BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 49 (7), 1928—1930 (1976)

# Optical Activation of Racemic α-Substituted Carbonyl Compounds Using Optically Active Amines

Hajime Matsushita, Masao Noguchi, and Sadao Yoshikawa*

*Central Research Institute, The Japan Tobacco and Salt Public Corporation, Umegaoka,*
*Midori-ku, Yokohama, Kanagawa 227*
**Department of Synthetic Chemistry, Faculty of Engineering, The University of*
*Tokyo, Hongo, Bunkyo-ku, Tokyo 113*

(Received February 19, 1976)

Hydrolysis of immonium salts of enamines consisting of optically active amines and racemic α-substituted carbonyl compounds with hydrochloric acid gave the corresponding optically active carbonyl compounds. The NMR spectra showed that the immonium salt is a mixture of two diastereomeric isomers. The mechanism of the optical activation is discussed on the basis of an isotope labeling experiment and the NMR spectra.

Optically active carbonyl compounds with an asymmetric carbon atom at the α-position of the carbonyl group are widespread in nature as terpenoids, steroids and alkaloids, their synthesis being considered of interest by many workers.1) The resolution of racemic carbonyl compounds,2) asymmetric destruction,3) asymmetric synthesis4) and asymmetric transformation5) has been reported. The asymmetric transformation by which racemic compounds are transformed into the corresponding optically active forms has not been much utilized, though nearly 100% yield of one enantiomer has been reported.6) Compounds with an active proton at the asymmetric carbon are suitable for the asymmetric transformation, but it is difficult to isolate their optically active forms since they undergo racemization easily.6) On the other hand, the compounds with an inactive proton at the asymmetric carbon are undesirable for their optical activation. The hydrolysis of the immonium salts of enamines of racemic α-substituted carbonyl compounds with optically active acids give the corresponding optically active carbonyl compounds and the original acids.7) Conversion of the stable α-substituted carbonyl compounds into the labile immonium salts is a key step in the optical activation. This paper deals with another method of optical activation of racemic α-substituted carbonyl compounds. The enamines consisting of racemic α-substituted carbonyl compounds and optically active amines were treated with acid, and hydrolysis of the salts gave the optically active carbonyl compounds. This is a new method to obtain optically active α-substituted carbonyl compounds from their racemic forms.

## Experimental

Optical rotations were determined with a JASCO Digital Automatic Polarimeter Model DIP 181. Gas chromatographic analyses were carried out on a 2 m column of 20% Carbowax 20 M on Cromosorb W with a Hitachi Gas Chromatograph, Model K 53. Nuclear magnetic resonance spectra were obtained with a JNM-PS-100 Spectrometer with tetramethylsilane as an internal standard.

S(+)-*2-Methylpiperidine.* *S*(+)-2-Methylpiperidine was obtained by resolution according to the method of Kostyanovsky *et al.*8)

R(−)-*2-Methylpyrrolidine.* *R*(−)-*O*,*N*-Ditosyl-L-prolinol was prepared according to the method described by Kostyanovsky *et al.*8) Anhydrous benzene (500 ml) and *R*(−)-*O*,*N*-ditosyl-L-prolinol (115 g, 0.28 mol) were placed in a 3 l four-necked round bottom flask equipped with a mechanical stirrer, a reflux condenser and a thermometer. Sodium bis(2-methoxyethoxy)aluminum hydride (700 g in benzene, 3.47 mol) was carefully added with vigorous stirring. The reaction mixture was refluxed and stirred for 5 days. It was then cooled, and ice-cold water was added with vigorous stirring. After separation of the benzene layer, the aqueous layer was made strongly basic with pellets of sodium hydroxide, and extracted with benzene. The separated benzene layer and the extracts were combined and extracted with three 100 ml portions of 6 M hydrochloric acid. The acid solution was made strongly basic with pellets of sodium hydroxide again, and extracted with ether. The ether solution was dried over anhydrous $Na_2SO_4$, and filtered. The solvent was distilled off and the residue was subjected to fractional distillation. All the fractions boiling up to 100 °C were collected (11.3 g, 47.7% yield based on the ditosylprolinol). This crude amine was subjected to the subsequent procedures without further purification.

