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Unconjugated Chiral Azomethines; Structure of N-Isobutylidene Derivatives of (*S*)-α-Amino Acid Esters

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Unconjugated chiral azomethines, N-isobutylidene derivatives of (*S*)-α-amino acid esters (I—VI) were synthesized. The structures of these compounds were confirmed by the infrared, mass spectrum and nuclear magnetic resonance (NMR) spectra.

The conformations were discussed by the NMR spectra. The characteristic absorption band for the unconjugated chiral azomethine compounds were observed nearly at 240 nm by the circular dichroism spectra.

Keywords——valine ester isobutylidene; alanine ester isobutylidene; chiral azomethine unconjugate; conformation amino acid NMR; configuration amino acid CD; CD azomethine unconjugate

Some azomethine compounds having the asymmetric carbon attached to the nitrogen atom are known as a main step substance in the biosyntheses of alkaloids. This fact stimulated us to synthesize the chiral azomethine compounds by condensing optically active α-amino acid esters with aldehydes. In this paper, we report the preparation of N-isobutylidene α-amino acid esters and also discuss the structure of the products.

The condensations of isobutyraldehyde and methyl isopropyl keton with corresponding esters of L-valine and L-alanine were carried out by the method of Bonnett, *et al.*[2] The results and spectral data of N-isobutylidene α-amino acid esters and their related compounds (I—VI) thus obtained are listed in Table I, II, III, and V.

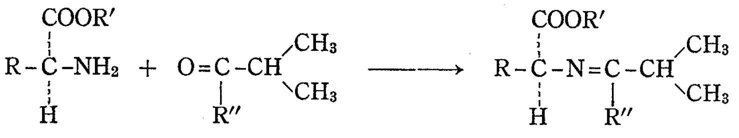

Chart 1

TABLE I. N-Isobutylidene Derivatives of (*S*)-α-Amino Acid Esters (I—VI)

Compounds	R	R′	R″	Yield (%)	bp (°C/mmHg)	IR (cap.) cm^{-1} $\nu_{C=O}$	IR (cap.) cm^{-1} $\nu_{C=N}$
I	$CH(CH_3)_2$	C_2H_5	H	96	83—86/9	1735(s)	1665(m)
II	$CH(CH_3)_2$	CH_3	H	82	81—83/8	1740(s)	1665(m)
III	CH_3	C_2H_5	H	71	59—62/5	1735(s)	1665(m)
IV	CH_3	CH_3	H	60	83—86/10	1740(s)	1665(m)
V	$CH(CH_3)_2$	C_2H_5	CH_3	74	78—82/5	1740(s)	1660(m)
VI	$CH(CH_3)_2$	CH_3	CH_3	71	60—65/2	1740(s)	1660(m)

s: strong m: medium.

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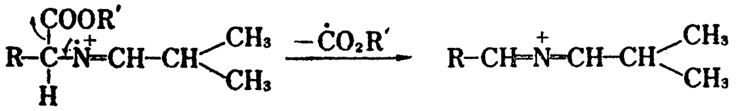
1) Location: *2-4-41, Ebara, Shinagawa, Tokyo.*

2) *a*) Z. Badr, R. Bonnett, T.R. Emerson, and W. Klyne, *J. Chem. Soc.*, **1965**, 4503; *b*) Z. Bade, R. Bonnett, W. Klyne, R.J. Swan, and J. Wood, *J. Chem. Soc.* (*C*), **1966**, 2047.

The infrared (IR) spectra of the reaction products (I—VI) showed the typical absorption band of C=N group at 1660—1665 cm^{-1}, and showed no band that could be assigned to the imino group due to enamine structure.[3]

In the mass (MS) spectra of I—IV, all of the molecular ion peaks (M^+) were observed very weakly, and the prominent peaks appeared each at *m/e* 126 and 98, which are respective 73 ($COOC_2H_5$) and 59 ($COOCH_3$) mass unit less than those of the M^+ peaks.[4] The metastable ion peaks of I—IV were quite in agreement with their calculated values as shown in Table II.

TABLE II. MS Spectral Data of Compounds I—IV

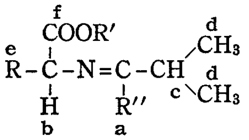


Compounds	M^+ *m/e* (%)	$(M-CO_2R')^+$ *m/e* (%)	m* Calcd.	m* Found
I	199(1.8)	126(100)	79.8	78
II	185(2.4)	126(100)	85.8	85
III	171(3.2)	98(100)	56.7	55
IV	157(3.0)	98(100)	61.1	61

m*: Metastable ion peak.

