[Chem. Pharm. Bull. 18(1) 61—74 (1970)]

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Studies on optically Active Amino Acids. XVIII.[1] Studies on α-Methyl-α-amino Acids. XIV.[1] Several Optical Properties of α-Methyl-α-amino Acids[2]

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Several optical properties of α-methyl-α-amino acids (I), whose absolute configurations have already been established in our laboratory, were investigated, and compared with those of protein derived L-amino acids (II).

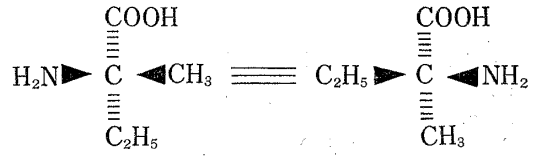
On N-dithiocarbethoxy α-methyl-α-amino acids (III) with the same absolute configuration, the opposite ORDand CD curves were observed in the same solvent. Moreover, changes of direction of ORD and CD curves were not found by changing the solvent. These results were clearly different from those obtained on N-dithiocarbethoxy L-amino acids (IV).

Examinations of Clough-Lutz-Jirgensons rule on I do not exhibit good relationships between absolute configurations and their positive values of $[M]_D^{HCl}-[M]_D^{H_2O}$. This reuslt was also different from that reported on II. However, hydantoin derivatives of I with (*S*)-configuration, showed large negative rotations with one exception, the same as those of II.

From these studies, it has become apparent that the hydantoin rule is most useful for the assignment of absolute configuration of I.

Relationships between absolute configurations of optically active α-methyl-α-amino acids (I) and signs of their circular dichroism (CD) was studied in a previous paper.[1] However, no general rule was found for results observed on protein derived optically active L-amino acids (II).[4]

As previously mentioned,[1] α-methyl-α-amino acids are interesting from a stereochemical point of view, as, it is evident that (+) isovaline, for instance, can be assigned either an L-or D-configuration, depending on whether it is considered a derivative of L-butyrine or D-alanine. Generally speaking, α-methyl-α-amino acids are composed of both characters of D- and L-configurations. Thus, investigation of the optical properties of α-methyl-α-amino acids, as compared with protein derived L-amino acids, is of interest.

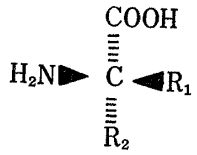


L-α-methylbutyrine D-α-ethylalanine

(+)-isovaline

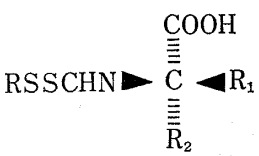
The Absolute Configuration of (+)-Isovaline

1) Part XVII and Part XIII: S. Yamada, K. Achiwa, S. Terashima, H. Mizuno, N. Takamura, and M. Legrand, *Chem. Pharm. Bull.* (Tokyo), **17**, 2608 (1969).
2) Presented at the 87th Annual Meeting of the Pharmaceutical Society of Japan, April 1967, Kyoto.
3) Location: *Hongo, Bunkyo-ku, Tokyo.*
4) Ordinary L-amino acid shows a positive Cotton effect on ORD and positive maximum on CD curves. J.P. Jennings, W. Klyne, and P.M. Scope, *J. Chem. Soc.*, **1965**, 294; M. Legrand and R. Viennet, *Bull. Soc. Chim. France.*, **1965**, 679.



I : $R_1=CH_3$; R_2=Alkyl, Aryl
II : $R_1=H$; R_2=Alkyl, Aryl

a : $R_2=CH_3-$
b : $R_2=C_2H_5-$
c : $R_2=HOCH_2-$
d : $R_2=CH_2=CH-$
e : $R_2=HOOCCH_2-$
f : $R_2=HOCH_2CH_2-$



III : $R_1=CH_3$; R_2=Alkyl, Aryl
IV : $R_1=H$; R_2=Alkyl, Aryl

g : $R_2=C_6H_5-$
h : $R_2=C_6H_5CH_2-$
i : $R_2=C_6H_5CH_2OCH_2CH_2-$
j : $R_2=C_6H_5SCH_2CH_2-$
k : $R_2=3,4-(MeO)_2C_6H_3CH_2-$
l : $R_2=3,4-(HO)_2C_6H_3CH_2-$

Optical rotatory dispersion (ORD) and circular dichroism (CD) of N-dithiocarbethoxy derivatives (III) of I,[5,6] the Clough–Lutz–Jirgensons rule,[7a] and the hydantoin rule[7b] for α-amino acids were examined for Ib-1, whose absolute configurations had been established in our laboratory,[8] to explore the relationship between optical properties and absolute configurations of these amino acids.

Table I. CD Data of (*S*)-N-Dithiocarbethoxy α-Methyl-α-amino Acids (III) and Their Cyclohexylamine Salts

Solv.	IIIb[a] ($R_2=C_2H_5$)				IIIg[a] ($R_2=C_6H_5$)			
	Free acid		Cyclohexylamine salt		Free acid		Cyclohexylamine salt	
	λ_{max}	$[\theta]$	λ_{max}	$[\theta]$	λ_{max}	$[\theta]$	λ_{max}	$[\theta]$
H_2O			326	−390			332	−2980
CH_3OH	340	− 35	347	−550	352	−2100	348	−3120
Dioxane	337	−112			351	−3220		
Benzene	355	−694			360	−2400		
$CHCl_3$	351	−805			356	−2760		

Solv.	IIIh[a] ($R_2=C_6H_5CH_2$)				IIIk ($R_2=3,4-(MeO)_2C_6H_3CH_2$)			
	Free acid		Cyclohexylamine salt		Free acid		Cyclohexylamine salt[b]	
	λ_{max}	$[\theta]$	λ_{max}	$[\theta]$	λ_{max}	$[\theta]$	λ_{max}	$[\theta]$
H_2O			336	+2400			334	+3060
CH_3OH	334	+2390	342	+2200	341	+3320	339	+2300
Dioxane	384	+3640			348	+4430		
Benzene	352	+1680			350	+2090		
$CHCl_3$	350	+1770			349	+1790		

a) Measurements were carried out using (*R*)-isomer. *b*) This salt contains one crystal of water.

5) *a*) B. Sjöberg, A. Fredga, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 5002 (1959); *b*) C. Djerassi, H. Wolf, and E. Bunnenberg, *ibid.*, **84**, 4552 (1965); *c*) C. Djerassi, K. Undheim, R.C. Sheppard, W.G. Terry, and B. Sjöberg, *Acta Chem. Scand.*, **15**, 903 (1961).
6) S. Yamada, K. Ishikawa, and K. Achiwa, *Chem. Pharm. Bull.* (Tokyo), **13**, 892 (1965).
7) J.P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, *a*) p. 83 and *b*) p. 94.
8) The absolute configurations of I used in this report were established in the following literature: *a*) S. Yamada, K. Achiwa, *Chem. Pharm. Bull.* (Tokyo), **14**, 537 (1966); *b*) S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 572 (1966); *c*) *Idem*, *ibid.*, **14**, 579 (1966); *d*) *Idem*, *ibid.*, **13**, 1399 (1965); *e*) *Idem*, *ibid.*, **14**, 1138 (1966); *f*) H. Mizuno, S. Terashima, K. Achiwa, and S. Yamada, *ibid.*, **15**, 1749 (1967); *g*) N. Takamura, S. Terashima, K. Achiwa, and S. Yamada, *ibid.*, **15**, 1776 (1967).

ORD and CD of N-Dithiocarbethoxy α-Methyl-α-amino Acids

To determine absolute configurations of α-amino acids, measurement of the ORD and CD curves of their N-dithiocarbethoxy derivatives (IV) in a wave length range of more than 250 mμ has been recommended, with no exception as an excellent method.[5] However, re-examination of this method[6] by changing the solvents used in ORD and CD measurements, showed that the Cotton Effects and CD curves were affected seriously by the solvents used. Successive solvent changes from methanol, dioxane, benzene, and chloroform generally shifted the Cotton effect sign of the ORD and CD curves, observed for IV, from positive to negative.

