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SYNTHESIS AND CHIROPTICAL PROPERTIES OF SOME N-(3-METHYL-2-QUINOXALOYL) L-AMINO ACIDS AND THEIR DIOXIDES

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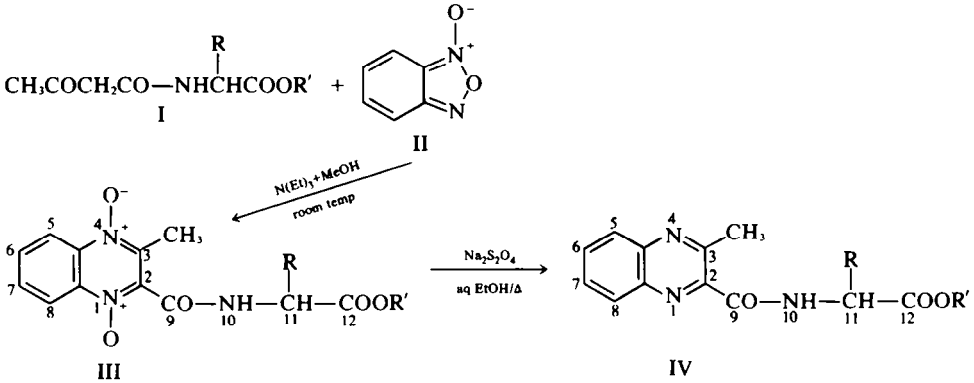
Abstract—A number of N-(3-methyl-2-quinoxaloyl) L-α-amino acids and esters, and their 1,4-dioxides have been prepared. The quinoxaline derivatives of *aliphatic* and *aromatic* L-α-amino acids exhibit enantiomorphic CD spectra in ethanol as well as in ethanolic KOH. However, the corresponding quinoxaline-1,4-dioxide derivatives of the L-α-*aliphatic* and L-α-*aromatic* amino acids show, in organic solvents, similar CD spectra. This behaviour is attributed to differences in conformational equilibria in both the quinoxaline and the quinoxaline-1,4-dioxide series. NMR and mass spectra of these compounds are discussed.

Quinoxaline-1,4-dioxides recently received considerable interest as potent antibacterial agents,[1] while some quinoxaline-peptides exhibit antibiotic and anti-tumour activity.[2] Of current interest also is the study of the chiroptical properties of heterocyclic and biomolecules.[3,4] During our work on heterocyclic derivatives of peptides, we have prepared several optically active L-α-amino acid derivatives containing these heterocyclic ring systems, and we describe here their synthesis and chiroptical properties.

The dioxides III (R=H, Table 1) have been obtained by the reaction of N-acetoacetyl L-α-amino acids I (R'=H) with benzofuroxan (II).[5] The best yields were obtained when the reaction was carried out in triethylamine–methanol. Compounds I were obtained from the reaction of the corresponding amino acids with diketene in an alkaline medium.[6]

Reduction of the dioxides III with sodium dithionite[7] gave the corresponding quinoxalines IV (Table 1). The methyl ester analogues of III (R'=Me) and of IV (R'=Me) have been obtained either by direct methylation with diazomethane, or by starting with the methyl esters of I (R'=Me).

As the reaction conditions are quite mild and the center of chirality is not affected, all the above compounds are expected to be optically pure. This was ascertained by the fact that a sample of compound **5a** showed no detectable racemization after dissolution in triethylamine–methanol for two weeks at room temperature. Furthermore, optical purity was determined for **12b**, as a model compound of the quinoxaline series IV, by NMR using $(tfc)_3Eu$ as the chiral lanthanide shift reagent (LSR method).[8] It can be seen from Fig. 1(a) that the DL-**12b** shows two resolved enantiomeric singlets for the methyl ester protons, and



No R

1 $CH(OH)CH_3$
2 CH_3
3 $CH_2CH(CH_3)_2$
4 $CH(CH_3)C_2H_5$
5 C_6H_5
6 $CH_2C_6H_5$
7
8 $CH_2C_6H_4$—OH(p)