In the nuclear magnetic resonance (NMR) spectra of I—IV, the signal for azomethine proton (–N=CH–) appeared at 7.48—7.56 ppm as a doublet (J=5.4—5.6 Hz), coupling with the adjacent isopropyl proton. There were no signals for the imino protons atributable to the enamine isomers. Concerning the tautomerism of azomethine system, it has been reported that the contribution of enamine structure is less than 5% at most.[5]

TABLE III. NMR Spectral Data of Compounds I—VI in $CDCl_3$ Solvent (ppm)



Compounds	a	b	c	d	e	f
I	7.48(d) J=5.6 Hz	3.35(d) J=7.3 Hz	2.2—2.7(m)	1.09(d) J=6.8 Hz	0.91(d), 0.87(d) J=6.8 Hz; 2.0—2.5(m)	4.19(q), 1.27(t) J=7.1 Hz
II	7.49(d) J=5.4 Hz	3.39(d) J=7.1 Hz	2.2—2.7(m)	1.09(d) J=6.8 Hz	0.89(d), 0.86(d) J=6.8 Hz; 2.0—2.5(m)	3.71(s)
III	7.56(d) J=5.4 Hz	3.86(q) J=6.8 Hz	2.2—2.7(m)	1.09(d) J=6.8 Hz	1.40(d) J=6.8 Hz	3.86(q), 1.26(t) J=7.1 Hz
IV	7.56(d) J=5.4 Hz	3.88(q) J=6.8 Hz	2.2—2.7(m)	1.09(d) J=6.8 Hz	1.40(d) J=6.8 Hz	3.72(s)
V	1.79(s)	3.77(d) J=7.5 Hz	2.57[a)] J=6.8 Hz	1.08(d) J=6.8 Hz	0.93(d), 0.89(d) J=6.6 Hz; 2.0—2.5(m)	4.16(q), 1.25(t) J=7.2 Hz
VI	1.78(s)	3.81(d) J=7.3 Hz	2.58[a)] J=6.8 Hz	1.09(d) J=7.0 Hz	0.92(d), 0.88(d) J=6.7 Hz; 2.0—2.5(m)	3.70(s)

a) Septet.

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3) D.J. Curran and S. Siggia, "The Chemistry of the Carbon-Nitrogen Double Bond," ed. by S. Patai, Interscience Publishers, Inc., 1970, pp. 149—180.

4) M. Fischer and C. Djerassi, *Chem. Ber.*, **99**, 1541 (1966); E. Schumacher and R. Taubenest, *Helv. Chim. Acta*, **49**, 1455 (1966).

5) D.A. Nelson and J.J. Worman, *Chem. Commun.*, **1966**, 487.

On the *syn-anti* isomerism of C=N bond, the *anti*-form is known to be stable and the energy barriers between the *syn*- and *anti*-forms are 23—24 kcal/mol.[6] Accordingly, the compounds I—IV were postulated the *anti*-form.

On the compounds I—VI, the singals of methyl protons (d) at the isobutylidene group were observed at 1.08—1.09 ppm with doublet peaks (J=6.8—7.0 Hz). The compounds I—IV gave the signals of methine protons (c) at 2.2—2.7 ppm with multiplet peaks, and the compounds V and VI gave a septet peaks at 2.57—2.58 ppm. The vicinal coupling constants of the proton (b) attached to the asymmetric carbon on the compounds I—VI were in the range of 6.8—7.5 Hz. Therefore, it was found that these values were larger than the proton coupling constant of valine, which has been reported as J=4.2—4.4 Hz.[7,8]

The chemical shifts of proton, which located at the asymmetric carbon on the compounds I and II, were observed at 3.35 and 3.39 ppm, respectively. Contrary to this, on III and IV, they were observed at 3.86 and 3.88 ppm, respectively. The chemical shifts of the corresponding protons at N-neopentylidene derivatives of valine and alanine esters were reported as 3.35 and 3.84 ppm, respectively.[2a]

The NMR spectra of the valine derivatives I, II, V, and VI showed four peaks, which are attributed as the signals of two methyl protons at isopropyl group. The chemical shifts of these doublet signals were centered around at 0.89—0.93 and 0.86—0.89 ppm with a difference about 0.03 ppm as depicted in the Fig. 1.