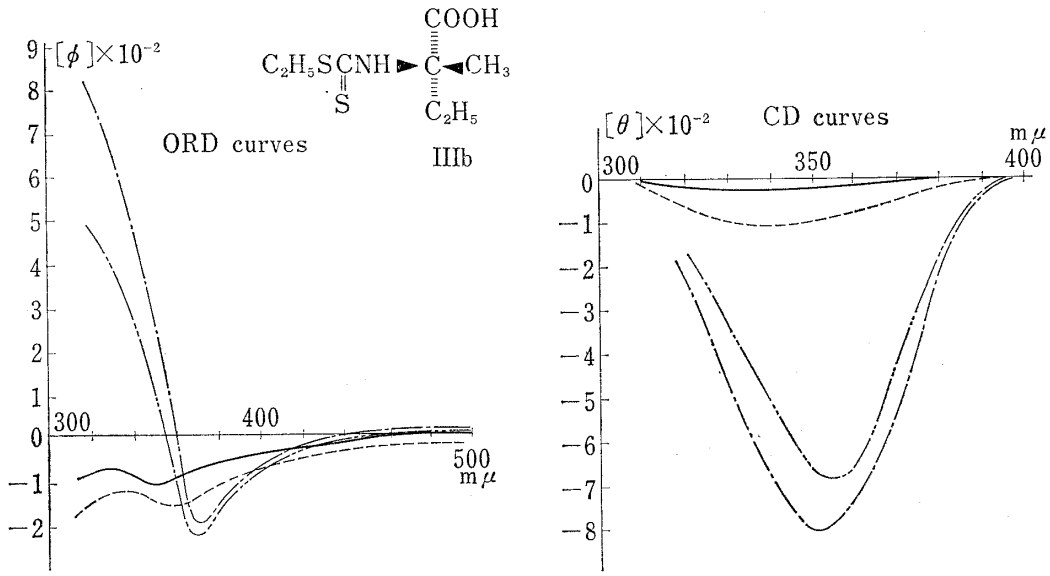


Fig. 1. ORD and CD Curves of (*S*)-N-Dithiocarbethoxy Isovaline (IIIb)

——— : in CH_3OH — — — : in $CHCl_3$ (1% EtOH)

------- : in dioxane ——— : in benzene

(*R*)-Isomer was used for measurements.

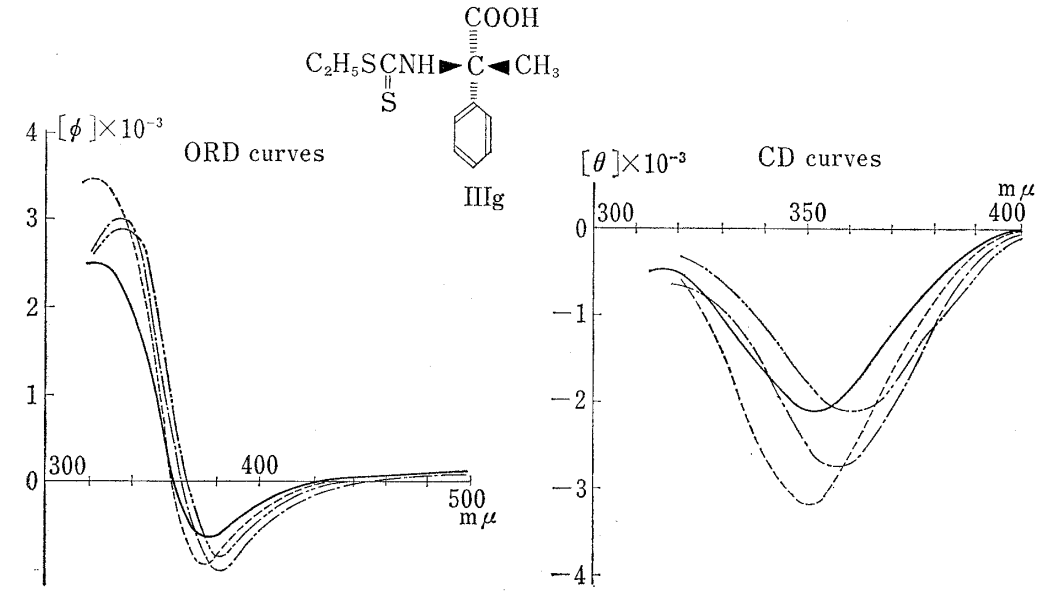


Fig. 2. ORD and CD curves of (*S*)-N-Dithiocarbethoxy α-Methylphenylglycine (IIIg)

——— : in CH_3OH — — — : in $CHCl_3$ (1% EtOH)

------- : in dioxane ——— : in benzene

(*R*)-Isomer was used for measurements.

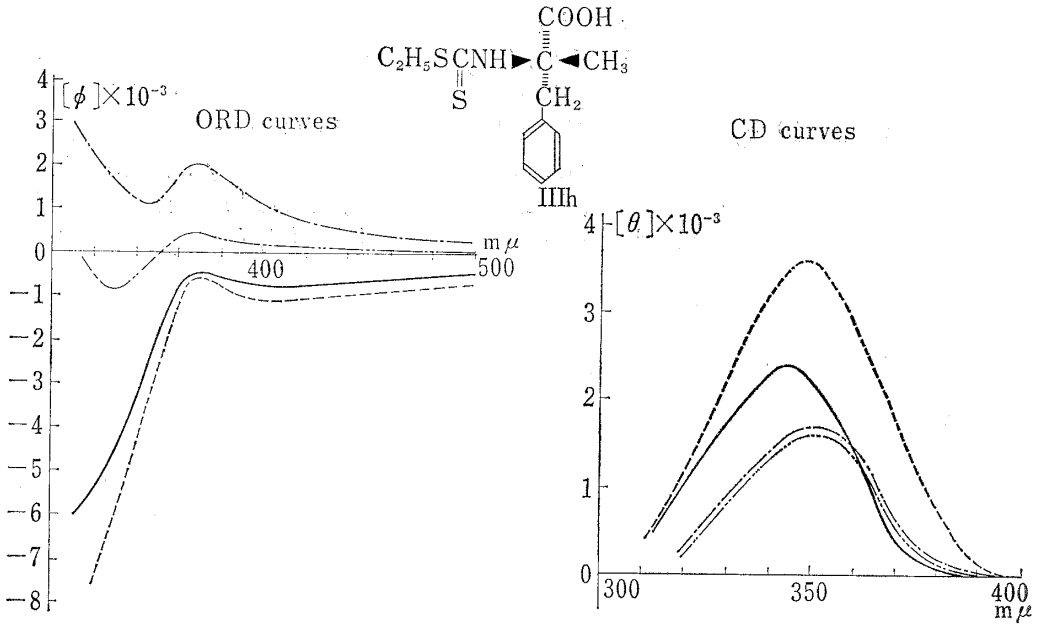
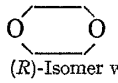
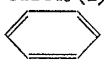


Fig. 3. ORD and CD Curves of (*S*)-N-Dithiocarbethoxy α-Methylphenylalanine (IIIh)

——— : in CH_3OH — — — : in $CHCl_3$ (1% EtOH)

-------- : in  ——— : in 

(*R*)-Isomer was used for measurements.

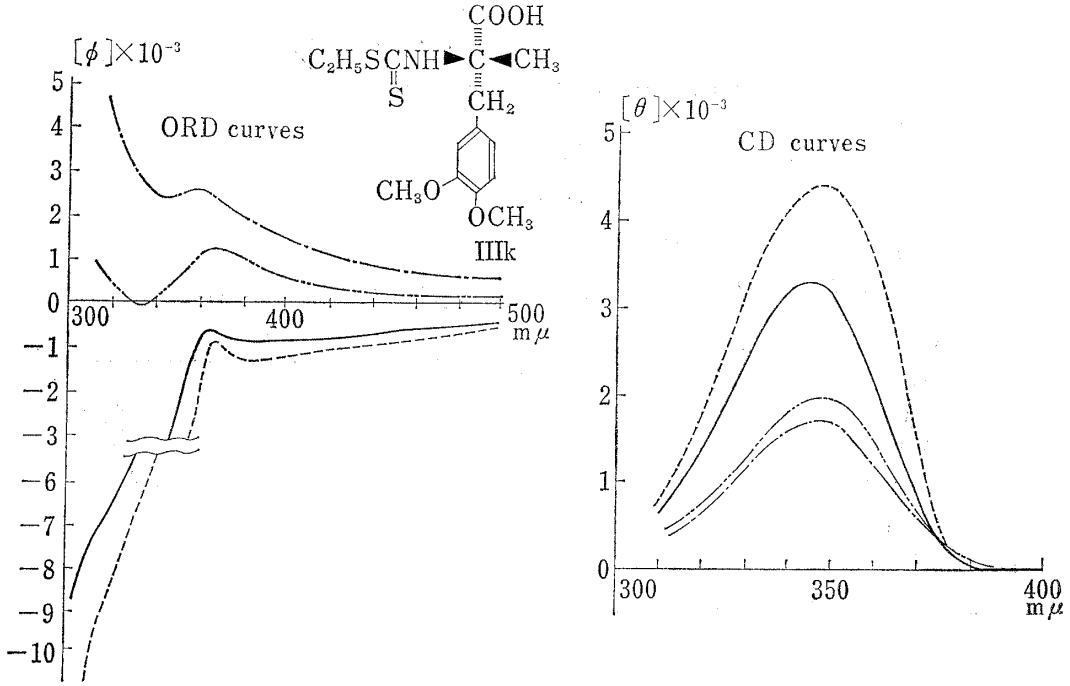
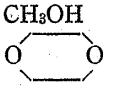
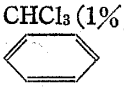


