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THE CIRCULAR DICHROISM OF SOME DERIVATIVES OF TETRAHYDRO-1,3-OXAZINE, TETRAHYDRO-1,4-OXAZINE(MORPHOLINE) AND 1,3-OXAZOLIDINE

(the late) W. Klyne and P. M. Scopes*
Department of Chemistry, Westfield College, Hampstead, London, NW3 7ST

and

N. Berova, J. Stefanovsky and B. J. Kurtev
Institute of Organic Chemisty, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria

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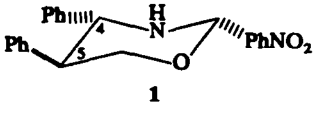
Abstract—The circular dichroism of some derivatives of tetrahydro-1,3-oxazine, tetrahydro-1,4-oxazine and 1,3-oxazolidine is described, and discussed in terms of configuration and preferred conformations.

Previous papers in this series[1] have described NMR and conformational studies on some derivatives of tetrahydro-1,3-oxazine,[2] tetrahydro-1,4-oxazine (morpholine)[3] and 1,3-oxazolidine.[4] The compounds included several pairs of chiral disubstituted derivatives of known absolute configuration and with related *cis* or *trans* arrangements of the two substituents. The circular dichroism (CD) spectra of these compounds have now been recorded and can be rationalised in terms of the preferred conformations.

Experimental data are presented in Table 1. The principal solvent was methanol but many of the compounds were also examined in dioxan. In each case the CD maxima recorded in dioxan were of the same sign and of the same order of magnitude as those for methanol, but more detailed fine structure was observed in the hydroxylic solvent.

Derivatives of tetrahydro-1,3-*oxazine*

The first pair of compounds have three aryl substituents on the tetrahydro-oxazine ring. (−) (2*S*,4*R*,5*S*)-*trans*-4,5-Diphenyl-2(*p*-nitrophenyl)-tetrahydro-1,3-oxazine **1** can adopt a conformation in which all three aryl substituents are in equatorial positions **1** whereas the C-5 epimer **2** must have at least one substituent axial. NMR evidence supports these conformations.[2]



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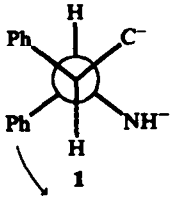

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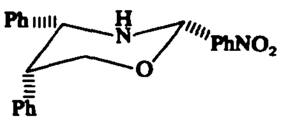

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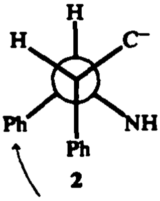

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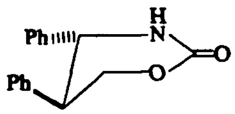

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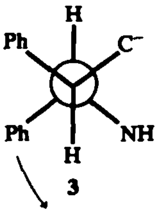

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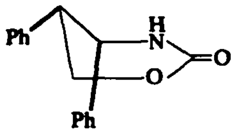

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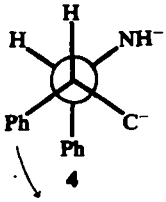

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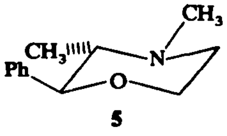
The CD spectra of both compounds show four distinct maxima, at about 320 nm, 268 nm, 220 nm and 195 nm. If the results for compounds **1** and **2** are compared with those for the corresponding oxazinones **3** and **4** it can be seen that the weak positive 320 nm band appears only for the compounds with the 2-p-nitrophenyl substituent, and this Cotton effect (CE) may therefore be ascribed to the isolated aromatic chromophore (*cf.* absorption maximum of p-nitrophenol in water, 317 nm[5]). The maxima centred at 268 nm are small and show fine structure characteristic of the ^1L_b transition of unsubstituted aromatic chromophores, but the remaining maxima near 220 nm and 195 nm are of the order of magnitude associated with the $\pi \rightarrow \pi^*$ transitions of extended dissymmetric systems such as the homoconjugated phenyl groups present in this case. For compound **1** the signs of the three bands are positive (268 nm), negative (220 nm) and negative (195 nm) but the signs are reversed for compound **2**. This sign reversal in the CD spectrum may be correlated directly with the sign of the torsion angle between the phenyl groups in the two compounds. Compound **1** has a negative torsion angle for the system Ph–C_5C_4–Ph whereas compound **2** has a positive angle the same in each case as the sign of the two short wavelength cotton effects.

