri tome, sa slabim iskorištenjem, nastaju 1,5-dihidro-9-hidroksi-8-metil-3*H*-[1,3]dioksepino[5,6-*c*]piridini **6**, međuprodukti u sintezi piridoksina (**8**). Sporedni su produkti te reakcije 4,7-dihidro-4-hidroksiimino-6-nitro-1,3-dioksepini **7**, čija je struktura potvrđena usporednom sintezom, tj. nitrozacijom **4** etil-nitritom.

Redoslijed reaktivnosti u nizu 5-supstituiranih-4,7-dihidro-1,3-dioksepina, izračunan semiempirijskom metodom AM1, predviđa da je 5-nitro- > 5-nesupstituirani- > 5-cijano- > 5-klor-4,7-dihidro-1,3-dioksepin i u suglasnosti je s eksperimentalnim