

Structural Characterization of Isomeric 2,3,5-Substituted Tetrahydropyrrolo[3,4-*d*]isoxazole-4,6-diones Prepared by Cycloaddition of *N*-Methyl-*C*-Arylnitrones to *N*-Phenyl- or *N*-Methylmaleimide

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1,3-Dipolar cycloaddition reactions of *N*-methyl-*C*-arylnitrones with *N*-phenyl- or *N*-methylmaleimide were studied. The reaction of *p*-dimethylamino-, 4-benzyloxy-3-methoxy-, *p*-nitro- and *p*-chloro-substituted phenylnitrones with *N*-phenylmaleimide gave *cis* and *trans* cycloadducts but that of the corresponding phenylnitrones with *N*-methylmaleimides only the *cis* adducts in the case of *p*-dimethylamino and 4-benzyloxy-3-methoxy substitution. All *cis* adducts attain a biased conformation whereas the *trans* forms are shown (by ^1H NMR at 233 K and ^{13}C NMR at 208 K) to be mixtures of two invertomers, namely *o*- (N-lone pair antiperiplanar to 3H; minor) and *i*-conformations (3H-C-C-3aH dihedral angle close to 90°; major). PM3 and DFT calculations at the B3LYP/6-31G(d) level of theory prove qualitatively that these two conformers of the *trans* adduct are of comparable stability and represent energy minima.

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Introduction.

After the important contribution of Huisgen [1], the application of 1,3-dipoles has become a cornerstone in organic synthesis [2]. In this field, one of the fundamental reactions is the 1,3-dipolar cycloaddition of alkenes to nitrones, since the product (isoxazolidine) is a very useful synthon [3]. A pair of diastereomeric isoxazolidines (Scheme 1) is often obtained in this cycloaddition reaction. Additionally, a small structural change in the nitron can lead to a significant change in the stereoselectivity of the cycloaddition [4]. Only a few reports [5-20] describe the regiochemical and stereochemical course of 1,3-dipolar cycloaddition of *N*-alkyl-*C*-phenylnitrones with alkenes. Apart from our preliminary report [21], no paper dealing with the effects of substituents on the stereochemistry of cycloaddition reactions of *N*-alkyl-*C*-(substituted)phenylnitrones with alkenes has been published. A recent paper on the synthesis of bisisoxazolidines, published when this paper was under preparation, also reported data for the conformational equilibria of *trans*-2,5-dimethyl-3-phenyl- and *trans*-2-methyl-3,5-diphenyltetrahydropyrrolo[1,3-*d*]isoxazole-4,6-diones [8].

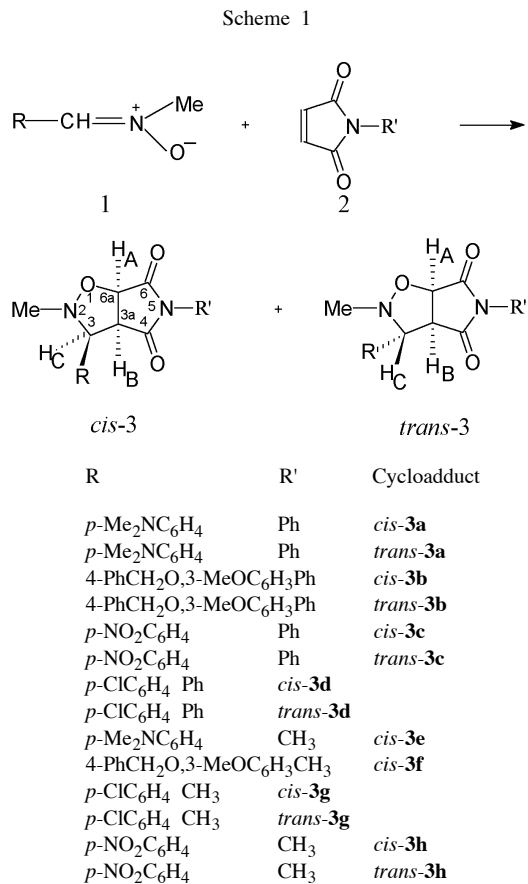
Results and Discussion.

