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Thermolysis of Oxime *O*-Allyl Ethers: A New Method for Pyridine Synthesis

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Thermolysis of cycloalkanone oxime *O*-allyl ethers in air gave the corresponding cycloalkenopyridines, providing a new method for the synthesis of cycloalkenopyridine derivatives.

Keywords——cycloalkanone oxime *O*-allyl ether; cycloalkenopyridine; thermolysis; *O*-allylhydroxylamine; cyclohexanone; tetrahydroquinoline

In 1973, Ranganathan and his co-workers reported the thermal rearrangement of oxime *O*-allyl ethers of benzaldehydes to the corresponding nitrones by preferential [2,3]-sigmatropic rearrangement.[1] Following this report, Rogers and Eckersley indicated that the reaction proceeded by a homolytic cleavage-recombination mechanism, at least in part, as a result of electron spin resonance (ESR) investigations.[2] Our interest in the thermal rearrangement of some oxime *O*-allyl ethers of cycloalkanones resulted in our finding a new method for constructing cycloalkenopyridines.[3,4] We report here the synthetic results obtained by the rearrangement of some cycloalkanone and acyclic ketone oxime *O*-allyl ethers.

Treatment of *N*-hydroxyphthalimide with allyl chloride in the presence of potassium carbonate in dimethyl sulfoxide gave *N*-allyloxyphthalimide (**1a**) in 95% yield. Hydrazinolysis of (**1a**) gave *O*-allylhydroxylamine (**2a**).[5] Treatment of cyclohexanone with the hydroxylamine (**2a**) in ethanol in the presence of sodium acetate gave cyclohexanone oxime *O*-allyl ether (**3a**) in good yield.

Heating of the oxime *O*-allyl ether (**3a**) in a sealed glass tube at 180 °C (bath temperature) under argon gave the isoxazolidine (**4**) as a major product (65% isolated yield) and 5,6,7,8-tetrahydroquinoline (**5a**) as a minor product (3% isolated yield). Structures of the products (**4**) and (**5a**) were assigned on the basis of spectroscopic evidence (see "Experimental"). Formation of the isoxazolidine (**4**) can be interpreted in terms of the cycloaddition of (**3a**) with the 1,3-dipole species (**6**), which is equivalent to the nitrone formed by [2,3]-sigmatropic rearrangement of (**3a**). On the other hand, when the thermolysis was carried out under air rather than argon, the tetrahydroquinoline (**5a**) was obtained in 50% yield along with water and a minute amount of the isoxazolidine (**4**). Though the mechanism of the reaction is not clear, we proposed the reaction sequence depicted in Chart 2 for the transformation reaction based on the following results and inference: (a) re-heating of the isoxazolidine (**4**) under air did not give the tetrahydroquinoline (**5a**),[6] (b) the thermolysis of (**3a**) in the presence of 2,6-di-(*tert*-butyl)-*p*-cresol as a radical scavenger did not affect the yield of (**5a**), and (c) these results suggest that oxygen participated in an ionic manner after nitrone formation.

In order to extend the applicability of the reaction for synthesizing cycloalkenopyridines, several cycloalkanone oxime *O*-allyl ethers (**3b—d**) were synthesized by using *O*-methallyl-*O*-crotyl-, and *O*-(α-methylallyl)hydroxylamine (**2b—d**), which were prepared in the same way as described for (**2a**). Thermolysis of the oxime *O*-allyl ethers thus obtained gave the correspond-

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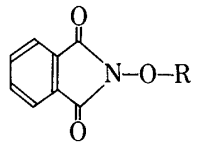
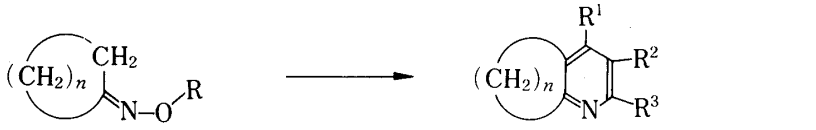


