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1,3-Oxazines and Related Compounds. X.[1] Ring Transformation of 1,3-Oxazin-4-ones into Pyridine Derivatives

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Ring transformations of 2-aryl-6-methyl-4*H*-1,3-oxazin-4-ones (**1**—**3**) with carbanions derived from various ketones, esters, lactones, and nitriles to give 3-acetyl-4,5,6-trisubstituted-2-pyridone derivatives **12** were explored. 1,3-Oxazin-4-ones (**1**—**3**) underwent initial attack of the carbanions at the 2-position of the ring to give the 2-substituted-2-aryl-3,4-dihydro-2*H*-1,3-oxazin-4-ones (**9a**—**o**). The dihydrooxazines (**9a**—**g**) bearing a quarternary-carbon substituent at the 2-position of the 1,3-oxazine ring were stable. In contrast, the dihydrooxazines (**9h**—**o**) which possess a tertiary-carbon substituent at the 2-position were converted into the ring-opened acetoacetamide derivatives (**11**) and subsequently recyclized to the corresponding 3-acetyl-2-pyridone derivatives (**12**).

Keywords——4*H*-1,3-oxazin-4-one; 3,4-dihydro-2*H*-1,3-oxazin-4-one; lithium diisopropylamide; lithium isopropylcyclohexylamide; butyllithium; ring transformation; carbanion; 3-acetyl-2-pyridone derivative

Ring transformations of 4*H*-1,3-oxazin-4-ones (**1**) with several nucleophiles to give a variety of heterocycles have been well investigated. Among them, transformation of **1** with typical active methylene compounds (**4**), such as diethyl malonate, ethyl acetoacetate, acetylacetone, and malononitrile to give pyridine derivatives (**5**) is useful for the synthesis of substituted pyridines.[2] On the other hand, in the previous paper[3] from this laboratory, we demonstrated that the oxazine **1** reacted with *N*-trimethylsilyllactams (**6**) in the presence of lithium diisopropylamide (LDA) to yield 3,4-dihydro-2*H*-1,3-oxazin-4-ones (**7**), as a result of the addition reaction of **6** across the C=N double bond of **1** (Chart 1). This was the first report of isolation of the adduct **7**, which is an important key intermediate in the ring transformation. In order to gain a better understanding of the ring transformation and also to

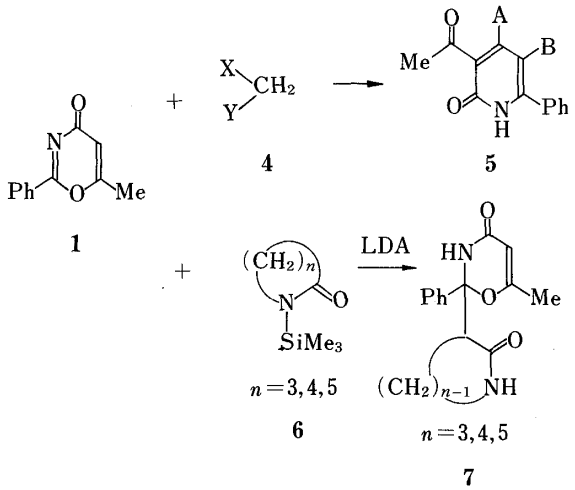


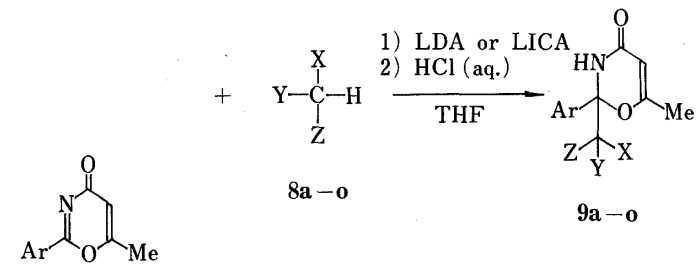
Chart 1

widen the scope of its synthetic utility, we have undertaken an investigation employing various carbanions derived from ketones, esters, lactones, and nitriles, and attempted to isolate the intermediates.

