Opposite CD Curves in Chromophoric Derivatives of 3-Substituted 5-and 6-Membered Cyclic Amines

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Absolute configuration was assigned to 3-isopropylpyrrolidine by chemical correlation with R-3-isopropylsuccinic acid. The comparison between CD curves of 3-substituted piperidines, morpholines and pyrrolidine having the same chirality shows that the chiroptical properties of these five and six-membered cyclic amine derivatives are opposite.

Our past researches on a large series of chromophoric derivatives of amino compounds having a chiral centre in a position adjacent to nitrogen atom, allowed us to enunciate semiempirical rules which correlate chiroptical properties and chiral centre absolute configuration (1).

These semiempirical rules can be safely applied in all those cases in which the classes of molecules under investigation: i) can assume a similar spatial arrangement for steric and/or electronic factors which severely limit their conformational freedom; ii) contain additional chromophoric groups which gave rise to an intrinsically disymmetric chromophore.

In the first case, in fact, the presence of a rotamer largely favoured influences, in a predominant way, the Cotton effect sign whereas in the second case, quite independently on the rotameric mixture composition, the Cotton effect is practically governed by the high amplitude of the disymmetric chromophore.

(A)   (B)
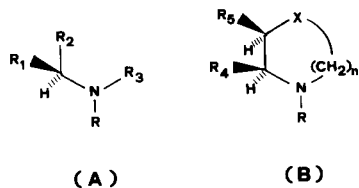
As far as pyridine N-oxide derivatives of A-type amines are concerned, the presence of both the above mentioned requisites have been thoroughly examined and verified by means of nmr (2) and X-rays (3) spectrometric methods. The data obtained from the ORD and CD measurements, together with the Cotton effect sign inversion observed in primary and secondary derivatives of amines having the same chirality, have been rationalized in a semiempirical rule. This rule relates the chiroptical properties to the position assumed by the substituent on the chiral centre with respect to the planar portion of the molecule.

Lately the research has been extended to B-type five and six-membered cyclic amines with only one chiral atom in α or β position (4,5). The analyses of the CD curves of these compounds indicate that in the α-substituted derivatives having the same absolute configuration, a Cotton ef-

fect of the same sign is always observed independently of the ring size. In the β-substituted derivatives a Cotton effect coherent with that one shown by the α-substituted amines was observed either in piperidine (4) or morpholine (5) derivatives. Two pyrrolidine derivatives investigated showed a Cotton effect which sign is opposite in respect to the one shown by the β-substituted six-membered cyclic amines having the same chirality.

Table I

UV and CD Data for 2-Pyrrolidinopyridine N-Oxide Derivatives

Pyridine N-oxide derivatives of	R_s	UV		CD	
		λ max (nm)	log ϵ	λ max (nm)	$[\theta]10^{-2}$ (a)
S-(-)-VIa	CH$_3$	342	3.61	342	-80
S-(-)-VIb	C$_2$H$_5$	340	3.58	338	-79
S-(-)-VIc	n-C$_3$H$_7$	340	3.54	338	-65
R-(-)-VId	iso-C$_3$H$_7$	340	3.60	338	-85
R-(-)-VIe	C$_6$H$_5$	337	3.63	337	-95

(a) Reported values are referred to optically pure amino compounds.

In order to examine the chiroptical behaviour of the substituted pyrrolidines, the research has been extended to other compounds corresponding to the general formula B with n = 1; X = CH$_2$; R$_4$ = H; R$_s$ = C$_2$H$_5$, n-C$_3$H$_7$, iso-C$_3$H$_7$.

These compounds have been obtained in an optically active form through the imide or the N-benzyl derivatives from the corresponding succinic acid according to the synthetic path shown in the figure.

The absolute configuration of the first two has been the subject of a recently published note (6). In the case of 3-isopropylpyrrolidine the synthesis has been carried out starting from the R-isopropylsuccinic acid with known optical purity.
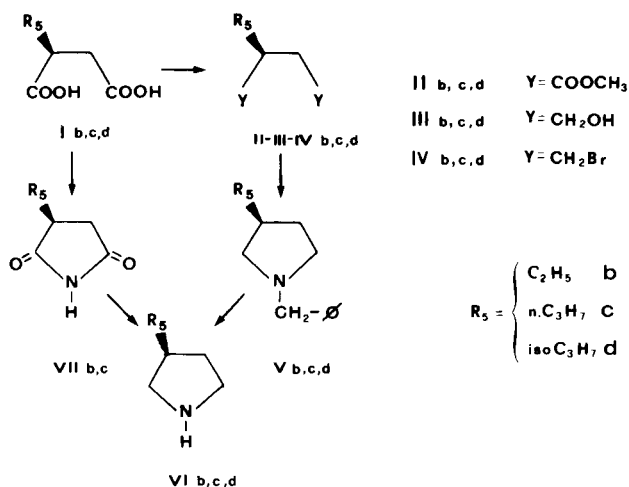
Previous (7) chemical correlations carried out on these classes of compounds through the same synthetic pathway used in this work, have proved that no racemization occurs. On this basis and knowing both the chirality and the $[\alpha]_D$ value of the starting isopropylsuccinic acid, the absolute R configuration and the specific maximum rotatory power of 19.5° can be assigned to the obtained (-)-3-isopropylpyrrolidine.