1a–d

a: R = CH_2–CH=CH_2
b: R = CH_2–C(Me)=CH_2
c: R = CH_2–CH=CH–Me
d: R = CH(Me)–CH=CH_2

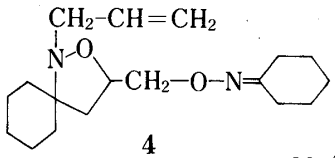
NH_2–O–R

2a–d



3a–d : $n=4$
3e–l : R = CH_2–CH=CH_2
n; cycloalkanone is indicated in Table I

5a : $R^1=R^2=R^3=H$, $n=4$
5b : $R^2=Me$, $R^1=R^3=H$, $n=4$
5c : $R^3=Me$, $R^1=R^2=H$, $n=4$
5d : $R^1=Me$, $R^2=R^3=H$, $n=4$
5e–l : $R^1=R^2=R^3=H$,
n; cycloalkeno-part is indicated in Table II



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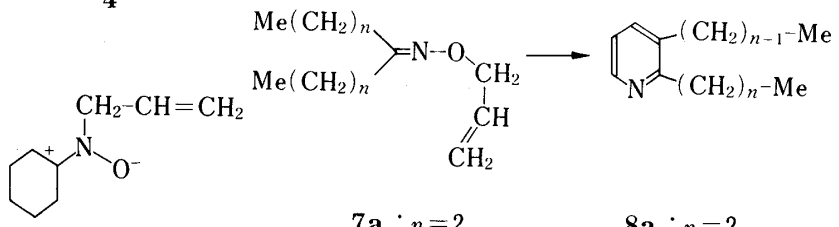

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7a : $n=2$
7b : $n=3$

8a : $n=2$
8b : $n=3$

Chart 1

ing cycloalkenopyridines in fair yields. The results are summarized in Table II. As indicated in Table II, the *O*-methallyl ether (**3b**) gave 3-methyl-5,6,7,8-tetrahydroquinoline (**5b**) as a sole product on heating, while the crotyl- (**3c**) and α-methylallyl ether (**3d**) yielded a mixture of 2-methyl- (**5c**) and 4-methyl-5,6,7,8-tetrahydroquinoline (**5d**) in ratios of 40 : 17 and 36 : 10, respectively, suggesting that the nitrone formation reaction, thought to be the first stage of the reaction to form the tetrahydroquinolines, proceeded in a "caged" homolysis-recombination manner.

Oxime *O*-allyl ethers of acyclic ketones gave 2,3-dialkylpyridines on heating: thermolysis of di-propyl- (**7a**) and di-butyl ketone oxime *O*-allyl ether (**7b**) yielded 2-propyl-3-ethyl-(**8a**) and 2-butyl-3-propylpyridine (**8b**) in 35 and 50% yields, respectively; both products were characterized as their picrates.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 215 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra

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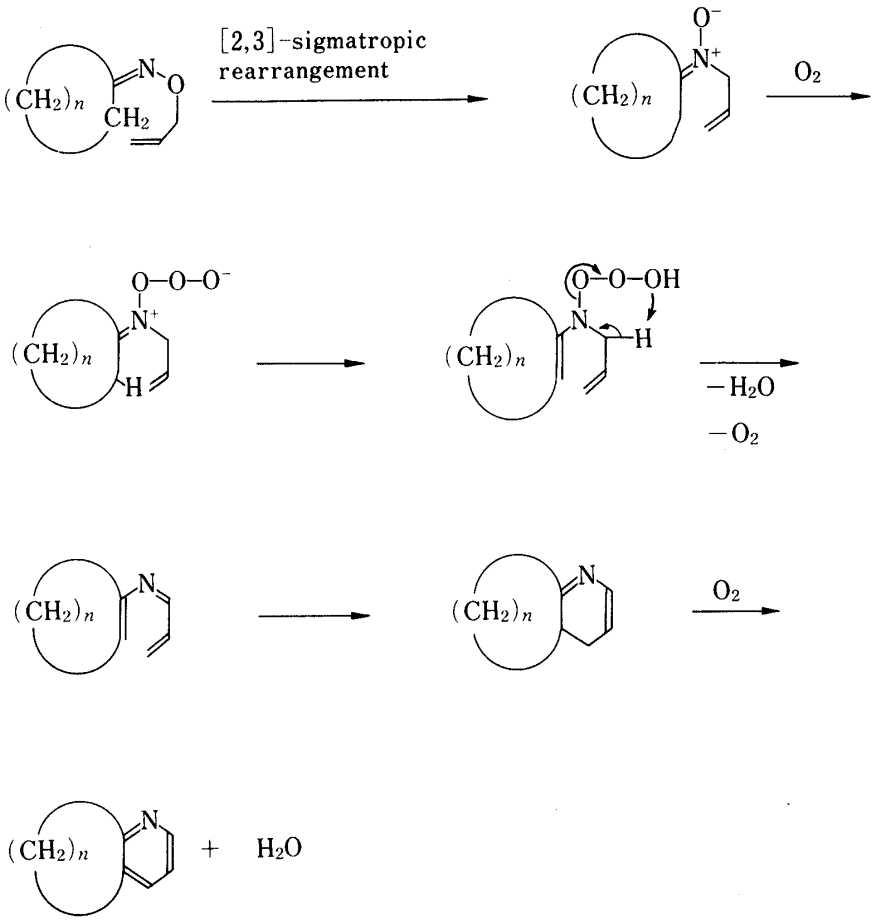