In this work, the cycloaddition of *N*-methyl-*C*-(substituted)phenylnitrones to *N*-phenyl-maleimide (Scheme 1) is studied. In an earlier paper [21] two of us reported the synthesis of some cycloadducts of *N*-methyl-*C*-(substituted)phenylnitrones with *N*-methylmaleimide (**3e-h**),

the structural characterization of which needs amendment. All $\text{R}' = \text{Ph}$ derivatives (**3a-3d**) gave both *cis* and *trans* forms with respect to the ring fusion and the substituent R (Scheme 1) whereas, of the 5-methyl substituted compounds prepared earlier [21], only the 2-*p*-chloro- (**3g**) and 2-*p*-nitrophenyl (**3h**) derivatives gave both forms, and only the *cis* form was found for the *p*-dimethylamino- (**3e**) and 4-benzyloxy-3-methoxyphenyl (**3f**) substituted derivatives.

In a recent paper [22] it was shown that 1,3-dipolar cycloaddition reactions of *N*-phenyl-*C*-arylnitrones to the C16-C17 π -bond in 16-dehydropregnenolone acetate proceed through the minor rotamer (*E*-isomer; for the formulas of the *E*- and *Z*-isomers see Scheme 2) of the nitrones. In another recent work [23] the cycloaddition reactions of *N*-benzyl-*C*-ethoxycarbonylnitrones in benzene solution have been stated to proceed mainly through the *E*-isomer of the nitron. Additionally intramolecular cycloadditions of *E*-isomers of nitrones to alkenes have been utilized as key steps in the syntheses of a number of important isoxazolidine derivatives [24-27]. Therefore, the *E*-isomer of nitrones should be considered as one of the effective dipoles besides the *Z*-isomer in 1,3-dipolar cycloaddition reactions [3,28].

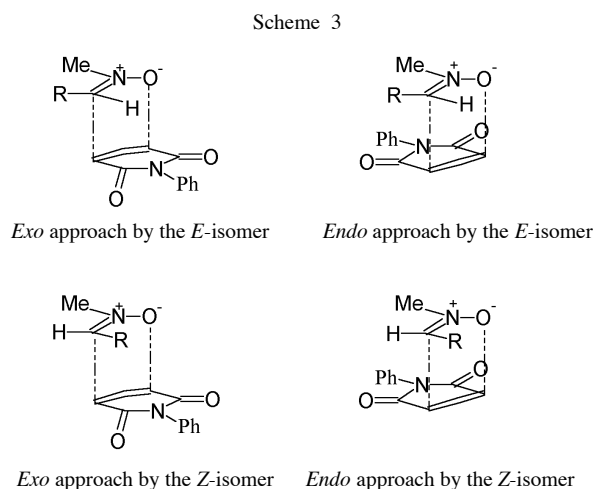
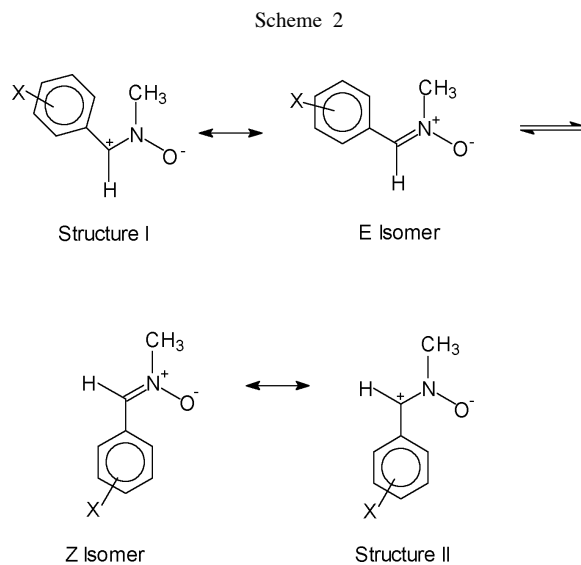
The *E*-isomer of *N*-methyl-*C*-phenylnitron can be present in solution in significant quantities [4] (~10% at room temperature), and it can undergo the dipolar cycloaddition faster than the *Z*-isomer for steric reasons [29,30]. The *E*-isomers of *N*-methyl-*C*-substituted-phenylnitrones can