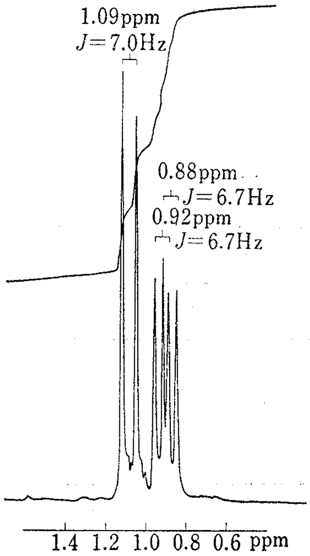
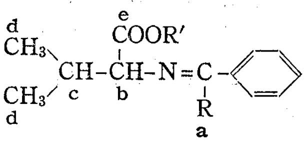


Fig. 1. NMR Spectrum of Compound VI at region of 0.5—1.5 ppm in $CDCl_3$ Solvent

To compare the NMR spectra, we, therefore, prepare the azomethine compounds such as benzylidene and methyl benzylidene derivatives of valine methyl and ethyl esters (VII—X). The results were listed in Table IV.

TABLE IV. NMR Spectral Data of Compounds VII—X in $CDCl_3$ Solvent (ppm)



Compounds	R	R′	a	b	c	d	e
VII	H	C_2H_5	8.23(s)	3.64(d) J=7.3 Hz	2.2—2.6(m)	0.98(d), 0.95(d) J=6.7 Hz	4.20(q), 1.26(t) J=7.1 Hz
VIII	H	CH_3	8.23(s)	3.67(d) J=8.0 Hz	2.2—2.6(m)	0.96(d), 0.94(d) J=6.7 Hz	3.71(s)
IX	CH_3	C_2H_5	2.23(s)	4.03(d) J=7.1 Hz	2.2—2.6(m)	1.00(d) J=6.8 Hz	4.17(q), 1.25(t) J=7.1 Hz
X	CH_3	CH_3	2.24(s)	4.06(d) J=6.8 Hz	2.2—2.6(m)	1.00(d) J=6.8 Hz	3.69(s)

On the compounds VII and VIII, the chemical shifts of protons (b) located at the asymmetric carbon were observed at 3.64 and 3.67 ppm, respectively. On the other hand, the signals of IX and X were observed at 4.03 and 4.06 ppm, respectively.

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6) D. Wurmb-Gerlich, F. Vögtle, A. Mannschreck, and H.A. Staab, *Ann. Chem.*, **708**, 36 (1967).
7) J. Feeney, P.E. Hansen, and G.C.K. Roberts, *Chem. Commun.*, **1974**, 465.
8) S. Fujiwara and Y. Arata, *Bull. Chem. Soc. Jpn.*, **36**, 578 (1963).

By the comparison of the chemical shifts of protons (b) of the azomethine compounds, it may be concluded that the compounds I and II, which the signals are observed at higher field, are situated on the conformation under the influence of a magnetic anisotropy of C=N bond, on the contrary the compounds IX and X take the conformation under the less influence of the magnetic anisotropy.

The two doublet ($J=6.7$ Hz) signals of two methyl protons at isopropyl group on VII and VIII were centered at 0.98, 0.95 ppm, and 0.96, 0.94 ppm, respectively. Contrary to this, on the compounds IX and X, one doublet ($J=6.8$ Hz) signals were centered both at 1.00 ppm that is, the conformation of IX and X were regarded as equivalent to the two methyl groups.

In connection with the above study, we have investigated the configurations of I—IV by circular dichroism (CD) method. It was known that the ultraviolet (UV) spectra unconjugated azomethine compounds showed the absorptions nearly at 240 nm ($\varepsilon=200$) as the $n\rightarrow\pi^*$ transition absorption of C=N bond.9) Among various studies on the CD spectra of chiral azomethine compounds, there is only one report on the unconjugated azomethine, (+)-3-methyl-N-cyclopentylidene *n*-butylamine, by Mason, *et al.*10) On the optical rotatory dispersion (ORD) of unconjugated chiral azomethine, there was a report by Bonnett, *et al.*9) The wave length and the molecular ellipticity ([θ]) of the CD absorption band can be approximated from the medians of wave lengths between the first and second extrema and the molecular amplitude refered to these ORD curve. Then, the CD bands of the chiral azomethine thus calculated are nearly at 240 nm, and [θ] are about 5×10^3.

The UV spectra of I—IV were observed at 216 nm ($\log\varepsilon=2.8$) in *n*-hexane. In methanol, they showed at 201 nm ($\log\varepsilon=2.8$) with 15 nm blue shift. However, in the region of 230—250 nm, we observed hardly discernible shoulder as shown in Fig. 2.

