Stereochemical Study on the Cycloaddition of a Cyclic Nitrone to 5-Methyl-2(5*H*)-furanone

Marta Figueredo, Josep Font*, and Pedro de March*

Unitat de Química Orgànica, Departament de Química, Universitat Autònoma de Barcelona, 08193-Bellaterra, Barcelona, Spain

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The 1,3-dipolar cycloaddition of 3,4,5,6-tetrahydropyridine 1-oxide (1) to 5-methyl-2(5*H*)-furanone (2) yields adducts 3, 4, and 5, whose stereochemistry has been established by a detailed study of their low-temperature ^{1}H-NMR spectra. The major adduct, 4, arises from an *exo* transition state and an *anti* approach, indicating the dominance of steric factors over secondary orbital interactions.

Stereochemische Analyse der Cycloaddition eines cyclischen Nitrons an 5-Methyl-2(5*H*)-furanon

Die 1,3-dipolare Cycloaddition von 3,4,5,6-Tetrahydropyridin-1-oxid (1) an 5-Methyl-2(5*H*)-furanon (2) liefert die Addukte 3, 4 und 5, deren Stereochemie durch sorgfältige Analyse der Tieftemperatur-^{1}H-NMR-Spektren bestimmt wurde. Das Hauptprodukt, 4, Ergebnis eines *exo*-Übergangszustandes und einer *anti*-Annäherung, weist auf die Überlegenheit sterischer Faktoren über sekundäre Orbitalwechselwirkungen hin.

1,3-Dipolar cycloadditions are becoming of increasing importance in the last years for the preparation of natural products, mainly alkaloids[1]. However, only very few cases employing 2(5*H*)-furanones (α,β-butenolides) as dipolarophiles have been described[2], in spite of the current use of these heterocycles as dienophiles in Diels-Alder reactions[3].

Since butenolides are good synthetic building blocks, more information is needed about the regio-, *endo/exo*, and diastereofacial selectivity of 1,3-dipolar cycloadditions with these substrates.

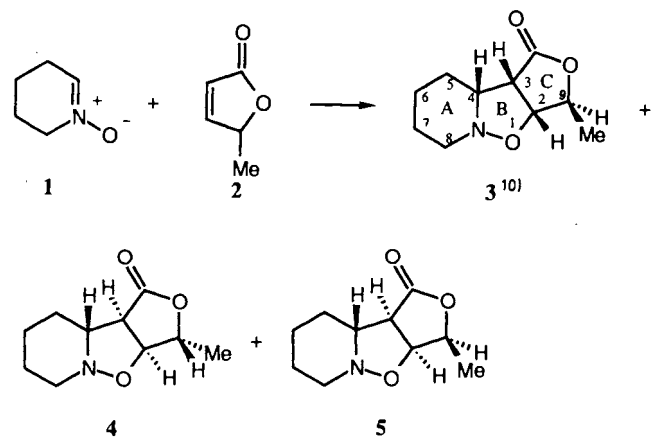
Among 1,3-dipoles, nitrones are particularly useful for synthetic applications. However, the precise stereochemical details of nitrone cycloadditions are difficult to establish[4], and therefore stereochemical reassignment of some cycloadducts has recently been required[4c]. Considerable efforts are still dedicated to study the *endo/exo* selectivity in 1,3-dipolar cycloadditions of cyclic and acyclic *N*-alkyl and *N*-aryl nitrones[4], being the cyclic ones, incapable of *E/Z* isomerization, the most appropriate substrates for this purpose. Moreover, the diastereofacial selectivity of nitrone cycloadditions has only scarcely been investigated[5], and up to now no data have been reported for reactions using cyclic nitrones.

We describe herein the cycloaddition reaction of 3,4,5,6-tetrahydropyridine 1-oxide[6] (1) to 5-methyl-2(5*H*)-furanone[7] (2), where the regio, *endo/exo*, and *syn/anti* selectivity can be studied simultaneously.

Results and Discussion

Reaction of nitrone 1 with butenolide 2 in boiling toluene yielded 84% of only three of the eight possible adducts. From an analysis of their complicated ^{1}H-NMR spectra, (see below), structures 3, 4, and 5 (formed in a ratio 1:5.1:2.3) were assigned to these compounds. Adduct 3 arises from an *endo* transition state with an *anti* approach, whereas 4 and 5 are the result of an *exo* transition state with *anti*-facial and *syn*-facial approaches, respectively.

Therefore, the reaction is regiospecific, following the electronic demand always observed in cycloadditions of nitrones to electron-deficient 1,2-disubstituted olefins[2d,4a,5,8], but it is not diastereospecific, although adduct 4 predominates, even more so when the reaction is carried out at lower temperature (chloroform, 40°C, 3:4:5 = 1:18.6:2.3). Since the purified isomer 3 was recovered unchanged after heating for 24 h in boiling toluene, cycloreversion does not occur. The reaction is hence kinetically controlled, and 4 is the most favoured stereoisomer.