Table 2

NMR Data for 2-Pyrrolidinopyridine N-Oxide Derivatives
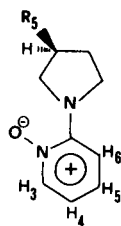
R_5	H_6	H_4	$H_5 + H_3$	Protons in R_5
CH_3	8.00	7.06	6.50-6.66	1.16 (d, 3H, CH_3)
C_2H_5	8.01	7.10	6.48-6.66	0.98 (t, 3H, CH_3CH_2), 1.34-1.70 (m, 2H, CH_2CH_3)
$n\text{-}C_3H_7$	8.03	7.06	6.45-6.70	0.90 (m, 3H, CH_3CH_2)
$iso\text{-}C_3H_7$	7.98	7.04	6.46-6.65	0.90-1.00(double d, 6H, isopropyl CH_3)
C_6H_5	8.03	7.08	6.50-6.70	7.26 (s, 5H, aromatic H)

All CD curves of pyridine N-oxide derivatives of β-substituted pyrrolidines with the indicated absolute configuration show, in methanol, a negative Cotton effect in the 330-340 nm region caused by the 2-aminopyridine

N-oxide chromophore. The spectroscopic data for all the 3-substituted pyrrolidines are summarized in Table I.

The comparison between these data and those obtained for the derivatives of the 3-substituted piperidines (4) and morpholines (5) having the same chirality, proves that the two series of cyclic amines with five and six members, respectively, have opposite chiroptical properties.

This behaviour can be ascribed to the fact that the presence of a substituent in the β-position of the pyrrolidine ring greatly influences the ring conformation. Thus the main contribution for the Cotton effect is given by the spatial disposition of the carbon atoms adjacent to the nitrogen. This hypothesis is also supported by the fact that, unlike six-membered cyclic amines, the Cotton effect amplitudes of β-substituted pyrrolidines are quite high and their absolute values do not change greatly on changing the R_5 group in the β-position.

These results show how inopportune it can be to apply or extend the semiempirical rules, which correlate the Cotton effect sign to the absolute configuration, to structures not completely similar to those for which the rule has been verified.

EXPERIMENTAL

General Procedure for the Preparation of 2-Pyrrolidinopyridine N-Oxide Derivatives.

The amino compounds (1 mmole) were reacted with 2-fluoropyridine-N-oxide (1.2 mmoles) in the presence of sodium bicarbonate (1 mmole) in water (5 ml) (in the case of $R\text{-}(\text{-})\text{-Vle}$ a mixture 1:1 of water-methanol was used). The reaction mixture was then extracted with dichloromethane. When the reaction was conducted in an aqueous alcohol medium the solution was first concentrated under vacuum.

After evaporation of the dichloromethane, highly viscous oils that can be stored in the dark at 0° were obtained. They were purified by column chromatography on silica (ratio 1:20) and by double microdistillation under high vacuum; on the distilled products were immediately determined the nmr, CD and UV spectra. In the nmr spectra the protons of the pyridine ring show a pattern in agreement with the data previously reported for the amines (A) (2) (Table 2).

$R\text{-}(+)\text{-}3\text{-Isopropyl-}N\text{-benzylpyrrolidine}$ (Vd).

$R\text{-}(+)\text{-}2\text{-Isopropyl-1,4-dibromobutane}$, $[\alpha]_D$ + 9° (neat) obtained as reported (8) from $R\text{-}(\text{-})\text{-}2\text{-isopropylsuccinic}$ acid with $[\alpha]_D\text{-}9°$ (water) [optical purity about 40% with respect to the maximum value reported (10)] (3 g), was reacted (9) with benzylamine. Compound $R\text{-Vd}$ (1 g) was obtained, bp 135°/l mm Hg, $[\alpha]_D$ + 0.21 (neat), d = 0.9344; nmr 0.80-0.88 (double d, 6H, isopropyl CH_3), 1.30-2.90 (m, 8H), 3.58 (s, 2H, benzyl CH_2), 7.10-7.30 (m, 5H, aromatic).

The Picrolonate had mp 134° which was crystallized from ethanol.

Anal. Calcd. for $C_{24}H_{29}N_5O_5$: C, 61.66; H, 6.25; N, 14.98. Found: C,

62.00; H, 6.05; N, 15.28.

R-(-)-3-Isopropylpyrrolidine (VId).

Compound *R*-Vd (1 g), dissolved in glacial acetic acid was hydrogenated in a Gallenkamp glass apparatus in the presence of 10% Pd/C (0.25 g) as catalyst at room temperature and 1 atmosphere . After 24 hours hydrogenation was completed. Compound *R*-VId (0.3 g) was obtained, bp 140°, [*a*]$_D$-7.8° (neat), d = 0.847; nmr: 0.84-0.98 (double d, 6H, isopropyl CH$_3$), 1.90 (s, 1H, NH). The picrolonate had mp 252°, crystals from ethanol.

Anal. Calcd. for C$_{17}$H$_{23}$N$_5$O$_5$: C, 54.10; H, 6.14; N, 18.56. Found: C, 54.32; H, 6.04; N, 18.69.

Acknowledgments.

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