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ON THE CHIROPTICAL PROPERTIES OF KETIMINE STRUCTURES DERIVED FROM 5-CHLORO-2-HYDROXYBENZOPHENONE

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Abstract—The CD curves of several ketimines derived from condensation of 5-chloro-2-hydroxybenzophenone with optically active amino compounds have been measured. The geometric relationship between the chromophoric groups in the amino moiety and the 5-chloro-2-hydroxybenzophenone chromophore, which depends on the absolute configuration and conformation of the molecule, is more important than chirality at the asymmetric C atom in determining the chiroptical properties of these compounds.

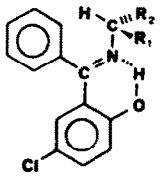
Recently[1] the 5-chloro-2-hydroxybenzophenone was introduced as a N-protecting reagent for amino acids in peptide synthesis. The resulting ketimine derivatives (A) present a particular rigid structure due to the presence of the C=N double bond, and the H-bond between the O and N atoms. In addition the presence of the bulky phenyl group near the single bond linking the nitrogen to the asymmetric carbon would be expected to further restrict the small degree of conformational freedom in these molecules. A study of the chiroptical properties of the ketimines was undertaken to evaluate

(i) if this chromophore could be used to determine the absolute configuration of chiral amino compounds.

(ii) if the presence of additional chromophoric groups in the R_1 and R_2 substituents of (A) regulates the sign of the Cotton effect as observed in other rigid structures such as pyridyl-N-oxide derivatives,[2] vinylogous amides,[3] vinylogous urethans[4] and nitropyridyl derivatives.[5]

The preparation of the amino acid derivatives (1-7) has been described elsewhere.[1]

Compounds (8–12) were obtained by refluxing equimolecular amounts of 5-chloro-2-hydroxybenzophenone and the amine in benzene. The NMR and IR spectra of the derivative are consistent with the proposed structure (A). The difficult exchange of the phenolic OH group of the ketimines with D_2O suggests the presence of a strong H-bond between the O and N atoms.



(A)

Table 1. Chiroptical and ultraviolet data of ketimine derivatives (1–12)*

Ketimine	derived from	in methanol				in dioxane	
		λ max	$[\theta]_{max}\cdot10^{-2}$	λmax	$[\theta]_{max}\cdot10^{-2}$	λ max	$[\theta]_{max}\cdot10^{-2}$
1	S-alanine	3.30 (415)	+ 6 (410)	3.55 (337)	+23 (335)	3.65 (338)	+32 (335)
2	S-valine	3.38 (415)	+5 (415)	3.53 (337)	+16 (335)	3.65 (338)	+30 (336)
3	S- serine	2.92 (415)	+5 (415)	3.49 (337)	+12 (335)	3.60 (337)	+14 (335)
4	S-phenylalanine	3.09 (415)	-14(415)	3.49 (340)	-47 (335)	3.56 (340)	-67 (335)
5	Im-N-benzyl-S-histidine	3.22 (415)	-14(415)	3.47 (340)	-44 (337)	3.62 (336)	-96 (335)
6	O-benzyl-S-tyrosine	3.15 (415)	-23 (410)	3.47 (340)	-61 (335)	3.61 (340)	-135 (335)
7	S-tryptophane	3.35 (415)	-47 (415)	3.56 (337)	-135(337)	3.68 (337)	-184 (339)
8	S-1-phenyl-1-amino--ethane	3.23 (415)	+51 (410)	3.60 (335)	+151(330)	3.65 (335)	+173 (335)
9	S-1-phenyl-2-amino--propane	3.31 (412)	+68(410)	3.37 (332)	+125 (330)	3.64 (335)	+147 (332)
10	S-1-(1-naphthyl)-1--aminoethane	3.28 (417)	+70(415)	3.61 (335)	+220(330)	3.67 (335)	+274 (332)
11	S-1-cyclohexyl-1--aminoethane	3.46 (412)	+35(410)	3.45 (335)	+ 31 (332)	3.66 (335)	+ 47 (330)
12	S-1-cyclohexyl-2--aminopropane	3.43 (412)	+38(410)	3.48 (335)	+45 (332)	3.57 (335)	+54 (330)

*Figures in brackets indicate the maxima position in nm.

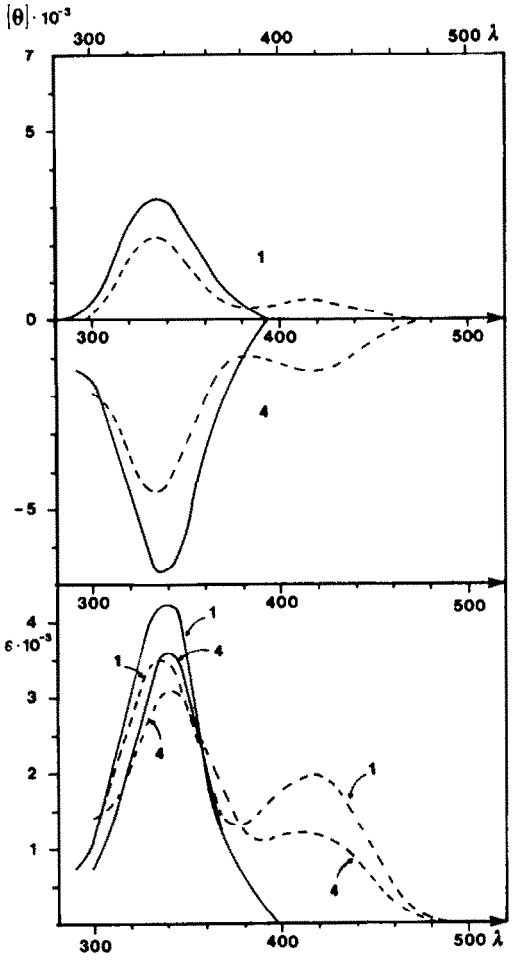


Fig. 1. CD and UV curves of S-alanine (1) and S-phenylalanine (4) derivatives in dioxane (——) and in methanol (– – –).