Fig. 4. ORD and CD Curves of (*S*)-N-Dithiocarbethoxy α-Methyl-β-(3,4-dimethoxyphenyl)alanine (IIIk)

——— : in CH_3OH — — — : in $CHCl_3$ (1% EtOH)

-------- : in  ——— : in 

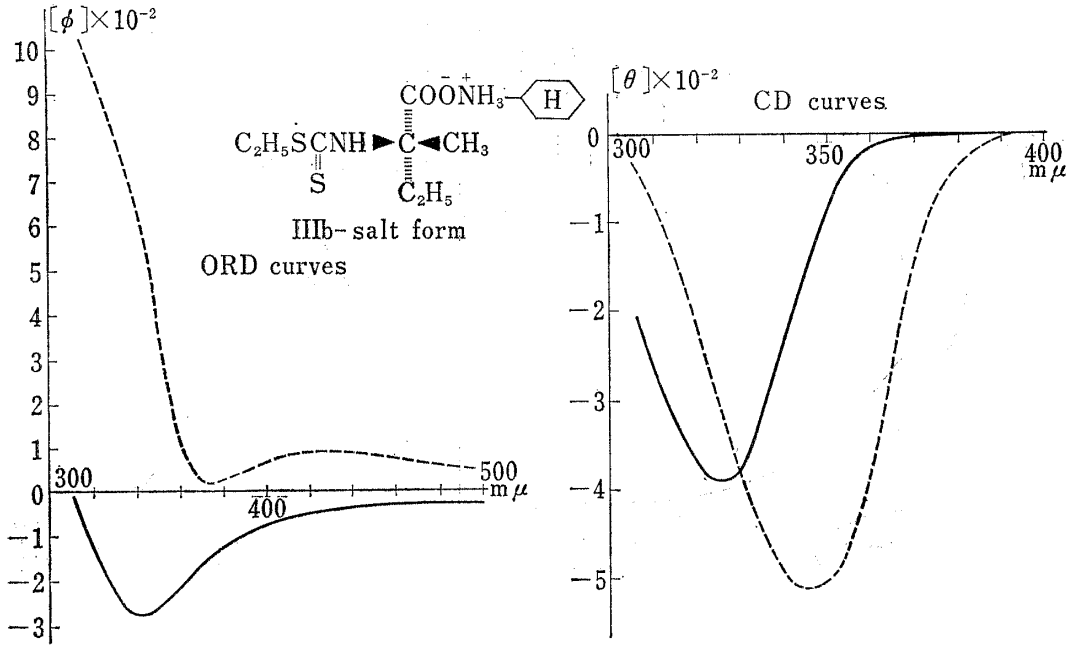


Fig. 5. ORD and CD Curves of Cyclohexylamine Salt of (*S*)-N-Dithiocarbethoxy Isovaline

———: in H_2O ---------- : in CH_3OH

(*R*)-Isomer was used for measurements.

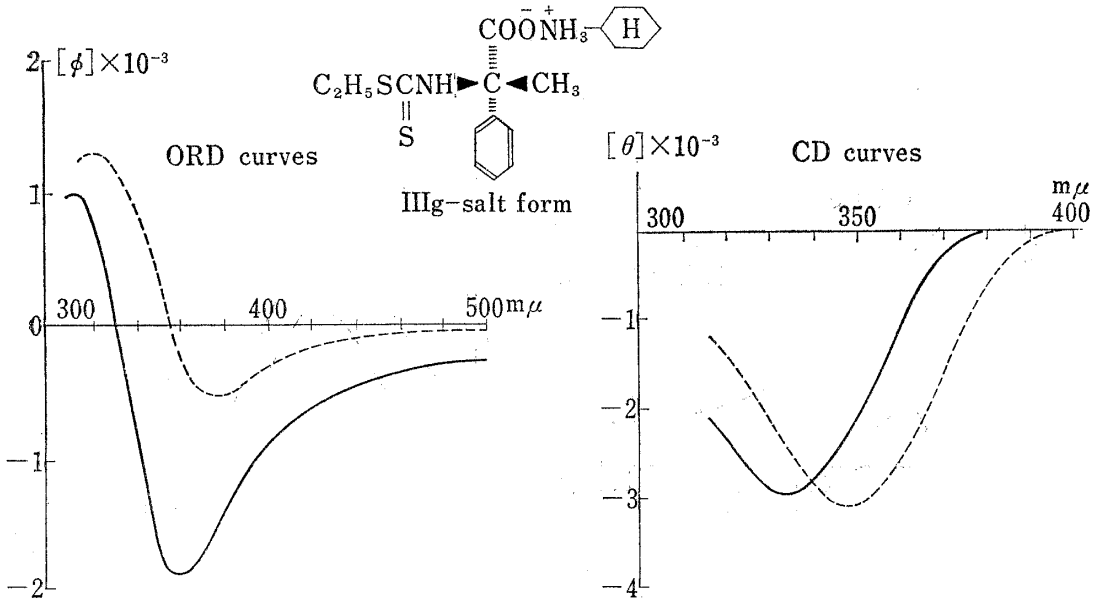


Fig. 6. ORD and CD Curves of Cyclohexylamine Salt of (*S*)-N-Dithiocarbethoxy α-Methylphenylglycine

———: in H_2O ----------: in CH_3OH

(*R*)-Isomer was used for measurements.

Moreover, all the ORD and CD curves of the amine salt of IV which were measured, showed positive Cotton effects and positive CD maxima when measured in water.[9]

The objectives of this study were to discover whether or not the same solvent effects as described above were observed for III and to determine the absolute configuration of III. Examinations were performed using N-dithiocarbethoxy derivatives (IIIb, g, h, k) of isovaline

9) S. Yamada, K. Ishikawa, and K. Achiwa, in preparation.

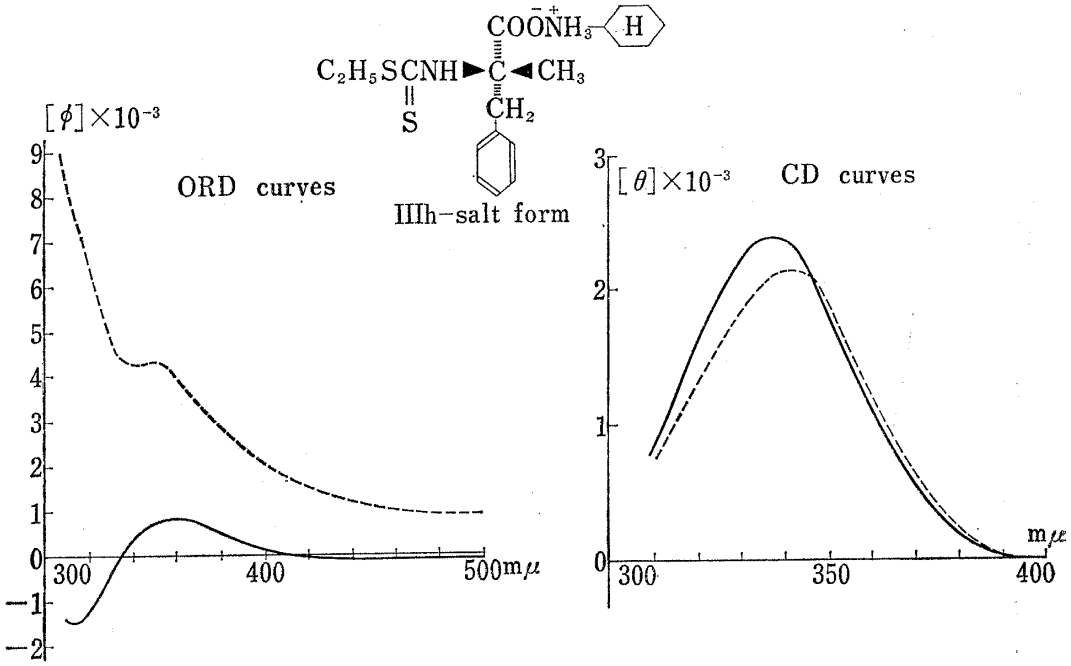


Fig. 7. ORD and CD Curves of Cyclohexylamine Salt of (*S*)-N-Dithiocarbethoxy α-Methylphenylalanine

————: in H_2O ----------: in CH_3OH
(*R*)-Isomer was used for measurements.

