Giancarlo Bettoni, Flaviano Morlacchi, Roberto Perrone, Vicenzo Tortorella
and Claudio Vetuschi

Istituto di Chimica Farmaceutica e Tossicologica, Università, 70126 Bari, Italy

Chiroptical properties of several 2 or 3 monosubstituted azetidines, pyrrolidines and piperi-
dines as free bases and N-[2-pyridyl N-oxide] derivatives has been examined. The absolute con-
figuration can be unambiguously established, independently on the nature of the substituent and
the size of the ring, only for 2-substituted N-[2-pyridyl N-oxide]amine derivatives. This behav-
iour is explained in terms of limited rotational freedom in these compounds.

where R = H or a chromophoric group
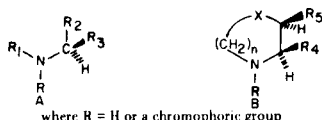
We have long been interested in the chiroptical proper-
ties of some chromophoric derivatives of primary and sec-
ondary open-chain amines with the general formula (A),
containing an asymmetric carbon center attached to the
nitrogen atom (2). It has been established that, when the
amine part contains a chromophoric group in addition to
that carried by the nitrogen, the sign of the Cotton effect
basically depends on the geometry of the homo-conju-
gated chromophore, resulting from the spatial arrange-
ment of two unsaturated groups. When R_3 is an alkyl
group, however, the sign and the absolute magnitude of
the Cotton effect depend on the presence of a favoured
conformer in the mixture of rotamers.

This regular behaviour has been observed with all the
amino derivatives (A) in which the chromophoric group R
greatly restricts free rotation about the N-R bond. In fact,
it has been found more recently (3) that, if the molecular
structure of R lacks the steric or electronic features needed
for the conformational stability of the compound (A),
then it is no longer possible to correlate the absolute con-
figuration of the amine with the sign of the Cotton effect
in the condensation product.

The work has now been extended to chiral cyclic am-
ines with the general formula (B), containing an asymmet-
ric carbon center in positions 2 and 3 with respect to the
amine nitrogen. The aim of this was twofold: partly to
examine the case of only steric hindrance to rotation about
the N-R bond, caused by substituents in the amine part,
and partly to test the validity of the above-mentioned
semi-empirical rule for compounds different from those
considered before.

Other authors have already examined the chiroptical

properties of some derivatives of these amines, namely
thiourethanes, dicarbamates, N-chloro derivatives, nitroso
derivatives, etc, (4).

The chromophore in the present work was the 2-pyridyl
N-oxide group, which is the R group we had used most
often before (2a,b). The cyclic amines examined had the
general formula (B), with R = H (see Table I). For many
of these absolute configuration first had to be determin-
ed by chemical correlations (5-10). The data in Tables
II and III show the physicochemical characteristics and the
chiroptical properties of the corresponding pyridyl N-ox-
ide derivatives.

The circular dichroism curves recorded in methanol for
the free amine (B) with R = H and without any additional
chromophoric groups in the substituents R_4 and R_5 (cf.
Table I) give no indication as to the configuration, because
they have no peaks at wavelengths greater than 210 nm,
and the shape of the dichroism curve in this region cannot
be classified, owing to strong absorption and the low ro-
tational strength in the compounds studied. Better results
have been obtained by using hydrocarbons as solvents (11).

In agreement with previous observations (12), amines
with a carboxyl group in R_4 or R_5 show a positive Cotton
effect centered on a position corresponding to an n → π*
transition. Only amines with an aromatic substituent in
R_4 next to the amine nitrogen gave a Cotton effect with
a fine structure in the region of 250-270 nm, the sign of
which was reversed on going from 2-phenylpiperidine (XII)
to 2-(2'-pyridyl)piperidine (XIII).

The introduction of the 2-pyridyl N-oxide group on the
nitrogen shifts the absorption maximum of these com-
pounds towards longer wavelengths, thus facilitating the
measurement of the circular dichroism. The data in Table
III show that all the compounds under consideration have
a dichroic maximum around 330 nm. All the compounds
with a substituent in position 2 that is oriented like R_4
give a negative Cotton effect, irrespective of the nature of
this substituent and of the size of the ring. If, however,
the substituent is further away from the chromophoric
group, the sign of the Cotton effect is no longer consistent.

