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Grignard Reaction and Products. V.[1] Reduction of Ketoximes to Aziridines with Grignard Reagents[2]

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For the purpose of expanding our former finding that cyclohexylmagnesium chloride acted as reductive reagent to convert a ketoxime to an aziridine,[4] following ten ketoximes were treated with cyclohexylmagnesium chloride or isobutylmagnesium bromide: Oximes (**4**—**13**) of dibenzyl ketone, phenyl benzyl ketone, 2-benzhydrylcyclohexanone, 2-benzoylcyclohexanone, 2-(1-phenyl)cyclohexylcyclohexanone, propiophenone, 4-phenyl-4-methylpentan-2-one, cyclohexanone, benzophenone and camphor. By this treatment, ketoximes (**4**—**10**) suffered reduction to be converted to aziridines. Among those, the cases of **9** and **10** were accompanied with Hoch-Campbell reaction. **12** and **13** were converted to ketimines by the same treatment.

It has been well-known as the Hoch-Campbell reaction that aliphatic ketoximes react with Grignard reagents to afford aziridines *via* addition of the reagents to azirine intermediates[5] (Chart 1).

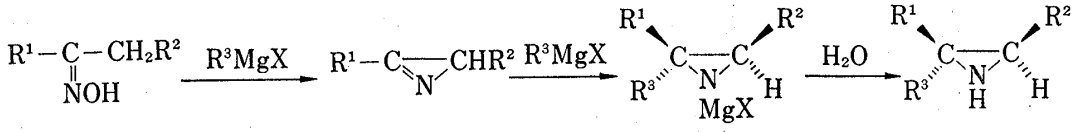


Chart 1

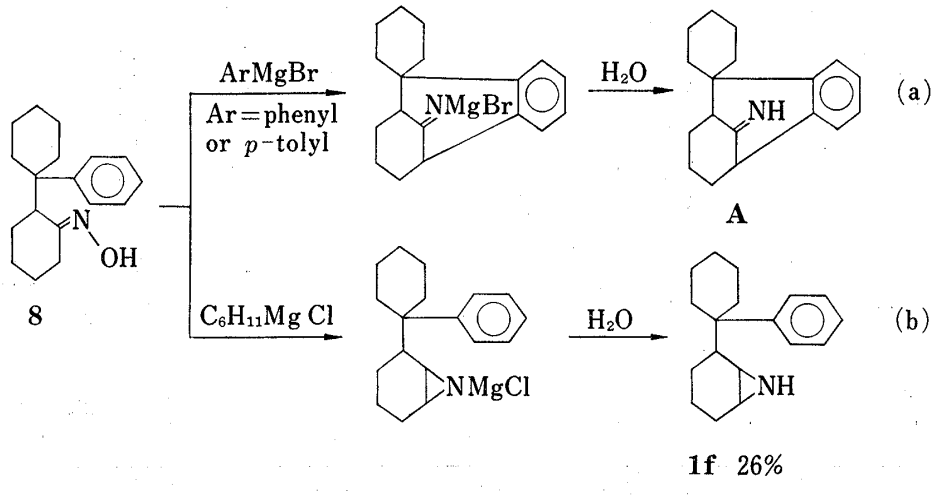
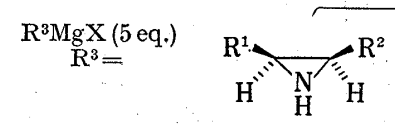
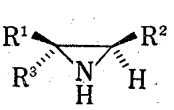
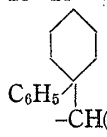
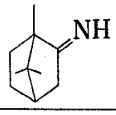