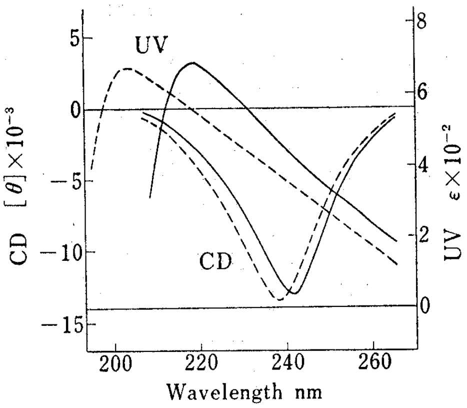

Fig. 2. UV and CD Spectra of Compound I in *n*-Hexane (——) and in Methanol (------)

The CD spectra of I and II showed the clear absorption bands nearly at 240 nm, [θ] about -12×10^3. These bands in methanol showed some nm blue shift compared with that of *n*-hexane.

It can be presumed that the typical band at 240 nm of the CD spectra is attributed as the $n\rightarrow\pi^*$ transition absorption of C=N bond, since the ester group is not placed in the plane of the chromophore N=CH group. In view of the above results, these compounds have torsion

Table V. UV and CD Spectral Data of Compounds I—IV

Compounds	Methanol		*n*-Hexane	
	The UV maxima λ, nm ($\log\varepsilon$)	The CD maxima λ, nm ([θ])	The UV maxima λ, nm ($\log\varepsilon$)	The CD maxima λ, nm ([θ])
I	201(2.81)	237(−13500)	217(2.84)	241(−13000)
II	201(2.80)	237(−12500)	216(2.83)	242(−12000)
III	201(2.83)	230(−6100)	216(2.80)	232(−7200)
IV	201(2.79)	230(−5600)	216(2.79)	232(−6300)

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9) R. Bonnett, N.J. David, J. Hamlin, and P. Smith, *Chem. Ind.*, **1963**, 1836; R. Bonnett and T.R. Emerson, *J. Chem. Soc.*, **1965**, 4508.

10) S.F. Mason and G.W. Vane, *Chem. Commun.*, **1965**, 540.

structure. The torsional direction on the configurations of these compounds, whose the α-amino acid is *levo*-form, are counterclockwise, and this resulted the negative Cotton effect.

The CD spectra of alanine derivatives (III and IV) showed the similar absorption band with the exception of about 10 nm blue shifts and the [θ] values are much smaller compared with those of valine derivatives (I and II). It may be considered that these small [θ] values depend on the racemization during the reaction and on the torsion angle of two chromophores. To verify this assumption, the [θ] of optically active valine and alanine ethyl esters which yielded upon the hydrogenolysis of I and III were measured. The results indicated that the racemization ratio were 6 and 26% for I and III, respectively.

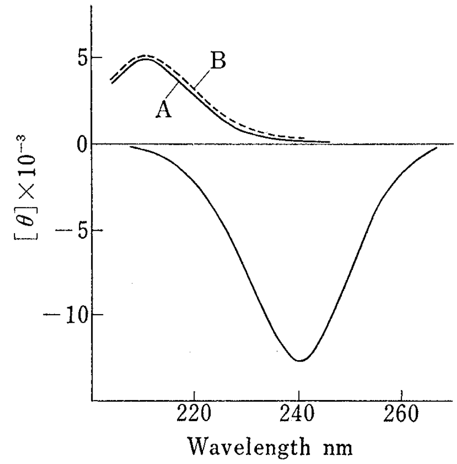
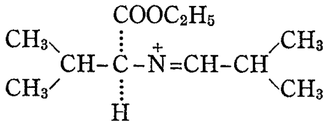
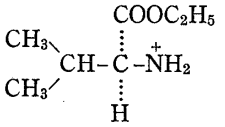


Fig. 3. CD Spectra of Compound I in Methanol (——), on treating with a trace of dil. HCl (——), and the corresponding L-α-Valine Ethyl Ester on treating with a trace of dil. HCl (------)



$\mathrm{(CH_3)_2CH{-}\overset{COOC_2H_5}{\underset{H}{C}}{-}\overset{+}{N}{=}CH{-}CH(CH_3)_2}$

A (——)



$\mathrm{(CH_3)_2CH{-}\overset{COOC_2H_5}{\underset{H}{C}}{-}\overset{+}{N}H_2}$

B (------)

Experimental studies of temperature dependence and solvent effect were attempted on the compound I. On the measurement of CD spectrum of I in *trans*-decaline, even the temperature rised to 100°, the band nearly at 240 nm did not change at all.