1 2 3[10] 4 5

The predominance of the *exo* transition state is in accordance with the results very recently reported by Ali[4a] for the cycloadditions of nitrone 1 to maleic anhydride and dimethyl maleate, and by Gandolfi[4c] for the reaction of 3,4-dihydroisoquinoline *N*-oxide with several *cis* olefins. Thus, the *exo* selectivity appears to be general for cycloadditions of cyclic *N*-alkyl and *N*-aryl nitrones to (*Z*)-disubstituted olefins, where the unfavourable steric interactions dominate over the favourable secondary orbital interactions in the *endo* transition state. The situation must be the opposite

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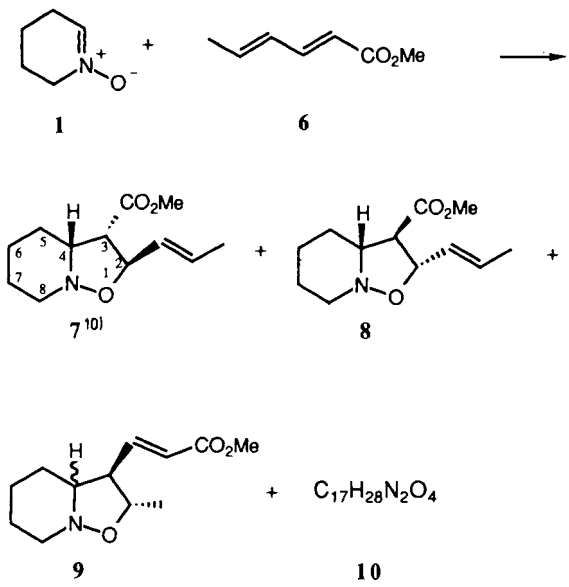
when using *trans* dipolarophiles, in which case *endo* adducts are obtained[4a,8].

As mentioned above, the ^{1}H-NMR spectra of adducts **3**, **4**, and **5** are complex. This is due both to the six-membered ring and nitrogen inversion processes. Therefore, the stereochemical assignment of these compounds was only possible by comparison of their 400-MHz ^{1}H-NMR spectra at 253 K in [D_6]acetone with those of the 1:1 adducts **7** and **8** obtained from the cycloaddition of nitrone **1** on the α,β-double bond of methyl sorbate[9] (**6**). This reaction was tested as a possible route for the preparation of some alkaloids, but it did not have any synthetic value, since it afforded a complex mixture, from which compounds **7**, **8**, **9**, and several 2:1 adducts **10** of undetermined structure were isolated.



The stereochemical relationship[10] between 2-H and 9-H in adducts **3**–**5** can be directly derived from $J_{2,9}$ = 2.0 Hz in **3**, 1.6 Hz in **4**, and 5.4 Hz in **5**[2g,11]. Thus, the *syn* or *anti* geometry is easily established for each compound. The expected *cis* fusion for rings B and C is confirmed by a $J_{2,3}$ value around 7 Hz in all three cases, while **7** and **8** with a *trans* fusion present $J_{2,3}$ = 5.6 and 5.8 Hz, respectively. It remains therefore to assign the relationship between 3-H and 4-H that will give us the *endo* or *exo* geometry in the transition state.

In the ^{1}H-NMR spectra of adducts **3** and **8** at 253 K signals of only one rigid conformer are observed. This is not the case for adducts **4**, **5**, and **7**, whose spectra show two sets of signals in a ratio of ca. 4:1, 15:1, and 4:1, respectively. Table 1 shows the chemical shifts of the most significant protons for the major conformer in the cycloadducts studied. Since the ^{1}H-NMR spectra of compounds **3**, **7**, and **8** present a very similar pattern, a facile correlation between their signals could be established. The δ values were assigned to each proton with the help of decoupling experiments on compound **7**. Thus, proton 4-H resonates at δ 2.27 (ddd), since irradiation at δ 2.77 (3-H) collapsed the former absorption to a broad doublet; the subsequent irradiation at δ 1.99 collapsed also the signal at δ 2.27 (4-H), and the absorptions at δ 1.36 (5-H_{ax}) and 1.17. This observation indicates that protons 5-H_{eq} and 6-H_{ax} appear at δ 1.99 and 1.17, respectively.

Table 1. ^{1}H-NMR chemical shifts (δ) for the major conformer present in the studied cycloadducts

	8-H_{eq}	8-H_{ax}	4-H	5-H_{eq}	5-H_{ax}
3	3.33	2.35	2.35	1.98	1.39
7	3.24	2.33	2.27	1.99	1.36
8	3.30	2.27	2.44	1.85	1.11
4	3.42 > δ > 2.96		3.22 > δ > 2.96	1.80 > δ > 1.20	
5	3.42 > δ > 2.92		3.42 > δ > 2.92	1.75 > δ > 1.16	

The value of the coupling constant $J_{3,4}$ in compound **3** is ca. 7.2 Hz, from which no stereochemical relation between these two protons could be derived, since $J_{3,4}$ was not measurable in adducts **4** and **5**. Moreover, the observed $J_{3,4}$ for **7** and **8** (10.0 Hz and 8.7 Hz, respectively) did not help to assign the stereochemistry[12].