*Preparation of Enamines.* Enamines of α-phenylpropionaldehyde (**1**), 2-methylcyclohexanone (**2**) and 2-ethylhexanal(**3**) were prepared by the usual azeotropic procedure using benzene as the solvent and purified by distillation. *R*(−)-2-methylpyrrolidine and *S*(+)-2-methylpiperidine were used as amine components of the enamines. *S*(+)-2-Methylpiperidine enamine of **1**: bp 129—130 °C (5 mmHg), 81% yield; MS *m*/*e* 215 ($M^+$), 200 (base); IR 1638 $cm^{-1}$ ($\nu_{C=C}$); NMR ($CDCl_3$) mixture of two geometrical isomers (92: 8 at room temperature), major isomer, 1.03 (N–C–$CH_3$, d, *J*=6.7 Hz), 2.09 (C=C–$CH_3$, s), 6.40 (N–CH=C, s), 7.30 (phenyl, m), minor isomer, 5.81 (N–CH=C, s); $[\alpha]_D^{23}$ −426° (neat). *S*(+)-2-Methylpiperidine enamine of **2**: bp 136 °C (8.5 mmHg), 32% yield; MS *m*/*e* 193 ($M^+$), 178 (base); 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); $[\alpha]_D^{23}$ −89° (neat), $[\alpha]_D^{23}$ −71.2° (*c*=5, benzene). *S*(+)-2-Methylpiperidine enamine of **3**: bp 97—99 °C (6 mmHg), 91.9% yield; MS *m*/*e* 209 ($M^+$), 166 (base); IR 1664 $cm^{-1}$ ($\nu_{C=C}$); NMR ($CDCl_3$) mixture of two geometrical isomers (60: 40 at room temperature), $[\alpha]_D^{23}$ −11.6° (neat). *R*(−)-2-Methylpyrrolidine enamine of **1**: bp 102—130 °C (5.5 mmHg), 76.1% yield; MS *m*/*e* 201 ($M^+$), 186 (base); IR 1631 $cm^{-1}$ ($\nu_{C=C}$); NMR ($CDCl_3$) mixture of two geometrical isomers (89: 11 at room temperature), major isomer, 1.17 (N–C–$CH_3$, d, *J*=6.3 Hz), 2.15 (C=C–$CH_3$, s), 6.40 (N–CH=C, s), 7.3 (phenyl, m), minor isomer, 1.17 (N–C–$CH_3$, d, *J*=6.3 Hz), 2.04 (C=C–$CH_3$, s), 6.11 (N–CH=C, s), 7.17 (phenyl, m); $[\alpha]_D^{23}$ +398° (*c*=2.90, benzene). *R*(−)-2-Methylpyrrolidine enamine of **2**: bp 93.5 °C (7.5 mmHg), 78.7% yield; MS 179 ($M^+$), 164 (base); IR 1638 $cm^{-1}$ ($\nu_{C=C}$);

NMR ($CDCl_3$) mixture of two geometrical isomers (85: 15 at room temperature), major isomer, 0.90 ($CH_3$–CH–C=C, d, $J$=6.0 Hz), 1.08 ($CH_3$–C–N, d, $J$=6.6 Hz), 4.30 ($CH_3$–C$\underline{H}$–C=C, t, $J$=4.0 Hz), minor isomer, 1.66 ($CH_3$–C=C, s); $[\alpha]^{23}_{D}$ +190.5° ($c$=2.31, benzene).

*The Hydrolysis of Enamines.* To a solution of enamine (0.02 mol) in benzene (30 ml) was added an equivalent aqueous hydrochloric acid with vigorous stirring in an ice bath. The reaction was continued until the completion of hydrolysis which was confirmed gas chromatographically. The benzene layer was separated, successively washed with water and 5% aqueous sodium carbonate and water, and dried over anhydrous $Na_2SO_4$, the optical rotation being then measured. The recovery of carbonyl compound was determined with a gas chromatograph. The same results were obtained by another method: Dry HCl gas was bubbled into a benzene solution (50 ml) of enamine (0.02 mol), and the solvent was removed completely under reduced pressure. The residue was dissolved in benzene (30 ml), and to the solution in an ice bath was added water (15 ml) dropwise with vigorous stirring. The subsequent procedure was the same as mentioned above.