Chart 2

were taken on JNN-PMX-60, Varian A-60D, and NEVA NV-21 spectrometers with tetramethylsilane as an internal standard in $CDCl_3$. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were taken on the NV-21 spectrometer with the same standard and the same solvent. Mass spectra were recorded on a JEOL JMS-01SG spectrometer. Preparative thin layer chromatography was carried out on Kieselgel 60 F_{254} (Merck) with appropriate solvents.

***O*-Allylhydroxylamine (2a)**——Allyl chloride (2.5 ml) was added dropwise with stirring to a suspension of anhydrous K_2CO_3 (4.3 g) and *N*-hydroxyphthalimide (5 g) in DMSO (50 ml) at 25 °C. When the addition was complete, the whole was stirred at room temperature for 24 h, then poured into cold water (500 ml). The deposited crystals were collected, washed with water, and dried. The crystals were recrystallized from EtOH to give *N*-allyloxyphthalimide (**1a**) (5.9 g) as prisms, mp 56—57 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1790 and 1730. ^{1}H-NMR ($CDCl_3$) δ: 4.71 (2H, d, J=7 Hz, O–CH_2–), 5.18—5.54 (2H, m, =CH_2), 6.12 (1H, m, –CH=), 7.72—7.89 (4H, m, aromatic H's). *Anal.* Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.13; H, 4.39; N, 6.81.

A mixture of *N*-allyloxyphthalimide (**1a**) (10 g), hydrazine hydrate (5 ml), and EtOH (100 ml) was heated under reflux for 2 h, and poured into 3% aqueous Na_2CO_3 (500 ml). The solution was extracted with ether. The ether extract was washed with water, dried ($MgSO_4$), and filtered. The filtrate was treated with dry HCl gas. Removal of ether gave allylhydroxylamine hydrochloride as a gum. Solid KOH was added to the hydrochloride in a distillation flask, and the mixture was subjected to distillation to give *O*-allylhydroxylamine (**2a**) (3.1 g), bp 80 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350. ^{1}H-NMR ($CDCl_3$) δ: 4.15 (2H, d, J=6 Hz, O–CH_2–), 5.05—5.44 (2H, m, =CH_2), 5.81 (1H, m, –CH=). MS *m/e*: 73.052 (calcd for 73.053).

O-Methallyl- (**2b**), *O*-crotyl- (**2c**), and *O*-(α-methyl)allylhydroxylamine (**2d**) were prepared in the same way as described above.

***O*-Methallylhydroxylamine (2b)**——Yield, 89%; bp 90 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400. ^{1}H-NMR ($CDCl_3$) δ: 1.74 (3H, s, Me), 4.07 (2H, s, O–CH_2–), 4.95 (2H, s, =CH_2), 5.32 (2H, s, NH_2). MS *m/e*: 87.065 (calcd for 87.068).

***O*-Crotylhydroxylamine (2c)**——Yield, 85%; bp 95—100 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400. ^{1}H-NMR ($CDCl_3$) δ: 1.72 (3H, d, J=5 Hz, Me), 3.98 (2H, d, J=5 Hz, O–CH_2–), 5.02 (2H, s, NH_2), 5.44—5.70 (2H, m, –CH=CH–). MS *m/e*: 87.069 (calcd for 87.068).