Two axial protons α to the nitrogen, 4-H and 8-H (δ 2.2–2.4) are observed in compounds **3**, **7** (major conformer), and **8**, implying a rigid *trans* fusion for rings A-B[13]. Now, the anisotropic effect of the carbonyl group on 4-H, 5-H_{ax}, and 5-H_{eq} was crucial for the stereochemical assignment: the carbonyl group deshields protons 5-H_{ax} and 5-H_{eq} in adducts **3** and **7**, and proton 4-H in compound **8** (see Table 1). This indicates a *trans* relationship between 3-H and 4-H in **8**, and a *cis* relationship in **3** and **7**.

Since the relative stereochemistry at centers 2, 3, and 9 in adducts **3** and **4** is the same, 3-H and 4-H should be *trans* in **4**. In this compound, the chemical shifts of the three protons α to the nitrogen are very different from those observed in adducts **3**, **7**, and **8** (see Table 1), indicating for rings A and B a *cis* fusion, in which an equilibrium between two possible chair conformations exists (molecular models). Adduct **5** presents a similar ^{1}H-NMR spectrum as **4**. This indicates an A/B *cis* fusion and a *trans* 3-H, 4-H relationship. Moreover, a *cis* relationship between 3-H and 4-H would imply an *endo* transition state and a *syn*-facial approach, with quite unfavourable steric interactions. As a matter of fact, this would be the transition state leading to the diastereoisomer not found with the same structure as the isolated adducts.

In conclusion, the complete stereochemical elucidation of the adducts isolated in the kinetically controlled reaction between the cyclic nitrone **1** and the cyclic (*Z*)-alkene **2**, using ^{1}H-NMR techniques only, has allowed us to establish the predominance of the *exo* transition state with *anti* approach for this type of cycloadditions.

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Experimental

IR: Perkin-Elmer 1310. – ^{1}H-NMR: Bruker AM-400 WB (400 MHz). – ^{13}C-NMR: Bruker WP 80 SY (20 MHz); chemical shifts (δ values) relative to TMS for protons and $CDCl_3$ or [D_6]acetone for carbons. – Mass spectra: Hewlett-Packard 5985 B (ionization energy 70 eV). – Flash chromatography: SiO_2, 230–400 mesh (SDS). – GLC: Hewlett-Packard 5890 A; capillary column Hewlett-Packard Ultra 1 (crosslinked, methyl silicone gurn, 12 m ×

0.2 m × 0.3 μm); oven: 140°C, injector: 165°C, detector: 180°C. – Elemental analyses: Run in "Consejo Superior de Investigaciones Cientificas". – Commercial reagents and solvents were purchased from standard chemical suppliers and used as such. Compounds **1**[6], **2**[7], and **6**[9] were prepared according to literature procedures and purified to match the reported physical and spectral data.

Reaction of 3,4,5,6-Tetrahydropyridine 1-Oxide (**1**) *with 5-Methyl-2(5H)-furanone* (**2**) *in Toluene:* A solution of **1** (prepared from 404 mg, 4.0 mmol, of *N*-hydroxypiperidine and 2.23 g, 9.7 mmol, of yellow HgO) in 20 ml of toluene was treated with a solution of 392 mg (4.0 mmol) of **2** in 2 ml of toluene for 15 h at reflux temperature. After cooling and removal of the solvent at reduced pressure, 873 mg of crude product was obtained. Purification by flash chromatography afforded the following fractions: **3** as an oil (80 mg, 10%) with hexane:ethyl acetate (70:30); a mixture of **4** and **5** (585 mg, 74%) with hexane:ethyl acetate (60:40). GLC analysis of this last fraction showed a ratio **4**:**5** equal to 69:31. Repeated column chromatography of this mixture allowed the isolation of pure samples of **4** and **5** (oils). GLC (retention time): **3** (5.45 min), **4** (5.85 min), **5** (6.55 min).