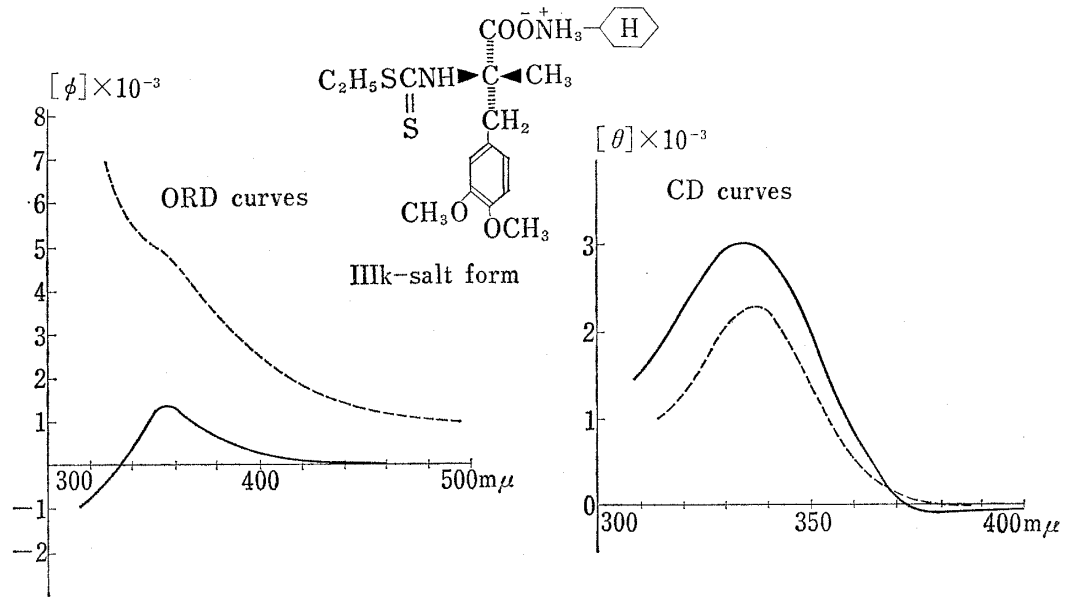


Fig. 8. ORD and CD Curves of Cyclohexylamine Salt of (*S*)-N-Dithiocarbethoxy α-Methyl-β-(3,4-dimethoxyphenyl)alanine

————: in H_2O ----------: in CH_3OH

(Ib),[8a] α-methylphenylglycine (Ig),[8f] α-methylphenylalanine (Ih),[8b,e] and α-methyl-β-(3,4-dimethoxyphenyl)alanine (Ik).[8b,c,d]

The results of ORD and CD measurements from these compounds are shown in Table II and Figure 1—8.

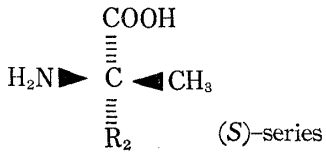
From these data, IIIb and IIIg showed negative Cotton effects in every solvent used when measurements were performed either in free acid form (Fig. 1 and 2) or in salt form as cyclohexylamine salt (Fig. 5 and 6). These negative Cotton effects are substantiated by negative CD curves which are centered around the 350 mμ absorption band. For IIIh and IIIk and their

cyclohexylamine salts, which have the same absolute configuration as IIIb and IIIg, the reverse results were obtained. Their compounds of free acid form and salt form always showed a positive Cotton effect and the corresponding positive CD maximum in the same solvents. Though the absolute configuration belonged to the same series, the opposite ORD and CD curves were observed in the same solvent. Magnitudes of ORD and CD curves changed slightly but changing direction of ORD and CD curves, was not observed for any α-methyl-α-amino acid by changing the solvent. These results differ from results indicating that N-dithiocarbethoxy-L-alanine (IVa) and N-dithiocarbethoxy-L-phenylalanine (IVh) showed positive Cotton effects and corresponding CD maxima in methanol, in contrast to negative effects and negative maxima CD in chloroform.[10] These differences in ORD and CD measurements, by changing the α-hydrogen of α-amino acids to the α-methyl group, cannot be explained by depending on the solvation or conformation in solution. From these data, it is dangerous to determine the absolute configuration of I using the ORD or CD curves of III.

Clough-Lutz-Jirgensons Rule on α-Methyl-α-amino Acids[11]

Applying the Clough-Lutz-Jirgensons rule to many α-amino acids shows that a good relationship can be observed between the L-(*S*-)-configuration of II and its positive value of $[M]_D^{HCl}-[M]_D^{H_2O}$. One representative exception to this is (+)isovaline.[7a] The scope and limitation of this rule for the determination of absolute configuration of α-methyl-α-amino acids was investigated. This rule had already been tested with amino acids, such as α-methylserine[7a,12] α-ethylserine,[12] and α-methyl-β-(3,4-dihydroxyphenyl)alanine[13] (α-methyl-DOPA). However, absolute configurations of these amino acids were not unequivocally determined. We reexamined the $[M]_D$ values in 1N hydrochloric acid and in water for all α-methyl-α-amino

Table II. Molecular Rotations of (*S*)-α-Methyl-α-amino Acids (I) measured in 1N HCl and H_2O[a]



(*S*)-series

Compds.	R_2	$[M]_D$ (1N HCl)[b]	$[M]_D$ (H_2O)[b]	$[M]_D$ (1N HCl)−$[M]_D$(H_2O)
Ib	C_2H_5–	+ 5.7°	+ 13.8°	− 8.1°
Ic	$HOCH_2$–	+ 5.7°	+ 6.0°	− 0.3°
Id	CH_2=CH–	+ 40.0°	+ 39.6°	+ 0.4°
Ie	$HOOCCH_2$–	+ 80.4°	+ 80.4°	0.0°
If	$HOCH_2CH_2$–	− 7.7°	− 20.7°	+13.0°
Ig	C_6H_5–[c]	+143°	+126°	+17.0°
Ih	$C_6H_5CH_2$–[d]	0.0°	− 34.8°	+34.8°
Ii	$C_6H_5CH_2OCH_2CH_2$–	+ 5.4°	− 38.6°	+44.0°
Ij	$C_6H_5SCH_2CH_2$–	+ 67.5°	0.0	+67.5°
Ik	3,4-$(MeO)_2C_6H_3CH_2$–[d]	+ 6.0°	− 27.8°	+33.8°
Il	3,4-$(HO)_2C_6H_3CH_2$–	− 3.2°	− 35.9°	+32.7°

a) Optical rotations were calculated from ORD charts.
b) c=0.2—0.9, temp. 11—28.5
c) This sample was not optically pure.
d) Measurements were carried out using (*R*)-isomer.

10) Part of these results was reported in ref. 6) as N-dithiocarbethoxy-L-phenylalanine in preparation.
11) A part of the results has been a subject of the preliminary communication (S. Yamada, S. Terashima, K. Achiwa, *Chem. Pharm. Bull.* (Tokyo), **13**, 227 (1965)).
12) E.M. Wilson and E.E. Snell, *J. Biol. Chem.*, **237**, 3180 (1962).
13) E.M. Tristram, J. tenBrocke, D.E. Reinhold, M. Sletzinger, and D.E. Williams, *J. Org. Chem.*, **29**, 2053 (1964).

acids, Ib-Il, which we synthesized and whose absolute configurations were established in our laboratory[8] including the tested amino acids mentioned above. Results are shown in Table II. For $[M]_D^{1N\ HCl}-[M]_D^{H_2O}$ values, note that only (*S*)(+)-isovaline (Ib) exhibited a negative value, as reported.[7a] Each of three amino acids, Ic, Id and Ie, possessed practically zero value, the rest showed positive rotations. This suggests that if the effective bulkiness of the R_2 group is far larger than the methyl group, the $[M]_D^{1N\ HCl}-[M]_D^{H_2O}$ value of I seems to be qualitatively positive, so far as has been tested. Some uncertainty exists as to how to utilize this tendency for the determination of absolute configuration of I.

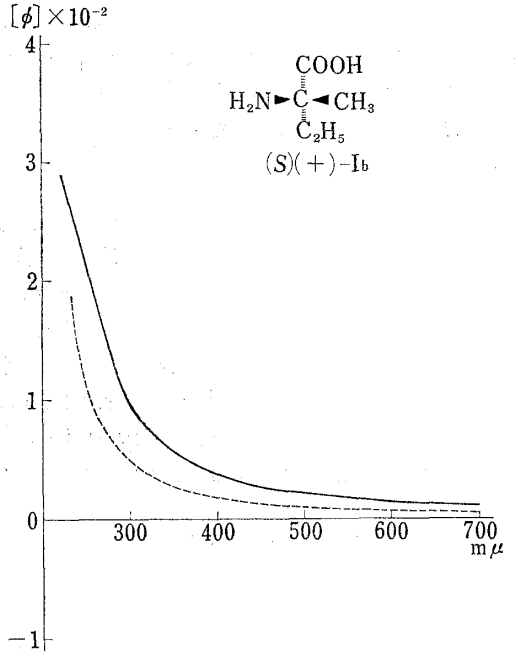


Fig. 9. ORD Curves of (*S*)(+)-Isovaline ((*S*)(+)-Ib)