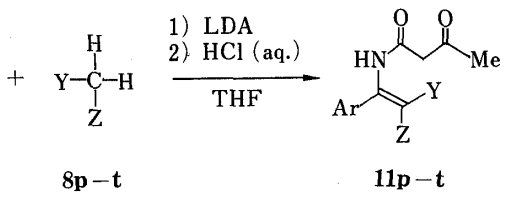
Treatment of 6-methyl-2-phenyl-4*H*-1,3-oxazin-4-one (**1**) with methyl cyclohexanecarboxylate (**8a**) in tetrahydrofuran (THF) at −70 °C in the presence of lithium isopropylcyclohexylamide (LICA), followed by quenching with 10% HCl at the same temperature gave 2-(1-methoxycarbonylcyclohexan-1-yl)-6-methyl-2-phenyl-3,4-dihydro-2*H*-1,3-oxazin-4-one (**9a**) in 89% yield. Structural assignment of the product **9a** was accomplished on the basis of analytical and spectroscopic data [infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR), and mass spectra (MS)] along with the following chemical evidence: hydrolysis of **9a** on heating with 10% HCl under reflux gave methyl 1-benzoylcyclohexanecarboxylate (**10**). The structure of the product **10** was confirmed by a comparison of the IR spectrum with that of an authentic sample obtained from **8a** and ethyl benzoate.

Ketones **8g**—**i**, esters **8a**, **d**, **j**, **m**, lactones **8n**, **o**, and nitriles **8e**, **f** were treated with **1**—**3** at −70 °C in the presence of LICA or LDA (LICA was used in the cases of **8a**—**g**, and LDA in the other cases) in the same manner as described above to give the corresponding adducts **9b**—**o**. The structures of these adducts were characterized on the basis of the spectroscopic and analytical data summarized in Table I.

Formation of the adducts depends on the reaction temperature; it was found that the adducts readily undergo ring opening at elevated temperature. For example, the reaction mixture prepared from **8j** and LDA in THF at −70 °C, when allowed to warm to 0 °C



	X	Y	Z	Ar
9a	–$(CH_2)_5$–		CO_2Me	Ph
9b	–$(CH_2)_5$–		CO_2Me	*p*-MeC_6H_4
9c	–$(CH_2)_5$–		CO_2Me	*p*-ClC_6H_4
9d	Me	Me	CO_2Me	Ph
9e	–$(CH_2)_5$–		CN	Ph
9f	Me	Me	CN	Ph
9g	Me	Me	$COCHMe_2$	Ph
9h	H		–$(CH_2)_4CO$–	Ph
9i	H		–$(CH_2)_5CO$–	Ph
9j	H	Ph	CO_2Et	Ph
9k	H	Ph	CO_2Et	*p*-MeC_6H_4
9l	H	Ph	CO_2Et	*p*-ClC_6H_4
9m	H	Me	CO_2Me	Ph
9n	H		–$(CH_2)_3OCO$–	Ph
9o	H		–$(CH_2)_4OCO$–	Ph



	Y	Z	Ar
11j	CO_2Et	Ph	Ph
11p	CN	Ph	Ph
11q	CN	Ph	*p*-MeC_6H_4
11r	CN	Ph	*p*-ClC_6H_4
11s	–$(CH_2)_3CO$–		Ph
11t	–$(CH_2)_2OCO$–		Ph

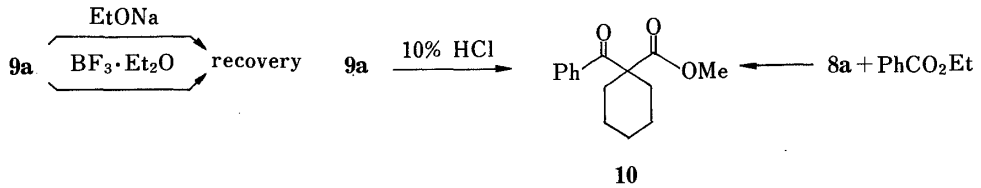


Chart 2

TABLE I. 3,4-Dihydro-2*H*-1,3-oxazin-4-ones **9a**—**o** from **1**—**3** and **8a**—**o**