9 CH_3
10 $CH_2CH(CH_3)_2$
11 $CH(CH_3)C_2H_5$
12 C_6H_5
13 $CH_2C_6H_5$

a: R' = H, b: R' = CH_3

Table 1. Analysis and physical data of III and IV

No	Molecular Formula	MP(°C) recryst. solvent	Yield %	$[\alpha]_{578}^{20}$ (c=1-2%)	% Analyses C, H, N,
1a	$C_{14}H_{15}N_3O_6$	225(dec.) (M)	65	+90.7°	requires:52.34 4.71 13.08 found :51.94 4.79 13.11
2a	$C_{13}H_{13}N_3O_5$	200(dec.) (E)	51	56.8°	requires:53.61 4.50 14.43 found :53.03 4.47 14.42
2b	$C_{14}H_{15}N_3O_5$	170 (M)	72	+59.6°	requires:55.08 4.95 13.76 found :55.20 5.02 13.70
3a	$C_{16}H_{19}N_3O_5$	206(dec.) (M)	68	+52.9°	requires:57.65 5.75 12.61 found :57.69 5.80 12.52
3b	$C_{17}H_{21}N_3O_5$	132 (W + M)	40	+29.2°	requires:58.78 6.09 12.10 found :58.39 5.99 12.07
4a	$C_{16}H_{19}N_3O_5$	152(dec.) (C + P)	62	+70.8°	requires:57.65 5.75 12.61 found :57.90 5.64 12.62
4b	$C_{17}H_{21}N_3O_5$	129 (W + M)	45	+41.7°	requires:58.78 6.09 12.10 found :58.84 5.98 11.96
5a	$C_{18}H_{15}N_3O_5$	217(dec.) (M)	78	+82.1°	requires:61.19 4.28 11.89 found :60.93 4.33 11.75
5b	$C_{19}H_{17}N_3O_3$	160-161 (M+W)	81	+62.9°	requires: 62.15 4.66 11.44 found : 62.53 4.65 11.51
6a	$C_{19}H_{17}N_3O_5$	204(dec.) (M)	76	+30.8°	requires: 62.15 4.66 11.44 found : 61.97 4.71 11.44
6b	$C_{20}H_{19}N_3O_5$	143 (M)	60	+19.4°	requires: 62.98 5.02 11.02 found : 62.96 4.94 11.10
7a	$C_{21}H_{18}N_4O_5$	188(dec.) (M)	85	+50.6°	requires: 62.06 4.46 13.79 found : 62.12 4.42 13.88
7b	$C_{23}H_{20}N_4O_5$	172 (M)	62	+120.6°	requires: 63.58 5.10 12.90 found : 63.39 5.24 12.97
8a	$C_{19}H_{17}N_3O_6$	154(dec.) (M)	57	+28.3°	requires: 59.52 4.47 10.69 found : 59.70 4.55 10.88
9a	$C_{13}H_{13}N_3O_3$	237 (E)	56	+80.3°	requires: 60.22 5.05 16.21 found : 60.04 4.93 16.20
9b	$C_{14}H_{15}N_3O_5$	86 (E+W)	69	+96.8°	requires: 61.53 5.54 15.38 found : 61.83 5.50 15.12
10a	$C_{16}H_{19}N_3O_3$	190-191 (M+W)	77	+27.4°	requires: 63.77 6.36 13.95 found : 63.87 6.33 13.83
10b	$C_{17}H_{21}N_3O_3$	67-68 (P)	86	+43.2°	requires: 64.74 6.71 13.32 found : 64.71 6.71 13.49
11a	$C_{16}H_{19}N_3O_3$	177-178 (M+W)	74	+39.1°	requires: 63.77 6.36 13.95 found : 63.54 6.32 14.04
11b	$C_{17}H_{21}N_3O_3$	54-55 (P)	82	+65.7°	requires: 64.74 6.71 13.32 found : 64.73 6.73 13.45
12a	$C_{18}H_{15}N_3O_3$	240-241 (M+W)	63	+10.1°	requires: 67.28 4.71 13.08 found : 66.49 4.79 13.18
12b	$C_{19}H_{17}N_3O_3$	105-106 (M+W)	90	-15.2°	requires: 68.05 5.11 12.53 found : 68.00 5.21 12.57
13a	$C_{19}H_{17}N_3O_3$	158-159 (M+W)	66	+79.8°	requires: 68.05 5.11 12.53 found : 68.28 4.99 12.57
13b	$C_{20}H_{19}N_3O_3$	137-138 (M+W)	92	+30.6°	requires: 68.75 5.48 12.03 found : 68.81 5.42 12.16
14a	$C_{21}H_{18}N_4O_3$	187-188 (M+W)	80	-71.7°	requires: 67.37 4.85 14.97 found : 67.47 4.85 15.06
14b	$C_{22}H_{20}N_4O_3$	178-179 (M+W)or (A+W)	88	+6.6°	requires: 68.03 5.19 14.43 found : 67.98 5.28 14.38

