Optical Activation of α-Substituted Carbonyl Compounds by Asymmetric Transformation

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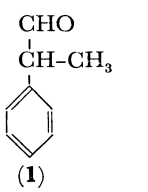
Immonium salts of enamines of racemic α-substituted carbonyl compounds with optically active acids gave, on hydrolysis with water, the corresponding optically active carbonyl compounds. Several reaction conditions were examined and a plausible reaction mechanism, an asymmetric transformation, was proposed. Rates of racemization for the (+)-α-phenylpropionaldehyde were also determined.

The synthesis of optically active carbonyl compounds has been considered of interest in the field of terpenoids, steroids and alkaloids.[1] Resolutions of racemic carbonyl compounds (chemical and biochemical),[2,3] asymmetric destruction,[4] asymmetric synthesis[5] and asymmetric transformation[6] have been reported. In the resolution and asymmetric destruction, the maximum theoretical yield of either pure enantiomer based on the original weight of the racemic material is obviously 50%. In an asymmetric synthesis, there are many restrictions and higher yields in optical activity usually give lower yields of the product. On the other hand, in the asymmetric transformation, although a resolution method, the theoretical yield of one pure enantiomer exceeds 50%. One enantiomer was obtained in nearly 100% yield by this method.[7]

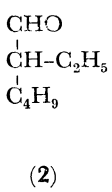
This paper deals with a phenomenon which can be accounted for by the asymmetric transformation. The enamines of racemic α-substituted carbonyl compounds were treated with optically active acids. Hydrolysis of the salts gave the optically active carbonyl compounds. This is a new method to get optically active α-substituted carbonyl compounds from their racemic forms.

Seven carbonyl compounds, α-phenylpropionaldehyde(**1**), 2-ethylhexanal(**2**), 2-methylcyclohexanone(**3**), 2-(2-cyanoethyl)cyclohexanone(**4**), methyl 3-(2-oxocyclohexyl)propionate(**5**), 2-(2-cyanoethyl)cyclopentanone(**6**) and methyl 3-(2-oxocyclopentyl)-propionate(**7**) were examined.

Pyrrolidine, piperidine and 2-methylpiperidine were used as the amine components of the enamines.



(**1**)



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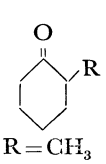
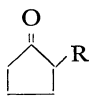


(**3**) R = CH_3
(**4**) R = CH_2CH_2CN
(**5**) R = $CH_2CH_2COOCH_3$



(**6**) R = CH_2CH_2CN
(**7**) R = $CH_2CH_2COOCH_3$

Experimental

Optical activities were determined with a JASCO Digital Automatic Polarimeter Model DIP 181. Gas chromatographic analyses were carried out on a 2 m column of 5% Carbowax 20M on Chromosorb W with a Hitachi Gas Chromatograph, Model K53.

Preparation of Enamines. Enamines of **1**, **2** and **3** were prepared by the usual azeotropic procedures with benzene as a solvent. Pyrrolidine enamines of **4**, **5**, **6** and **7** were synthesized according to the method of Stork *et al.*[8] The enamines obtained were directly subjected to the subsequent procedures without further purification.

Pyrrolidine enamine of **1**: bp 108—109 °C (6.5 mmHg), 91% yield; IR 1635 cm^{-1} ($\nu_{C=C}$). Piperidine enamine of **1**: bp 84—109 °C (7 mmHg), 85.9% yield; Mass *m/e* 201 (M^+, Parent); IR 1637 cm^{-1} ($\nu_{C=C}$); NMR($CDCl_3$) mixture of two geometrical isomers, 1.97 and 2.09 (C=C–CH_3, s), 5.82 and 6.11 (N–CH=C, s). 2-Methylpiperidine enamine of **1**: bp 129—130 °C (5 mmHg), 71.2% yield; Mass *m/e* 215 (M^+), 200 (Parent); IR 1638 cm^{-1} ($\nu_{C=C}$); NMR($CDCl_3$) mixture of two geometrical isomers though one isomer existed in a 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).

Pyrrolidine enamine of **2**: bp 95—96.5 °C (9 mmHg), 92.3% yield; Mass *m/e* 181 (M^+), 138 (Parent); IR 1658 cm^{-1} ($\nu_{C=C}$).

Piperidine enamine of **2**: This was reported by Opitz *et al.*[9] 2-Methylpiperidine enamine of **2**: bp 97—99 °C (6 mmHg), 93.8% yield; Mass *m/e* 209 (M^+), 166 (Parent); IR 1664 cm^{-1} ($\nu_{C=C}$); NMR($CDCl_3$) 5.12 (N–CH=C, s). Pyrrolidine enamine of **3**: This was reported by House and Schellenbaum.[10]

Piperidine enamine of **3**: This was reported by Gurowitz and Jaseph.[11] 2-Methylpiperidine enamine of **3**: bp 136 °C (8.5 mmHg), 65% yield; Mass *m/e* 193 (M^+), 178 (Parent); IR 1634 cm^{-1} ($\nu_{C=C}$): NMR($CDCl_3$) 0.83 (N–C–CH_3, d, *J* 6.0 Hz), 1.70 (CH_3–C–C–N, s).