Chart 2

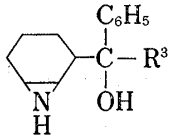
1) *a*) T. Taguchi, Studies in Stereochemistry. LIII; *b*) Part IV: Y. Masuoka, Y. Kawazoe, and T. Taguchi, *Yakugaku Zasshi*, **95**, 609 (1975).
2) Presented at the Meeting of Kyushu Branch, Pharmaceutical Society of Japan, Fukuoka, Feb. 1975.
3) Location: *Maedashi, Higashi-ku, Fukuoka, 812, Japan*; *a*) To whom correspondences should be addressed.
4) *a*) T. Taguchi, K. Miyano, Y. Shimizu, and Y. Kawazoe, *Tetrahedron Letters*, **1968**, 4105; *b*) K. Miyano and T. Taguchi, *Chem. Pharm. Bull.* (Tokyo), **18**, 1799 (1970); *c*) *Idem, ibid.*, **18**, 1806 (1970).
5) *a*) J. Hoch, *Compt. Rend.*, **198**, 1865 (1934); *b*) K.N. Campbell, *J. Org. Chem.*, **8**, 99, 103 (1943); *ibid*, **9**, 178. 184 (1944); *c*) H.R. Henze and W.D. Compton, *J. Org. Chem.*, **22**, 1036 (1957); *d*) S. Eguchi and Y. Ishii, *Bull. Chem. Soc. Japan*, **36**, 1434 (1963).

In contrast with this reaction, new reactions of two types were found in our laboratory during studying the Grignard reaction of 2-(1-phenyl)cyclohexylcyclohexanone oxime (**8**) (Chart 2): a) The reaction of **8** with arylmagnesium bromide caused an intramolecular ring-closure to afford spiro[bicyclo[3.3.1]-3,4-benzononan-9-imine-2,1′-cyclohexane] (**A**).[4] The availability of this reaction to other ketoximes was examined.[6] b) When cyclohexylmagnesium chloride was allowed to react with **8**, it caused the reductive ring-closure to afford 2-(1-phenyl)cyclohexyl-7-azabicyclo[4.1.0]heptane (**1f**).[4c] Since then, this new formation reaction of aziridines has been investigated further to know the scope and the limitation.

Table I. Aziridines and Ketimines resulted from the Grignard Reaction of Ketoximes (**4**—**13**)

Compd. No.	R^1–C(=NOH)–CH_2R^2	R^3MgX (5 eq.) R^3=	Products; Yield (%)						Ketimines	
										
4	$R^1=C_6H_5CH_2$, $R^2=C_6H_5$	$(CH_3)_2CHCH_2$	**1a**[7a]	47		—			—	
		cyclo-C_6H_{11}		5		—			—	
5	$R^1=R^2=C_6H_5$	$(CH_3)_2CHCH_2$	**1b**[7b]	49		—			—	
		cyclo-C_6H_{11}		7		—			—	
6	R^1–R^2= $(C_6H_5)_2CH$–$CH(CH_2)_3$–	$(CH_3)_2CHCH_2$	**1c**	48		—			—	
		cyclo-C_6H_{11}		16		—			—	
7	R^1–R^2= C_6H_5CO–$CH(CH_2)_3$–	$(CH_3)_2CHCH_2$	**1d**[a]	24		—			—	
		cyclo-C_6H_{11}	**1e**[a]	1[b]		—			—	
8	R^1–R^2= 	$(CH_3)_2CHCH_2$	**1f**	2[c]		—			—	
		cyclo-C_6H_{11}		26[4c]		—			—	
9	$R^1=C_6H_5$, $R^2=CH_3$	$(CH_3)_2CHCH_2$	**1g**[7c]	34	**2a**	6			—	
		cyclo-C_6H_{11}		8	**2b**	43			—	
		$C_6H_5CH_2CH_2$		15	**2c**	42			—	
10	$R^1=C_6H_5$–C(CH_3)(CH_3)–CH_2, R^2=H	$(CH_3)_2CHCH_2$	**1h**	32	**2d**	7			—	
		cyclo-C_6H_{11}		1[c]	**2e**	11			—	
		$C_6H_5CH_2CH_2$		6[c]	**2f**	32			—	
		$(C_6H_5)_2CHCH_2$		1[c]		—			—	
11	R^1–R^2=–$(CH_2)_4$–	$(CH_3)_2CHCH_2$		—	**2g**	8			—	
		cyclo-C_6H_{11}		—	**2h**	22			—	
12	benzophenone oxime	$(CH_3)_2CHCH_2$		—		—	**3a**	$(C_6H_5)_2C$=NH	—	48
		cyclo-C_6H_{11}		—		—			—	37
13	camphor oxime	$(CH_3)_2CHCH_2$		—		—	**3b**		—	30
		cyclo-C_6H_{11}		—		—			—	15

a) The carbonyl function suffered the Grignard reaction at the same time:



1d: R^3=isobutyl
1e: R^3=cyclohexyl

b) As N-tosyl deriv.
c) As N-phenylcarbamoyl deriv.

