OPTICAL ACTIVATION METHOD FOR RACEMIC α-SUBSTITUTED CARBONYL COMPOUNDS

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The optical activation of racemic α-substituted carbonyl compounds
by the hydrolysis of enamines with optically active α-pipecoline was
reported.   Solvent effect on the optical activation was also examined.

The asymmetric transformations have been reported by many workers.[1]   Generally,
the compounds with an active proton at the asymmetric carbon are suitable for the
asymmetric transformation, but it is difficult to isolate the optically active forms
because of their easiness to racemization.[1]   On the other hand, the compounds with an
inactive proton at the asymmetric carbon are undesirable for their optical activation,
because they are not preferable for the asymmetric transformation.   Such compounds
with an inactive proton at the asymmetric carbon will be able to be activated if they
are converted to some appropriate labile derivatives.   In a previous paper,[2] it was
described that the hydrolysis of the immonium salts of enamines of racemic
α-substituted carbonyl compounds with optically active acids gave the corresponding
optically active carbonyl compounds.   Conversion of the stable α-substituted carbonyl
compounds to the labile immonium salts was a key step in the optical activation.

This paper deals with another method of the optical activation of racemic
α-substituted carbonyl compounds.   As shown in Scheme I, (+)-α-pipecoline enamines of
the racemic compounds were synthesized and hydrolysis of them gave the corresponding
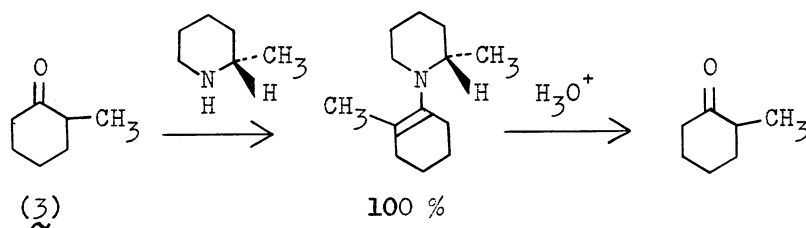optically active carbonyl compounds.

α-Phenylpropionaldehyde (1)
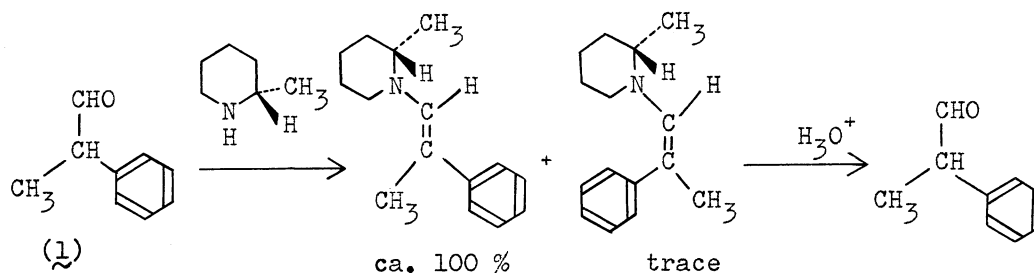
DL-Form   Enamine   Optically Active
                                                             Form

2-Ethylhexanal (2)
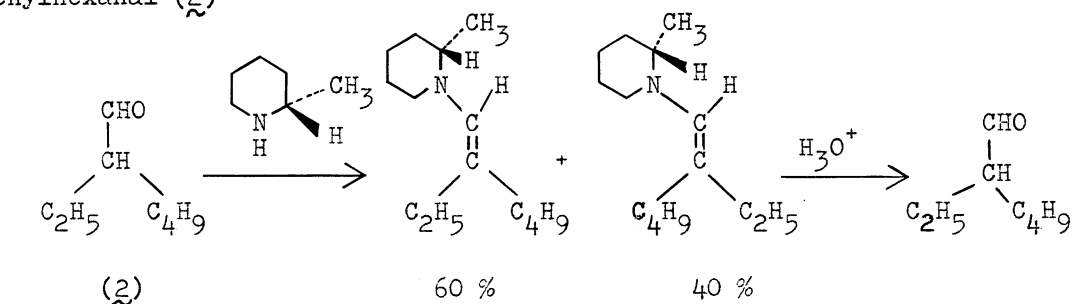
DL-Form   Enamine   Optically Active
                                                             Form