even be more stabilized by electron-releasing substituents than the unsubstituted one (Scheme 2, Structure I). Hence, *E*-isomers of *N*-methyl-*C*-(*p*-dimethylaminophenyl)nitron (1a) and *N*-methyl-*C*-(4-benzyloxy-3-methoxyphenyl)nitron (1b) should be present in solution in appreciable amounts. Two of us recently reported [21] that the cycloaddition reactions of 1a and 1b with *N*-methylmaleimide gave only *cis* cycloadducts. This was explained by postulating that the secondary orbital interaction of the *E*-isomers with the dipolarophile through an *endo* transition state is effective [31], and this leads to *cis* cycloadducts. Although the absolute magnitude of this kind of interactions is small its impact on the stereochemical outcome is very important [32-34]. In the present work, we allowed the same nitrones (1a and 1b) to react with *N*-phenylmaleimide and obtained both the *cis* and the *trans* cycloadducts. In this case the secondary orbital interaction through the *endo* transition state is not sufficiently effective (due to steric repulsion of the phenyl group) to favor formation of the *endo* transition state (Scheme 3).

In general, the electron-withdrawing substituents of *N*-methyl-*C*-substituted-phenylnitrones should not stabilize the *E*-isomers (Structure I, Scheme 2), and therefore the *Z*-isomers should predominate in solution

[22,23,25,26]. The *endo* and *exo* transition states leading to the *trans* and *cis* cycloadducts are now of comparable energies [5] (*exo* and *endo* approach of the *Z*-isomer, Scheme 3). Hence, a mixture of *cis* and *trans* stereoisomers was formed from the reaction of the *Z* isomers of nitrones 1c and 1d with *N*-phenylmaleimide.



R: *p*-(CH₃)₂NC₆H₄, 4-C₆H₅CH₂O,3-CH₃OC₆H₃, *p*-O₂NC₆H₅, *p*-ClC₆H₅

Stereochemical Assignments.

For each experiment with *N*-phenylmaleimide, the cycloaddition products were checked by TLC. Nitrones with electron-releasing or electron-withdrawing substituents always gave two products, the *cis* and *trans* adducts.

The stereochemical assignments of *cis*-(3a-h) and *trans*-(3a-d, 3g and 3h; Scheme 1) were made on the basis of the magnitude of H3, H3a and H3a, H6a coupling constants

Table 1

Selected ^1H NMR chemical shifts (ppm, relative to $\delta(\text{CHCl}_3) = 7.26$ ppm) at 298 K for *cis* adducts and 233 K for *trans* adducts of **3a-3h**. The *i*- and *o*-forms of *trans* isomers represent the two invertomers of their *trans* forms (Scheme 3).

Compound	H-3	H-3a	H-6a	2-CH ₃ -	5-CH ₃	N(CH ₃) ₂	CH ₂ O	CH ₃ O
<i>cis</i> - 3a	3.82	3.78	5.05	2.68		2.94		
<i>trans</i> - 3a (<i>i</i> , 69%)	4.54	3.91	5.11	2.32		2.99		
<i>trans</i> - 3a (<i>o</i> , 31%)	3.67	3.93	5.18	2.68		2.98		
<i>cis</i> - 3b	3.89	3.82	5.03	2.69			5.12	3.75
<i>trans</i> - 3b (<i>i</i> , 54%)	4.51	3.87	5.07	2.34			5.19	3.89
<i>trans</i> - 3b (<i>o</i> , 46%)	3.67 ₅	3.86	5.13	2.67			5.18	3.90
<i>cis</i> - 3c	4.06	3.94	5.09	2.73				
<i>trans</i> - 3c (<i>i</i> , 61%)	4.72	3.94	5.18	2.37				
<i>trans</i> - 3c (<i>o</i> , 39%)	3.99	3.86	5.18	2.75				
<i>cis</i> - 3d	3.93	3.85	5.05	2.69				
<i>trans</i> - 3d (<i>i</i> , 67%)	4.59	3.90	5.12	2.34				
<i>trans</i> - 3d (<i>o</i> , 33%)	3.77	3.85	5.15	2.70				
<i>cis</i> - 3e	3.79	3.69	4.88	2.61		3.06		
<i>cis</i> - 3f	3.76	3.68	4.87	2.62	3.01		5.13	3.82
<i>cis</i> - 3g	3.80	3.70	4.88	2.62	2.99			
<i>trans</i> - 3g (<i>i</i> , 66%)	4.45	3.73	4.98	2.28	3.10			
<i>trans</i> - 3g (<i>o</i> , 34%)	3.59	3.69	5.01	2.62	3.05			
<i>cis</i> - 3h	3.95	3.79	4.93	2.66	2.99			
<i>trans</i> - 3h (<i>i</i> , 66%)	4.55	3.63	5.02	2.41	3.12			
<i>trans</i> - 3h (<i>o</i> , 34%)	3.65	3.58	5.02	2.58	3.07			