6) K. Imai, Y. Kawazoe, and T. Taguchi, *Yakugaku Zasshi*, **94**, 452 (1974).
7) *a*) K. Kotera, Y. Matsukawa, H. Takahashi, T. Okada, and K. Kitahonoki, *Tetrahedron*, **24**, 6177 (1968); *b*) A. Hassner, G.J. Mattews, and F.W. Fowler, *J. Am. Chem. Soc.*, **91**, 5046 (1968); *c*) M.Y. Shandala, M.D. Solomon, and E.S. Waight, *J. Chem. Soc.*, **1965**, 892.

TABLE II. Microanalyses, IR and Mass Spectra of Aziridines (1 and 2) and Ketimines (3) resulted from the Grignard Reaction of Ketoximes (4—13)

Compd. No.	mp (bp) (°C)	Appearance (recryst. solvt.)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1} (NH)
1a	42—44	needles (petroleum ether)	$C_{15}H_{15}N$	86.08 (86.11)	7.22 (7.13)	6.69 (6.65)	3180
1b	82—83.5	needles (petroleum ether)	$C_{14}H_{13}N$	86.12 (86.44)	6.71 (6.84)	7.17 (7.10)	3276
1c	114.5—116.5	prisms (ligroin)	$C_{19}H_{21}N$	86.64 (86.67)	8.04 (8.05)	5.32 (5.33)	3297
1d[a]	177.5—179.5	prisms (ligroin)	$C_{24}H_{32}O_3NSCl$[e]	64.06 (64.27)	7.17 (7.33)	3.11 (3.11)	3226
1e[b]	230—232	prisms (acetone)	$C_{26}H_{33}O_3NS$[f]	71.04 (71.05)	7.57 (7.57)	3.19 (3.13)	—
1f[c]	164—166	prisms (EtOAc)	$C_{25}H_{30}ON_2$	80.17 (80.20)	8.07 (8.22)	7.48 (7.43)	3305
1g[c]	93.5—95.5	needles (*n*-hexane)	$C_{16}H_{16}ON_2$	76.16 (76.56)	6.39 (6.44)	11.10 (10.94)	3261
1h[c]	85—86.5	prisms (ligroin)	$C_{19}H_{22}ON_2$	77.52 (77.67)	7.53 (7.56)	9.52 (9.54)	3240
2a[b]	107.5—109	plates (petroleum benzin)	$C_{20}H_{25}O_2NS$	69.94 (69.82)	7.34 (7.31)	4.08 (4.00)	—
2b[b]	177—179	plates (EtOAc)	$C_{22}H_{27}O_2NS$	71.51 (71.55)	7.37 (7.34)	3.79 (3.79)	—
2c	(100—110[d] (0.045 mmHg))	oil	$C_{17}H_{19}N$	86.03 (85.66)	8.07 (8.10)	5.90 (5.91)	3241[g] 3291
2d[b]	84—85.5	needles (*n*-hexane)	$C_{23}H_{31}O_2NS$	71.65 (71.45)	8.10 (8.12)	3.63 (3.52)	—
2e	(115—125[d] (0.08 mmHg))	oil	$C_{18}H_{27}N$	83.99 (84.18)	10.57 (10.26)	5.44 (5.58)	3293[g]
2f	68.5—70	needles (*n*-hexane)	$C_{20}H_{25}N$	85.97 (85.76)	9.02 (8.91)	5.01 (5.04)	3247
2f[b]	94—96	plates (ligroin)	$C_{27}H_{31}O_2NS$	74.79 (74.71)	7.21 (7.10)	3.23 (3.22)	—
2g[b]	113—115	prisms (EtOAc)	$C_{17}H_{25}O_2NS$	66.41 (66.40)	8.20 (8.03)	4.56 (4.44)	—
2h	(80—90[d] (0.3 mmHg))	oil	$C_{12}H_{21}N$	80.38 (79.93)	11.81 (11.62)	7.81 (8.10)	3240[g]
2h[b]	148—149.5	plates (EtOAc)	$C_{19}H_{27}O_2NS$	68.43 (68.35)	8.16 (8.03)	4.20 (4.21)	—
3a·HCl	286—287	prisms (EtOH–ether)	$C_{13}H_{12}NCl$	71.72 (71.56)	5.56 (5.63)	6.43 (6.29)	1655 (C=N$^+$)
3b·HCl	288—289	needles (EtOH–ether)	$C_{10}H_{18}NCl$	63.99 (63.91)	9.67 (9.51)	7.46 (7.37)	1695 (C=N$^+$)