2-Methylcyclohexanone (3)

DL-Form   Enamine   Optically Active
                                                             Form

Racemic α-pipecoline was resolved according to the method of Kostyanovsky et al.[3]

(+)-α-Pipecoline enamines of α-phenylpropionaldehyde(1), 2-ethylhexanal(2) and

2-methylcyclohexanone(3) were prepared by the usual azeotropic procedures using benzene

as the solvent: (+)-α-pipecoline enamine of (1), bp 129-130°C (5 mmHg), 93.1 % yield,

$[\alpha]_D^{23}$ -426°(neat), IR 1638 cm^{-1} $(\nu_{C=C})$, NMR(CDCl$_3$) mixture of two geometrical

isomers, the existence of one isomer being of trace amount, 1.03 (N-C-CH$_3$, d,

J 6.7 Hz), 2.09 (C=C-CH$_3$, s), 6.40 (N-CH=C, s); (+)-α-pipecoline enamine of (2), bp

97-99°C (6 mmHg), 91.9 % yield, $[\alpha]_D^{23}$ -11.6°(neat), IR 1634 cm^{-1} $(\nu_{C=C})$, NMR(CDCl$_3$)

Two geometrical isomers were observed, and the ratio of their existence was 60 : 40;

(+)-α-pipecoline enamine of (3), bp 136°C (8.5 mmHg), 58.0 % yield, $\left[\alpha\right]_D^{23}$ -89°(neat),

$\left[\alpha\right]_D^{23}$ -71.2°(c=5, benzene), IR 1634 cm^{-1} $(\mathcal{V}_{C=C})$, NMR(CDCl$_3$) any peak due to the

vinyl proton was not observed, 0.83 (N-C-CH$_3$, d, J 6.0 Hz), 1.70 (CH$_3$-C=C-N, s). To a

benzene solution of the enamine in an ice bath, an equivalent aqueous hydrochloric acid

was added with vigorous stirring. The reaction was continued until the completion of

the hydrolysis which was confirmed gas-chromatographically. The benzene layer was

separated, washed until the amine was removed completely, and dried. Then the optical

activity was measured. The recovery of the carbonyl compound was determined with a

gas chromatograph. The optical rotations and recoveries of the carbonyl compounds are

summarized in Table I.

Table I Optical Activation of Carbonyl Compounds

	$\left[\alpha\right]_D^{23}$ in benzene		Recovery (%)
(1)	-80.8°	(c=25.0)	91
(2)	-0.098°	(c=3.19)	85
(3)	-2.87°	(c=42.2)	77

The recovery was calculated based on each enamine. The optical rotation of the

optically pure (1) has not been known, but that of a mixture of (1) and acetophenone,

$\alpha_{obs.}$ +75.80°, was reported by Cram.[4] Optical rotations of (2) were determined at

several other wave lengths as well as at 589 nm (D line); $\left[\alpha\right]_D^{23}$ -0.102°, $\left[\alpha\right]_{546}^{23}$ -0.138°,

$\left[\alpha\right]_{435}^{23}$ -0.255°, $\left[\alpha\right]_{365}^{23}$ -0.499°. Those of the optically pure (2) have not been known.

The optical rotation of the optically pure (3) was reported as $\left[\alpha\right]_D^{26}$ +12.01°,

$\left[\alpha\right]_D^{26}$ +14.2° in CHCl$_3$. Calculated from these data, the optical yield might be

estimated about 20 %.

Solvent effect on the optical activation was examined by the hydrolysis of the

enamine of (1) with acidic water in various solvents. As shown in Table II, in

non-polar solvents, such as benzene and dioxane, high optically active (1) was

obtained.

Table II   Solvent Effect on Optical Activation

	Benzene	Dioxane	CHCl$_3$	EtOH	H$_2$O
$\left[\alpha\right]_D^{23}$	-80.8°	-71.6°	-51.1°	-1.12°	-2.07°
	(c=25.0)	(c=10.8)	(c=21.3)	(c=26.8)	(c=17.9)

More details including considerations of the optical activation mechanism
will be published later.

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