Salt of Enamines and Their Hydrolysis. The preparation and hydrolysis of the salt of piperidine enamine of **1** with D-10-camphorsulfonic acid (**8**) were carried out as follows.

Acid **8** (0.02 mmol) was added to a benzene solution (30 ml) of **1** (0.02 mmol), and the mixture was stirred until **8** was completely dissolved. Water (15 ml) was added dropwise to the solution in an ice bath with vigorous stirring. The reaction was continued until completion of the hydrolysis which was confirmed by gas chromatography. The benzene layer was separated, successively washed with water, 5% aqueous sodium carbonate and water, dried over anhydrous sodium sulfate; the optical activity was then measured.

Recovery of the carbonyl compound was determined with

a gas chromatograph. The same procedure was applied to the other enamines except for those of **4**, **5**, **6** and **7**. These were subjected to synthesis, after which the solvent (dioxane) was replaced with benzene, and the benzene solutions were then subjected to the same procedure as that for the enamine of **1**. The liberated carbonyl compounds were isolated by vacuum distillation, and the optical rotation of the distillates were measured.

Examination of the Solvent Effect. The immonium salt of **1** with **8** in several solvents was similarly hydrolyzed. The solvent was distilled off *in vacuo* and the residue was dissolved in benzene. The solution was washed and dried as in the case of the enamine of **1** and its optical activity was measured.

Rapid racemization took place when a few drops of 0.05 M KOH alcoholic solution were added to the solution.

Results and Discussions

Hydrolysis of the Immonium Salts. The results of the hydrolysis of the immonium salts are summarized in Table 1. Fairly optically active carbonyl compounds were obtained in all the cases examined. No by-products other than each carbonyl compounds were detected in the benzene solution. As blank experiments, phenylacetaldehyde and cyclohexanone, which have no asymmetric carbons, were examined. The immonium salts of *N*-(2-phenyl-1-propenyl)-piperidine[12] and *N*-(1-cyclohexenyl)piperidine[12] were treated according to the same procedure. Contamination of **8** was found to be negligible. The optical rotations of the α-phenylpropionaldehyde recovered were the most active ones of all, although that of the pure enantiomer is still unknown.

Investigation of Racemization. Optically active **1** was easily racemized with acid or base at 23 °C. The racemization rates in the presence of 12.5% CH_3COOH or $N(C_2H_5)_3$ in benzene, and 0.7% *p*-toluenesulfonic acid or 0.25% D-10-camphorsulfonic acid in benzene–ethanol (1 : 1) were measured. In every case, a plot of log α_0/α *vs.* time gives a straight line. The half-life period for each case was 200.7, 18.8, 21.8 and 19.9 min. Optically active **3** was racemized very quickly with a strong base, such as KOH. On the other hand, the racemization of **8** could not be detected under these conditions. This shows that the observed optical rotations were not due to the contamination of **8**. The rate of racemization of **1** was fairly high in the presence of **8**, which indicates that the real optical activity attained would have been larger than the observed activity.

Table 1.

Carbonyl compounds	Amines	$[\alpha]_D^{23}$	Recovery (%)
1	Piperidine	+16.2 (*c* 3.67)	89.6
	Pyrrolidine	+13.8 (*c* 7.10)	84.1
	2-Methyl-piperidine	+15.9 (*c* 1.15)	92.0
2	Piperidine	+0.22 (*c* 55.1)	82.5
	Pyrrolidine	+0.18 (*c* 20.5)	62.8
	2-Methyl-piperidine	+0.11 (*c* 28.8)	78.0
3	Piperidine	+0.63 (*c* 2.30)	73.1
	Pyrrolidine	+0.39 (*c* 10.8)	88.8
	2-Methyl-piperidine	+0.89 (*c* 20.1)	80.0
4	Pyrrolidine	+0.058 (neat)	51.5
5	Pyrrolidine	+0.085 (neat)	39.1
6	Pyrrolidine	+0.018 (neat)	42.2
7	Pyrrolidine	+0.011 (neat)	38.8
Phenyl-acetaldehyde	Piperidine	+0.000 (*c* 11.5)	80.7
	Pyrrolidine	+0.000 (*c* 22.4)	68.9
Cyclohexanone	Piperidine	+0.000 (*c* 18.1)	62.3
	Pyrrolidine	+0.000 (*c* 57.1)	71.2

The Effect of Acid Component. The piperidine enamine of **1** was treated with each of several optically active acids in benzene solution, and the resulting mixture was hydrolyzed in an ice bath. The rate and the end point of the hydrolysis were measured by gas chromatography. The results are shown in Table 2. The salt with **8** was hydrolyzed rapidly, and gave high active **1**. On the other hand, the rates of hydrolysis of those with the other acids were slow, and the activities of the products were low. This tendency was also observed with other immonium salts. The most suitable acid among the acids examined was **8**. Its strong acidity as well as its steric factor might largely contribute to the introduction of optical activity.

