Department of Chemistry,
Tohoku University,
Katahira-cho, Sendai

Yutaka Fujise (藤瀬 裕)
Shô Itô*[4] (伊東 椒)

Received March 4, 1966

---

*[4] To whom all correspondences should be addressed.

[Chem. Pharm. Bull. 14(7) 800~802 (1966)]

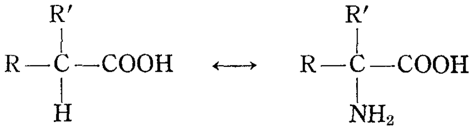
UDC 547.466.2.03 : 541.65

Determination of the Absolute Configuration of α-Methylphenylglycine by the Thermal Decomposition of the Azidoformate

In the previous communication,[1] the authors reported that the thermal decomposition of $S(+)$-2-methylbutyl azidoformate ($S(+)$-I) in diphenyl ether afforded $R(+)$-4-ethyl-4-methyl-2-oxazolidinone ($R(+)$-II) with nearly 100% retention of configuration. Accordingly, the results obtained suggested that this nitrene insertion reaction may be applicable to one of the methods for the determination of absolute configuration of a carboxylic acid (III) which has optically active tertiary C-H bond, or a α-alkyl-α-amino acid (IV) from the point of the reaction mechanism, if either one of the absolute configurations would be clear.


$S(+)$-I $R(+)$-II

Fig. 1.


III IV

R, R'≠H

Fig. 2.

On the absolute configuration of α-methylphenylglycine (2-amino-2-phenylpropionic acid) (IVa), which is one of the important α-alkyl-α-amino acids used frequently for the studies on the reaction mechanism,[2] Cram, *et al.*[2e] have deduced the absolute configuration of (+)-IVa to be *S*-series from the Freudenberg displacement rule and their studies on the carbanion chemistry. On the other hand, Maeda[2d] assumed that (+)-IVa is either *R*- or D-series without any convincing evidence. The discrepancy in these assignments cited above prompted us to undertake the examination of the correlation of the absolute configuration of IVa with that of hydratropic acid (2-phenylpropionic acid) (IIIa) whose absolute configuration has been already established,[3] using the thermal decomposition of the azidoformate prepared from IIIa.

The chemical scheme we employed is illustrated in Chart 1. A mixture of (+)-α-methylphenylglycine ((+)-IVa)(optical purity 82%[2a]) obtained from the resolution of

---

[1] S. Yamada, S. Terashima, K. Achiwa: This Bulletin, **13**, 751 (1965).

[2] *a*) A. McKenzie, G. W. Clough: J. Chem. Soc., **101**, 390 (1912). *b*) A. McKenzie, J. Myles: Ber., **65**, 209 (1932). *c*) W. A. Bonner, J. A. Zderic: J. Am. Chem. Soc., **78**, 3218 (1956). *d*) G. Maeda: Nippon Kagaku Zasshi, **77**, 1011 (1956). *e*) D. J. Cram, L. K. Gaston, H. Jäger: J. Am. Chem. Soc., **83**, 2183 (1961). *f*) S. Mitsui, E. Sato: Nippon Kagaku Zasshi, **86**, 416 (1965).

[3] *a*) W. A. Bonner, J. A. Zderic: J. Am. Chem. Soc., **81**, 3336 (1959) and the ref. 15~22 therein. *b*) F. A. A. Elhafez, D. J. Cram: *Ibid.*, **74**, 5846 (1952) and the ref. 9 therein. *c*) W. A. Bonner, J. A. Zderic, G. A. Casalette: *Ibid.*, **74**, 5086 (1952) and ref. 6~11 therein.