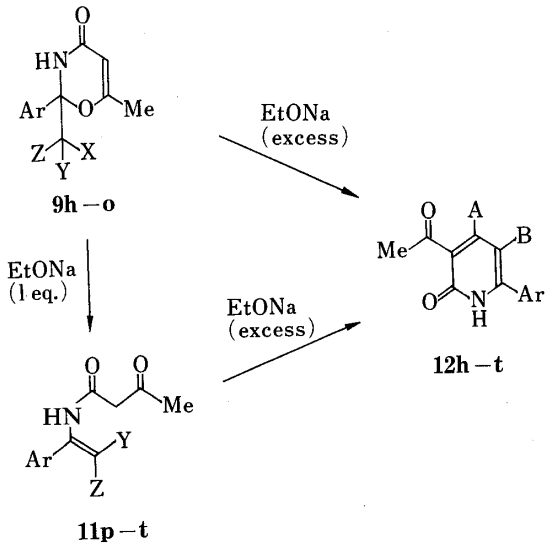
Product No.	Yield (%)	mp (°C) (Recrystn. solvent)	Formula (*m/e* M^+)	Analysis (%) Calcd (Found) C	H	N	IR *v* (KBr) cm^{-1}	NMR ($CDCl_3$) δ
9a	89	146—147 (Et_2O–C_6H_6)	$C_{19}H_{23}NO_4$ (329)	69.28 (69.06	7.04 6.88	4.25 4.00)	3190 1730 1670	0.93—2.66 (10H, m), 2.00 (3H, s), 3.57 (3H, s), 5.06 (1H, s), 7.20 (1H, br), 7.30 (5H, s)
9b	76	161—163 (Et_2O–C_6H_6)	$C_{20}H_{25}NO_4$ (343)	69.95 (70.00	7.33 7.43	4.08 3.83)	3200 1730 1670	0.86—2.70 (10H, m), 1.96 (3H, s), 2.30 (3H, s), 3.56 (3H, s), 5.03 (1H, s), 7.10 (4H, s), 7.26 (1H, br)
9c	88	165—167 (Et_2O–C_6H_6)	$C_{19}H_{22}ClNO_4$ (363)	62.73 (62.68	6.09 6.14	3.85 3.79)	3180 1730 1670	0.90—2.66 (10H, m), 1.96 (3H, s), 3.60 (3H, s), 5.03 (1H, s), 7.16 (1H, br), 7.20 (4H, s)
9d	80	130—131 (Et_2O–C_6H_6)	$C_{16}H_{19}NO_4$ (289)	66.42 (66.27	6.62 6.68	4.84 4.82)	3175 1730 1675	1.26 (3H, s), 1.50 (3H, s), 2.00 (3H, s), 3.60 (3H, s), 5.06 (1H, s), 7.38 (5H, s), 7.61 (1H, br)
9e	83	248—249 (dec.) (MeOH)	$C_{18}H_{20}N_2O_2$ (296)	72.95 (72.78	6.80 6.72	9.45 9.51)	3190 2250 1670	0.95—2.34 (10H, m), 2.10 (3H, s), 5.26 (1H, s), 7.43 (5H, s), 8.93 (1H, br)[a]
9f	77	154—155 (MeOH)	$C_{15}H_{16}N_2O_2$ (256)	70.29 (70.41	6.29 6.18	10.93 10.85)	3160 2250 1670	1.40 (3H, s), 1.57 (3H, s), 2.17 (3H, s), 5.47 (1H, s), 7.43 (5H, s), 9.13 (1H, br)[b]
9g	71	171—173 (Et_2O–C_6H_6)	$C_{18}H_{23}NO_3$ (301)	71.73 (71.58	7.69 7.71	4.65 4.73)	1710 1660	0.70 (3H, d, J=7 Hz), 0.96 (3H, d, J=7 Hz), 1.33 (3H, s), 1.40 (3H, s), 1.93 (3H, s), 2.86 (1H, m), 5.03 (1H, s), 7.30 (5H, s), 7.61 (1H,br)