————: in H_2O

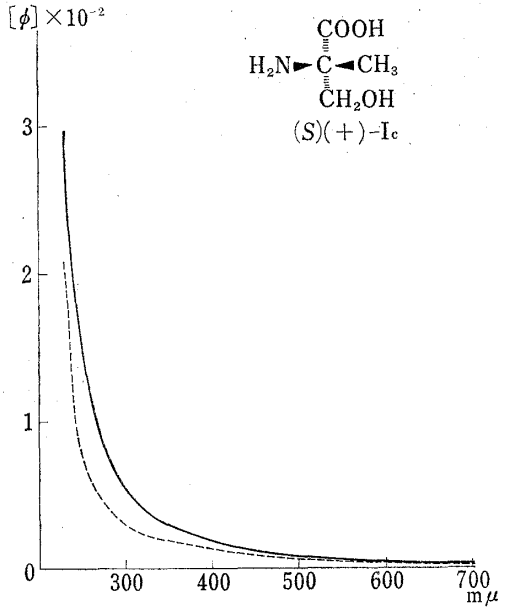


Fig. 10. ORD Curves of (*S*)(+)-α-Methylserine ((*S*)(+)-Ic)

----------: in 1N HCl

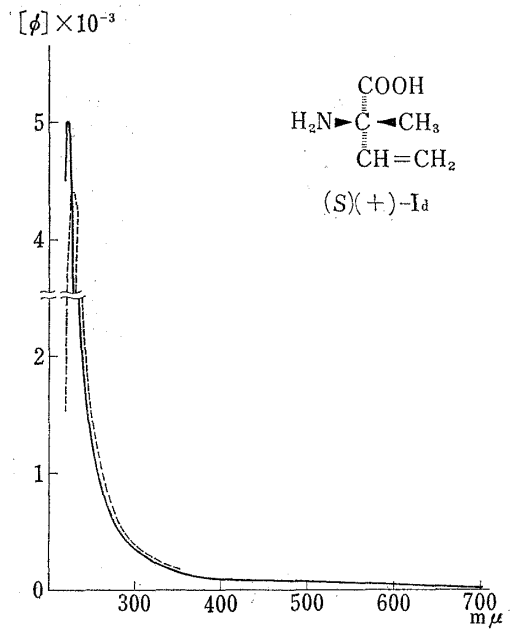


Fig. 11. ORD Curves of (*S*)(+)-2-Amino-2-methyl-3-butenoic Acid ((*S*)(+)-Id)

————: in H_2O

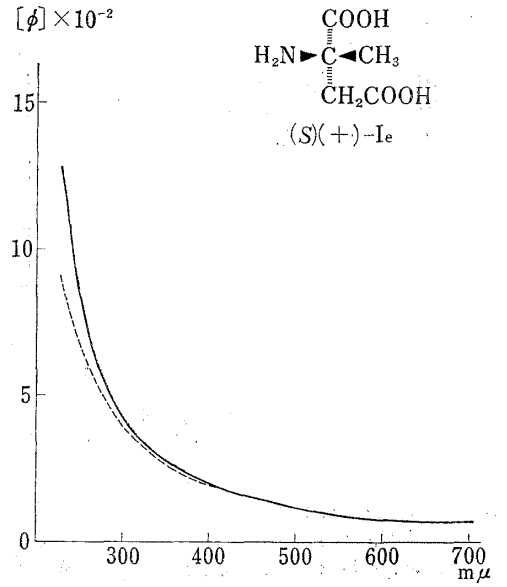


Fig. 12. ORD Curves of (*S*)(+)-α-Methylaspartic Acid ((*S*)(+)-Ie)

----------: in 1N HCl

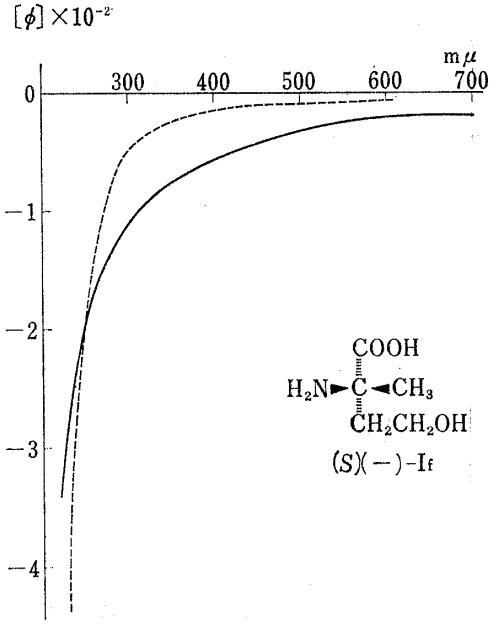


Fig. 13. ORD Curves of (*S*)(−)-α-Methylhomoserine ((*S*)(−)-If)

———: in H_2O

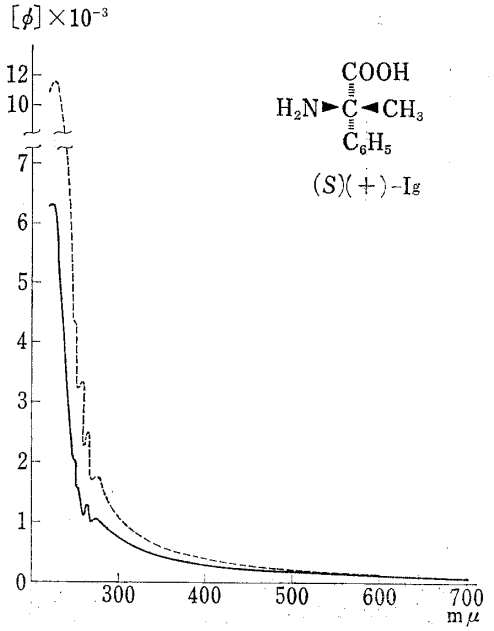


Fig. 14. ORD Curves of (*S*)(+)-α-Methylphenylglycine ((*S*)(+)-Ig)

----------: in 1N HCl

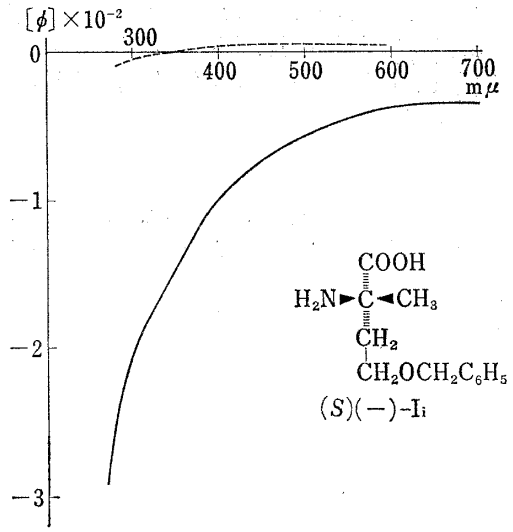


Fig. 15. ORD Curves of (*S*)(−)-2-Amino-4-benzyloxy-2-methylbutyric Acid ((*S*)-(−)-Ii)

———: in H_2O

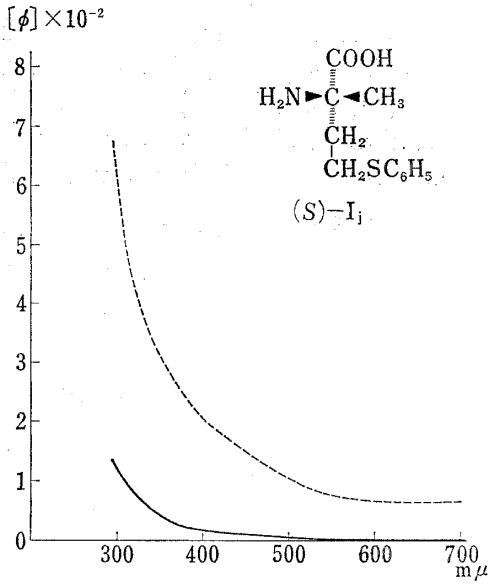


Fig. 16. ORD Curves of (*S*)-2-Amino-4-phenylthio-2-methylbutyric Acid ((*S*)-Ij)

----------: in 1N HCl

Next, the change of the $[M]$ value of I in 1N hydrochloric acid and in water with wavelength—optical despersion curve of I—was examined.[14–16] Results are shown in Figures 9—18. The values of $[M]^{HCl}-[M]^{H_2O}$ at various wavelengths down to 224 mμ were tested for L-leucine,

14) ORD curves of Ih-isomer in 3N hydrochloric acid and in water have been reported from our laboratory (see ref. 8e).

15) Application of the Clough–Lutz–Jirgensons rule for Il was also reported for wavelengths from 578 mμ to 405 mμ (see ref. 13).

16) Specific rotation of (+) and (−) α-methylserine in 5N hydrochloric acid and in a neutral solution at various wavelength has been described (see ref. 12).