Table I

CD Data for Free Amino Compounds

Compound	n	X	R4	R5	CD λ max (nm)	[θ]·10^{-2}	Abs. conf. references
S-(-)-I	0	-----	COOH	H	217	+12	(12)
R-(-)-II		-S-	COOH	H	217	+ 9	(13)
S-(-)-III		-CHOH-	COOH	H	215	+ 6	(14)
S-(-)-IV	1	-CH₂-	COOH	H	215	+ 6	(15)
R-(-)-V		-CH₂-	CH₃	H	-----	-----	(16)
S-(-)-VI		-CH₂-	C₆H₅	H	260	+40	(7)
R-(+)-VII		-CH₂-	H	CH₃	-----	-----	(17)
S-(+)-VIII		-CH₂-	H	C₆H₅	-----	-----	(10)
S-(-)-IX		-CH₂-	COOH	H	212	+13	(18)
R-(-)-X		-CH₂-	CH₃	H	-----	-----	(12,18)
R-(-)-XI		-CH₂-	C₂H₅	H	-----	-----	(19)
S-(-)-XII		-CH₂-	C₆H₅	H	260	+ 3	(9)
S-(-)-XIII	2	-CH₂-	β-pyridyl	H	260	-42 (a)	(20)
R-(-)-XIV		-CH₂-	H	COOH	217	+ 5	(21)
R-(-)-XV		-CH₂-	H	COOC₂H₅	-----	-----	(5)
R-(-)-XVI		-CH₂-	H	CH₃	-----	-----	(5,6)
S-(+)-XVII		-CH₂-	H	C₆H₅	-----	-----	(8)
8aR-(+)-XVIII		-CH₂-	trans-decahydroquinoline		-----	-----	(22)

(a) Optical purity 65%.

Thus, the compounds substituted in position 3 exhibit a positive or a negative Cotton effect according to whether the ring has five or six members, though the chirality remains the same.

This behaviour might be attributed to the fact that the substituents in position 2 strongly restrict free rotation about the N-R bond, hence they condition the chiroptical properties of the pyridyl N-oxide derivatives of the corresponding amines, these properties being connected exclusively with the orientation of the substituent.

When, however, the substituent is in position 3, the pyridyl N-oxide group has greater rotational freedom, so that the sign of the Cotton effect of these compounds depends mainly on the conformational changes in the ring structure.

This hypothesis was confirmed by recording the circular dichroism curve for the pyridyl N-oxide derivative of 8a-R-trans-decahydroquinoline (XVIII), which can be regarded as a piperidine ring substituted in positions 2 and 3. The Cotton effect observed for this compound was found to agree with that expected from the orientation of the 2-substituent according to the absolute configuration established before (22).

It can be concluded from these observations that the investigation of the chiroptical properties of pyridyl N-oxide derivatives of cyclic amines substituted in position

2 permits their absolute configuration to be established unambiguously.

EXPERIMENTAL

General Procedure for the Preparation of N-[2-Pyridyl N-oxide]-amino Acid Derivatives.

Amino acid (1 mmole), 2-fluoropyridine N-oxide (1.2 mmoles), sodium bicarbonate (3 mmoles), dissolved or suspended in water (1-3 ml.) were stirred at room temperature for 48 hours. By careful acidification with diluted hydrochloric acid, solid precipitates were obtained which were purified, after decoloration with active charcoal, by crystallization. Physical and analytical data are reported in Table II.

General Procedure for the Preparation of N-[2-Pyridyl N-oxide]-amino Derivatives.

The amino compound (1 mmole) was reacted with 2-fluoropyridine N-oxide (1.2 mmoles) in the presence of sodium bicarbonate (1 mmole) in a mixture (1:1) of water-ethanol (5 ml.) at room temperature for 3 days. The reaction mixture was then concentrated under vacuum and extracted with dichloromethane.