The same correlation can be seen for (−)(4*R*,5*S*)-*trans*-3-methyl-4,5-diphenyltetrahydro-1,3-oxazine, which has the same configuration and conformation as **1**, but lacks the C-2 aryl substituent and carries an additional N-methyl group. The two low wavelength CEs are negative in accordance with the negative torsion angle between the chromophores **1** but in contrast to results for compound **1** the ^1L_b band is also negative. The difference suggests that the 260 nm bands in the CD spectra of **1** and **2** may be influenced by the presence of the C-2 aryl group and may result from the interaction of all three aromatic chromophores, but that when only two aromatic groups are present the signs of all three CEs are the same as that of the torsion angle between the two chromophores.

This suggestion is confirmed by the CD spectra of the pair of oxazinones **3** and **4** which differ in the configuration of the phenyl substituent at C-5 and consequently in the conformation of the oxazinone ring. For the *trans* compound **3** the conformation with both phenyl groups equatorial[2] is closely similar to that for the *trans* oxazine, but the *cis* compound **4** adopts a conformation[2] in which the C_5 phenyl is essentially equatorial instead of axial (as in the corresponding oxazine **2**). The Newman projections for these conformations show that the Ph—C_5—C_4—Ph torsion angle is negative for both compounds, and this correlates well with the observed CD spectra which show three negative CEs for both compounds at ca 260 nm, 218 nm and 195 nm. A comparison between the two oxazinones and the oxazine lacking a C-2 substituent shows that the CD spectra are very similar and indicates that the carbamate chromophore makes no significant contribution to the observed circular dichroism.

*Derivatives of tetrahydro-*1,4-*oxazine*(*morpholine*)

The morpholine and morpholone derivatives which we have examined have only one aromatic substituent and lack any extended conjugated system. It is not surprising therefore that the magnitude of the observed CEs is generally smaller than for the diphenyl derivatives discussed above. The morpholine derivatives **5** and **6** each adopt a chair conformation with the single phenyl group equatorial and the C-3 methyl group equatorial and axial respectively.[3] Both compounds, which differ in the configuration of the phenyl group at C-2, show a negative CE at 200/210 nm but the longer wavelength ^1L_b bands at 260 nm are opposite in sign, compound **5** negative and compound **6** positive. The conformation of the six-membered ring[3] is an important feature in interpreting the CD of the morpholones **7** and **8** (for which both NH and N-methyl compounds are available). The atoms C—N—CO—C lie in one plane and the chirality of the twisted ring for the preferred conformation in the *trans* series **7** is opposite to that for the *cis* compound **8**; this opposite ring chirality gives rise to the CD bands of opposite sign. However, the NMR spectrum of the *trans*-compound **7**[3] indicates the presence of a small proportion of the pseudo diaxial isomer in addition to the more stable pseudo diequatorial isomer because of allylic strain[6,7] and this may explain the complex spectrum observed at low wavelengths for compound **7** (R = CH_3).



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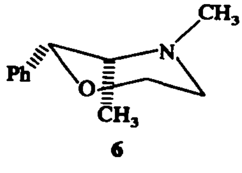

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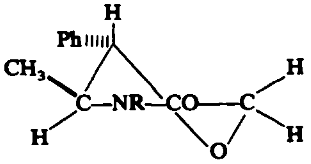

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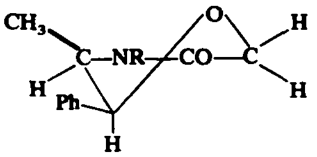

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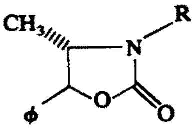
In addition to the aromatic ring, the morpholones also contain a lactam (amide) chromophore absorbing in the accessible spectral region at about 220 nm, and as expected the CD spectra show a maximum at this wavelength, which is *not* present in the corresponding morpholines **5** and **6**. The sign of this maximum is negative for the *trans* isomers **7** (R = H) and **7** (R = Me) and positive for the *cis* isomers **8** (R = H) and **8** (R = Me) and as for the other maxima the opposite signs reflect the opposite chirality of the ring of the predominant conformers.