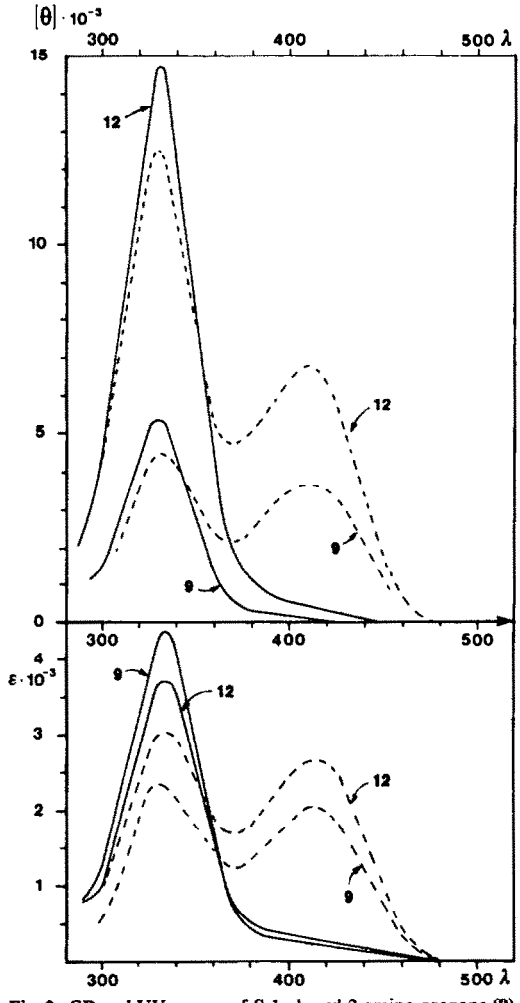


Fig. 2. CD and UV curves of S-1-phenyl-2-amino-propane (9) and S-1-cyclohexyl-2-amino-propane (12) derivatives in dioxane (——) and in methanol (– – –).

The UV and CD spectra were run in dioxane and in methanol. All compounds show an absorption band in the region 335–340 nm; and in methanol an additional band near 415 nm is also present. In all compounds the Cotton effect associated with these transitions has the same sign.

Typical examples are illustrated in Figs. 1 and 2 and the UV and CD maxima are given in Table 1.

These data demonstrate that the chiroptical properties

Table 2. Analytical figures of ketimine derivatives (8–12)

Compounds	$[\alpha]_D$	Resonance position		Elemental analysis					
				calcd.			found		
		CH_3	CH	C	H	N	C	H	N
8	+120°	146	425	75.11	5.40	4.17	75.46	5.60	4.07
9	+340°	121	338	75.51	5.76	4.03	75.29	5.98	3.80
10	+413°	161	517	77.82	5.23	3.63	78.16	5.43	3.53
11	+ 86°	108	305	73.78	7.07	4.10	73.52	6.87	3.92
12	+ 29°	113	335	74.24	7.36	3.94	74.08	7.31	3.48

of these ketimine derivatives are influenced by the conformational freedom around the C–N linkage and, mainly, by the presence of a chromophoric grouping in R_1 and in R_2. In fact if R_2 is a carboxyl function (**1–3**) or an aromatic group (**8–10**) a positive Cotton effect is observed.

When both R_1 and R_2 contain chromophores the chromophore which absorbs at higher wavelength predominates. For example, the aromatic amino acid derivatives (**4–7**) yield a negative Cotton effect which is opposite to that shown by alkyl amino acid derivatives belonging to the same stereochemical series.

When no chromophoric groups are present in the amino moiety of the ketimine derivatives (**11** and **12**) the Cotton effect depends on the percent of the preferred rotamer in solution, however their amplitude is smaller than that shown by the corresponding compounds where the cycloalkyl group is replaced by an aromatic ring.

EXPERIMENTAL

Microanalyses were conducted by Dr. R. De Leonardis, Istituto di Chimica Farmaceutica Bari, with a "Hewlett-Packard" mod 185 C, H, N, Analyzer. The m.ps, determined with a "Tottoli" apparatus, are not corrected. Optical rotations were determined in methanol with a "Roussel-Jouan" electronic micropolarimeter and CD curves with a Cary 61 dichograph. IR and NMR spectra (in CCl_4) were determined with a "Perkin-Elmer" mod 257 and with a "Varian" HA-100 spectrometers respectively; resonance positions are expressed in c/s in respect to TMS as internal standard.

N - (*α* - *Phenyl* - 5 - *chloro* - 2 - *hydroxybenzylidene*) - *aminoderivatives* (**1–12**). The preparation of the amino acid derivatives (**1–7**) has been described elsewhere.[1]

Compounds (**8–12**) were obtained by reacting the corresponding amines with equimolecular amounts of 5-chloro-2-hydroxybenzophenone in dry benzene in the presence of the molecular sieve (type 3A). After 24 hr refluxing the filtered soln was evaporated and the residue was distilled under vacuum. All the ketimine derivatives of amines were viscous yellow oils, except (**8**) which crystallised from hexane (m.p. 92°).

Their rotations in MeOH, the resonance positions (c/s) in CCl_4 of the Me group doublets and of the H atom on the asymmetric carbon (quartets for **8** and **10**) and the elemental analyses are summarized in Table 2.

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