## Results and Discussion

*Hydrolysis of Enamines.* The results are summarized in Table 1. The optical rotation of pure **1** is not known. Though the determination of the specific rotation of **1** was attempted by the method of Goering,[9] no pseudocontact-shift differences for enantiomers could be observed in the presence of tris-[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]-europium(III). Cram reported the optical rotation of a mixture of **1** and acetophenone, $\alpha_{obs}$ +75.80°.[10] The optical rotation of the pure **2** was reported to be $[\alpha]^{18}_{D}$ +14.21° ($l$=0.5).[11] Calculating from this value, the optical yields are estimated to be 20.2% (in the case of $S$(+)-2-methylpiperidine) and 6.20% (in the case of $R$(−)-2-methylpyrrolidine). The optical activation of **3** was examined only in the case of $S$(+)-2-methylpiperidine. Optical rotations of the recovered **3** were determined at several other wave lengths as well as at 589 nm (D line): $[\alpha]^{23}_{577}$ −0.102°, $[\alpha]^{23}_{546}$ −0.138°, $[\alpha]^{23}_{435}$ −0.255°, $[\alpha]^{23}_{365}$ −0.499°. From the results in Table 1, six membered ring amine seems to contribute to the optical activation more effectively than the five membered amine. The difference in the ability of the optical activation can be attributed to the difference of the *exo* double bond stability. The higher degree overlapping of the lone pair on the nitrogen atom with the π-orbital of *exo* double bond and more favorable conformation of five membered ring with *exo* double bond seem to make the immonium salt with five membered amine more stable and less reactive than that with six membered amine.[12,13] Greater stability and smaller reactivity of the salt with five membered ring amine would be unfavorable for asymmetric transformation by proton exchange.

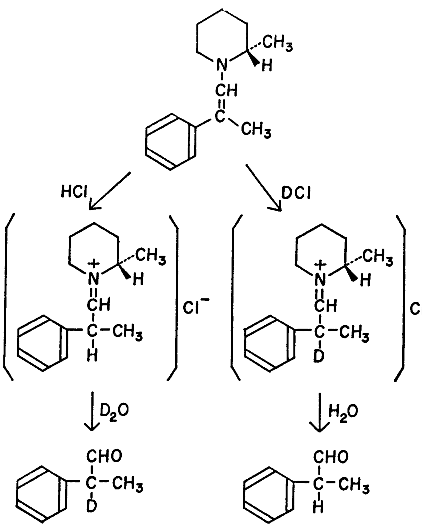
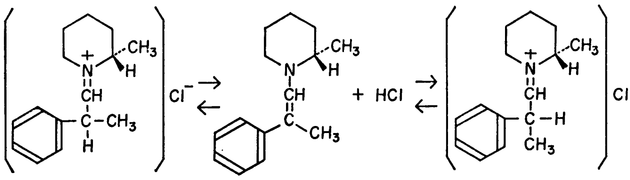


Fig. 1.

*Isotopic Labeling Study.* As shown in Fig. 1, hydrolysis of the immonium salt of HCl and 2-methylpiperidine enamine of **1** in $D_2O$ gave deuterated **1**, but not that of the salt of DCl and the enamine in $H_2O$.

This suggests that the proton exchange at the asymmetric α-carbon of an immonium salt occurs easily. The reversible protonation in favor of one diastereomeric immonium salt results in an optically active **1**. Similar proton exchange reactions *via* enamine were reported by Leonard and Sauers.[14]



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.[7] The mechanism of this optical activation was considered to be the same as the asymmetric transformation reported by Read and McMath.[15] The result of the isotopic labeling study also supports the mechanism.

*NMR Spectra of Enamine and Immonium Salts.* Dry HCl or DCl gas was bubbled into a solution of optically

TABLE 1. OPTICAL ROTATION OF SOME CARBONYL COMPOUNDS RECOVERED FROM THE IMMONIUM SALTS

| Amine component | Carbonyl component | Recovered carbonyl compound $[\alpha]^{23}_{D}$ | Optical yield % | Recovery % |
|---|---|---|---|---|
| $S$(+)-2-Methylpiperidine | **1** | −80.8 ($c$ 25.0) | | 91 |
| | **2** | −2.87 ($c$ 42.2) | 20.2[a] | 77 |
| | **3** | −0.098 ($c$ 3.19) | | 85 |
| $R$(−)-2-Methylpyrrolidine | **1** | +51.6 ($c$ 8.11) | | 71 |
| | **2** | + 0.881 ($c$ 15.5) | 6.20[a] | 60 |

a) Based on reported optically pure **2**, $[\alpha]^{18}_{D}$ +14.21.[11]