9h	Trace	129—130 (C_6H_6)	$C_{17}H_{19}NO_3$ (285)	71.56 (71.67	6.71 6.65	4.91 4.80)	3260 1700 1660	1.80 (3H, s), 1.46—2.80 (8H, m), 3.06—3.43 (1H, m), 5.03 (1H, s), 6.69 (1H, br), 7.13—7.70 (5H, m)
9i	78	128—130 (Et_2O)	$C_{18}H_{21}NO_3$ (299)	72.21 (72.05	7.07 7.03	4.68 4.51)	3250 1700 1665	1.83 (3H, s), 1.06—2.70 (10H, m), 3.23—3.56 (1H, m), 5.00 (1H, s), 7.13—7.50 (6H, m)
9j	85	142 (Et_2O–C_6H_6)	$C_{21}H_{21}NO_4$ (351)	71.78 (71.55	6.02 6.03	3.99 4.04)	3250 1740 1665	0.86 (3H, t, J=7 Hz), 1.40 (3H, s), 3.90 (2H, q, J=7 Hz), 4.26 (1H, s), 4.86 (1H, s), 7.06 (1H, br), 7.26 (10H, s)
9k	76	144—145 (Et_2O–C_6H_6)	$C_{22}H_{23}NO_4$ (365)	72.31 (72.10	6.34 6.05	3.86 3.60)	3200 1745 1670	1.13 (3H, t, J=7 Hz), 1.90 (3H, s), 2.30 (3H, s), 4.10 (2H, q, J=7 Hz), 4.26 (1H, s), 5.03 (1H, s), 7.0—7.66 (10H, m)
9l	63	127—129 (Et_2O)	$C_{21}H_{20}ClNO_4$ (385)	65.37 (65.39	5.22 5.12	3.63 3.39)	3180 1735 1670	0.93 (3H, t, J=7 Hz), 1.76 (3H, s), 3.90 (2H, q, J=7 Hz), 4.26 (1H, s), 4.93 (1H, s), 7.16—7.73 (10H, m)
9m	74	142 (Et_2O)	$C_{15}H_{17}NO_4$ (275)	65.44 (65.25	6.22 6.35	5.09 4.85)	3170 1735 1665	1.43 (3H, d, J=7 Hz), 1.86 (3H, s), 3.16 (1H, q, J=7 Hz), 3.40 (3H, s), 5.03 (1H, s), 7.06 (1H, br), 7.13 (5H, s)
9n	Trace	137.5—139 (C_6H_6)	$C_{16}H_{17}NO_4$ (287)	66.88 (67.07	5.96 5.96	4.88 4.74)	3200 1735 1665	1.66—2.65 (4H, m), 1.83 (3H, s), 3.13—3.46 (1H, m), 4.10—4.36 (2H, m), 5.03 (1H, s), 6.90 (1H, br), 7.30 (5H, s)
9o	80	152—153 (C_6H_6)	$C_{17}H_{19}NO_4$ (301)	67.76 (67.70	6.36 6.48	4.65 4.67)	3250 1725 1660	1.65—2.83 (6H, m), 1.83 (3H, s), 3.23—3.56 (1H, m), 4.03—4.30 (2H, m), 5.01 (1H, s), 7.10—7.63 (6H, m)