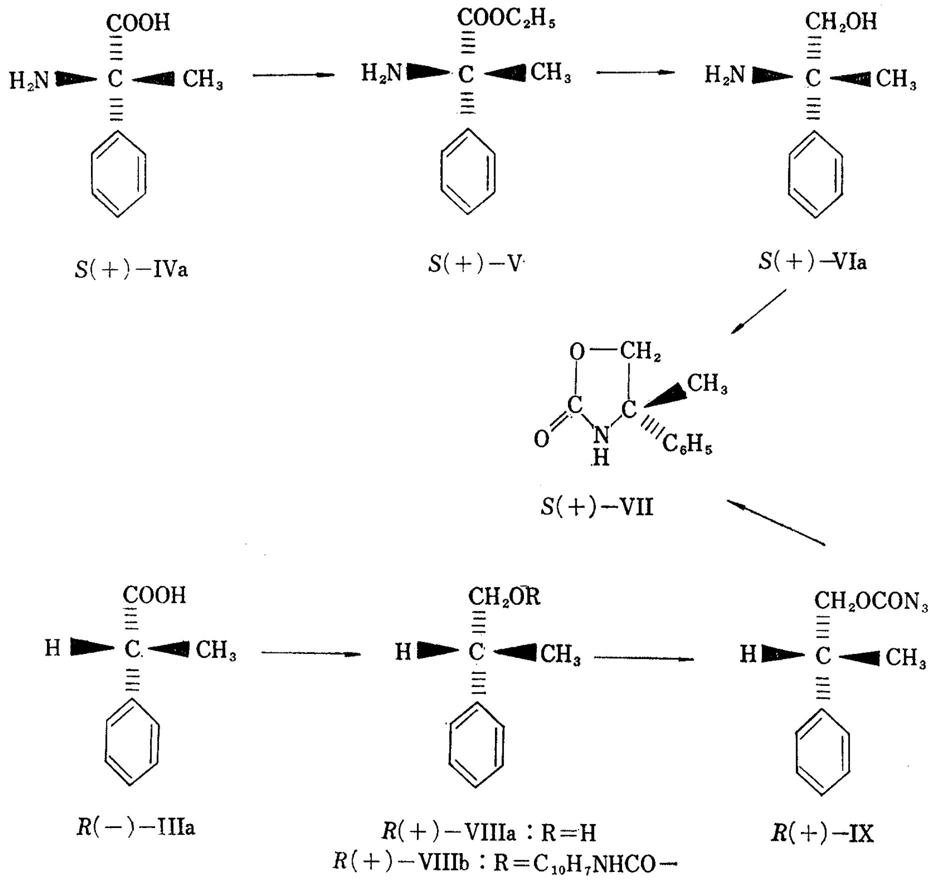


Chart 1.

DL-IVa[4] using quinine,[2a] and thionyl chloride in ethanol was refluxed for 6 hr. to give (+)-ethyl α-methylphenylglycinate ((+)-V) in a 63% yield as colorless oil, b.p$_{5.5}$ 108~109.5°, α_D^{16} +0.993° (l=0.1, neat)(optical purity 89%[2e]). IR ν_{max}^{Cap} cm^{-1} : 1733, 1603, 1496, 1235, 701. A reflux of (+)-V with sodium borohydride in 75% aq. ethanol[5] gave (+)-2-amino-2-phenyl-1-propanol ((+)-VIa) in a 70% yield as viscous oil, b.p$_4$117~120.5°, $[\alpha]_D^{23}$ +14.3° (c=0.978, EtOH). IR ν_{max}^{Cap} cm^{-1} : 3340~3060, 1605, 1599, 1064, 1046, 1029, 763, 701. This amino alcohol gave neutral oxalate ((+)-VIb) as white needles, m.p. 235°(decomp.), $[\alpha]_D^{23}$ +7.0°(c=0.770, H_2O). *Anal.* Calcd. for $C_{20}H_{28}O_2N_2$: C, 61.21; H, 7.19; N, 7.14. Found : C, 61.45; H, 7.21; N, 7.37. A reflux of (+)-VIa thus obtained with diethyl carbonate in the presence of sodium methylate[1,6,7] afforded crude (+)-4-methyl-4-phenyl-2-oxazolidinone ((+)-VII), which was purified through silica gel column, m.p. 93~94.5°, $[\alpha]_D^{27}$ +101° (c=0.912, EtOH). Recrystallizations from benzene-hexane twice gave pure (+)-VII as white plates, m.p. 93.5~94.5°, $[\alpha]_D^{24}$ +104° (c=0.894, EtOH). *Anal.* Calcd. for $C_{10}H_{11}O_2N$: C, 67.78; H, 6.26; N, 7.91. Found : C, 67.91; H, 6.21; N, 8.11. IR ν_{max}^{KBr} cm^{-1}: 3260, 1765, 1719, 1043, 760, 697. IR ν_{max}^{Cap} cm^{-1} : 3240, 1757, 1603, 1042.

On the other hand, *R*(−)-hydratropic acid (*R*(−)-IIIa)(b.p$_4$122~124°, $[\alpha]_D^{24}$ −33.7° (c=4.930, EtOH))(optical purity 42%[8]), obtained from the resolution of DL-IIIa[9] with strychinine,[8] was treated with lithium aluminum hydride in ether[10] to give *R*(+)-2-phenyl-

---

[4] Org. Syn., Coll. Vol. III, p. 88.
[5] H. Seki, K. Koga, H. Matsuo, T. Oki, I. Matsuo, S. Yamada : This Bulletin, **13**, 995 (1965).
[6] A. H. Homeyer : U. S. pat. 2,399,118 (1946) (C. A., **40**, 4084 (1946).).
[7] M. S. Newman, W. M. Edwards : J. Am. Chem. Soc., **76**, 1840 (1954).
[8] H. S. Raper : J. Chem. Soc., **123**, 2558 (1925).
[9] *a*) Org. Syn., Coll. Vol. III. p. 727, 733. *b*) C. L. Arcus, J. Kenyon : J. Chem. Soc., **1939**, 916.