The residue obtained from evaporation of the organic solvent

Table II

Physical and Analytical Data for N-[2-Pyridyl N-Oxide]amino Derivatives (a)

N-[2-Pyridyl N-Oxide] Derivatives of	formula	crystallized from	m.p. °C	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
S-(-)-I	$C_9H_{10}N_2O_3$	Methanol	220 dec.	55.66	55.41	5.19	5.40	14.43	14.31
R-(-)-II	$C_9H_{10}N_2O_3S$	Water	192 dec.	47.79	47.57	4.46	4.53	12.39	12.20
R-(-)-V	$C_{10}H_{14}N_2O$	(b)		67.38	66.91	7.92	8.00	15.72	15.64
S-(-)-VI	$C_{15}H_{16}N_2O$	(b)		74.97	74.66	6.71	6.87	11.66	11.62
R-(+)-VII	$C_{10}H_{14}N_2O$ picrate	Ethanol	138-140	47.18	47.20	4.21	4.23	17.19	17.19
S-(+)-VIII	$C_{15}H_{16}N_2O$ picrate	Ethanol	148-149	53.73	53.84	4.08	4.31	14.92	14.61
S-(-)-IX	$C_{11}H_{14}N_2O_3$	Methanol-water	203 dec.	59.45	59.56	6.35	6.63	12.60	12.63
R-(-)-X	$C_{11}H_{16}N_2O$	Benzene-n-Hexane	112-113	68.72	68.76	8.39	8.40	14.57	14.51
R-(-)-XI	$C_{12}H_{18}N_2O$	Dichloromethane-n-Hexane	56-57	69.87	69.50	8.80	8.80	13.58	13.37
S-(-)-XII	$C_{16}H_{18}N_2O$	oil		75.56	75.84	7.13	7.14	11.02	11.04
S-(-)-XIII	$C_{15}H_{17}N_3O$	oil		70.56	70.74	6.71	6.48	16.46	16.41
R-(-)-XIV	$C_{11}H_{14}N_2O_3$	Methanol-ether	163-164	59.45	59.12	6.35	6.52	12.60	12.59
R-(-)-XV	$C_{13}H_{18}N_2O_3$	oil		62.38	62.12	7.25	7.31	11.19	11.24
R-(-)-XVI	$C_{11}H_{16}N_2O$	Dichloromethane-n-Hexane	148-149	68.72	68.79	8.39	8.16	14.57	14.68
S-(+)-XVII	$C_{16}H_{18}N_2O$	oil		75.56	75.28	7.13	6.84	11.01	11.27
8aR-(+)-XVIII	$C_{14}H_{20}N_2O$ HCl	Ethanol-ether	135	62.55	62.63	7.88	8.07	10.42	10.30

(a) Derivatives of compounds S-(-)-III and S-(-)-IV have been reported elsewhere (2a). (b) Purified by sublimation (120-130°; 0.03 mm Hg).

Table III

Uv and CD data for N-[2-Pyridyl N-Oxide]amino Derivatives

N-[2-Pyridyl N-Oxide] Derivatives of	UV λ max (nm)	log ε	CD λ max (nm)	$[\theta]$ 10^{-2}
S-(-)-I	330	3.63	329	-178
R-(-)-II	325	3.53	325	-168
S-(-)-III	335	3.61	335	-172
S-(-)-IV	335	3.59	335	-142
R-(-)-V	330	3.52	337	- 79
S-(-)-VI	335	3.61	337	- 64
R-(+)-VII	342	3.61	342	+ 37 (a)
S-(+)-VIII	337	3.63	337	+ 95
S-(-)-IX	325	3.53	325	-187
R-(-)-X	327	3.49	328	- 79
R-(-)-XI	332	3.53	332	-125
S-(-)-XII	315	3.36	332	- 71 (b)
S-(-)-XIII	315	3.44	330	- 9 (c)
R-(-)-XIV	325	3.53	332	- 20
R-(-)-XV	323	3.51	330	- 20
R-(-)-XVI	328	3.50	323	- 11
S-(+)-XVII	325	3.53	323	- 43
8aR-(+)-XVIII	320	3.08	325	- 10 (d)

(a) Optical purity 46%. (b) Optical purity 50%. (c) Optical purity 65%. (d) Optical purity 76%.

was purified by column chromatography on silica gel (ratio 1:20). Liquid derivatives were then distilled twice under vacuum. Solid derivatives were crystallized or sublimed. Physical and analytical data are reported in Table II.