(3R,3aS*,9aR*,9bR*)-Octahydro-3-methyl-1H-furo[3',4':4,5]-isoxazolo[2,3-a]pyridin-1-one* (**3**): IR (neat): $\tilde{\nu}$ = 2920 cm^{-1}, 2840, 1765, 1200. – ^1H NMR ([D$_6$]acetone, 253 K): δ = 1.18 (qt, $J_{8ax,7ax} \approx J_{8ax,8eq} \approx J_{8ax,9ax} \approx$ 13.0 Hz, $J_{8ax,7eq} \approx J_{8ax,9eq} \approx$ 4.0 Hz, 1H, 8-H$_{ax}$), 1.33 (d, J = 6.4 Hz, 3H, 3-CH$_3$), 1.39 (dddd, $J_{9ax,8ax} \approx J_{9ax,9a} \approx$ 13.2 Hz, $J_{9ax,9eq}$ = 11.6 Hz, $J_{9ax,8eq}$ = 4.0 Hz, 1H, 9-H$_{ax}$), 1.46 (qt, $J_{7ax,6ax} \approx J_{7ax,7eq} \approx J_{7ax,8ax} \approx$ 13.0 Hz, $J_{7ax,6eq} \approx J_{7ax,8eq} \approx$ 4.3 Hz, 1H, 7-H$_{ax}$), 1.66–1.78 (m, 2H, 7-H$_{eq}$ and 8-H$_{eq}$), 1.98 (br. d, $J_{9eq,9ax}$ = 13.4 Hz, 1H, 9-H$_{eq}$), 2.30–2.40 (m, 2H, 9a-H and 6-H$_{ax}$), 3.33 (br. d, $J_{6eq,6ax}$ = 9.2 Hz, 1H, 6-H$_{eq}$), 3.53 (dd, $J_{9b,3a} \approx J_{9b,9a} \approx$ 7.2 Hz, 1H, 9b-H), 4.45 (qd, J = 6.4 Hz, $J_{3,3a}$ = 2.0 Hz, 1H, 3-H), 4.47 (dd, $J_{3a,9b}$ = 7.2 Hz, $J_{3a,3}$ = 2.0 Hz, 1H, 3a-H). – ^{13}C NMR (CDCl$_3$, 298 K): δ = 20.1 (3-CH$_3$), 23.3/24.3/25.9 (C-7/C-8/C-9), 51.0/55.1 (C-9b/C-6), 68.6 (C-9a), 81.2/83.1 (C-3/C-3a), 174.2 (C=O). – MS: *m/z* (%) = 197 (M$^+$, 0.7), 124 (2), 99 (10), 82 (14), 69 (21), 55 (55), 43 (92), 41 (100).

C$_{10}$H$_{15}$NO$_3$ (197.2) Calcd. C 60.90 H 7.67 N 7.10
Found C 60.95 H 7.70 N 6.64

A pure sample of **3** was dissolved in toluene and heated at reflux temperature for 16 h. GLC analysis of the solution showed that no other isomers were present.

(3R,3aS*,9aS*,9bR*)-Octahydro-3-methyl-1H-furo[3',4':4,5]-isoxazolo[2,3-a]pyridin-1-one* (**4**): IR (neat): $\tilde{\nu}$ = 2920 cm^{-1}, 2840, 1765, 1200. – ^1H NMR ([D$_6$]acetone, 253 K): δ = 1.20–1.80 (m, 6H, 2 × 7-H, 2 × 8-H, and 2 × 9-H), 1.32 (d, J = 7.0 Hz, 3H, 3-CH$_3$), 2.96 (dddd, J = 14.9 Hz, J' = 10.9 Hz, J'' = 3.7 Hz, J''' = 0.6 Hz, 1H, 6-H/9a-H), 3.18–3.22 (m, 1H, 6-H/9a-H), 3.38–3.42 (m, 2H, 6-H/9a-H and 9b-H), 4.50 (qt, J = 7.0 Hz, $J_{3,3a}$ = 1.6 Hz, 1H, 3-H), 4.53 (br. d, $J_{3a,9b}$ = 7.2 Hz, 1H, 3a-H). Some signals corresponding to a minor conformer were also clearly observed: 1.34 (d, J = 6.9 Hz, 3-CH$_3$), 2.16 (ddd), 2.45 (ddd), 3.32 (m), 4.37 (dd, $J_{3a,9b}$ = 7.5 Hz, $J_{3a,3}$ = 1.2 Hz, 3a-H), 4.57 (qd, J = 6.9 Hz, $J_{3,3a}$ = 1.2 Hz, 3-H). – ^{13}C NMR (CDCl$_3$, 270 K): δ = 19.3/21.1/24.7 (C-7/C-8/C-9), 19.8 (CH$_3$, SEFT), 49.6 (C-6, SEFT), 53.5 (C-9b), 63.5 (C-9a), 80.9/82.8 (C-3/C-3a), 176.4 (C=O). Signals of the minor conformer: 20.0 (CH$_3$, SEFT), 22.9/23.8/28.5 (C-7/C-8/C-9), 53.1 (C-9b), 54.3 (C-6, SEFT), 70.4 (C-9a), 79.2/82.2 (C-3/C-3a), 175.6 (C=O). – MS: *m/z* (%) = 197 (M$^+$, 14), 124 (9), 100 (48), 99 (100), 84 (93), 69 (59), 55 (50), 41 (85).