The long wavelength ^1L_b bands arising from the aromatic chromophore are negative in sign for the *trans* isomer and positive for the *cis* isomer in agreement with the equivalent maxima for the morpholines where the *cis* and *trans* isomers also have opposite configurations for the phenyl group. The only exception is the *cis* disubstituted N-methyl compound **8** R = Me for which the fine structure of the ^1L_b band is very complex, probably because of more restricted vibration. At short wavelengths, direct comparison between the spectra of the morpholines and morpholones is not possible because of the overlap of the $\pi \rightarrow \pi^*$ transition of the aromatic and amide chromophores in the morpholones and because of conformational inhomogeneity in the *trans* series.

Derivatives of 2-*oxazolidone*

The derivatives examined are *trans*-**9** and *cis*-**10**-4,5-disubstituted derivatives with either —NH— or —NCH_3— in the five-mentioned heterocyclic ring. Only one of the two substituents is an aryl group and the magnitude of the CEs is much less than that of the CEs for the diphenyloxazinones (**3** and **4**).



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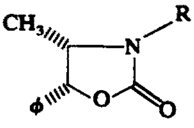

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The maximum at 260 nm is very small, positive for the (5*R*)-compounds and negative for the (5*S*). If these observations are compared with those for the morpholine series it can be seen that in each case the (*R*) configuration at the carbon carrying the aromatic substituent leads to a negative maximum at 260 nm (**5**, **7** and **9**) and the (*S*)-configuration (**6**, **8** and **10**) to a positive maximum.

The second aromatic CE for the oxazolidones occurs at 207/210 nm and is negative for both the *trans* and the *cis* series despite the opposite configuration at C_5. In the *trans* isomer **9** the phenyl substituents are quasi-equatorial and in the *cis* isomer **10** there is a tendency to adopt the same conformation.[4] Therefore in both compounds the sign of the torsion angle for the system CH_3—C_4—C_5—Ph is negative, although the torsion angle is much bigger for the *trans* than for the *cis* isomer. This is in good agreement with the greater magnitude of the short wavelength CEs for **10** than for **9**. Between the two aromatic bands, the *trans* compounds also show a small positive maximum at ca 223 nm. This is echoed in the *cis* compounds by a negative shoulder at ~215/220 nm on the longer wavelength side of the 210 nm aromatic band and could indicate a small negative maximum largely masked by the greater magnitude of the aromatic band.

EXPERIMENTAL

Cd spectra were measured in Sofia on a Roussel-Jouan Dichrograph Mark III and in London on a Dichrograph Mark II.

Table 1. Circular dichroism of some tetrahydrooxazine and oxazolidone derivatives