a) Compound formed by aziridine ring opening in N-tosylation reaction of **1d** with tosyl chloride. Free base: (**1d**) bp 128—138°[d] (0.06 mmHg), IR $\nu_{max}^{CCl_4}$ cm^{-1} 3329 (NH)

b) N-Tosyl deriv. Free base: (**2a**) bp 60—70°[d] (0.085 mmHg), IR $\nu_{max}^{liq.film}$ cm^{-1} 3260 (NH). (**2b**) bp 100—110°[d] (0.15 mmHg), IR $\nu_{max}^{liq.film}$ cm^{-1} 3239 (NH). (**2d**) bp 90—100°[d] (0.06 mmHg), IR $\nu_{max}^{liq.film}$ cm^{-1} 3247 (NH). (**2g**) bp 50—60°[d] (0.95 mmHg), IR $\nu_{max}^{liq.film}$ cm^{-1} 3253 (NH).

c) N-Phenylcarbamoyl deriv. Free base: (**1g**) bp 54—64°[d] (0.9 mmHg), IR $\nu_{max}^{liq.film}$ cm^{-1} 3280, 3360 (NH), (**1h**) bp 60—70°[d] (0.06 mmHg), IR $\nu_{max}^{liq.film}$ cm^{-1} 3232 (NH).

d) bath temperature

e) Mass Spectrum *m/e* 449 (M^+)

f) Mass Spectrum *m/e* 439 (M^+)

g) liquid film

Quite recently, a group of french authors[8] reported the same reaction without explaining the details of discovery of this reaction (b) although they cited our report.[4c] Such being the circumstances, we wish to report results achieved in our study on this new formation reaction of aziridines.

Ten ketoximes (**4**—**13**) were used as substrates for this reaction (Table I). Among those, **5**—**10** and **13** can exist as geometrical isomers, *E*- and *Z*-form.[9] As configurations of **5**, **8**, **9** and **13** prepared from ketones by the usual method have been already known as *E*-form for the former three and *Z*-form for the last,[4,10] only those of the remainders must be assigned.

2-Benzhydrylcyclohexanone oxime (**6**) was converted to a lactam by the Beckmann rearrangement. With reference to nuclear magnetic resonance (NMR) spectrum of ε-caprolactam which shows absorptions due to $C\underline{H}_2CONH$ at 2.34 ppm (lit.[11] 2.31 ppm) and to $CONHC\underline{H}_2$ at 3.18 ppm (lit.[11] 3.12 ppm), the absorption at 2.34 ppm (2H, m) in NMR spectrum of the lactam derived from **6** is attributable to $C\underline{H}_2CONH$. This means that the lactam is identified as 7-benzhydrylperhydroazepin-2-one and accordingly the parent oxime (**6**) is *E*-form.

The NMR spectrum of 4-methyl-4-phenylpentan-2-one oxime (**10**) shows signals due to C_3-methylene at 2.49 (s) and 2.73 (s) ppm in ratio of about 9: 1, indicating that the compound is an isomeric mixture. It is known that the α-methylene protons of a ketoxime shift by about 0.24 ppm to lower field when they are deshielded by *syn*-hydroxyl group of the oximido function.[12] This knowledge indicates that about 90% of the oxime (**10**) is *E*-form and the remainder is *Z*-form.