***O*-(α-Methylallyl)hydroxylamine (2d)**——Yield, 86%; bp 97—100 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=6 Hz, Me), 3.77—4.19 (1H, m, O–CH–), 4.93—5.27 (2H, m, =CH_2), 5.47—6.02 (1H, m, –CH=).

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MS *m/e*: 87.065 (calcd for 87.068).

Cyclohexanone Oxime *O*-Allyl Ether (3a)——A solution of cyclohexanone (9g), *O*-allylhydroxylamine (**2a**) hydrochloride (10g), anhydrous NaOAc (8g), and anhydrous Na_2CO_3 (10g) in EtOH (50 ml) was refluxed for 2 h. After evaporation of the solvent, the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried ($MgSO_4$), and evaporated to dryness to give cyclohexanone oxime *O*-allyl ether (**3a**) as an oil. Yield, 13g; bp 65 °C/6.5 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$) δ: 4.50 (2H, td, J=1.5 and 5 Hz, O–CH_2–), 5.03—5.44 (2H, m, =CH_2), 5.70—6.34 (1H, m, –CH=). MS *m/e*: 153.115 (calcd for 153.115).

Cyclohexanone oxime *O*-methallyl- (**3b**), *O*-crotyl- (**3c**), and *O*-(α-methyl)allyl ether (**3d**) were also prepared according to the procedure described above.

Cyclohexanone Oxime *O*-Methallyl Ether (3b)——Yield, 94%; bp 87 °C/17 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (3H, s, Me), 4.45 (2H, s, O–CH_2–), 4.93 (2H, br s, =CH_2). MS *m/e*: 167.134 (calcd for 167.131).

Cyclohexanone Oxime *O*-Crotyl Ether (3c)——Yield, 92%; bp 93 °C/17 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670. ^{1}H-NMR ($CDCl_3$) δ: 1.72 (3H, d, J=5 Hz, Me), 4.47 (2H, d, J=5 Hz, O–CH_2–), 5.63—5.82 (2H, m, –C<u>H</u>=C<u>H</u>–). MS *m/e*: 167.129 (calcd for 167.131).

Cyclohexanone Oxime *O*-(α-Methyl)allyl Ether (3d)——Yield, 94%; bp 79 °C/10 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=6 Hz, Me), 4.38—4.81 (1H, m, O–<u>C</u>H–), 4.99—5.32 (2H, m, =CH_2), 5.67—6.23 (1H, m, –CH=). MS *m/e*: 167.133 (calcd for 167.131).

All the other oxime *O*-allyl ethers indicated in Table I were prepared in the same way as above.

Table I. Physical and Spectral Data and Yields of Oxime *O*-Allyl Ethers

Oxime *O*-allyl ether	bp (°C/mm)	IR cm^{-1} ($CHCl_3$)	MS *m/e* (Calcd)	Yield (%)
Cyclopentanone (**3e**)	70/12	1650	139.099 (139.099)	91
Cycloheptanone (**3f**)	83/13	1620	167.130 (167.130)	94
Cyclooctanone (**3g**)	90/2	1630	181.146 (181.146)	92
Cyclododecanone (**3h**)	120/2	1645	237.210 (237.209)	92
2-Methylcyclohexanone (**3i**)	65/3	1635	167.128 (167.130)	92
3-Methylcyclohexanone (**3j**)	70/3	1640	167.129 (167.130)	94
4-Methylcyclohexanone (**3k**)	65/3	1640	167.129 (167.130)	92
α-Tetralone (**3l**)	125/3	1645	201.116 (201.115)	97
Di-*n*-propyl ketone (**7a**)	44/3	1625	169.147 (169.146)	90
Di-*n*-butyl ketone (**7b**)	47/3	1630	197.177 (197.177)	91