* Abbreviation used: A: Acetone, C: Chloroform, E: Ethanol, M: Methanol, P: Petroleum ether (60-80°)

** Measured in dimethylformamide for the acids (1a-14a), and in chloroform for the esters (2b - 14b).

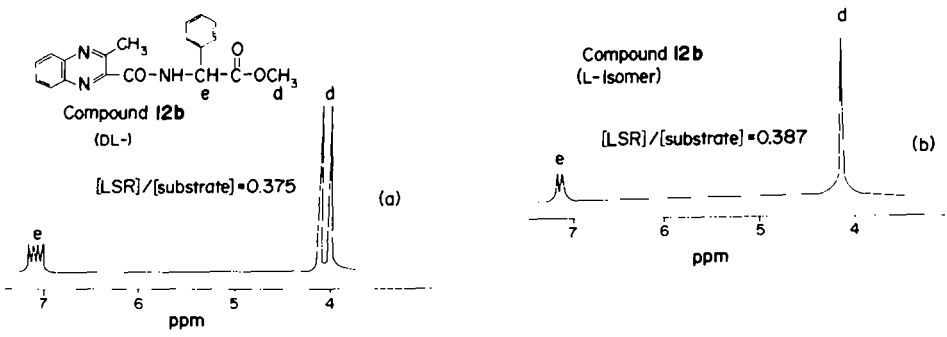


Fig. 1. Optishift NMR spectra of **12b**: (a) DL- (b) L-isomer.

Table 2. CD and UV spectral data of III and IV

No	Solvent	$\lambda_{max}(\Delta\varepsilon)$	$\lambda_{max}(\varepsilon) \times 10^{-3}$
1a	A	340(+0.30), 269(+2.91), 232(+1.26), 207(-2.65), 196(+0.16).	392(2.9), 380(2.6), 280sh(3.5), 268(9.1), 260sh(7.3), 225(17.2), 204(29.8)
	E	340(+0.52), 267(+3.65), 237(+1.13), 208(-4.41).	383(12.7),369(11.1),267(27.2), 260sh(19.2),232(21.1),205(13.3).
2b	A	363(-0.29), 320(+0.08), 268(+3.19), 227(+1.44), 205(-2.44).	394(11.5),377(9.8), 360sh(5.9), 268(25.3),260sh(15.7),228(20.3), 206(11.2).
	E	331(+0.20), 266(+3.48), 232(+1.46), 205(-2.55).	383(12.7),367(10.8),346sh(5.9), 266(26.6),260sh(19.1),231(21.3), 205(13.1).
3a	A	367(-0.24), 325(+0.27), 268(+2.60), 233(+1.64), 205(-3.90).	393(8.9), 380sh(7.8),360sh(4.9), 268(20.6),260sh(13.8),228(20.1), 205(16.2).
	E	361(-0.30), 320(+0.54), 267(+5.20), 235(+1.39), 206(-5.37).	384(12.9),370sh(11.3),267(27.0), 260sh(19.4),232(21.7),205(13.8).
3b	A	372(-0.24), 333(+0.21), 267(+3.91), 225(+1.61), 203(-3.10).	394(11.7),378(9.4), 359sh(5.9), 267(25.7),261sh(17.1),227(21.6), 206(13.3).
	E	326(+0.46), 266(+4.12), 230(+1.61), 205(-3.94).	385(12.2),370(10.8),350sh(6.2), 267(25.9),260sh(19.0),233(20.7), 206(12.7).
4a	A	370(-0.20), 325(+0.25), 268(+2.49), 232(+1.78),205(-3.33).	393(9.7), 379(8.4),360sh(5.3), 268(21.5),260sh(13.5),228(18.5), 205(11.2).
	E	357(-0.34), 318(+0.61), 267(+4.72), 235(+1.33), 205(-5.23).	384(12.1),370sh(10.7),267(25.5), 260sh(17.8),232(20.5),205(13.1).
4b	A	370(-0.26), 330(+0.23),268(+4.22), 227(+1.84), 204(-3.26).	395(10.2),378(8.7), 358sh(5.3), 268(22.9),260sh(14.4),227(20.3), 205(15.9).
	E	325(+0.86), 267(+5.31), 233(+1.95), 205(-4.95).	383(11.6),369(10.3), 349sh(6.2), 267(25.0),260sh(17.6), 232(21.6), 206(15.1).
5a	A	396(+0.33), 346(+0.36), 267(+1.46), 218(+13.89), 199(+8.79), 194(-18.81).	396(9.2), 380(8.4), 360sh(5.6), 267(21.8),232(18.1), 205(20.8).
	E	390(+0.10), 344(+0.37), 266(+3.84), 221(+11.64), 200(+8.52).	382(10.6), 370(9.3), 267(23.4), 259sh(17.2),231(19.6),205(21.2).
5b	A	395(+0.32), 370(+0.44), 267(+1.21), 219(+10.93), 198(+5.90).	394(9.8), 377(8.3), 347sh(4.0), 268(22.9)260sh(15.7),230(22.1), 205(23.0).
	E	394(+0.20), 338(+0.42), 265(+4.54), 221(+8.90), 207(-2.13), 199(+4.55).	390(11.0),370(10.0), 350sh(6.3), 267(24.6),259sh(18.2),235(22.0), 205(23.1).
6a	A	400(+ve), 360(+0.17), 268(+1.49), 217(+5.74), 196(+12.03).	393(10.7), 380(9.3), 360sh(5.9), 268(24.2), 205(22.8).
	E	396(+0.19), 340(+0.46), 266(+0.81), 217(+6.72), 197(+10.98).	384(12.9), 370(11.5),350sh(6.7), 265(27.4),260sh(19.7),232(22.5), 205(22.9).