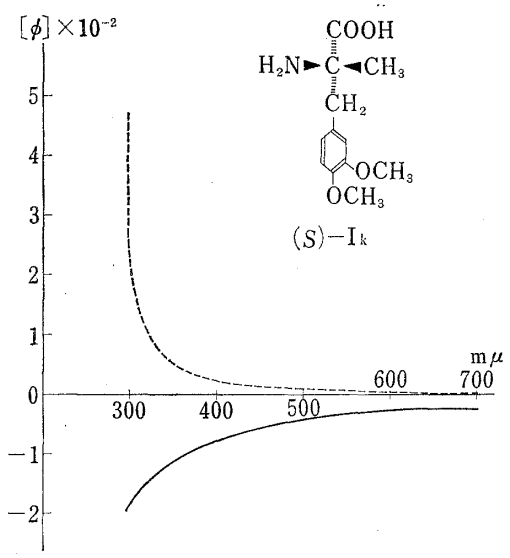


Fig. 17. ORD Curves of (*S*)-α-Methyl-β-(3,4-dimethoxyphenyl)alanine ((*S*)-Ik)
(*R*)-isomer was used for measurement
———: in H_2O

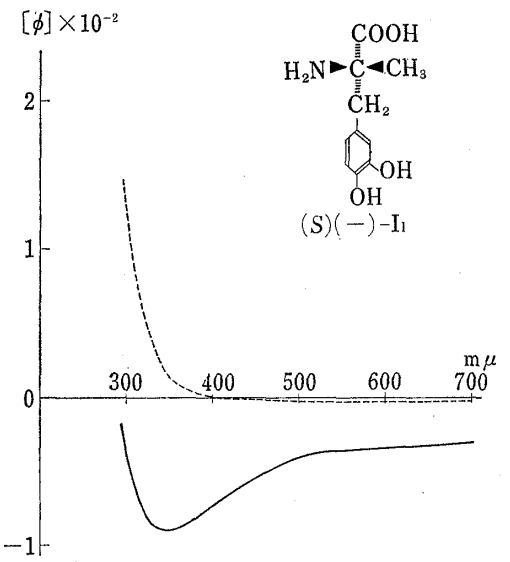


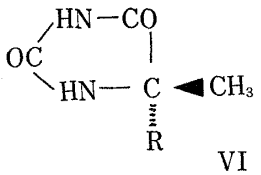
Fig. 18. ORD Curves of (*S*)(−)-α-Methyl-β-(3,4-dihydroxyphenyl)alanine ((*S*)(−)-Il)
----------: in 1N HCl

L-glutamic acid and L-lysine.[17] Results are in complete accordance with the above pattern for sodium D-line rotations. In the case of α-methyl-α-amino acids I, as shown in Fig. 9—18, various curve combinations were obtained. The values of $[M]^{1N\ HCl}-[M]^{H_2O}$ for (*S*)(+)Ib, and (*S*)(+)-Ic were always negative at all wavelength measured from 700 mμ to 225 mμ (Fig. 9 and 10), for (*S*)(+)Ig, (*S*)(−)-Ii, (*S*)-Ij, (*S*)(−)-Ik and (*S*)(−)Il (Fig. 14—18) they were constantly positive at similar wavelengths. For (*S*)(+)Id, (*S*)(+)-Ie and (*S*)(−)-If[18] peculiar values were observed at limited wavelengths (Fig. 11—13).

Hydantoin Rule for α-Methyl-α-amino Acids

Hydantoin derivatives of protein derived L-amino acids (II) are known to possess very large negative $[M]_D$ values. On this basis, a single rotational measurement of an optically

TABLE III. Molecular Rotations of Hydantoin Derivatives (VI) of (*S*)-α-Methyl-α-amino Acids (I)



VI (*S*)-series

Compds.	R	$[M]_D$ (in EtOH)(temp. °C)
b	C_2H_5	− 31°(25)[a]
c	$HOCH_2$	− 66°(18)[a]
d	CH_2=CH	− 52°(27)[a]
g	C_6H_5	+222°(17)
h	$C_6H_5CH_2$	− 86°(18)[b]
k	3,4-$(MeO)_2C_6H_3CH_2$	− 95°(27)[b]
l	3,4-$(HO)_2C_6H_3CH_2$	−119°(H_2O)(25)[c]

a) See ref 8 g). *b*) (*R*)-Isomer was used for measurement. *c*) See ref 13).

17) I.P. Dirkx, F.L.J. Sixma, *Rec. Trav. Chim.*, **83**, 522 (1964).
18) If (M.D. Armstrong, *J. Am. Chem. Soc.*, **71**, 3399 (1949)) and Id may form γ-lactone in acidic solution.

active hydantoin should suffice to establish the configuration of its parent amino acid.[7b] This method is disadvantageous in that hydantoin derivative generally recemizes easily. We examined the hydantoin derivatives of I to investigate the relationship between optical properties and absolute configuration, as the hydantoin derivatives of I do not racemize because they have no hydrogen atom at the α-carbon of amino acids. Hydantoin derivatives of Ib[19] and Il[13] have been reported to have negative rotations.

Seven optically active hydantoin derivatives; VIb, c, d, g, h, k, and l, were prepared from their corresponding (*S*)-α-methyl-α-amino acids.[8] Their optical rotations were measured and the results are summarized in Table III.

As shown in Table III, all hydantoin derivatives (VI) of (*S*)-configuration showed negative rotations, except VIg. Although presently available data are still too scant to establish the concept with certainty, they strongly suggest that levorotatory hydantoins are derived from (*S*)-α-methyl-α-amino acids, whereas the dextrorotatory derivatives have R-configuration. This levorotatory rotation in hydantoin derivatives of S configuration is due to a stereochemical optical contribution difference between a methyl group and another substituent (R in Table III) at the asymmetric center on the $n\rightarrow\pi^*$ carbonyl chromophore of a fixed hydantoin ring system at lower wavelength. Only in VIg, was a large dextrorotatory rotation observed. The inversion of the $[M]_D$ value was unexpected. At present it is ascribed to the electronic transition effect, $\pi\rightarrow\pi^*$, of the phenyl group, responsible for absorption at about 260 mμ, which is optically active to the asymmetric center of the hydantoin ring. In VId, ethylenic chromophores at lower wavelengths had no special effects on the rotatory properties of the VI type compound at the sodium D line, showing negative rotation.

Of these investigations for the assignment of absolute configuration in α-methyl-α-amino acids, the hydantoin rule seems the most useful if *R* (Table III) does not significantly effect the asymmetric center.

Experimental[20]

N-Dithiocarbethoxy α-Methyl-α-amino Acids (III) and Their Cyclohexylamine Salts——To a mixture of I (0.005 mole) and K_2CO_3 (0.0075 mole) in H_2O (30 ml) and EtOH (30 ml) was added carbon disulfide (0.010 mole) under stirring at room temperature. The whole was stirred for 1.5 hr, then EtBr (0.010 mole) was added. The reaction mixture was stirred overnight at room temperature. Evaporation of EtOH, and addition of H_2O gave an oil, which was extracted with ether. The aqueous layer was made acidic by adding hydrochloric acid under cooling. An oil obtained was extracted from this with ether. Combined ether layers were washed with H_2O, and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave an oil. This was dissolved in a small amount of ether (3 ml). Cyclohexylamine (0.0075 mole) was added dropwise to the ether solution. Precipitated crystals were collected, recrystallized from a mixture of iso-Pr_2O and MeOH. Yield, mp and analytical data are summarized in Table IV.

Diluted hydrochloric acid was added to the cyclohexylamine salt and the oil obtained was extracted with ether. The ether layer was washed with H_2O and dried over anhyd. Na_2SO_4. Evaporation of the ether solution gave III, which was used immediately for ORD and CD measurements.

ORD and CD Measurements of N-Dithiocarbethoxy α-Methyl-α-amino Acids (III) and Their Cyclohexylamine Salts

(*R*)-N-Dithiocarbethoxy Isovaline (IIIb)——ORD (c=0.206, MeOH) $[\phi]^{20}$ (mμ): +2.0° (500), +107° (352, peak), +64° (330, trough), +86° (315). ORD (c=0.206, dioxane) $[\phi]^{23}$ (mμ): +26° (500), +170° (355, peak), +128° (330, trough), +170° (315). ORD (c=0.210, benzene) $[\phi]^{22}$ (mμ): +4.2° (500), +216° (372, peak), −483° (320). ORD (c=0.204, $CHCl_3$) $[\phi]^{21}$ (mμ): −13° (500), +208° (371, peak), −825° (320).

19) H. Sobotka, M.F. Holzmann, and J. Kahn, *J. Am. Chem. Soc.*, **54**, 4697 (1932). In this paper (+) ethylmethylhydantoin was prepared from (−) isovaline. At the time, the absolute configuration of (−) isovaline was not determined. According to our report (see ref. 8a) it was found to be R series.

20) All melting points are uncorrected. IR spectra were measured using a Spectrometer, Model 402, Japan Spectroscopic Co., Ltd. Optical activities were measured with a Yanagimoto Photo Direct Reading Polarimeter, Model OR-20. ORD and CD curve measurements were performed using a Spectrometer, Model ORD/UV-5, Japan Spectroscopic Co., Ltd.

