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X RAY CRYSTALLOGRAPHY OF (+)-$(R)_P$ METHYL PHENYL PHOSPHORAMIDATE OF ETHYL L-PHENYLALANINATE

Toru Koizumi*, Yoshiko Kobayashi, and Eiichi Yoshii

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University,

Sugitani, Toyama 930-01, Japan

Masayuki Takamoto, Kazuhide Kamiya, and Hiroyuki Asakawa

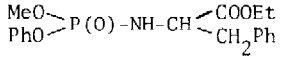
Central Research Division, Takeda Chemical Industries, Ltd., Juso-honmachi,

Yodogawa-ku, Osaka 532, Japan

Summary : The absolute configuration of (+)-$(R)_P$ methyl phenyl phosphoramidate of ethyl L-phenylalaninate 1 was determined by X ray crystallography.

The stereochemical study of the solvolysis of phosphoric acid esters has been a subject of considerable recent interest.[1] For this investigation the chiral phosphates of the known absolute configurations are indispensable. The absolute configurations of the hitherto known simple chiral phosphates, however, have been assigned only on the basis of NMR[2] and Mass[3] spectral analyses of their diastereomeric precursors, and X ray crystallography, the most conclusive method, has not been applied for the determination of their absolute configurations.[4]

We here describe the X ray determination of the absolute configuration of a simple phosphate derivative, one of the diastereomers of methyl phenyl phosphoramidate of ethyl L-phenylalaninate 1,[5] which is potentially useful as a key chiral compound for the chemical correlation.



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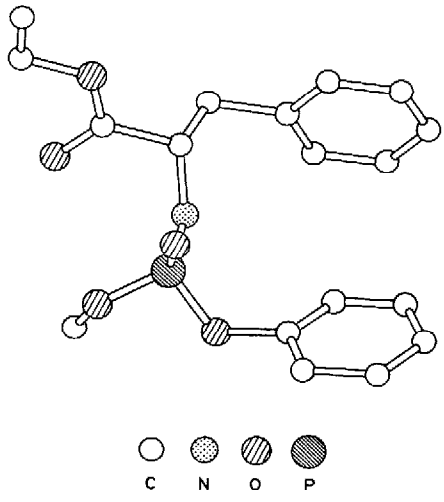
The phosphoramidate 1 (mp 59°, $[\alpha]_D$=32.9°) was repeatedly recrystallized from isopropyl ether-n-hexane to give the desired single crystals. The crystal data are : $C_{18}H_{22}NO_5P$, mw 363.3; Orthorhombic, space group $P2_12_12_1$, a=8.682(8), b=40.79(3). c=5.345(4) Å, U=1893(3)Å^3; z=4, D_x=1.275g·cm^{-3}. Using monochromated M_oK_α radiation(λ=0.7107Å), 2035 independent reflections up to 2θ=50° were measured with a Rigaku AFC-5 diffractometer. A total of 1216 reflections with $F_o \geq 3\sigma(F_o)$ were used for the calculations. The structure was solved by direct methods (MULTAN) and refined by the least-squares method (XRAY) to a residual R of 0.118.

A perspective view of the molecule is shown in Figure. The absolute configuration of the phosphorus was determined as R on the basis of the known S configuration of ethyl L-phenylalaninate.[6]



Based on the X ray result, the absolute configurations of (+) methyl phenyl phosphoramidate and (-) ethyl methyl phenyl phosphate stereospecifically derived from 1 could be determined as R and S respectively. Since the almost all known chiral phosphates[1,5, 7,8] could be correlated chemically with the above mentioned compounds, their absolute configurations may now in principle be established.[9]

References and Notes

1) W. A. Blaettler, and J. R. Knowles, *J. Amer. Chem. Soc.*, 101, 510(1979) and references cited therein.

2) D. B. Cooper, C. R. Hall, J. M. Harrison, and T. D. Inch, *J. Chem. Soc. Perkin I*, 1977, 1969; C. R. Hall, and T. D. Inch, *J. Chem. Soc. Perkin I*, 1979, 1646.

3) S. J. Abbott, S. R. Jones, S. A. Weinman, F. M. Bockhoff, F. W. McLafferty, and J. R. Knowles, *J. Amer. Chem. Soc.*, 101, 4323(1979); S. J. Abbott, S. R. Jones, S. A. Weinman, and J. R. Knowles, *Ibid.*, 100, 2558(1978).

4) Although the absolute configurations of cyclophosphamide and uridine 2', 3'-cyclic phosphorothioate derivatives have been determined by X ray crystallography, they are not useful as the key chiral compounds for the chemical correlation because the conversion of these compounds to the known simple phosphates is rather difficult. Literatures for cyclophosphamide : D. A. Adamaik, R. Kinas, W. Saenger, W. J. Stec, *Angew. Chem. Intern. Ed.*, 16, 330(1977); I. L. Karle, J. M. Karle, W. Egan, G. Zon, and J. A. Brandt, *J. Amer. Chem. Soc.*, 99, 4803(1977). For uridine 2',3'-cyclic phosphorothioates: F. Eckstein, *Angew. Chem. Intern. Ed.*, 14, 160(1975) and references cited therein.

5) Y. Kobayashi, T. Koizumi, and E. Yoshii, *Chem. Pharm. Bull.*, 27, 1641(1979).

6) This was confirmed by the recovery of ethyl ester hydrochloride of L-phenylalanine after HCl catalyzed ethanolysis of the substance 1.

7) C. R. Hall, and T. D. Inch, *J. Chem. Soc. Perkin I*, 1979, 1104.

8) T. Koizumi, Y. Kobayashi, H. Amitani, and E. Yoshii, *J. Org. Chem.*, 42, 3459(1977).

9) For example, the absolute configuration of 2R-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxaza-phospholidine-2-thione, an important intermediate for various chiral phosphorus compounds, is now confirmed by the reaction sequences described in the reference 7. The validity of the spectral method is also confirmed.

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