The configuration of 2-benzoylcyclohexanone oxime (**7**) can not be determined by the Beckmann reaction, because the reaction causes ring-closure to convert **7** to the isoxazol derivative. The NMR spectrum of **7** shows that *e*- and *a*-hydrogen signals of C_6-methylene appeared at 2.94 (m) and 2.18 (m) ppm respectively. On the other hand, corresponding two hydrogen signals of 2-benzoylcyclohexanone locate closely and appear as an unresolving multiplet centered at 2.55 ppm (2H). Thus, the signal of *a*-hydrogen at C_6 of **7** shifts fairly to higher field in comparison with the corresponding *a*-hydrogen signal of the parent ketone. This phenomenon supports the assignment of the oxime (**7**) as *E*-form, because it is known that in alicyclic ketoxime, the signal of α-*a*-hydrogen which is in *syn*-relationship with the hydroxyl group of oximido function shifts to higher field[13] (Table III).

Table III. NMR Spectra of Ketoximes

Compd. No.	Solvent	100 MHz, δ ppm
6	CCl_4	2.13 (1H, m, H_{6a}), 2.76 (1H, m, H_{6e}), 3.18 (1H, m, H_2)
	DMSO-d_6	2.19 (1H, m, H_{6a}), 2.64 (1H, m, H_{6e}), 3.33 (1H, m, H_2)
7	DMSO-d_6	2.18 (1H, m, H_{6a}), 2.94 (1H, m, H_{6e}), 4.28 (1H, t, H_2)
10[a]	CCl_4	2.49 (1.8H, s, 3-CH_2), 2.73 (0.2H, s, 3-CH_2)

a) isomeric mixture

8) Y. Diab, A. Laurent, and P. Mison, *Tetrahedron Letters*, **1974**, 1605; *idem*, *Bull. Soc. Chim. France*, **1974**, 2202.

9) E.L. Eliel, *J. Chem. Educ.*, **48**, 163 (1971).

10) *a*) S.S. Jenkins, *J. Am. Chem. Soc.*, **55**, 703 (1933); *b*) G.J. Karabatsos and R.A. Taller, *Tetrahedron*, **24**, 3347 (1968); *c*) Z.W. Wolkowski, J. Cassan, L. Elegant, and M. Azzaro, *C.R. Acad. Sci.*, **272**, 1244 (1971).

11) H. Conroy, "Advances in Organic Chemistry; Methods and Results," Vol. 2, ed. by R.A. Raphael, E.C. Taylor, and H. Wynberg, Interscience Publishers, Inc., New York, N.Y., 1960, pp. 265—328.

12) A.C. Huitric, D.B. Roll, and J.R. DeBoer, *J. Org. Chem.*, **32**, 1661 (1967).

The ten ketoximes (**4**—**13**) were treated with 5 molar equivalents of Grignard reagents. As the reagents, cyclohexylmagnesium chloride and isobutylmagnesium bromide were used in major cases and 2-phenylethylmagnesium bromide and 2,2-diphenylethylmagnesium bromide in minor cases. The reductive aziridine formation reaction occurred in 7 cases (**4**—**10**), of which two cases (**9**, **10**) were accompanied with the Hoch-Campbell reaction. In other

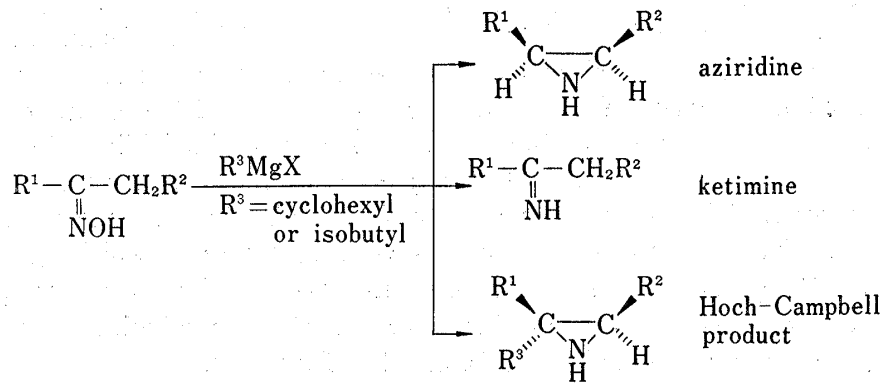
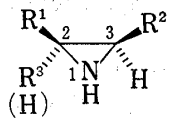


