Optical Rotatory Dispersion of *N*-(2-Pyridyl *N*-oxide)amino-acids: Empirical Correlation of Cotton Effect with Chromophoric Substituents

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OPTICAL ROTATORY DISPERSION has been widely used to establish absolute configurations of amino-acids. Amino-acids and some of their suitable derivatives have been widely investigated. In particular, derivatives which result from the stepwise degradation of peptides have been taken into consideration.[1] The well known phenylthiohydantoins are not convenient for this purpose because they racemize easily.[1]

Recently, a new method for the sequential degradation of peptides using 2-fluoropyridine *N*-oxide has been suggested.[2] We felt that it would be profitable to examine the rotatory dispersion of pyridyl *N*-oxide derivatives (I) in order to correlate the Cotton effect with the configurations of the amino-acids.

The preference given to these derivatives was justified by the following considerations: (i) 2-fluoropyridine *N*-oxide condenses easily with free amino-groups; (ii) no racemisation occurs during cleavage of the *N*-terminal amino-acid; (iii) the resulting derivatives shown an ultraviolet spectrum similar to that of 2-methylaminopyridine *N*-oxide[3] with a maximum near to 330 mμ.

Even if the absorption is strong at this wavelength ($\log \epsilon \sim 3{\cdot}7$ in methanol), the recording spectropolarimeters now available make it possible to perform o.r.d. measurements through this absorption band.*

The o.r.d. curves of several amino-acid derivatives have been studied and the absorption band centred at 330 mμ was found to be optically active. The resulting data led us to divide the compounds studied into two different groups (Table):

Group 1: Derivatives with no group in R absorbing above 215 mμ.

Group 2: Derivatives having groups in R absorbing between 215 and 330 mμ.

TABLE

O.r.d. curves amplitudes of compound (I)§ (L-*series*)

Group	*N*-(2-Pyridyl *N*-oxide) derivatives of:	*a***
1	Alanine	+ 62
	α-Aminobutyric acid	+ 38
	Norvaline	+ 22
	Valine	+ 55
	Leucine	+ 30
	Isoleucine	+ 38
	Alloisoleucine	+ 49
	Homoserine	+ 46
	Threonine	+ 83
2	Methionine	− 13
	S-Methylcysteine	− 24
	Phenylalanine	−152
	α-Aminophenylacetic acid	−287
	Tyrosine	−185
	Tryptophan	−259

§ The compounds listed have been prepared from Fluka CHR amino-acids and 2-fluoropyridine *N*-oxide. They are crystalline products and gave correct elemental analyses.

** The amplitudes reported are the algebraic differences between the molecular rotations of the first and second extrema in the o.r.d. curve divided by a 100. Since the medium values of several independent measurements taken for enantiometric pairs agreed to within 5%, the amplitudes for the L-isomer only are given in each case.

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* O.r.d. curves were measured with a Cary Model 60 spectropolarimeter at 25° in methanol solution.

(I)

$H_2N{\cdot}CHR^1R^2$

(II)

The *N*-(2-pyridyl *N*-oxide)-L-amino-acids exhibit a Cotton effect which is positive if they belong to the first group and negative if they belong to the second, the reverse being true of members of the D-series (Figure 1).

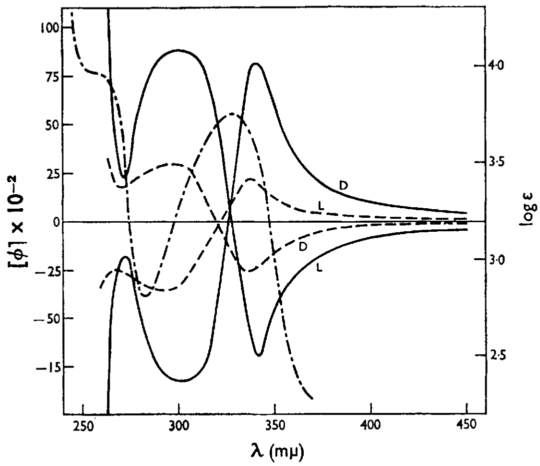

FIGURE 1. *O.r.d. curves of* N-(2-*pyridyl* N-*oxide*)-*phenylalanine* (——) *and* N-(2-*pyridyl* N-*oxide*)-*valine* (......). *U.v spectrum of* N-(2-*pyridyl* N-*oxide*)-*valine* (–·–·–).