Table 2

The values of H3, H3a and H3a, H6a coupling constants (Hz) in *cis* and *trans* isomers (Scheme 1). The values for the *i*- and *o*-invertomers of the *trans* adducts were measured at 233 K.

Compound	$J_{3,3a}$	$J_{3a,6a}$
<i>cis</i> - 3a	8.9	7.3
<i>trans</i> - 3a (<i>i</i>)	0	7.6
<i>trans</i> - 3a (<i>o</i>)	8.3	7.7
<i>cis</i> - 3b	8.9	7.2
<i>trans</i> - 3b (<i>i</i>)	0	7.3
<i>trans</i> - 3b (<i>o</i>)	7.5	7.7
<i>cis</i> - 3c	8.7	7.5
<i>trans</i> - 3c (<i>i</i>)	0	7.5
<i>trans</i> - 3c (<i>o</i>)	7.1	7.6
<i>cis</i> - 3d	8.8	7.3
<i>trans</i> - 3d (<i>i</i>)	0	7.3
<i>trans</i> - 3d (<i>o</i>)	7.5	7.7
<i>cis</i> - 3e	8.3	7.5
<i>cis</i> - 3f	8.5	7.3
<i>cis</i> - 3g	8.6	7.3
<i>trans</i> - 3g (<i>i</i>)	0	7.4
<i>trans</i> - 3g (<i>o</i>)	7.8	7.5
<i>cis</i> - 3h	8.5	7.3
<i>trans</i> - 3h (<i>i</i>)	0	7.2
<i>trans</i> - 3h (<i>o</i>)	7.4	7.2

(Table 2) and NOE effects. The *cis* configuration was proven in one case (*cis*-**3c**) by observed NOEs. The irradiation of this signal corresponding to H3 gave an 8.5% and that of H6a a 9.7% enhancement of the signal corresponding to H3a. Correspondingly, the irradiation of the signal corresponding to H3a enhanced the signals corresponding to H3 (10.7%) and H6a (12.0%). Based on the strong NOEs, it was deduced that H3, H3a, and H6a are all on the same side of the isoxazole ring. The relative configuration

of the rest of the cases was concluded by comparison of the H3, H3a and H3a, H6a coupling constants. Also the available literature data support these conclusions [8,22-24].

The NMR experiments revealed that the *trans*-isomers were mixtures of two conformations. At room temperature they gave broad signals which at 233 K (^1H) and at 208 K (^{13}C) separated to two sets of signals (Tables 1-3) indicating that the *trans*-isomers indeed are mixtures of the *i*- (major) and *o*- (minor) conformers (*cf.* Figure 1) [8]. The *trans*-isomers were examined by NOE difference experiments at low temperatures in four cases (*trans*-**3a**, *trans*-**3c**, *trans*-**3d**, and *trans*-**3h**). Irradiation of H3a enhanced the signal of H6a (3.9–19.6%) but not significantly the signal of H3 (0.8% in one case). Conversely, irradiation of H6a enhanced the signal of H3a (1.8–9.3%), but irradiation of H3 enhanced only weakly (1.7–2.7%) the signal of H3a in three cases. As a conclusion, H3a and H6a are on the same side of the isoxazole ring, but H3 is on the opposite side. Furthermore, irradiation of the isoxazole N-methyl signals of the *i*- and *o*-forms at low temperatures resulted in faint 0–2% enhancements of the H3 signals of the major forms and 2–3% enhancements of the H3 signals of the minor forms. Thus, the former were assigned as the *i*-invertomers (N-methyl and H3 on the opposite sides of the isoxazole ring), in agreement with their crystal

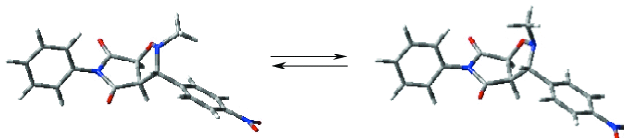


Figure 1. The PM3 optimized *i*- (left) and *o*-conformations (right) of *trans*-**3c**.