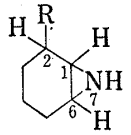
Chart 3

TABLE IV. NMR Spectra of Aziridines (**1** and **2**) produced by the Grignard Reaction of Ketoximes (**4**—**11**)



Compd. No.	100 MHz (in CCl_4) δ ppm			
	NH	H_2	H_3	Others
1a	0.96 (1H, broad),	3.24 (1H, d, J=6.0 Hz),	2.37 (3H, m, CH_2, H_3)	
1b	1.32 (1H, broad),	3.58 (2H, broad, H_2, H_3)		
1c[a]	0.20 (1H, broad)			2.50 (1H, m)[e]
1d				2.55 (1H, t)[e]
1e[b]	—			2.52 (1H, m)[d,e]
1g	1.00 (1H, s),	3.18 (1H, d, J=6.0 Hz),	2.33 (1H, quintet, J=6.0 Hz)	
1h	0.27 (1H, broad),	1.04 (1H, m)		
	—	1.55 (1H, m)[c],	1.73 (2H, m)[c]	
2a	0.42 (1H, s)	—	1.97 (1H, q)	
2b	0.32 (1H, broad)	—	2.04 (1H, q)	
2c	0.36 (1H, broad)	—	2.04 (1H, q)	
2d	−0.075 (1H, s)	—	1.20 (2H, d)	
2e	−0.33 (1H, s)	—		
2f	−0.36 (1H, s)	—		
2g	0.05 (1H, broad)	—		
	—	—	2.96 (1H, m)[d]	
2h	−0.11 (1H, broad)	—		
	—	—	2.85 (1H, m)[d]	

a) 60 MHz
b) in $CDCl_3$
c) N-phenylcarbamoyl deriv.
d) N-tosyl deriv.
e) C_2-H in 7-azabicyclo[4.1.0]heptane deriv.



13) W.F. Trager and A.C. Huitric, *Tetrahedron Letters*, **1966**, 825.

cases, cyclohexanone oxime (**11**) was converted solely to Hoch-Campbell products (**2g, h**) and camphor oxime (**13**) solely to the ketimine derivative (**3b**) in analogy with the case of benzophenone oxime (**12**) which is impossible of ring-closure to aziridine (Table I, Chart 3). Table I indicates that among Grignard reagent used, isobutylmagnesium bromide is most favorable for the reductive aziridine (**1**) formation and 2-phenylethyl- and 2,2-diphenylethylmagnesium bromide are unfavorable for the same purpose.

The characterization of products (Table I) was carried out by their microanalyses (Table II), IR (Table II), Mass (Table II) and NMR (Table IV) spectral data. As these tables indicate, some products were isolated and submitted to these measurements in the form of N-tosyl or N-phenylcarbamoyl derivative. These data were consistent with the proposed structures of all products. The configuration of isomeric 2,3-disubstituted aziridines (**1**) formed by the reductive cyclization was established as follows; An aziridine can fuse with cyclohexanone ring only in *cis*-fashion. This is the case for **1c, 1d, 1e** and **1f**. The other aziridines (**1a, 1b** and **1g**) were identical with the known compounds *cis*-configuration of which has been already confirmed.[7] In NMR spectrum of such a *cis*-aziridine, the coupling constant ($J_{2,3}$) of methine proton has been established to be the order of 6.0 Hz.[14] The coincidence with this value supports further the configuration given to **1a** and **1g** (Table IV).