Table II. Reaction Times and Yields of Alkenopyridines

Oxime *O*-allyl ether	Alkenopyridine	Heating time (h)	Yield (%)
3e	2,3-Cyclopentenopyridine (**5e**)	30	30
3f	2,3-Cycloheptenopyridine (**5f**)	50	55
3g	2,3-Cyclooctenopyridine (**5g**)	48	65
3h	2,3-Cyclododecenopyridine (**5h**)	48	60
3i	8-Methyl-5,6,7,8-tetrahydroquinoline (**5i**)	35	35
3j	5- and 7-Methyl-5,6,7,8-tetrahydroquinoline (**5j**) and (**5j′**)	40	40
3k	6-Methyl-5,6,7,8-tetrahydroquinoline (**5k**)	40	40
3l	Benzo[*h*]-5,6-dihydroquinoline (**5l**)	50	61
7a	2-Propyl-3-ethylpyridine (**8a**)	15	35
7b	2-Butyl-3-propylpyridine (**8b**)	20	50
3b	3-Methyl-5,6,7,8-tetrahydroquinoline (**5b**)	40	41
3c	2- and 4-Methyl-5,6,7,8-tetrahydroquinoline (**5c**) and (**5d**)	40	40+17
3d	**5c** and **5d**	40	36+10

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TABLE III. Physical and Spectral Data for the Pyridine Derivatives

Product	Picrate mp °C (Lit. mp)	Formula (Free base)	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR ($CDCl_3$) δ (J=Hz) [Free base]
5e	176—178 (181—182)[7]	$C_{14}H_{12}N_4O_7$ (C_8H_9N)		a)		6.99 (1H, dd, J=5 and 8, pyridine-β-H), 7.48 (1H, d, J=8, γ-H), 8.33 (1H, d, J=5, α-H)
5f	135—137 (138—139)[7]	$C_{16}H_{16}N_4O_7$ ($C_{10}H_{13}N$)	51.23, (51.06,	4.30, 4.29,	14.74 14.89)	6.97 (1H, dd, J=5 and 8, β-H), 7.33 (1H, dd, J=2 and 8, γ-H), 8.23 (1H, dd, J=2 and 5, α-H)
5g	148—150 (150—151)[7]	$C_{17}H_{18}N_4O_7$ ($C_{11}H_{15}N$)	52.33, (52.30,	4.57, 4.65,	14.12 14.35)	7.02 (1H, dd, J=5 and 8, β-H), 7.37 (1H, dd, J=2 and 8, γ-H), 8.36 (1H, dd, J=2 and 5, α-H)
5h	152—153	$C_{21}H_{26}N_4O_7$ ($C_{15}H_{23}N$)	56.45, (56.49,	5.90, 5.87,	12.41 12.55)	6.97 (1H, dd, J=4 and 8, β-H), 7.40 (1H, d, J=8, γ-H), 8.33 (1H, d, J=4, α-H)
5i	124—126	$C_{16}H_{16}N_4O_7$ ($C_{10}H_{13}N$)	51.13, (51.06,	4.16, 4.29,	14.68 14.89)	1.37 (3H, d, J=7, Me), 6.94 (1H, dd, J=5 and 8, β-H), 7.30 (1H, dd, J=2 and 8, γ-H), 8.35 (1H, dd, J=2 and 5, α-H)
5j+5j′	169—171	$C_{16}H_{16}N_4O_7$ ($C_{10}H_{13}N$)	51.01, (51.06,	4.22, 4.29,	14.73 14.89)	1.10 and 1.29 (3H×2, d, J=6 and 7, respectively, Me), 6.96 (1H×2, dd, J=5 and 8, β-H), 7.32 (1H×2, dd, J=2 and 8, γ-H), 8.29 (1H×2, dd, J=2 and 5, α-H)
5k	158—159	$C_{16}H_{16}N_4O_7$ ($C_{10}H_{13}N$)	51.00, (51.06,	4.21, 4.29,	14.80 14.89)	1.10 (3H, d, J=6, Me), 7.01 (1H, dd, J=5 and 8, β-H), 7.35 (1H, dd, J=2 and 8, γ-H), 8.35 (1H, dd, J=2 and 5, α-H)
5l	184—186	$C_{19}H_{14}N_4O_7$ ($C_{13}H_{11}N$)		b)		2.90 (4H, s, CH_2×2), 7.05 (1H, dd, J=5 and 8, β-H), 7.45 (1H, dd, J=2 and 8, γ-H), 8.45 (1H, dd, J=2 and 5, α-H)
8a	150	$C_{16}H_{18}N_4O_7$ ($C_{10}H_{15}N$)		c)		7.00 (1H, dd, J=5 and 8, β-H), 7.38 (1H, dd, J=2 and 8, γ-H), 8.32 (1H, dd, J=2 and 5, α-H)
8b	154—155	$C_{18}H_{22}N_4O_7$ ($C_{12}H_{19}N$)		d)		6.95 (1H, dd, J=5 and 8, β-H), 7.35 (1H, dd, J=2 and 8, γ-H), 8.31 (1H, dd, J=2 and 5, α-H)
5b	182—184 (182—183)[7]	$C_{16}H_{16}N_4O_7$ ($C_{10}H_{13}N$)	51.01, (51.06,	4.25, 4.29,	14.64 14.89)	2.23 (3H, s, Me), 7.14 (1H, s, γ-H), 8.18 (1H, s, α-H)
5c	152—154	$C_{16}H_{16}N_4O_7$ ($C_{10}H_{13}N$)	50.96, (51.06,	4.26, 4.29,	14.81 14.89)	2.47 (3H, s, Me), 6.86 (1H, d, J=8, β-H), 7.23 (1H, d, J=8, γ-H)
5d	178—181	$C_{16}H_{16}N_4O_7$ ($C_{10}H_{13}N$)	51.17, (51.06,	4.12, 4.29,	14.84 14.89)	2.21 (3H, s, Me), 6.87 (1H, d, J=5, β-H), 8.21 (1H, d, J=5, α-H)