Table 3

Selected ^{13}C NMR chemical shifts (ppm, relative to $\delta(\text{CDCl}_3) = 77.00$ ppm) at 298 K for *cis* adducts and 208 K for *trans* adducts of **3a-3h**. The *i*- and *o*-forms of *trans* isomers represent the two invertomers of the *trans* forms (Scheme 3).

Compound	C-3	C-3a	C-4	C-6	C-6a	2-CH ₃	5-CH ₃	N(CH ₃) ₂	CH ₂ O	CH ₃ O
<i>cis</i> - 3a	75.08	53.84	172.86	175.57	76.13	42.55		40.35		
<i>trans</i> - 3a (<i>i</i>)	70.16	55.24	173.47	174.38	75.32	39.27		~40.5		
<i>trans</i> - 3a (<i>o</i>)	74.09	57.78	170.89	174.12	75.85	43.46		~40.5		
<i>cis</i> - 3b	75.42	54.26	171.90	174.59	76.37	42.66			70.90	55.93
<i>trans</i> - 3b (<i>i</i>)	71.07	55.74	173.81	175.21	75.42	39.34			70.14	55.95
<i>trans</i> - 3b (<i>o</i>)	75.52	57.76	171.34	174.76	75.71	42.98			70.08	55.85
<i>cis</i> - 3c	74.51	54.50	171.47	173.89	76.25	42.65				
<i>trans</i> - 3c (<i>i</i>)	70.16	55.23	173.47	174.38	75.32	39.27				
<i>trans</i> - 3c (<i>o</i>)	74.09	57.78	170.89	174.12	75.85	43.39				
<i>cis</i> - 3d	74.89	54.26	171.77	174.29	76.31	42.58				
<i>trans</i> - 3d (<i>i</i>)	70.42	55.38	173.60	174.88	75.35	39.07				
<i>trans</i> - 3d (<i>o</i>)	74.82	57.76	171.10	174.51	75.71	43.09				
<i>cis</i> - 3e	74.83	54.26	173.04	175.33	76.18	42.44	24.87	44.31		
<i>cis</i> - 3f	75.18	54.34	173.14	175.57	76.31	42.51	24.81		70.90	55.95
<i>cis</i> - 3g	74.62	54.34	172.96	175.25	76.21	42.45	24.97			
<i>trans</i> - 3g (<i>i</i>)	70.07	55.46	174.57	175.68	75.46	39.26	25.57			
<i>trans</i> - 3g (<i>o</i>)	74.54	57.91	172.27	175.50	76.00	42.90	25.36			
<i>cis</i> - 3h	74.27	54.53	172.49	174.82	76.19	42.54	24.97			
<i>trans</i> - 3h (<i>i</i>)	69.79	55.30	174.31	175.07	75.36	39.14	25.57			
<i>trans</i> - 3h (<i>o</i>)	73.86	57.92	171.88	174.99	75.84	43.17	25.38			

structure [8] and the latter as the *o*-invertomers (N-methyl and H3 on the same side of the isoxazole ring).

Calculations.

In order to verify the presence of the *i*- and *o*-conformers for the *trans* adducts and the similarity of their relative stabilities we applied semiempirical (PM3 Hamiltonian [35,36], MOPAC 6.0 [37]) and density functional theory (DFT, B3LYP/6-31G(d) [38-42], Gaussian 98W [43]) quantum chemical calculations to search for the minimum energy conformations of *trans*-**3a**, *trans*-**3c**, and *trans*-**3d**. Vibrational analysis calculations (Gaussian 98W [42], 1 bar, 233.15 K, and a scaling factor of 0.9804 [44]) were performed for the DFT-optimized structures at the same level of theory as the optimizations to verify that all optimized structures are true minima on the potential energy surface (PES) and to provide ΔH° and ΔG° values by subtraction of the sums of the electronic and thermal enthalpies and free energies, respectively. The results are collected in Table 4. The calculations gave a good qualitative agreement with two minima corresponding to the *i*-

and *o*-conformations although the stability of the major *i*-invertomer was somewhat overestimated at the PM3 level of theory in each case. The DFT energies and the derived *i*:*o* ratios are slightly better in agreement with the experimental observations in comparison to the PM3 results.