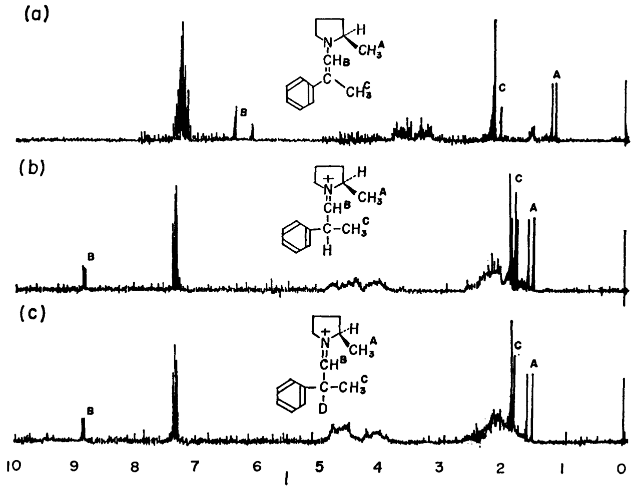
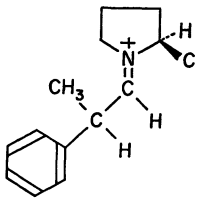
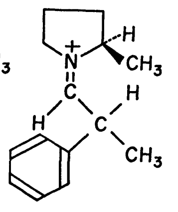


Fig. 2.

active 2-methylpyrrolidine enamine of **1** in $CDCl_3$. The solution has a color varying from initially light yellow to dark-brown at the end. The immonium salt thus prepared was confirmed by NMR spectra. Figure 2 shows NMR spectra of the enamine (a), the immonium salt with HCl (b) and the immonium salt with DCl (c). The existence of two geometrical isomers of the enamine is observed from (a). Their ratio can be obtained by the measurement of peak areas. The spectra of immonium salt, (b) and (c), showed two diastereomeric isomers. Displacement of the balance in favor of one diastereomeric immonium salt can be observed. Possibility of the existence of geometrical isomer (B) can be neglected by consideration of the steric interaction using models (Corey-Pauling-Koltum type and Dreiding type). The mechanism of the optical activation is considered to be an asymmetric, reversible protonation to the enamine and successive hydrolysis of the immonium salt.



(A)



(B)

## References

1) K. Hiroi and S. Yamada, *Chem. Pharm. Bull.*, **23**, 1103 (1975); K. Nagasawa, H. Takahashi, K. Hiroi, and S. Yamada, *Yakugaku Zasshi*, **95**, 33 (1975).

2) J. W. Scott, R. Borer, and G. Saucy, *J. Org. Chem.*, **37**, 1659 (1972); H. Nohira and H. Miura, *Nippon Kagaku Kaishi*, **1975**, 1122; L. M. Kogan, V. E. Gulaya, and I. V. Torgov, *Tetrahedron Lett.*, **1967**, 4673.

3) G. Bredig and K. Fajas, *Chem. Ber.*, **41**, 752 (1908).

4) R. Kuhn, H. E. Driesen, and H. J. Haas, *Justus Liebigs Ann. Chem.*, **718**, 78 (1968); G. Otani and S. Yamada, *Chem. Pharm. Bull.*, **21**, 2130 (1973).

5) Marckwald and A. McKenzie, *Chem. Ber.*, **32**, 2120 (1899).

6) H. Leuchs, *Chem. Ber.*, **54**, 830 (1921).

7) H. Matsushita, M. Noguchi, M. Saburi, and S. Yoshikawa, *Bull. Chem. Soc. Jpn.*, **48**, 3715 (1975).

8) R. G. Kostyanovsky, I. M. Gella, V. I. Markov, and Z. E. Samojlova, *Tetrahedron*, **30**, 39 (1974).

9) H. L. Goering, J. N. Eikenberry, and G. S. Koermer, *J. Am. Chem. Soc.*, **93**, 5913 (1971).

10) D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3883 (1949).

11) G. A. C. Gough, H. Hunter, and J. Kenyon, *J. Chem. Soc.*, **1926**, 2052.

12) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

13) W. D. Gurowitz and M. A. Joseph, *J. Org. Chem.*, **32**, 3289 (1967).

14) N. J. Leonard and R. R. Sauers, *J. Am. Chem. Soc.*, **79**, 6210 (1957).

15) J. Read and A. M. McMath, *J. Chem. Soc.*, **1925**, 1572.