Table IV. Cyclohexylamine Salts of Optically Active N-Dithiocarbethoxy α-Methyl-α-amino Acids (III)

Compds.	Starting amino acids H_2N ► C(COOH, R_1) ◄ R_2			
	R_1	R_2	Optical rotation	Configuration
Ib	CH_3	C_2H_5	$[\alpha]_D^{19}$ −10.3°(c=1, H_2O)	R
Ig	CH_3	C_6H_5	$[\alpha]_D^{14}$ −63.3°(c=0.584, NHCl)	R
Ih[a]	CH_3	$C_6H_5CH_2$	$[\alpha]_D^{17}$ + 6.0°(c=1.33, H_2O)	R
Ik[b]	3,4-$(MeO)_2$-$C_6H_3CH_2$-	CH_3	$[\alpha]_D^{26}$ − 5.9°(c=0.9, MeOH)	S

Compds.	Cyclohexylamine salts of III: mp (decomp.) (°C)	Appearance	Yield (%)	Analyses (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ib	163—164	colorless needles	32	52.48	8.99	8.74	52.70	8.65	8.89
Ig	166—167	colorless needles	35	58.66	7.66	7.60	58.71	7.63	7.36
Ih	149—149.5	colorless needles	32	59.65	7.91	7.32	59.87	7.98	7.48
Ik	111—113	colorless prisms	33	54.75	7.88	6.08	55.08	7.72	6.25

a) This sample was the hydrochloride with ½H_2O as crystal water.
b) This sample was the hydrochloride with H_2O as crystal water.

$CD_{max}[\theta]_{340}^{20}$ +35 (c=0.206, MeOH); $CD_{max}[\theta]_{337}^{23}$ +112 (c=0.206, dioxane); CD_{max} $[\theta]_{355}^{22}$ +694 (c=0.210, benzene); CD_{max} $[\theta]_{351}^{21}$ +805 (c=0.204, $CHCl_3$).

Cyclohexylamine Salt of (*R*)-N-Dithiocarbethoxy Isovaline (IIIb)——ORD (c=0.238, H_2O)$[\phi]^{21.5}$ (mμ): +31° (500), +280° (342, peak), 0° (310). ORD (c=0.105, MeOH) $[\phi]^{19.5}$ (mμ): −61° (500), −25° (371, peak), −1040° (315).

CD_{max} $[\theta]_{326}^{21.5}$ +390 (c=0.238, H_2O); CD_{max} $[\theta]_{347}^{19.5}$ +550 (c=0.105. MeOH).

(*R*)-N-Dithiocarbethoxy α-Methylphenylglycine (IIIg)——ORD (c=0.232, MeOH)$[\phi]^{18.5}$ (mμ); −93° (500), +650° (376, peak), −2550° (326, trough), −2500° (320). ORD (c=0.204, dioxane)$[\phi]^{16.5}$ (mμ): −92° (500), +948° (372, peak), −3500° (324, trough), −3430° (314). ORD (c=0.258, benzene)$[\phi]^{20.5}$ (mμ): −125° (500), +897° (380, peak), −2920° (337, trough), −2550° (320). ORD (c=0.214, $CHCl_3$)$[\phi]^{21.5}$ (mμ): −75° (500), +1043° (380, peak), −3020° (335, trough), −2580° (230).

CD_{max} $[\theta]_{352}^{18.4}$ +2100 (c=0.232, MeOH); CD_{max} $[\theta]_{351}^{17}$ +3220 (c=0.204, dioxane); CD_{max} $[\theta]_{360}^{21}$ +2400 (c=0.258, benzene); CD_{max} $[\theta]_{356}^{22}$ +2760 (c=0.214, $CHCl_3$).

Cyclohexylamine Salt of (*R*)-N-Dithiocarbethoxy α-Methylphenylglycine (IIIg)——ORD (c=0.110, H_2O) $[\phi]^{14}$ (mμ): +308° (500), +1870° (358, peak), −1000° (314, trough), −920° (310). ORD (c=0.204, MeOH) $[\phi]^{23}$ (mμ): +31° (500), +597° (372, peak), −1300° (trough), −1290° (316).

CD_{max} $[\theta]_{332}^{14}$ +2980 (c=0.110, H_2O); CD_{max} $[\theta]_{348}^{23}$ +3120 (c=0.204, MeOH).

(*R*)-N-Dithiocarbethoxy α-Methylphenylalanine (IIIh)——ORD (c=0.24, MeOH) $[\phi]^{20}$ (mμ): +470° (500), +560° (366, trough), +6020 (310). ORD (c=0.208, dioxane) $[\phi]^{20}$ (mμ): +680° (500), +1070° (397), +630° (368, trough), +8570° (310). ORD (c=0.200, benzene) $[\phi]^{21.5}$ (mμ): 0° (500), −780° (366, trough), +920° (330, peak), +253° (314). ORD (c=0.202, $CHCl_3$) $[\phi]^{23}$ (mμ): −460° (500), −2030° (366, trough), −1100° (342, peak), −3080° (310).

CD_{max} $[\theta]_{344}^{20}$ −2390 (c=0.24, MeOH); CD_{max} $[\theta]_{348}^{20}$ −3640 (c=0.208, dioxane); CD_{max} $[\theta]_{352}^{21.5}$ −1680 (c=0.200, benzene); CD_{max} $[\theta]_{350}^{23}$ −1770 (c=0.202, $CHCl_3$).

Cyclohexylamine Salt of (*R*)-N-Dithiocarbethoxy α-Methylphenylalanine (IIIh)——ORD (c=0.208, H_2O) $[\phi]^{20.5}$ (mμ): +74° (500), −814° (358, trough), +1480° (313, peak). ORD (c=0.204, MeOH) $[\phi]^{20}$ (mμ): −950° (500), −4300° (354, trough), −4400° (336, peak), −9350° (306).

CD_{max} $[\theta]_{336}^{20.5}$ −2400 (c=0.208, H_2O); CD_{max} $[\theta]_{342}^{20}$ −2200 (c=0.204, MeOH).

(*S*)-N-Dithiocarbethoxy α-Methyl-β-(3,4-dimethoxyphenyl)alanine (IIIk)——ORD (c=0.109, MeOH) $[\phi]^{22}$ (mμ): −485° (500), −880° (388), −560° (365, peak), −8730° (305). ORD (c=0.110, dioxane) $[\phi]^{20}$ (mμ): −690° (500), −1250° (394), −806° (367, peak), −10850° (310). ORD (c=0.114, benzene) $[\phi]^{20}$ (mμ): +150° (500), +1260° (360, peak), −90° (333, trough), +900° (312). ORD (c=0.114, $CHCl_3$) $[\phi]^{23.5}$ (mμ): +600° (500), +2640° (360, peak), +2340° (343, trough), +4680° (317).

CD_{max} $[\theta]^{22}_{341}$ +3320 (c=0.109, MeOH); CD_{max} $[\theta]^{20}_{346}$ +4430 (c=0.110, dioxane); CD_{max} $[\theta]^{20}_{350}$ +2090 (c=0.114, benzene); CD_{max} $[\theta]^{23.5}_{349}$ +1790 (c=0.114, $CHCl_3$).

Cyclohexylamine Salt of (*S*)-N-Dithiocarbethoxy α-Methyl-β-(3,4-dimethoxyphenyl)alanine (IIIk)——ORD (c=0.110, H_2O) $[\phi]^{22}$ (mμ): +76° (500), +144° (355, peak), −760° (318). ORD (c=0.124, MeOH) $[\phi]^{20}$ (mμ): +1000° (500), +5000° (350, shoulder), +6780° (325).

CD_{max} $[\theta]^{22}_{334}$ +3060 (c=0.110, H_2O); CD_{max} $[\theta]^{20}_{339}$ +2300 (0.124, MeOH).

ORD Measurements of α-Methyl-α-amino Acids (I)

(*S*)(+)-Isovaline ((*S*)(+)-Ib)[8a,b]——ORD (c=0.473, H_2O) $[\phi]^{15}$ (mμ): +11.8° (700), +13.8° (589), +20.1° (500), +27.0° (450), +38.1° (400), +56.9° (350), +95.6° (300), +213° (250), +386° (224). ORD (c=0.507, 1N HCl) $[\phi]^{15}$ (mμ): +5.5° (700), +5.7° (589), +9.0° (500), +12.5° (450), +17.3° (400), +27.4° (350), +49.7° (300), +111° (250), +184° (233).

(*S*)(+)-α-Methylserine ((*S*)(+)-Ic)[8g]——ORD (c=0.888, H_2O) $[\phi]^{11}$ (mμ): +3.4° (700), +6.0° (589), +9.4° (500), +12.7° (450), +18.8° (400), +29.5° (350), +53.6° (300), +144° (250), +295° (230). ORD (c=0.624, 1N HCl) $[\phi]^{23}$ (mμ): +2.7° (700), +5.7° (589), +6.5° (500), +9.9° (450), +13.0° (400), +18.7° (350), +29.3° (300), +74.5° (250), +204° (230).