(3R,3aR*,9aS*,9bS*)-Octahydro-3-methyl-1H-furo[3',4':4,5]-isoxazolo[2,3-a]pyridin-1-one* (**5**): IR (neat): $\tilde{\nu}$ = 2920 cm^{-1}, 2840, 1765, 1200. – ^1H NMR ([D$_6$]acetone, 253 K): δ = 1.16–1.58 (m, 4H), 1.30 (d, J = 6.2 Hz, 3H, CH$_3$), 1.60–1.75 (m, 2H), 2.92 (ddd, J = 14.9 Hz, J' = 12.9 Hz, J'' = 4.0 Hz, 1H), 3.30–3.42 (m, 3H), 4.70 (qd, J = 6.2 Hz, $J_{3,3a}$ = 5.4 Hz, 1H, 3-H), 4.77 (dd, $J_{3a,9b}$ = 7.0 Hz, $J_{3a,3}$ = 5.4 Hz, 1H, 3a-H). Some signals corresponding to a minor conformer were also clearly observed: 1.31 (d, J = 6.2 Hz, CH$_3$), 2.15 (ddd), 2.48 (ddd), 4.63 (dd, J = 7.0 Hz, J' = 5.2 Hz, 3a-H). – ^{13}C NMR (CDCl$_3$, 270 K): δ = 14.0 (CH$_3$, SEFT), 18.8/21.8/24.7 (C-7/C-8/C-9), 49.7 (C-6, SEFT), 55.2 (C-9b), 63.2 (C-9a), 76.2/80.4 (C-3/C-3a), 176.9 (C=O). Observed signals of the minor conformer: 23.1, 23.9, 28.9, 54.5, 71.2, 77.5, 78.1. – MS: *m/z* (%) = 197 (M$^+$, 0.7), 124 (1), 99 (4), 69 (14), 55 (41), 43 (100), 42 (62), 41 (84).

4 + **5**: C$_{10}$H$_{15}$NO$_3$ (197.2) Calcd. C 60.90 H 7.67 N 7.10
Found C 60.82 H 7.57 N 7.00

Reaction of **1** *with* **2** *in CHCl$_3$:* To a stirred solution of **1** (prepared from 404 mg, 4.0 mmol, of *N*-hydroxypiperidine and 2.23 g, 9.7 mmol, of yellow HgO) in 17 ml of CHCl$_3$, a solution of **2** (392 mg, 4.0 mmol) in 2 ml of CHCl$_3$ was added and the mixture heated at 40°C for 17 h. The solvent of the cooled solution was evaporated under reduced pressure to give 861 mg of crude product. Purification by flash chromatography afforded 466 mg (59%) of pure **4** and 107 mg (14%) of different mixtures of adducts **3**, **4**, and **5**.

Reaction of **1** *with Methyl (2E,4E)-2,4-Hexadienoate* (**6**) *in CHCl$_3$:* A solution of **1** (prepared from 404 mg, 4.0 mmol, of *N*-hydroxypiperidine and 2.23 g, 9.7 mmol, of yellow HgO) in 17 ml of CHCl$_3$ was treated with a solution of **6** (510 mg, 4.0 mmol) in 5 ml of CHCl$_3$ at reflux temperature for 16 h. After cooling and solvent removal under reduced pressure, 988 mg of crude product was obtained. This crude was purified by flash chromatography (hexane:ethyl acetate, 4:1), affording the following fractions: **6** (210 mg, 41%); **7** (40 mg, 4.4%); a mixture of **7** and **8** (130 mg, 14%); and **8** (128 mg, 14%). Both compounds 7 and **8** were isolated as oils.