Table 2. Effect of acid component

Acids	Time (min)	$[\alpha]_D^{23}$	Recovery (%)
L-Tartaric acid	80	−0.93 (*c* 7.3)	97.8
D-Camphoric acid	75	+2.61 (*c* 3.4)	53.3
D-Quinic acid	80	+0.56 (*c* 3.2)	29.8
8	35	+16.2 (*c* 3.67)	89.6

Solvent Effect. The immonium salts of the enamines of **1** with **8** were prepared in several solvents and subjected to hydrolysis. The amount of water used for the hydrolysis did not affect the activity. In non-polar aprotic solvents, such as benzene, high optically active **1** was obtained (Table 3). It is known that strong acid components and non-polar solvents are preferable for the stability of immonium salts.[13] The result of the solvent effects as well as the acid components suggests that the stability of an immonium salt is an important factor for the introduction of optical activity.

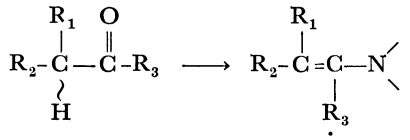
Mechanism of Introduction of Optical Activity. Enamines have been studied and applied by many workers since they were first described by Mannich and Davidsen.[12] The structure of enamines and their salts,[13] and mechanism of the hydrolysis[8] have been subjects of great interest.

It was found that formation of an enamine causes deprotonation from the α-carbon of the carbonyl compound, and formation of the immonium salt causes protonation to the carbon, which is the first step of hydrolysis. We found no evidence of the formation of immonium salts. However, the above mechanism seems to be appropriate to account for the observed stereospecificity. When the enamine of a racemic α-substituted carbonyl compound is

Table 3. Solvent effect on optical activity

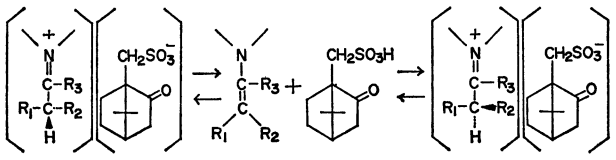
		Benzene	Dioxane	CH_3CN	EtOH	MeOH	H_2O
Piperidine enamine	$[\alpha]_D^{23}$	+16.2 (c 3.67)	+10.0 (c 1.81)	+2.81 (c 2.10)	+0.091 (c 23.3)	+0.100 (c 31.9)	+0.000 (c 50.8)
	Recovery (%)	89.6	28.0	42.3	61.7	78.0	89.7
Pyrrolidine enamine	$[\alpha]_D^{23}$	+18.3 (c 6.77)	+11.8 (c 3.88)	+1.08 (c 11.3)	+0.026 (c 35.5)	+0.082 (c 41.3)	+0.000 (c 67.1)
	Recovery (%)	84.1	32.7	38.1	49.9	58.9	92.3

formed by the removal of the α-hydrogen atom, such an enamine has an enantiotropic plane but no asymmetric α-carbon atom.

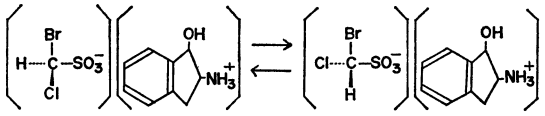


Racemic form Enamine

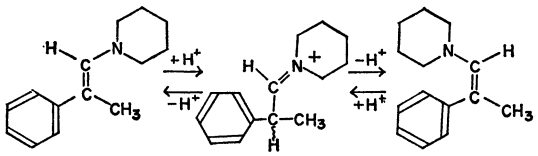
Addition of an optically active acid causes the protonation of the α-carbon to form the immonium salt. The immonium salt would exist as an equilibrium mixture of two diastereomeric isomers. The enamine could be considered to be an intermediate of the isomers in the solution.



Displacement of the balance of the interconversion reactions in favor of one diastereomeric isomer results in an optically active carbonyl compound. The lability of the enamine is shown by the equilibrium of the two geometrical isomers of the piperidine enamine of **1**. The proportion of the two isomers depends on temperature. Attainment of the equilibrium was fairly rapid, and accelerated by the use of some acid.



The mechanism mentioned above seems to be an asymmetric transformation reported by Read and McMath.[14] They reported the equilibrium of the two diastereomeric chlorobromomethanesulfonic acid with an equivalent of active 1-hydroxy-2-aminoindan in a dilute acetone solution, the resulting solution exhibit mutarotation. An examination of the rotation at equilibrium shows that the solution contains 81% of the salt of one isomer and 19% of that of the other one. Attempts to liberate the active acid from the solution were not successful.



From the mechanism of the asymmetric transformation, the factor which determines the degree of optical activity is considered to be the stability of diastereomeric immonium salts.

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