(*S*)(+)-2-Amino-2-methyl-3-butenoic Acid ((*S*)(+)-Id)[8g]——ORD (c=0.612, H_2O) $[\phi]^{28.5}$ (mμ): +26.2° (700), +39.6° (589), +60.2° (500), +82.6° (450), +113° (400), +178° (350), +352° (300), +1260° (250), +4990° (222, peak), +4510° (220). ORD (c=0.604, 1N HCl) $[\phi]^{26.5}$ (mμ): +26.7° (700), +40.0° (589), +60.6° (500), +82.1° (450), +114° (400), +190° (350). +356° (300). +1485° (250), +4380 (230, peak), +1525° (220).

(*S*)(+)-α-Methylaspartic Acid ((*S*)(+)-Ie)[8b]——ORD (c=0.264, H_2O) $[\phi]^{16}$ (mμ): +74.0° (700), +80.4° (589), +120° (500), +152° (450), +200° (400), +274° (350), +428° (300), +820° (250), +1270° (228). ORD (c=0.282, 1N HCl) $[\phi]^{16}$ (mμ): +67.8° (700), +80.4° (589), +120° (500), +153° (450), +193° (400), +264° (350), +394° (300), +672° (250), +893° (226).

(*S*)(−)-α-Methylhomoserine ((*S*)(−)-If)[8d]——ORD (c=0.336, H_2O) $[\phi]^{23}$ (mμ): −19.1° (700), −20.7° (589), −34.9° (500), −44.8° (450), −59.5° (400), −75.5° (350), −113° (300), −194° (250), −340° (223). ORD (c=0.327, 1N HCl) $[\phi]^{23}$ (mμ): −7.7° (589), −8.1° (500), −11.1° (450), −15.5° (400), −23.6° (350), −49.4° (300), −190° (250), −439° (231).

(*S*)(+)-α-Methylphenylglycine ((*S*)(+)-Ig)[8f,21]——ORD (c=0.256, H_2O) $[\phi]^{17.5}$ (mμ): +72.6° (700), +126° (589), +181° (500), +226° (450), +310° (400), +468° (350), +782° (300), +1072° (274, peak), +1030° (268, trough), +1290° (265, peak), +1095° (262, trough), +1611° (255, shoulder,), +2090° (250, shoulder), +6200° (222). ORD (c=0.532, 1N HCl) $[\phi]^{19.5}$ (mμ): +93.2° (700), +143° (589), +203° (500), +295° (450), +403° (400), +634° (350), +1092° (300), +1770° (274, peak), +1710° (268, trough), +2480° (264, peak), +2330° (262, trough), +3340° (258, peak), +3250° (256, trough), +4350° (250, shoulder), +11500° (228, peak), +10800° (222).

(*S*)(−)-2-Amino-4-benzyloxy-2-methylbutyric Acid ((*S*)(−)-Ii)[8d]——ORD (c=0.300, H_2O) $[\phi]^{17}$ (mμ): −35.7° (700), −38.6° (589), −59.6° (500), −72.7° (450), −95.3° (400), −131° (350), −203° (300), −291° (270). ORD (c=0.330, 1N HCl) $[\phi]^{17}$ (mμ): +5.4° (589—400), 0° (350), −4.0° (300), −9.4° (280).

(*S*)-2-Amino-4-phenylthio-2-methylbutyric Acid ((*S*)-Ij)[8d]——ORD (c=0.358, H_2O) $[\phi]^{22}$ (mμ):[22] 0° (700—589), +8.1° (500), +12.2° (450), +18.1° (400), +43.3° (350), +121° (300), +132° (296). ORD (c=0.353, 1N HCl) $[\phi]^{22}$ (mμ):[23] +66.8° (700), +67.5° (589), +109° (500), +150° (450), +206° (400), +308° (350), +628° (300), +665° (296).

(*R*)-α-Methyl-β-(3,4-dimethoxyphenyl)alanine ((*R*)-Ik)[8d]——ORD (c=0.387, H_2O) $[\phi]^{18}$ (mμ)[24]: +25.8° (700), +27.8° (589), +41.1° (500), +57.6° (450), +79.6° (400), +114° (350), +187° (300), +195° (296). ORD (c=0.435, 1N HCl)[25] $[\phi]^{18}$ (mμ): −4.3° (700), −6.0° (589), −8.1° (500), −13.1° (450), −24.6° (400), −50.5° (350), −214° (300), −461° (296).

(*S*)(−)-α-Methyl-β-(3,4-dihydroxyphenyl)alanine ((*S*)(−)-Il)[8c,8d]——ORD (c=0.354, H_2O) $[\phi]^{18}$ (mμ): −30.0° (700), −35.9° (589), −40.5° (500), −54.8° (450), −71.4° (400), −86.9° (350), −89.3° (300, trough),

21) This sample was 94% optically pure.
22) The (*S*)(+)-hydrochloride[8d] was used for measurement after its aqueous solution was neutralized with an equivalent amount of NaOH.
23) The (*S*)(+)-hydrochloride[8d] was used directly. Its concentration was corrected.
24) The (*R*)(−)-hydrochloride[8d] was used for measurement after its aqueous solution was neutralized using an equivalent amount of NaOH.
25) The (*R*)(−)-hydrochloride[8d] was used directly. Its concentration was corrected.

$-38.2°$ (300), $-19.2°$ (295). ORD ($c=0.557$, 1N HCl) $[\phi]^{18}$ (mμ): $-2.3°$ (700), $-3.2°$ (589), $-2.7°$ (500), $-0.8°$ (450), 0° (400), $+14.1°$ (350), $+129°$ (300), $+146°$ (295). ORD data reported in ref. 13 were similar to those obtained by us.

Syntheses of Hydantoin Derivatives

(*R*)(+)-5-Benzyl-5-methylhydantoin ((*R*)(+)-VIh)——A mixture of *R*(+)-α-methylphenylalanine hydrochloride (mp 209.5—213.5°, $[\alpha]_D^{25}$ +5.9° ($c=0.950$, H_2O))[8e] (0.46 g, 0.0020 mole) and KNCO (0.81 g, 0.01 mole) in H_2O (5 ml) was refluxed for 2 hr. After cooling, conc. HCl (1.6 ml) was added to the reaction mixture and the whole was refluxed for another 30 min. Crystals, precipitated after the reaction mixture cooled, were collected (0.17 g, 42%), and showed a mp of 219°. Two recrystallizations from H_2O–EtOH gave analytical samples as colorless needles, mp 223°, $[\alpha]_D^{18}$ +42.2° ($c=0.218$, EtOH). *Anal.* Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.68; H, 6.08; N, 13.72. IR ν_{max}^{KBr} cm^{-1}: 3275, 3195, 1769, 1734, 1713, 1408, 782, 735, 705.

(*S*)(+)-5-Phenyl-5-methylhydantoin (*S*)(+)-VIg)——(*S*)(+)-α-Methylphenylglycine ((*S*)(+)-Ig)[8f] (mp >250°, $[\alpha]_D^{20}$ +65.2° ($c=0.426$, H_2O))(1.65 g, 0.010 mole) was treated the same as above. Needles, precipitated after the reaction mixture cooled, were collected. They weighed 0.70 g (37%), and showed a mp of 237°. Several recrystallizations from EtOH and hexane afforded a pure sample as colorless needles, mp 238°, $[\alpha]_D^{1}$ +117° ($c=0.728$, EtOH). *Anal.* Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.19; H, 5.24; N, 14.62. IR ν_{max}^{KBr} cm^{-1}: 3290, 3200, 1770, 1727, 1401, 782, 732, 694.

(*R*)(+)-5(3,4-Dimethoxybenzyl)-5-methylhydantoin ((*R*)(+)-VIk)——(*R*)(−)-α-Methyl-β-(3,4-dimethoxyphenyl)alanine hydrochloride (mp 169—171.5° (decomp.), $[\alpha]_D^{28}$ −7.1° ($c=1.282$, MeOH)) (2.9 g, 0.010 mole) was treated the same as (*R*)(+)-α-methylphenylalanine hydrochloride. Pale violet powder, precipitated after the reaction mixture cooled, was collected. It weighed 1.0 g (38%), and showed a mp of 263° (decomp.). Three recrystallizations from MeOH gave a pure sample as colorless prisms, mp 262.5—264° (decomp.), $[\alpha]_D^{27}$ +36° ($c=0.186$, EtOH). *Anal.* Clacd. for $C_{13}H_{16}O_4N_2$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.30; H, 6.06; N, 10.82. IR ν_{max}^{KBr} cm^{-1}: 3300, 1772, 1729, 1023, 808, 790, 763.

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