Methyl (2R,3S*,3aR*)-Hexahydro-2-[(1E)-1-propenyl]-2H-isoxazolo[2,3-a]pyridin-3-carboxylate* (**7**): IR (neat): $\tilde{\nu}$ = 2920 cm^{-1}, 2830, 2800, 1740, 1445. – ^1H NMR ([D$_6$]acetone, 253 K): δ = 1.17 (qt, $J_{5ax,4ax} \approx J_{5ax,5eq} \approx J_{5ax,6ax} \approx$ 12.9 Hz, $J_{5ax,4eq} \approx J_{5ax,6eq} \approx$ 4.0 Hz, 1H, 5-H$_{ax}$), 1.36 (dddd, $J_{4ax,3a} \approx J_{4ax,5ax} \approx$ 12.7 Hz, $J_{4ax,4eq}$ = 11.3 Hz, $J_{4ax,5eq} \approx$ 3.9 Hz, 1H, 4-H$_{ax}$), 1.49 (qt, $J_{6ax,5ax} \approx J_{6ax,6eq} \approx J_{6ax,7ax} \approx$ 12.7 Hz, $J_{6ax,5eq} \approx J_{6ax,7eq} \approx$ 4.0 Hz, 1H, 6-H$_{ax}$), 1.63 (d, J = 5.2 Hz, 3H, CH$_3$), 1.60–1.82 (m, 2H, 5-H$_{eq}$ and 6-H$_{eq}$), 1.99 (m, 1H, 4-H$_{eq}$), 2.27 (ddd, $J_{3a,4ax}$ = 12.6 Hz, $J_{3a,3}$ = 10.0 Hz, $J_{3a,4eq}$ = 2.5 Hz, 1H, 3a-H), 2.33 (ddd, $J_{7ax,6ax}$ = 12.3 Hz, $J_{7ax,7eq}$ = 9.0 Hz, $J_{7ax,6eq}$ = 3.0 Hz, 1H, 7-H$_{ax}$), 2.77 (dd, $J_{3,3a}$ = 10.0 Hz, $J_{3,2}$ = 5.6 Hz, 1H, 3-H), 3.24 (br. d, $J_{7eq,7ax}$ = 9.0 Hz, 1H, 7-H$_{eq}$), 3.66 (s, 3H, OCH$_3$), 4.47 (m, 1H, 2-H), 5.57–5.62 (m, 2H, 2 × =CH). Some signals corresponding to a minor conformer were also clearly visible: 2.75–2.82 (m), 2.98–3.04 (m), 3.50–3.56 (m), 4.53 (dd, J = J' = 8.0 Hz, 2-H), 5.53–5.69 (m). Irradiation at δ 2.77 collapsed the signal at δ 2.27 to a broad doublet. Irradiation at δ 1.99 reduced the signals at δ 2.27 (dd), 1.36 (ddd), and 1.17 (dddd). – ^{13}C NMR (CDCl$_3$, 250 K): δ = 17.6 (CH$_3$), 22.6/23.8/27.9 (C-4/C-5/C-6), 52.1 (OCH$_3$), 54.7/57.8 (C-3/C-7), 70.0 (C-3a), 78.9 (C-2), 129.4/130.3 (2 × =CH), 171.5 (C=O). Some signals corresponding to a minor conformer were also observed: 19.0, 53.4, 64.3, 83.9, 131.4. – MS: *m/z* (%) = 225 (M$^+$, 13), 100 (52), 99 (100), 69 (41), 55 (29), 41 (74).

C$_{12}$H$_{19}$NO$_3$ (225.3) Calcd. C 63.98 H 8.50 N 6.22
Found C 64.03 H 8.28 N 5.88

Methyl (2R,3S*,3aS*)-Hexahydro-2-[(1E)-1-propenyl]-2H-isoxazolo[2,3-a]pyridin-3-carboxylate* (**8**): IR (neat): $\tilde{\nu}$ = 2920 cm^{-1}, 2830, 2800, 1740, 1445. – ^1H NMR ([D$_6$]acetone, 253 K): δ = 1.11 (m, $J_{4ax,4eq}$ = $J_{4ax,5ax}$ = 12.1 Hz, $J_{4ax,3a}$ = 11.1 Hz, $J_{4ax,5eq}$ = 3.8 Hz,

1 H, 4-H_{ax}), 1.19 (qt, $J_{5ax,4ax} \approx J_{5ax,5eq} \approx J_{5ax,6ax} \approx 12.7$ Hz, $J_{5ax,4eq} \approx J_{5ax,6eq} \approx 4.0$ Hz, 1 H, 5-H_{ax}), 1.44 (qt, $J_{6ax,5ax} \approx J_{6ax,6eq} \approx J_{6ax,7ax} \approx 12.9$ Hz, $J_{6ax,5eq} \approx J_{6ax,7eq} \approx 4.0$ Hz, 1 H, 6-H_{ax}), 1.65 (dd, J = 6.5 Hz, J' = 1.8 Hz, 3 H, CH_3), 1.58–1.76 (m, 2 H, 5-H_{eq} and 6-H_{eq}), 1.85 (m, 1 H, 4-H_{eq}), 2.27 (ddd, $J_{7ax,6ax}$ = 12.5 Hz, $J_{7ax,7eq}$ = 9.5 Hz, $J_{7ax,6eq}$ = 3.0 Hz, 1 H, 7-H_{ax}), 2.44 (ddd, $J_{3a,4ax}$ = 11.1 Hz, $J_{3a,3}$ = 8.7 Hz, $J_{3a,4eq}$ = 2.4 Hz, 1 H, 3a-H), 3.00 (dd, $J_{3,3a}$ = 8.7 Hz, $J_{3,2}$ = 5.8 Hz, 1 H, 3-H), 3.30 (m, 1 H, 7-H_{eq}), 3.64 (s, 3 H, OCH_3), 4.65 (dd, J = 8.4 Hz, $J_{2,3}$ = 5.8 Hz, 1 H, 2-H), 5.46 (ddq, J_{trans} = 15.3 Hz, J = 8.4 Hz, ^5J = 1.8 Hz, 1 H, $CH{=}CH{-}CH_3$), 5.74 (dq, J_{trans} = 15.3 Hz, J = 6.5 Hz, 1 H, $CH{=}CH{-}CH_3$). – ^{13}C NMR ($CDCl_3$, 240 K): δ = 17.7 (CH_3), 22.8/23.6/26.0 (C-4/C-5/C-6), 51.9 (OCH_3), 54.8/55.5 (C-3/C-7), 69.1 (C-3a), 79.5 (C-2), 127.2/132.6 (2 × =CH), 171.8 (C=O). – MS: m/z (%) = 225 (M^+, 22), 194 (4), 100 (63), 99 (100), 69 (29).