a) MS m/e: 119.073 (119.073 for C_8H_9N). b) MS m/e: 181.088 (181.089 for $C_{13}H_{11}N$).
c) MS m/e: 149.122 (149.120 for $C_{10}H_{15}N$). d) MS m/e: 177.151 (177.152 for $C_{12}H_{19}N$).

Thermolysis of the Oxime *O*-Allyl Ether (3a)——a) Under Argon: Heating of the oxime *O*-allyl ether (**3a**) (200 mg) in a sealed glass tube at 180—190 °C (bath) for 20 h gave a brown oil. The crude product was separated by preparative thin layer chromatography (silica gel F_{254} (Merck), $CHCl_3$: MeOH = 50 : 2) to give the oxazolidine (**4**) (130 mg) as an oil: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1645. ^{1}H-NMR ($CDCl_3$) δ: 3.33 (2H, td, J=1.5 and 6 Hz, $-CH_2-N$), 4.09 and 4.10 (1H each, d, J=4 and 6 Hz, $CH-C\underline{H}_2-O$), 4.18—4.50 (1H, m, $-\underline{C}H-O$), 5.04—5.31 (2H, m, $=CH_2$), 5.83—6.27 (1H, m, $-CH=$). ^{13}C-NMR ($CDCl_3$) ppm: 53.3 (t), 67.0 (s), 74.8 (t), 75.4 (d), 116.3 (t), 135.8 (d), 160.4 (s). MS m/e: 306.233 (calcd for 306.231), and the tetrahydroquinoline (**5a**) (6 mg), which was characterized as its picrate: picrate mp 158—

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159 °C (lit.[7] mp 158—159 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1580 and 1450. ^{1}H-NMR ($CDCl_3$) δ: 7.04 (1H, dd, J=4 and 6 Hz, pyridine-β-H), 7.38 (1H, dd, J=2 and 6 Hz, γ-H), 8.41 (1H, dd, J=2 and 4 Hz, α-H). *Anal.* Calcd for $C_9H_{11}N \cdot C_6H_3N_3O_7 \cdot 1/4C_2H_5OH$: C, 49.80; H, 4.18; N, 14.99. Found: C, 49.92; H, 3.92; N, 14.78.

b) Under Air: Heating of the oxime *O*-allyl ether (**3a**) (300 mg) in the same manner as in a), but under air rather than argon, for 70 h gave an oily product which was taken up in $CHCl_3$. The solution was washed with 5% HCl and water, dried, and concentrated to dryness to give the isoxazolidine (**4**) (5 mg), which was identical with (**4**) obtained above. The HCl washings were basified with Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to dryness to leave an oil. The oil was subjected to preparative thin layer chromatography on silica gel with the same plate and solvent system as above to give the tetrahydroquinoline (**5a**) (130 mg).

Other results obtained by thermolysis of oxime *O*-allyl ethers derived from various cycloalkanones and acyclic ketones are summarized in Table II. Thermolysis of the *O*-allyl ethers was carried out in the same manner as in the case of cyclohexanone oxime *O*-allyl ether, under air.

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