Mass Spectra.

The elemental compositions of all products were determined by accurate mass measurements. The electron ionization mass spectra also showed that all products were split back to the starting materials under EI conditions, the base peak being always (or almost so, especially when there was no benzyl substitution) that of *N*-methyl-*C*-(substituted phenyl)nitron (**1a-h**). 5-*N*-Phenyl substituted derivatives (**3a-d**) gave also a clear peak of *N*-phenylmaleimide.

EXPERIMENTAL

Melting points were taken on a Buchi apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-821PC Fourier Transform IR spectrometer. Preparative thin layer chromatography (TLC) was performed on a silica gel HF₂₅₄ (Merck). Solvents were dried using standard procedures.

^1H and ^{13}C NMR.

Chemical shifts for ^1H NMR and ^{13}C NMR are reported in parts per million (Tables 1 and 3, respectively) relative to the solvent signals ($\delta(\text{CHCl}_3) = 7.26$ ppm and $\delta(\text{CDCl}_3) = 77.00$ ppm, respectively). ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were recorded either on a JEOL JNM-LA400 (operating at 399.78 MHz for ^1H and 100.54 MHz for ^{13}C) or a JEOL JNM-A500 (^1H , 500.16 MHz; ^{13}C , 125.78 MHz) spectrometer. Dry nitrogen was bubbled through the samples

Table 4

Relative computational enthalpy and free energy differences of the *i*- and *o*-forms of *trans*-**3a**, *trans*-**3c**, and *trans*-**3d** and their computational and experimental ratios at 233.15 K.

Compound	$\Delta H^\circ(\text{PM3})$, kJ mol ⁻¹	$\Delta H^\circ(\text{DFT})$, kJ mol ⁻¹	$\Delta G^\circ(\text{DFT})$ / kJ mol ⁻¹	<i>io</i> (DFT)	<i>io</i> (exptl)
<i>trans</i> - 3a (<i>i</i> → <i>o</i>)	7.53	6.45	5.06	93/7	69/31
<i>trans</i> - 3c (<i>i</i> → <i>o</i>)	2.93	1.75	0.35	55/45	61/39
<i>trans</i> - 3d (<i>i</i> → <i>o</i>)	5.86	3.44	1.69	71/29	67/33

in order to remove dissolved oxygen (paramagnetic). Correct assignments of the chemical shifts were confirmed with the aid of standard two-dimensional PDQF-COSY (Phase Sensitive Double Quantum Filtered Correlation Spectroscopy), f_1 -decoupled CHSHF (^{13}C , ^1H Shift correlation; $^1J_{\text{CH}} = 145$ Hz), HMBC-BIRD (Heteronuclear Multiple Bond Correlation with a preceding Bilinear Rotation Decoupling Sequence; $^nJ_{\text{CH}} = 8$ Hz, 540 ms BIRD delay) NMR methods and one-dimensional nuclear Overhauser effect (NOE) difference experiments. The relative intensity of -100 was given to the irradiated signal in order to gain comparable percentage intensities for the NOE enhanced signals.

Mass Spectrometry.

Mass spectra were recorded on a VG ZabSpec-ooTOF spectrometer (VG Analytical, Manchester, UK) at 70 eV using a direct insertion probe. Accurate mass measurements were performed at a resolving power of 8000-10000 by the peak matching technique using PFK as a reference compound.

Syntheses.

N-Methyl-*C*-substituted-phenylnitrones were prepared by the literature method [45].

3-(*p*-Dimethylaminophenyl)-2-methyl-5-phenyltetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*cis*-**3a**).