$C_{12}H_{19}NO_3$ (225.3) Calcd. C 63.98 H 8.50 N 6.22
Found C 63.93 H 8.81 N 6.13

Reaction of **1** *with* **6** *in Toluene:* To a solution of **1** (prepared from 404 mg, 4.0 mmol, of *N*-hydroxypiperidine and 2.23 g, 9.7 mmol, of yellow HgO) in 20 ml of toluene was added a solution of **6** (510 mg, 4.0 mmol) in 2 ml of toluene, and the mixture was heated for 19 h at reflux temperature. After cooling and evaporation of the solvent under reduced pressure, 947 mg of crude material was obtained. Purification by flash chromatography afforded the following fractions: **6** (170 mg, 33%) with hexane:ethyl acetate (80:20); **7** (67 mg, 5%) and **9** (139 mg, 10%) with hexane:ethyl acetate (50:50); 2:1 adducts (**10**) (443 mg, 46%) with ethyl acetate.

Methyl (2E)-3-{(2R,3S*)-Hexahydro-2-methyl-2H-isoxazolo-[2,3-a]pyridin-3-yl}-2-propenoate* (**9**): IR (neat): $\tilde{\nu}$ = 2920 cm^{-1}, 2840, 2800, 1725, 1660, 1445. – ^{1}H NMR ([D_6]acetone, 253 K): δ = 1.13–1.27 (m, 2 H, 4-H_{ax} and 5-H_{ax}), 1.20 (d, J = 6.0 Hz, 3 H, CH_3), 1.48 (m, 1 H, 6-H_{ax}), 1.59–1.76 (m, 3 H, 4-H_{eq}, 5-H_{eq}, and 6-H_{eq}), 2.31 (ddd, $J_{7ax,6ax}$ = 11.9 Hz, $J_{7ax,7eq}$ = 9.3 Hz, $J_{7ax,6eq}$ = 3.0 Hz, 1 H, 7-H_{ax}), 2.32 (ddd, $J_{3a,4ax}$ = 10.0 Hz, $J_{3a,3}$ = 7.1 Hz, $J_{3a,4eq}$ = 2.8 Hz, 1 H, 3a-H), 2.79 (ddd, J = 11.0 Hz, $J_{3,3a}$ = 7.1 Hz, $J_{3,2}$ = 4.2 Hz, 1 H, 3-H), 3.31 (br. d, $J_{7eq,7ax}$ = 9.3 Hz, 1 H, 7-H_{eq}), 3.66 (s, 3 H, OCH_3), 3.74 (dq, J = 6.0 Hz, $J_{2,3}$ = 4.2 Hz, 1 H, 2-H), 5.89 (d, J_{trans} = 15.4 Hz, 1 H, $CH{=}CH{-}CO_2Me$), 6.89 (dd, J_{trans} = 15.4 Hz, J = 11.0 Hz, 1 H, $CH{=}CH{-}CO_2Me$). – ^{13}C NMR ([D_6]acetone, 250 K): δ = 19.0 (CH_3), 24.1/24.8/26.5 (C-4/C-5/C-6), 51.6 (OCH_3), 55.6 (C-3 and C-8), 70.3 (C-3a), 96.5 (C-2), 122.5 ($CH{=}CH{-}CO_2Me$), 148.3 ($CH{=}CH{-}CO_2Me$), 166.4 (C=O). – MS: m/z (%) = 225 (M^+, 8), 122 (14), 100 (74), 99 (100), 69 (46), 55 (38), 41 (41).

$C_{12}H_{19}NO_3$ (225.3) Calcd. C 63.98 H 8.50 N 6.22
Found C 64.03 H 8.28 N 5.88

10: MS: m/z (%) = 324 (M^+, 6), 293 (3), 225 (5), 181 (18), 124 (32), 100 (100), 99 (93), 84 (82), 69 (21), 55 (31), 41 (37).