REFERENCES AND NOTES

(1) Some of the results of this work has been presented at the Fifth International Congress of Heterocyclic Chemistry held in Ljubljana, Yugoslavia, July, 1975.

(2a) V. Tortorella and G. Bettoni, Ann. Chim. (Rome), 58, 286 (1968); (b) V. Tortorella, G. Bettoni and R. Perrone, Gazz. Chim. Ital. 103, 1083 (1973); (c) V. Tortorella and N. Tangari, ibid., 103, 1037 (1973); (d) G. Bettoni, V. Tortorella, A. Hope and B. Halpern, Tetrahedron, 31, 2383 (1975).

(3a) G. Bettoni, S. Catsiotis, R. Perrone and V. Tortorella, Gazz. Chim. Ital., 107, 111 (1977); (b) G. Bettoni, S. Catsiotis and C. Franchini, Farmaco, Ed. Sci., 31, 367 (1977).

(4) P. Crabbe', "ORD and CD in Chemistry and Biochemistry," Academic Press, New York, N. Y., 1972.

(5) G. Bettoni, E. Duranti and V. Tortorella, Gazz. Chim. Ital., 102, 189 (1972).

(6) G. Bettoni, R. Perrone and V. Tortorella, ibid., 102, 196 (1972).

(7) F. Morlacchi, V. Losacco and V. Tortorella, ibid., 105, 349 (1975).

(8) F. Morlacchi, M. D'Ambruoso and V. Tortorella, Chim.

Ind. (Milan), 56, 456 (1974).

(9) C. Vetuschi, A. Ottolino and V. Tortorella, Gazz. Chim. Ital., 105, 935 (1975).

(10) G. Bettoni, C. Cellucci and V. Tortorella, J. Heterocyclic Chem., 13, 1053 (1976).

(11) R. G. Kostyanovsky, I. M. Gella, V. I. Markov and Z. E. Samojlova, Tetrahedron, 30, 39 (1974).

(12) J. Cimerman-Craig and S. K. Roy, Tetrahedron, 21, 391 and 401 (1965).

(13) S. Ratner and H. T. Clarke, J. Am. Chem. Soc., 59, 200 (1937).

(14) J. Zussman, Acta Cryst., 4, 72, 493 (1951).

(15) D. A. Buckingham, L. G. Marzilli, I. E. Maxwell, A. M. Sargeson and H. C. Freeman, Chem. Commun., 583 (1969).

(16) P. Karrer and K. Erhardt, Helv. Chim. Acta, 34, 2202 (1951).

(17) D. Fles and T. Ghyczy, Croat, Chem. Acta, 36, 27 (1964).

(18) H. Ripperger and K. Schreiber, Tetrahedron, 21, 1485 (1965).

(19a) H. Ripperger, K. Schreiber and F. J. Sych, J. Prakt. Chem., 312, 471 (1970); (b) H. C. Beyerman, S. Van Der Bosch, J. H. Breuker and L. Maat, Rec. Trav. Chim., 90, 755 (1971).

(20) R. Lukes, A. A. Arojan, J. Kovar and K. Blaha, Collect. Czech. Chem. Commun., 27, 751 (1962).

(21) H. Ripperger and K. Schreiber, Chem. Ber., 102, 2864 (1969).

(22a) H. Ripperger and K. Schreiber, Tetrahedron, 25, 737 (1969); (b) R. A. Johnson, H. C. Murray, L. M. Reineke and G. S. Fonken, J. Org. Chem., 33, 3207 (1968).