a) In CF_3COOH–$CDCl_3$. *b*) In CF_3COOH.

TABLE II. Ring-Opened Compounds **11j**, **p**—**t** from **1**—**3** and **8j**, **p**—**t**

Product No.	Yield (%)	mp (°C) (Recrystn. solvent)	Formula (*m/e* M^+)	Analysis (%) Calcd (Found) C	H	N	IR ν (KBr) cm^{-1}	NMR[a] δ
11j	83	99—100 (Et_2O)	$C_{21}H_{21}NO_4$ (351)	71.78 (71.53	6.02 6.08	3.99 4.12)	1730 1710 1680	1.90 (3H × 1/3, s), 2.23 (3H × 2/3, s) 3.47 (2H × 2/3, s), 5.07 (2H × 1/6, s) 7.03 (10H, s), 11.3 (1H, br), 12.93 (2H × 1/6, s)
11p	67	158—159 (MeOH)	$C_{19}H_{16}N_2O_2$ (304)	74.98 (75.28	5.30 5.20	9.21 9.16)	3150 2210 1725 1675	2.23 (3H, s), 3.75 (2H, s), 7.40 (10H, m), 9.23 (1H, br)
11q	64	160—161 (MeOH)	$C_{20}H_{18}N_2O_2$ (318)	75.45 (75.45	5.70 5.73	8.80 8.59)	3150 2210 1725 1680	2.26 (3H, s), 2.36 (3H, s), 3.73 (2H, s), 7.20—7.60 (9H, m), 9.16 (1H, br)
11r	61	167—168 (MeOH)	$C_{19}H_{15}ClN_2O_2$ (338)	67.36 (67.38	4.46 4.71	8.27 8.18)	3230 2210 1725 1680	2.26 (3H, s), 3.73 (2H, s), 7.43—7.74 (9H, m), 9.23 (1H, br)
11s	74	81—83 (Et_2O)	$C_{16}H_{17}NO_3$ (271)	70.83 (70.83	6.32 6.53	5.16 4.96)	1720 1660	1.70—2.66 (6H, m), 1.90 (3H × 3/8, s), 2.19 (3H × 5/8, s), 3.47 (2H × 5/8, s), 4.96 (1H × 3/8, s), 7.35 (5H, s), 12.22 (1H, br), 12.53 (1H × 3/8, br)
11t	74	96—98 (Et_2O–C_6H_6)	$C_{15}H_{15}NO_4$ (273)	65.92 (65.86	5.53 5.51	5.13 4.98)	3275 1740 1720 1690	2.23 (3H, s), 2.83 (2H, t, J=7 Hz), 3.50 (2H, s), 4.33 (2H, t, J=7 Hz), 7.40 (5H, s), 10.83 (1H, br)

a) CF_3COOH was used as a solvent in the cases of **11p**—**r**, while $CDCl_3$ was used in the other cases.



	A	B	Ar
12h	–$(CH_2)_4$–		Ph
12i	–$(CH_2)_5$–		Ph
12j	OH	Ph	Ph
12k	OH	Ph	*p*-MeC_6H_4
12l	OH	Ph	*p*-ClC_6H_4
12m	OH	Me	Ph
12n	OH	$(CH_2)_3$–OH	Ph
12o	OH	$(CH_2)_4$–OH	Ph
12p	NH_2	Ph	Ph
12q	NH_2	Ph	*p*-MeC_6H_4
12r	NH_2	Ph	*p*-ClC_6H_4
12s	–$(CH_2)_3$–		Ph
12t	OH	$(CH_2)_2$–OH	Ph