A mixture of *N*-methyl-*C*-(*p*-dimethylaminophenyl)nitron (2.81 mmol, 0.500 g) and *N*-phenylmaleimide (2.89 mmol, 0.500 g) in benzene (50 mL) was refluxed for 9 h. Benzene was then evaporated under reduced pressure. The residue was dissolved in hot methanol and recrystallized to give *cis*-**3a** (0.279 g, 38%); mp 173.4-174.8 °C; IR (KBr): 1720.4 cm^{-1} (C=O); MS (EI, 70eV): m/z (RA%) 351 (14.5, $\text{M}^{+\bullet}$), 178(100), 173(21). $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_3$: Calcd 351.1583; Found (HRMS) 351.1582. For ^1H and ^{13}C NMR, see Tables 1-3.

3-(*p*-Dimethylaminophenyl)-2-methyl-5-phenyltetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*trans*-**3a**).

The solution remaining from the above procedure was evaporated to dryness under reduced pressure. The residue was recrystallized from benzene-diethyl ether (1:6) to give *trans*-**3a** (0.2983 g, 41%); mp 159.1-160.3 °C; IR (KBr): 1712.7 cm^{-1} (C=O); MS (EI, 70eV): m/z (RA%) 351 (12, $\text{M}^{+\bullet}$), 178(100), 173(32). $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_3$: Calcd 351.1583; Found (HRMS) 351.1586. For ^1H and ^{13}C NMR see Tables 1-3.

3-(4-Benzyloxy-3-methoxyphenyl)-2-methyl-5-phenyltetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*cis*-**3b**).

A mixture of *N*-methyl-*C*-(4-benzyloxy-3-methoxyphenyl)nitron (4.28 mmol, 1.160 g) and *N*-phenylmaleimide (5.137 mmol, 0.890 g) in benzene (50 ml) was refluxed for 10 h. Benzene was then evaporated under reduced pressure. The residue was recrystallized from benzene-diethyl ether (1:6) to give *cis*-**3b** (0.804 g, 42%); mp 169.4-170.0 °C; IR (KBr): 1720.4 cm^{-1} (C=O); MS (EI, 70eV): m/z (RA%) 444 (8, $\text{M}^{+\bullet}$), 271(24), 173(32). $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_5$: Calcd 444.1686; Found (HRMS) 444.1688. For ^1H and ^{13}C NMR see Tables 1-3.

3-(4-Benzyloxy-3-methoxyphenyl)-2-methyl-5-phenyltetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*trans*-**3b**).

The solution remaining from the above procedure was evaporated to dryness under reduced pressure. The residue was recrystallized from benzene-diethyl ether (1:6) to give *trans*-**3b** (0.653 g, 34%); mp 129.5-131.5 °C; IR (KBr): 1718.5 cm^{-1} (C=O); MS (EI, 70eV): m/z (RA%) 444 (17, $\text{M}^{+\bullet}$), 271(29), 173(26). $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_5$: Calcd 444.1685; Found (HRMS) 444.1688. For ^1H and ^{13}C NMR see Tables 1-3.

2-Methyl-3-(*p*-nitrophenyl)-5-phenyltetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*cis*-**3c** and *trans*-**3c**).

A mixture of *N*-methyl-*C*-(*p*-nitrophenyl)nitron (1.20 mmol, 0.215 g) and *N*-phenylmaleimide (1.20 mmol, 0.212 g) in benzene (50 mL) was refluxed for 8 h. Benzene was then evaporated under reduced pressure. The residue was subjected to thin-layer chromatography (eluent, methanol:benzene:petroleum ether, 1:4:2) to yield *cis*-**3c** (0.1323 g, 31%, R_f = 0.26) and *trans*-**3c** (0.1136 g, 27%, R_f = 0.49); *cis*-**3c**: mp 117.8-119.2 °C; IR (KBr): 1720.4 cm^{-1} (C=O); MS (EI, 70eV): m/z (RA%) 353 (100, $\text{M}^{+\bullet}$), 180(66), 179(91), 173(97). $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_5$: Calcd 353.1012; Found (HRMS) 353.1014. For ^1H and ^{13}C NMR see Tables 1-3; *trans*-**3c**: mp 177.6-178.9 °C; IR (KBr): 1716.5 cm^{-1} (C=O); MS (EI, 70eV): m/z (RA%) 353 (100, $\text{M}^{+\bullet}$), 180(30), 179(62.5), 173(69). $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_5$: Calcd 353.1012; Found (HRMS) 353.1017. For ^1H and ^{13}C NMR see Tables 1-3.