$C_{17}H_{28}N_2O_4$ (324.4) Calcd. C 62.94 H 8.70 N 8.63
Found C 62.87 H 9.08 N 8.49

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1: 34418-91-2 / **2**: 591-11-7 / **3**: 121097-73-2 / **4**: 121155-23-5 / **5**: 121155-24-6 / **6**: 689-89-4 / **7**: 121097-74-3 / **8**: 121155-25-7 / **9**: 121097-75-4

[1] [1a] For a review see: A. Padwa, *1,3-Dipolar Cycloaddition Chemistry*, John Wiley and Sons, New York 1984. – Other examples: [1b] J. J. Tufariello, G. B. Mullen, J. J. Tegeler, E. J. Trybulsky, S. C. Wong, Sk. A. Ali, *J. Am. Chem. Soc.* **101** (1979) 2435. – [1c] W. R. Roush, A. E. Walts, *J. Am. Chem. Soc.* **106** (1984) 721. – [1d] A. P. Kozikowsky, P. Park, *J. Am. Chem. Soc.* **107** (1985) 1763. – [1e] S. F. Martin, M. S. Dappen, B. Dupre, C. J. Murphy, *J. Org. Chem.* **52** (1987) 3706.

[2] [2a] M. Frank-Neumann, *Angew. Chem., Int. Ed. Engl.* 7 (1968) 65; *Angew. Chem.* **80** (1968) 42. – [2b] R. Metelli, C. F. Bettinetti, *Synthesis* **1970**, 365. – [2c] S. W. Pelletier, Z. Djarmati, S. Lajsic, I. Micovic, D. T. C. Yang, *Tetrahedron* **31** (1975) 1659. – [2d] J. J. Tufariello, J. P. Tette, *J. Org. Chem.* **40** (1975) 3866. – [2e] K. Tomioka, F. Sato, K. Koga, *Heterocycles* **17** (1982) 311. – [2f] J. Mann, A. Thomas, *J. Chem. Soc., Chem. Commun.* **1985**, 737. – [2g] F. Fariña, M. V. Martín, F. Sánchez, *Heterocycles* **24** (1986) 2587. – [2h] S. Hanessian, P. J. Murray, *J. Org. Chem.* **52** (1987) 1170. – [2i] L. Fisera, P. Oravec, *Collect. Czech. Chem. Commun.* **52** (1987) 1315.

[3] [3a] B. de Lange, B. L. Feringa, *Tetrahedron Lett.* **29** (1988) 5317. – [3b] R. M. Ortuño, M. Ballesteros, J. Corbera, F. Sánchez-Ferrando, J. Font, *Tetrahedron* **44** (1988) 1711. – [3c] J. Corbera, J. Font, M. Monsalvatje, R. M. Ortuño, F. Sánchez-Ferrando, *J. Org. Chem.* **53** (1988) 4393.

[4] [4a] Sk. A. Ali, M. I. M. Wazeer, *Tetrahedron* **44** (1988) 187. – [4b] Sk. A. Ali, M. I. M. Wazeer, *J. Chem. Soc., Perkin Trans. 1*, **1988**, 597. – [4c] M. Burdisso, A. Gamba, R. Gandolfi, R. Oberti, *Tetrahedron* **44** (1988) 3735.

[5] A. J. Blake, A. C. Forsyth, R. M. Paton, *J. Chem. Soc., Chem. Commun.* **1988**, 440.

[6] [6a] J. Thesing, W. Sirrenberg, *Chem. Ber.* **92** (1959) 1748. – [6b] W. Sabel, *Chem. Ind. (London)* **1966**, 1216.

[7] R. M. Ortuño, J. Cardellach, J. Font, *J. Heterocycl. Chem.* **24** (1987) 79.

[8] [8a] B. G. Murray, A. F. Turner, *J. Chem. Soc. C*, **1966**, 1338. – [8b] R. Huisgen, H. Hauck, R. Grashey, H. Seidl, *Chem. Ber.* **101** (1968) 2568. – [8c] M. Joucla, F. Tonnard, D. Grée, J. Hamelin, *J. Chem. Research (S)* **1978**, 240. – [8d] J. J. Tufariello, G. E. Lee, P. A. Senaratne, M. Al-Nuri, *Tetrahedron Lett.* **1979**, 4359.

[9] Y. Ueda, C. E. Damas, B. Belleau, *Can. J. Chem.* **61** (1983) 1996.

[10] The unsystematic numbering of the compounds **3**–**5**, 7, and **8** assists in discussing the substituent effects and in assigning the spectral data. Systematic names are used in the Experimental.

[11] C. Jaime, R. M. Ortuño, J. Font, *J. Org. Chem.* **51** (1986) 3946; C. Jaime, R. M. Ortuño, J. Font, *ibid.* **52** (1987) 5500.

[12] Although S. Murahashi et al. for an observed J = 6 Hz for similar protons in ethyl hexahydro-2-methylpyridinoisoxazole-3-carboxylate stated *trans* stereochemistry: S. Murahashi, H. Mitsui, T. Watanabe, S. Zenki, *Tetrahedron Lett.* **24** (1983) 1049.

[13] E. Gössinger, *Monatsh. Chem.* **112** (1981) 1017.

[76/89]