Chart 3

TABLE III. Pyridine Derivatives **12h—t** from **9** or **11**

Product No.	Yield (%)	mp (°C) (Recrystn. solvent)	Formula (*m/e* M^+)	Analysis (%) Calcd (Found) C	H	N	IR ν (KBr) cm^{-1}	NMR (CF_3COOH)[c] δ
12h	72	235—236 (dec.)[a] (EtOH)	—	—	—	—	1680	1.30—1.90 (4H, m), 2.32 (3H, s), 2.30—2.60 (2H, m), 2.60—2.92 (2H, m), 7.40 (5H, s), 12.45 (1H, br)[d]
12i	69	206—207 (dec.) (Acetone)	$C_{18}H_{19}NO_2$ (281)	76.84 (76.78	6.81 6.73	4.98 4.86)	1680	1.47—2.02 (6H, m), 2.63—3.33 (4H, m), 2.83 (3H, s), 7.53 (5H, m)
12j	85	253—254 (dec.) (MeOH)	$C_{19}H_{15}NO_3$ (305)	74.74 (74.59	4.95 5.03	4.59 4.51)	1660	2.46 (3H, s), 7.16 (10H, s), 11.0 (1H, br), 15.4 (1H, s)[d]
12k	83	212—213 (dec.) (MeOH)	$C_{20}H_{17}NO_3$ (319)	75.22 (75.40	5.37 5.28	4.39 4.34)	1660	2.26 (3H, s), 2.90 (3H, s), 7.06—7.53 (9H, m)
12l	81	246—248 (dec.) (MeOH)	$C_{19}H_{14}ClNO_3$ (339)	67.16 (67.42	4.15 4.25	4.12 4.21)	1660	2.93 (3H, s), 7.06—7.53 (9H, m)
12m	86	242 (dec.) (MeOH)	$C_{14}H_{13}NO_3$ (243)	69.12 (69.03	5.39 5.30	5.76 5.81)	1660	2.17 (3H, s), 2.90 (3H, s), 7.57 (5H, s)
12n	85	229—230 (dec.) (MeOH)	$C_{16}H_{17}NO_4$ (287)	66.88 (66.94	5.96 6.06	4.88 4.69)	1660	1.76—2.26 (2H, m), 2.56—3.23 (3H, m), 2.86 (3H, s), 4.23—4.45 (2H, m), 7.53 (5H, s)
12o	84	169—170 (MeOH)	$C_{17}H_{19}NO_4$ (301)	67.76 (67.57	6.36 6.31	4.65 4.61)	1660	1.33—2.03 (4H, m), 2.46—3.01 (3H, m), 2.90 (3H, s), 4.10—4.51 (2H, m), 7.57 (5H, s)
12p	85	310—312 (dec.) (MeOH)	$C_{19}H_{16}N_2O_2$ (304)	74.98 (74.89	5.30 5.26	9.21 9.32)	1650	2.88 (3H, s), 7.23 (10H, m)
12q	79	294 (dec.) (MeOH)	$C_{20}H_{18}N_2O_2$ (318)	75.45 (75.70	5.70 5.87	8.80 8.62)	1665	2.26 (3H, s), 2.85 (3H, s), 7.06—7.85 (9H, m)
12r	77	313—315 (dec.) (Acetone)	$C_{19}H_{15}ClN_2O_2$ (338)	67.36 (67.41	4.46 4.51	8.27 8.36)	1665	2.85 (3H, s), 7.05—7.56 (9H, m)
12s	75	273—276 (dec.)[b] (MeOH)	—	—	—	—	1645	2.30—2.53 (2H, m), 2.92 (3H, s), 3.22 (2H, t, J=8 Hz), 3.65 (2H, t, J=8 Hz), 7.65 (5H, s)
12t	83	226—227 (dec.) (MeOH)	$C_{15}H_{15}NO_4$ (273)	65.92 (65.93	5.53 5.60	5.13 4.94)	1660	2.70—3.26 (2H, m), 2.90 (3H, s), 4.00 (1H, m), 4.57 (2H, m), 7.60 (5H, s)

a) Ref. 4, mp 235 °C (dec.). *b*) Ref. 4, mp 273—276 °C (dec.). *c*) Signals due to the protons of –OH, $-NH_2$, and –NH groups on the pyridine nuclei were not observed. *d*) In $CDCl_3$.

followed by quenching with 10% HCl, afforded the ring-opened **11j**, mp 99—100 °C, in 83% yield.

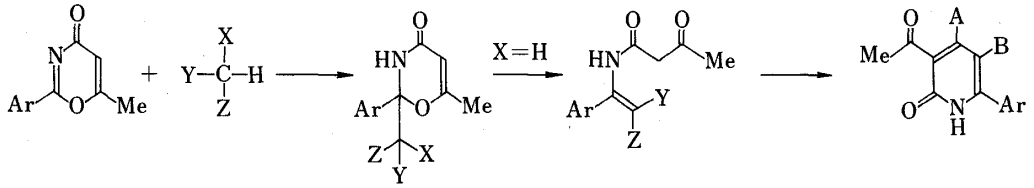
It was concluded that the dihydro-1,3-oxazines **9a—g**, bearing a quaternary-carbon substituent at the 2-position of the 1,3-oxazine ring, are more stable than the adducts **9h—o**, bearing a tertiary-carbon substituent at the 2-position. This was confirmed by the following chemical evidence: the oxazines **9a—g** were found to be stable to base and acid under anhydrous conditions, *e.g.* treatment of **9a** with EtONa in ethanol or BF_3 etherate in $CHCl_3$ resulted in quantitative recovery of **9a**. In contrast, the oxazines **9h—o** were easily converted to the ring-opened **11h—o**, *e.g.* treatment of **9j** with one equivalent of EtONa in ethanol at 0 °C for 90 min afforded the ring-opened **11j** quantitatively.