3-(*p*-Chlorophenyl)-2-methyl-5-phenyltetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*trans*-**3d**).

A mixture of *N*-methyl-*C*-(*p*-chlorophenyl)nitron (7.264 mmol, 1.232 g) and *N*-phenylmaleimide (8.717 mmol, 1.510 g) in benzene (50 mL) was refluxed for 10 h. Benzene was then evaporated off under reduced pressure. The residue was recrystallized from benzene-diethyl ether (1:6) to give *trans*-**3d** (1.437 g, 48%); mp 177-177.3 °C; IR (KBr): 1716.5 cm^{-1} (C=O); MS (EI, 70 eV): m/z (RA%) 342 (79, $\text{M}^{+\bullet}$), 169(92), 168(95), 173(17). $\text{C}_{18}\text{H}_{15}\text{ClN}_2\text{O}_3$: Calcd 342.0771; Found (HRMS) 342.0762. For ^1H and ^{13}C NMR see Tables 1-3.

3-(*p*-Chlorophenyl)-2-methyl-5-phenyltetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*cis*-**3d**).

The solution remaining from the procedure above was evaporated to dryness under reduced pressure. The residue was recrystallized from benzene-diethyl ether (1:6) to give *cis*-**3d** (0.744 g, 30%); mp 83.7-85.2 °C; IR (KBr): 1716.5 cm^{-1} (C=O); MS (EI, 70eV): m/z (RA%) 342 (73, $\text{M}^{+\bullet}$), 169(82), 168(93), 173(21). $\text{C}_{18}\text{H}_{15}\text{ClN}_2\text{O}_3$: Calcd 342.0771; Found (HRMS) 342.0776. For ^1H and ^{13}C NMR see Tables 1-3.

3-(*p*-Dimethylaminophenyl)-2,5-dimethyltetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*cis*-**3e**) [7].

Compound *cis*-**3e** has MS (EI, 70 eV): m/z (RA%) 289 (24, $\text{M}^{+\bullet}$), 178(100). $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_3$: Calcd 289.1426; Found (HRMS) 289.1426. For ^1H and ^{13}C NMR see Tables 1-3.

3-(4-Benzyloxy-3-methoxyphenyl)-2,5-dimethyltetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*cis*-**3f**) [7].

Compound *cis*-**3f** has MS (EI, 70 eV): m/z (RA%) 382 (14, $\text{M}^{+\bullet}$), 271(8). $\text{C}_{21}\text{H}_{22}\text{ClN}_2\text{O}_5$: Calcd 382.1529; Found (HRMS) 382.1536. For ^1H and ^{13}C NMR see Tables 1-3.

3-(*p*-Chlorophenyl)-2,5-dimethyltetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*cis*-**3g**) [7].

Compound *cis*-**3g** has MS (EI, 70 eV): m/z (RA%) 280 (73, $\text{M}^{+\bullet}$), 169(74), 168(100). $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{O}_3$: Calcd 280.0615;

Found (HRMS) 280.0624. For ^1H and ^{13}C NMR see Tables 1–3.

3-(*p*-Chlorophenyl)-2,5-dimethyltetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*trans*-**3g**) [7].

Compound *trans*-**3g** has MS (EI, 70 eV): m/z (RA%) 280 (75, M^+), 169(79), 168(100). $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{O}_5$: Calcd 280.0615; Found (HRMS) 280.0613. For ^1H and ^{13}C NMR see Tables 1–3.

2,5-Dimethyl-3-(*p*-nitrophenyl)tetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*cis*-**3h**) [7].

Compound *cis*-**3h** has MS (EI, 70 eV): m/z (RA%) 291 (86, M^+), 180 (39), 179(100). $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_5$: Calcd 291.0855; Found (HRMS) 291.0853. For ^1H and ^{13}C NMR see Tables 1–3.

2,5-Dimethyl-3-(*p*-nitrophenyl)tetrahydropyrrolo[3,4-*d*]isoxazol-4,6-dione (*trans*-**3h**) [7].

Compound *trans*-**3h** has MS (EI, 70 eV): m/z (RA%) 291 (100, M^+), 180(28), 179(89). $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_5$: Calcd 291.0855; Found (HRMS) 291.0853. For ^1H and ^{13}C NMR see Tables 1–3.

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