This characteristic band was not altered in methanol with a mild alkaline conditions. But under the acidic conditions with a trace of hydrochloric acid, this band disappeared completely and a new band was clearly observed at 211 nm, [θ]+5.1×10^3, as shown in Fig. 3. This new band should be assigned to the n→π* transition absorption of the ester group, because of the UV spectra are known to be observed nearly at 210 nm as ester group.[11] On the measurement of (*S*)-α-valine ethyl ester in methanol with a trace of hydrochloric acid, the absorption band at 212 nm, [θ]+5.2×10^3 was observed, and this spectra coincided well with that of compound I. Hence, it may be concluded that the bands nearly at 240 nm of the CD spectra are the characteristic absorption for the unconjugated chiral azomethine compounds having the asymmetric carbon attached to the nitrogen atom.

Experimental

The boiling points were uncorrected. The IR spectra were recorded with a Hitachi Model-215, MS spectra with a Hitachi RMS-4, and UV spectra with a Hitachi Model-323 instrument. The NMR spectra in $CDCl_3$ were run on a Jeol JNM-FX-100 spectrometer using tetramethylsilane as an internal standard and given in δ-unit. The CD spectra were measured with a Jasco J-40 spectropolarimeter using 0.1—0.2 cm cell. The sample concentrations were 0.1—0.5 g/100 ml, and this instrument was calibrated with *d*-camphorsulfonic acid as a standard.

Compounds——The specific rotations ($[\alpha]_D$) of L-valine and L-alanine used in this experiments were measured at 24—28°. Then, +26.2 (c=2.03, 5 N HCl aq.) and +13.5 (c=2.06, 5 N HCl aq.) were observed, respectively, and the optical purity of these compounds were obtained 98 and 96% by the calculation for $[\alpha]_D$ of the literature.[12]

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11) W.D. Closson and P. Haug, *J. Am. Chem. Soc.*, **86**, 2384 (1964).

12) M.C. Otey, J.P. Greenstein, M. Winitz, and S.M. Birnbaum, *J. Am. Chem. Soc.*, 77, 3112 (1955).

The α-amino acid esters were synthesized in the usual way. The CD absorption bands of L-valine and L-alanine ethyl ester were measured in the methanol with a trace of hydrochloric acid, and the respective results of 212 nm, $[\theta]$ $+5.2\times10^3$ and 208 nm, $[\theta]$ $+4.9\times10^3$ were observed.

General Procedure for the Preparation of N-Isobutylidene Derivatives of (*S*)-α-Amino Acid Esters (I—IV)——Isobutyraldehyde (0.048 mol) was added to L-α-amino acid ester (0.04 mol) with stirring at 0°. After the reaction for 1.5 hr, *n*-hexane (*ca.* 30 ml) was added to the reaction mixture, and the solution was dried over anhydrous $MgSO_4$. The solvent was removed, and the residual oil was distilled *in vacuo* to yield colorless liquid. The distillation temperature and the yield are given in Table I.

N-Pentylidene Derivatives of (*S*)-α-Valine Esters (V—VI)——Methyl isopropyl ketone (0.04 mol) and L-valine ester (0.02 mol) were dissolved in anhydrous benzene (*ca.* 30 ml), and the mixture was refluxed for 72 hr in a flask fitted with a Soxhlet extractor containing calcium chloride. After evaporation of the solvent, the residual oil was distilled *in vacuo* to yield colorless liquid.

Hydrogenolysis of N-Isobutylidene (*S*)-α-Valine Ethyl Ester (I)——I (2.9 g) was dissolved in 40 ml of EtOH, dil. HCl (1 ml), and 10% Pd–C (200 mg) were added to the solution. The mixture was shaken in hydrogen at room temperature and atmospheric pressure. After the absorption of H_2 (2 mol) ceased, the catalyst was filtered off and the solvent was evaporated. The residue was taken in NH_3 alkaline solution and extracted with ethyl acetate. After the solvent was removed, the residual oil distilled *in vacuo*, and 1.5 g of colorless oil of bp 65—68° (8 mmHg) was obtained. This compound was identical with valine ethyl ester by the IR spectrum. The absorption of 212 nm, $[\theta]+4.9\times10^3$ was observed by the CD spectrum.

Hydrogenolysis of N-Isobutylidene (*S*)-α-Alanine Ethyl Ester (III)——III (2.7 g) was dissolved in 30 ml of EtOH, dil. HCl (1 ml), and 10% Pd–C (200 mg) were added to the solution. The mixture was worked up similarly as above, and 0.9 g of colorless oil bp 73—78° (10 mmHg) was obtained. This compound was identical with alanine ethyl ester by the IR spectrum. The absorption of 208 nm, $[\theta]+3.6\times10^3$ was obtained by the CD spectrum.