In similar reactions of **1—3** with phenylacetonitrile (**8p**), cyclopentanone (**8s**), and γ-butyrolactone (**8t**), however, the expected dihydro-1,3-oxazines were not obtained even by

quenching at −70 °C, and the corresponding ring-opened **11p—t** was isolated instead as a sole product (Table II).

Compound **11** is considered to be another key intermediate in the ring transformation of **1**. Cyclization of **11** to a pyridine derivative by treatment with base was easily achieved. When **11j** was treated with excess EtONa in ethanol at room temperature overnight, the cyclized **12j** was obtained in 82% yield. In addition, transformation of **9** to **12** by a one-pot procedure was carried out. A solution of **9j** was stirred with excess EtONa at room temperature overnight to yield **12j** in 86% yield. Table III summarizes the results of the transformation of **9** and **11** to pyridines **12**, together with the spectral and analytical data.

Accordingly, it seems reasonable to explain the ring transformation of 1,3-oxazines into pyridines **12** in terms of the sequential steps shown in Chart 4.



1—3 **8** **9** **11** **12**

Chart 4

Experimental

Melting points were obtained in a Mel-Temp melting point apparatus with an open capillary tube, and are uncorrected. IR spectra were taken on a Shimadzu IR-400 or IR-430 spectrometer. ^{1}H-NMR spectra were measured on a JEOL JNM-PMX 60 instrument. Chemical shifts are reported in δ values downfield relative to internal tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate. The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. Diisopropylamine and *N*-isopropyl-*N*-cyclohexylamine were freshly distilled from CaH_2. THF was distilled from $LiAlH_4$ directly before use. A 10% BuLi hexane solution (Nakarai Chemicals, Ltd.) was used as received.

Preparation of 6-Methyl-2-(4-methylphenyl)-4*H*-1,3-oxazin-4-one (2)——Diketene was added dropwise to a solution of ethyl 4-methylbenzimidate (81.5 g, 0.5 mol) in dry benzene (100 ml) with stirring. A few drops of acetic acid were added to the mixture. The whole solution was refluxed for 3 h and then allowed to stand at room temperature overnight. The precipitate formed was collected by filtration and recrystallized from benzene to give **2** (75%), mp 176—178 °C. IR ν_{max}^{KBr} cm^{-1} 1670. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.40 (3H, s), 6.00 (1H, s), 7.23 (2H, d, J=8 Hz), 8.06 (2H, d, J=8 Hz). *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.58; H, 5.42; N, 6.81.

Preparation of 2-(4-Chlorophenyl)-6-methyl-4*H*-1,3-oxazin-4-one (3)——The oxazine **3** was prepared from ethyl 4-chlorobenzimidate and diketene in 71% yield in the same manner as described above, mp 161—163 °C (benzene). IR ν_{max}^{KBr} cm^{-1} 1670. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 6.03 (1H, s), 7.40 (2H, d, J=8 Hz), 8.10 (2H, d, J=8 Hz). *Anal.* Calcd for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.71; H, 3.50; N, 6.26.

Reactions of 1—3 with 8a—o, Giving Dihydrooxazine 9. General Procedure——A 10% BuLi hexane solution (6.5 ml, 10 mmol) was added dropwise to a solution of diisopropylamine (1.01 g, 10 mmol) (in the case of **9a—g**, *N*-isopropyl-*N*-cyclohexylamine was used) in THF (10 ml) with stirring over a period of 10 min. After completion of the addition, stirring was continued for a further 10 min. A solution of **8** (10 mmol) in THF (20 ml) was added dropwise to the resulting solution with stirring. A solution of **1—3** (10 mmol) in THF (30 ml) was added with stirring over a period of 1 h. Stirring was continued for a further 2 h and acidified with 10% HCl. During these procedures, the temperature was kept at −70 °C. The reaction mixture was concentrated under reduced pressure and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The remaining crude product **9** was purified by recrystallization from the solvent indicated in Table I.