The Hoch-Campbell reaction products (**2**) are not the objectives in the present study. Therefore, the configuration of them was assigned previsionally on basis of the stereochemical proposal that the reaction arises by approach of the Grignard reagent from less hindered side of the azirine intermediate[15] (Chart 1).

Experimental

All melting and boiling points were uncorrected. IR spectra were recorded with a JASCO DS-701G spectrometer. NMR spectra were obtained with JEOL C-60H spectrometer at 60 MHz and PS-100 spectrometer at 100 MHz using TMS as an internal standard. s=singlet, d=doublet, q=quartet, m=multiplet. Mass spectra were recorded using JMS-01SG mass spectrometer.

Ketoximes (**4**—**13**) prepared according to techniques described in the literatures; dibenzylketoxime (**4**) mp 123—124° (lit.[16] mp 122°), *E*-phenylbenzylketoxime (**5**) mp 97—98° (lit.[10a] mp 98°), *E*-2-benzhydrylcyclohexanone oxime (**6**) mp 141—143° (li.t[6] mp 141—143°), *E*-2-benzoylcyclohexanone oxime (**7**) mp 138—140° (lit.[6] mp 138.5—140°), *E*-2-(1-phenyl)cyclohexylcyclohexanone oxime (**8**) mp 126—128° (lit.[4] mp 127—128°), *E*-propiophenone oxime (**9**) mp 53—54° (lit.[5b] mp 53—54°), 4-methyl-4-phenylpentan-2-one oxime (**10**) mp 60—63° (lit.[6] mp 62—63.5°), cyclohexanone oxime (**11**) mp 88—89° (lit.[17] mp 89°), benzophenone oxime (**12**) mp 141—142° (lit.[18] mp 141—142°) and *Z*-camphor oxime (**13**) mp 117—118° (lit.[19] mp 118—119°).

The Grignard Reaction of Ketoximes (4—13)——General Method: A Grignard reagent was prepared by the usual method from Mg (0.16 mole) and an alkyl halide (0.15 mole) dissolved in abs. ether (75 ml). After the formation of the reagent completed, ether was removed by evaporation as much as possible. To the vessel was added dry toluene (75 ml) and then a dry hot toluene solution (30—50 ml) containing a ketoxime (0.03 mole) dropwise with stirring at refluxing temperature. After addition, reflux was continued for additional 2—3 hr and the mixture was allowed to stand overnight. The mixture was hydrolyzed with sat. aqueous NH_4Cl at 0—10° and the toluene layer was separated and extracted with 10% HCl (400 ml). The HCl extract was made alkaline with 30% aqueous NaOH and the appearing oily layer was extracted with ether, washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on Al_2O_3 (Merck, neutral activity I) or silica gel (Merck, 70—325 mesh), and then by recrystallization or distillation. Results are shown in Table I, II and IV.

N-Phenylcarbamoyl Derivative——A mixture of an aziridine (2 mmole) and phenyl isocyanate (2 mmole) in 30 ml of abs. ether was allowed to stand at room temperature for 24 hr, and the mixture was evaporated

14) A. Hassner and C.C. Heathcock, *Tetrahedron Letters*, **1964**, 1125.
15) G. Alvernhe and A. Laurent, *Bull. Soc. Chim. France*, **1970**, 3304.
16) P.W. Neber and A. Uber, *Ann.*, **467**, 59 (1928).
17) A. Baeyer, *Ann.*, **278**, 88 (1893).
18) A. Lachman, "Organic Synthesis," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, N.Y., 1943, p. 70.
19) M. Nazir, Naeemuddin, I. Ahmed, M.K. Bhatty, and Karimullah, *Pakistan J. Sci. Ind. Res.*, **10**, 13 (1967) [*C.A.*, **68**, 9270 (1968)].

to dryness. The residue was chromatographed on silica gel (Merck, 70—325 mesh), and then recrystallized. Results are shown in Table II.

***p*-Toluenesulfonyl Derivative**——A mixture of an aziridine (2 mmole) and tosyl chloride (3 mmole) in dry pyridine (5 ml) was allowed to stand at room temperature for 24 hr. The mixture was poured into 10% H_2SO_4. The separating oil was extracted with $CHCl_3$, washed with water, dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed on silica gel (Merck, 70—325 mesh). Results are shown in Table II.