1-propanol (R(+)-VIIIa) in a 71% yield as colorless oil, b.p$_{5.5}$ 88~90.5°, α_D^{24} +0.717° (l=0.1, neat)(optical purity 40%[10]). This alcohol gave α-naphthyl urethane derivative (R(+)-VIIIb), m.p. 102.5°, α_D^{23} +5.9° (c=0.988, EtOH). *Anal.* Calcd. for $C_{20}H_{19}O_2N$: C, 78.66; H, 6.27; N,4.59. Found : C, 78.87; H, 6.32; N, 4.58. IR ν_{max}^{KBr} cm^{-1} : 3260, 1688, 1600, 1530. The alcohol (+)-VIIIa was treated with phosgene in benzene, followed with sodium azide in aq. methanol to afford R(+)-2-phenyl-1-propyl azidoformate (R(+)-IX) in a 93% yield, α_D^{23} +0.222° (l=0.1, neat). IR ν_{max}^{Cap} cm^{-1} : 2185(sh), 2140, 1756, 1730, 1230, 1150, 700. The thermal decomposition of R(+)-IX in diphenyl ether[1] at 200±10°, followed by the purification using the procedure as reported previously[1] gave (+)-4-methyl-4-phenyl-2-oxazolidinone ((+)-VII) in a 4% yield, m.p. 68.5~74.5°, α_D^{25} +43.9° (c=1.026, EtOH). Infrared spectrum of this (+)-VII in solid state showed that this sample was contaminated with a fair amount of DL-VII,[*1] but in chloroform it was superimposable with those of DL-VII[*1] and (+)-VII obtained from S(+)-IVa. Thin-layer chromatography of this sample in two different solvent systems showed a single spot respectively, whose Rf value was as same as those of DL-VII.[*1] Rf value : 0.2 ($CHCl_3$), 0.6 (hexane-AcOEt=1:1). Recrystallizations of crude (+)-VII twice gave (+)-VII with a low optical purity as white plates, m.p. 80.5~81.5°,[*2] $[\alpha]_D^{17}$ +9.3° (c=0.172, EtOH). *Anal.* Calcd. for $C_{10}H_{11}O_2N$: C, 67.78; H, 6.26; N, 7.91. Found : C, 67.90; H, 6.43; N, 8.11. Infrared spectra of this sample were identical with those of DL-VII[*1] in solid state and chloroform solution.

From the results obtained above, it has been concluded that the absolute configuration of (+)-α-methylphenylglycine ((+)-IVa) should be shown to be S-configuration on the assumption that the thermal decomposition of azidoformate proceeded with the retention of configuration, and this conclusion is in agreement of Cram's proposal. In this case, the retention percentage of the reaction was also nearly 100%. The determination of the absolute configuration of IVa using chemical correlation method is now in progress in our laboratory.

Faculty of Pharmaceutical Sciences,
University of Tokyo, Hongo,
Tokyo, Japan

Shun-ichi Yamada (山田俊一)
Shiro Terashima (寺島孜郎)
Kazuo Achiwa (阿知波一雄)

Received March 25, 1966

[*1] DL-VII was prepared from DL-IVa similarly to (+)-VII.[7] m.p. 81.5~82.5°. (lit.,[7] m.p. 79.6~80°).

[*2] Mixed melting point with (+)-VII obtained from (+)-IVa showed m.p. 73.5~78°.

10) E.L. Eliel, J.P. Freeman : J. Am. Chem. Soc., **74**, 923 (1952).

[Chem. Pharm. Bull. 14(7) 802~804 (1966)]

UDC 615.779.925-011 : 547.682.07

Synthesis of Bisanhydroaklavinone

In 1956, Strelitz, *et al.*[1] isolated a pigment antibiotics, aklavine, from Streptomyces. Afterwards, in 1960, Ollis, *et al.*[2] obtained aklavinone (I), the aglycone of the antibiotics, on a mild acid hydrolysis of aklavine and also bisanhydroaklavinone by dehydration of I, and established their structures by the degradative and physical methods. We have prepared methyl 2-ethyl-5,7-dihydroxy-6,11-dioxo-6,11-dihydro-1-naphthacenecarboxylate

---

1) F. Strelitz, H. Flon, U. Weiss, I.N. Asheshov : J. Bacteriol., **72**, 90 (1956).

2) W.D. Ollis, J.J. Gordon, L.M. Jackmann, I.O. Sutherland : Tetrahedron Letters, No. 8, 28 (1960).