Hydrolysis of 9a to 10——A suspension of **9a** (300 mg) in 10% HCl (20 ml) was heated under reflux for 10 min. The reaction mixture was concentrated under reduced pressure, followed by extraction with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual liquid was distilled under a vacuum to give **10**, bp 110—115 °C (bath temperature)/2 Torr, 150 mg, 63%. IR ν_{max}^{neat} cm^{-1}: 1735, 1690. ^{1}H-NMR

($CDCl_3$) δ: 1.33—2.31 (10H, m), 3.63 (3H, s), 7.33 (5H, s). *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.94; H, 7.53. The IR spectrum of **10** was identical with that of an authentic sample prepared by the procedure described below.

Synthesis of 10——A 10% BuLi hexane solution (6.5 ml, 10 mmol) was added dropwise to a solution of *N*-isopropyl-*N*-cyclohexylamine (1.41 g, 10 mmol) in THF (10 ml) with stirring. After completion of the addition, stirring was continued for a further 10 min. A solution of methyl cyclohexanecarboxylate (1.42 g, 10 mmol) in THF (20 ml) was added dropwise to the resulting solution. The whole was stirred for 10 min, and then a solution of ethyl benzoate (1.50 g, 10 mmol) in THF (20 ml) was added dropwise with stirring. During these procedures, the temperature was kept at −70 °C. The temperature was raised gradually to 0 °C, then the reaction was quenched with 10% HCl. The reaction mixture was concentrated under reduced pressure, followed by extraction with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting liquid was distilled under a vacuum to give **10**, 1.08 g, in 44% yield, bp 83—85 °C/2 Torr. The IR spectrum of **10** was identical with that of a sample prepared by the hydrolysis of **9a** as described above.

Reactions of 1—3 with 8p—t Giving Ring-Opened Compounds 11. General Procedure——A 10% BuLi hexane solution (6.5 ml, 10 mmol) was added dropwise to a solution of diisopropylamine (1.01 g, 10 mmol) in THF (10 ml) with stirring over a period of 10 min. After completion of the addition, stirring was continued for a further 10 min. To the resulting solution, a solution of **8** (10 mmol) in THF (20 ml) was added dropwise. A solution of an oxazine **1**—**3** (10 mmol) in THF (30 ml) was then added with stirring over a period of 1 h. Stirring was continued for a further 2 h, then the reaction was quenched with 10% HCl. During these procedures, the temperature was kept at −70 °C. The reaction mixture was concentrated under reduced pressure and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual crude product was purified by recrystallization from the solvent indicated in Table II.

Reaction of 1 with 8j Giving Ring-Opened 11j——A 10% BuLi hexane solution (6.5 ml, 10 mmol) was added dropwise to a solution of diisopropylamine (1.01 g, 10 mmol) in THF (10 ml) with stirring over a period of 10 min. After completion of the addition, stirring was continued for a further 10 min. To the resulting solution, a solution of ethyl phenylacetate **8j** (1.64 g, 10 mmol) in THF (20 ml) was added dropwise. A solution of the oxazine **1** (1.87 g, 10 mmol) in THF (30 ml) was then added with stirring over a period of 1 h. During these procedures, the temperature was kept at −70 °C. The reaction mixture was allowed to warm to 0 °C, neutralized with 10% HCl, and then concentrated under reduced pressure, followed by extraction with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual crude product was recrystallized from ether to give **11j** in 83% yield.

Synthesis of 11j from 9j——Sodium metal (0.12 g, 5 mmol) was dissolved in absolute ethanol (20 ml), then **9j** (1.75 g 5 mmol) was added and the mixture was stirred for 90 min in an ice-bath. Then 10% HCl was added to the reaction mixture and the whole was concentrated under reduced pressure, followed by extraction with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual solid was recrystallized from ether to give **11j** quantitatively.

Synthesis of Pyridine Derivatives 12 from 9 or 11——Sodium metal (0.23 g, 10 mmol) was dissolved in absolute ethanol (30 ml), then **9** or **11** (2 mmol) was added, and the resulting solution was stirred at room temperature overnight. Next 10% HCl was added to the reaction mixture and the whole was concentrated under reduced pressure. The resulting solid was washed successively with H_2O and ether, then purified by recrystallization from the solvent indicated in Table III.

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