The Beckmann Rearrangement of 2-Benzhydrylcyclohexanone oxime (6)——The Formation of 7-Benzhydrylperhydroazepin-2-one: To an acetone (40 ml) solution of the ketoxime (6) (2.0 g) was added 10% aqueous NaOH (5.0 ml) and then a solution of TsCl (1.5 g) in acetone (5.0 ml) under ice-cooling. After allowing to stand overnight, precipitating NaCl was removed by filtration and the filtrate was concentrated *in vacuo* at 40°. The residue was extracted with $CHCl_3$, washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from ether and then from benzene–*n*-hexane to give 1.3 g (67%) of needles, mp 131.5—133.5°. *Anal.* Calcd. for $C_{19}H_{21}ON$: C, 81.68; H, 7.57; N, 5.01. Found: C, 81.72; H, 7.60; N, 5.00. IR ν_{max}^{KBr} cm^{-1}: 3197 (NH), 1668 (C=O). NMR (in CCl_4), δ ppm: 2.34 (2H, m, $C\underline{H}_2CONH$).

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Studies on Anticoccidial Agents. VII.[1] An Improved Synthesis of α^4-Norpyridoxol

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The Diels-Alder reaction of 5-ethoxy-4-methyloxazole with unsymmetrical dienophiles was investigated and it was found that steric interaction during the course of the Diels-Alder reaction of an unsymmetrical dienophile with oxazole affected the structural isomeric distribution of the resulting products. On the basis of the above result, α^4-norpyridoxol has been synthesized by the Dields-Alder reaction of 5-ethoxy-4 methyloxazole with allyl alcohol or its derivatives. With the latter, acid hydrolysis of the adduct was necessary to obtain the title compound.

In the previous papers[3] we stated that α^4-norpyridoxol (I), 4-deoxypyridoxol (II) and their esters had the anticoccidial activity. For determination of the relationship between the structure and activity, some analogous pyridoxols[1,3b,4,5] modified at the 2, 3, 4 and 5 positions have been also synthesized and α^4-norpyridoxol and several ester derivatives were found to be the most desirable compounds.

The preparation of α^4-norpyridoxol (I) has already been reported by Perez-medina, *et al.*,[6] Yoshikawa, *et al.*[7] and us,[3b] and recently Chekhum, *et al.*[8] described a new synthetic

1) Part VI: Y. Morisawa, M. Kataoka, T. Sakamoto, and F. Saito, *Agr. Biol. Chem.*, **40**, 101 (1976).
2) Location: *Hiromachi 1-2-58, Shinagawa-ku, Tokyo.*
3) *a*) Y. Morisawa, M. Kataoka, T. Watanabe, N. Kitano, and T. Matsuzawa. *J. Med. Chem.*, **17**, 1083 (1974); *b*) Y. Morisawa, M. Kataoka, T. Watanabe, N. Kitano, and T. Matsuzawa, *J. Med. Chem.*, **17**, 1235 (1974); *c*) Y. Morisawa, M. Kataoka, and T. Watanabe, *J. Org. Chem.*, **40**, 1051 (1975).
4) M. Kataoka, T. Sakamoto, F. Saito, and Y. Morisawa, *Agr. Biol. Chem.*, **39**, 1283 (1975).
5) Y. Morisawa, M. Kataoka, T. Watanabe, N. Kitano, and T. Matsuzawa, *Agr. Biol. Chem.*, **39**, 1275 (1975).
6) L.A. Perez-Medina, R.P. Mariella, and S.M. McElvain, *J. Am. Chem. Soc.*, **69**, 2574 (1947).
7) T. Yoshikawa, F. Ishikawa, Y. Omura, and T. Naito, *Chem. Pharm. Bull.* (Tokyo), **13**, 973 (1965).
8) V.P. Chekhum, E.N. Struchkova, E.N. Zvonkova, M.I. Struchkova, T.P. Belova, and R.P. Evstigneeva, *Khim. Geterosikl, Soedin* **1974**, 100.