Name	Formula	Solvent	Δε	λ(nm)	Δε	λ(nm)	Δε	λ(nm)
(−)(2*S*,4*R*,5*S*)-*trans*-4,5-diphenyl	**1**	M	+0.07	320				
2(*p*.nitrophenyl)tetrahydro-1,3-			+0.46 m	269	−4.39 m	218	−72.63 m	192
oxazine			+0.43	263				
		D	+0.76 m	269	−1.03 m	218		
(+)(2*S*,4*R*,5*R*)-*cis*-4,5-diphenyl-	**2**	M	+0.12 m	320				
2(*p*.nitrophenyl)tetrahydro-1,3-			−1.17 m	268	+5.63 m	221	+23.07 m	195
oxazine		D	−0.90 m	266	+3.94 m	224	+6.05!	212
(−)(4*R*,5*S*)-*trans*-2-oxo-4,5-	**3**	M	−0.32	267				
diphenyltetrahydro-1,3-			−0.41 m	259	−19.75 m	218	−70.90 m	193
oxazine			−0.28	253				
		D	−0.29	266				
			−0.38 m	259	−16.95 m	218		
			−0.29	253				
(−)(4*R*,5*R*)-*cis*-2-oxo-4,5-	**4**	M	−0.41	267				
diphenyltetrahydro-1,3-			−0.46 m	260	−16.00 m	213	−20.00!	202
oxazine			−0.36	253				
		D	−0.50	268				
			−0.59 m	261	−18.40 m	216		
			−0.44	254				
(−)(4*R*,5*S*)-*trans*-3-methyl-4,5-		M	−0.35	266				
diphenyltetrahydro-1,3-			−0.42 m	259	−14.57 m	217	−7.63!	200
oxazine			−0.42	250				
(+)(2*S*,3*S*)-*trans*-3,4-dimethyl	**5**	M	−0.02	265				
2-phenylmorpholine			−0.03 m	260	−0.65 m	202	−0.89 m	197
			−0.02	249				
(−)(2*R*,3*S*)-*cis*-3,4-dimethyl-	**6**	M	+0.28	266				
2-phenylmorpholine			+0.31 m	260	−3.05 m	212		
			+0.19	254				
(+)(2*S*,3*S*)-*trans*-3-methyl-	**7**,R = H	M	−0.02	267				
2-phenyl-5-morpholone			−0.03 m	261	−2.96 m	221	+3.26 m	198
			−0.03	256			−7.41!	190
		D			−4.02 m	222	+1.12!	213
(+)(2*S*,3*S*)-*trans*-3,4-dimethyl-	**7**,R = CH_3	M	−0.01	266	−1.73	227		
2-phenyl-5-morpholone			−0.02 m	261	−2.36 m	219	+1.90 m	202
			−0.02	257	−2.28	213	+3.80!	193
		D			−3.36 m	220		

Table (*continued*)

Name	Formula	Solvent	Δε	λ(nm)	Δε	λ(nm)	Δε	λ(nm)
(−)(2*R*,3*S*)-*cis*-3-methyl-2-phenyl-5-morpholone	**8**,R = H	M	+0.27	267				
			+0.28 m	261	+9.45 m	220	−48.86!	193
			+0.15	257				
(−)(2*R*,3*S*)-*cis*-3,4-dimethyl-2-phenyl-5-morpholone	**8**,R = CH_3	M	−0.08	272				
			+0.04	267	+5.11 m	219	−21.65 m	194
			−0.08	264				
			+0.02	261				
			−0.09	251				
			−0.18	246				
		D			+3.71 m	222	−5.64!	208
(+)(4*S*,5*S*)-*trans*-4-methyl-5-phenyl-2-oxazolidone	**9**,R = H	M	−0.04 m	258	+0.10!	221		
		D	−0.02	267				
			−0.04 m	261	+0.09!	224		
			−0.04	256				
(+)(4*S*,5*S*)-*trans*-3,4-dimethyl-5-phenyl-2-oxazolidone	**9**,R = CH_3	M	−0.05	267				
			−0.05 m	261	+0.14 m	231	−1.57 m	210
			−0.05	256			−5.25 m	193
		D	−0.03	267				
			−0.06 m	261	+0.15 m	223	−1.48!	212
			−0.05	257				
(−)(4*S*,5*R*)-*cis*-4-methyl-5-phenyl-2-oxazolidone	**10**,R = H	M	+0.11	267			−3.46 m	213
			+0.12 m	261			−14.96 m	192
			+0.08	256				
		D	+0.11	268				
			+0.13 m	262			−2.70 m	214
			+0.08	255				
(−)(4*S*,5*R*)-*cis*-3,4-dimethyl-5-phenyloxazolidone	**10**,R = CH_3	M	+0.10	267			−3.72 m	207
			+0.10 m	261			−5.50!	202
			+0.07	255				
		D	+0.08	267			−2.77 i	211
			+0.11 m	261			−3.18!	208
			+0.09	255				

M = methanol; D = dioxan; m = maximum; i = inflexion; ! = lowest wavelength measured

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