In the case of some amines having a phenyl group directly attached to the asymmetric carbon, it has been shown that when the phenyl is replaced by a cyclohexyl[4] or an ethyl group[5] the sign of the Cotton effect in the o.r.d. curves for some of their derivatives is inverted. The chromophoric group influence on o.r.d. curves has been cited as evidence also for amino-acids[6] and for some of their derivatives, *i.e.*, phenylthiohydantoins,[1] thiobenzoyl[7] and dimedone[8] derivatives.

If we take into account the influence of every chromophore present in the molecule, the results obtained here with pyridyl *N*-oxide derivatives of the monocarboxylic α-amino-acids can be generalized.

The compound (I) obtained from an L-amino-acid is projected with the hydrogen atom below and the other groups in the plane (Figure 2) (*cf.* projections used for *RS* convention).[9] The three substituents lying in the plane of the ring are then read according to the increasing wavelength of their absorption maximum. When this occurs in a clockwise order, then the Cotton effect is positive; when the sequence is anticlockwise, the Cotton effect is negative.†

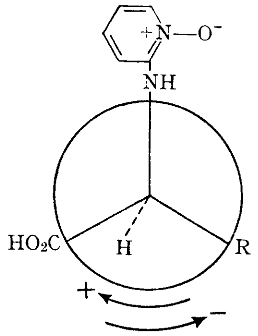

FIGURE 2. *Three-dimensional model of the compound* (I) *from an* L-*amino-acid.*

According to this procedure, since the carboxyl group has an absorption maximum around 215 mμ, all the L-series derivatives of the first group in the Table will have a positive Cotton effect. Conversely those of the second group, in which R contains a chromophore‡ with an absorption maximum at a wavelength higher than 215 mμ, will have negative Cotton effect.

The curve amplitude of the first-group compounds decreases with the length and increases with branching of the carbon chain. Additional asymmetric centres seem to be unimportant.

In the second group, the data obtained so far suggest that the curve amplitude increases (i) when the difference between the wavelength of absorption maximum of the carboxyl group and that of the chromophore contained in R increases; (ii) when the distance between the chromophore and the asymmetric carbon atom decreases.

Further studies are now in progress on compounds with the general formula (II), in order to

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† In the attempt to assign the sign of optical rotation at 589 mμ (ref. 10) and of Cotton effect in o.r.d. curves (ref. 11) analogous schemes have been suggested in the past. However these schemes have considered parameters different from those reported here.

‡ The reported wavelengths (ref. 12) for the absorption maximum of phenylalanine, tyrosine, and tryptophan are 267, 275, and 280 mμ respectively. An absorption maximum at 240 mμ is reported (ref. 6a, d) for methionine.

determine how the different absorption of the two substituents influences the sign and the amplitude of the Cotton effect in the o.r.d. curve of their *N*-[2-pyridyl *N*-oxide] derivatives.

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[1] C. Djerassi, K. Undheim, R. C. Sheppard, W. G. Terry, and B. Sjöberg, *Acta Chem. Scand.*, 1961, **15**, 903.

[2] (a) D. Sarantakis, J. K. Sutherland, C. Tortorella, and V. Tortorella, *Chem. Comm.*, 1966, 105; (b) V. Tortorella and G. Bettoni, *Gazzetta*, 1967, **97**, 85; (c) V. Tortorella, G. Tarzia, and G. Bettoni, to be published.

[3] A. R. Katritzky, *J. Chem. Soc.*, 1957, 191.

[4] A. La Manna, V. Ghislandi, P. M. Scopes, and R. J. Swan, *Il Farmaco, Edizione Scientifica* (*Pavia*), 1965, **20**, 842.

[5] S. Yamada, K. Ishikawa, and K. Achiwa, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 921.

[6] (a) J. A. Shelmann in C. Djerassi, ed., "Optical Rotatory Dispersion" McGraw-Hill, New York, 1960, 210; (b) J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 1965, 294; (c) T. M. Hooker and C. Tanford, *J. Amer. Chem. Soc.*, 1964, **86**, 4989; (d) K. Bláhá, I. Frič, and P. Hermann, *Coll. Czech. Chem. Comm.*, 1965, **30**, 304.

[7] B. Sjöberg, K. Karlen, and R. Dahlbom, *Acta Chem. Scand.*, 1962, **16**, 1071.

[8] P. Crabbé and B. Halpern, *Chem. and Ind.*, 1965, 346.

[9] R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 1956, **12**, 81.

[10] R. E. Marker, *J. Amer. Chem. Soc.*, 1936, **58**, 976.

[11] B. Sjöberg, D. Cram, L. Wolf, and C. Djerassi, *Acta Chem. Scand.*, 1962, **16**, 1079.

[12] "Organic Electronic Spectral Data", Interscience, New York, vol. I, II, III, IV.