Table 2. (*Contd.*)

6b	A	365(-0.17), 340(+ve), 315(-ve), 266(+0.35), 258(+1.19), 215(+4.80).	394(9.3), 378(8.7), 360sh(5.0), 268(21.3),260sh(14.0),228(19.1), 205(22.6).
	E	366(-0.19), 266(+0.47), 216(+4.64), 197(+4.84).	384(10.6), 369(9.5), 349sh(5.6), 266(23.2),260sh(16.9),232(19.8), 205(21.1).
7a	A	396(+0.27), 368(+0.45), 270(+1.96), 226(+4.38),211sh(-1.30), 200(-2.85), 190(+1.95).	393(10.9), 378(9.6), 360sh(6.1), 289(6.8), 268(29.6), 260sh(19.1), 223(48.9).
	E	365(+0.67), 287(+0.62), 269(+1.88), 224(+3.00), 199(-4.68).	384(12.1), 370(10.8), 290(6.8), 283sh(9.4),267(30.5),259sh(21.1), 232sh(22.8),222(48.6),199(30.7).
7b	A	378sh(+0.25),340(+0.57),278sh(+0.95), 268(+3.04), 218(+4.43), 205(-3.25).	395(6.4), 377(5.4), 352sh(3.2), 289(7.3), 280sh(10.4), 268(21.7), 260sh(15.4),222(48.9), 205(42.7).
	E	340(+0.78), 267(+3.32), 224(+2.41), 203(-4.68).	383(6.3), 370(5.9), 290(7.7), 280sh(9.1), 267(19.9),222(42.8).
9a	E	320(+0.59), 295(+0.61), 244(+2.43), 225(-0.93), 213(+1.03).	326(6.7), 319(7.4), 240(29.7), 201(37.5).
9b	E	319(+0.60), 294(+0.76), 243(+3.29), 225(-1.55), 214(+0.81).	326(6.5), 319(7.1), 239(29.3), 200(36.7).
10a	E	335(+0.33), 322(+0.20), 292(+0.70), 242(+1.35), 228(-0.95), 214(+0.93), 200(-5.60).	320(6.9), 241(31.4), 203(39.3).
	E/KOH	317(+1.04), 240(+1.20), 230(-0.43), 217(+0.46), ~200(-ve).	321(6.6), 241(33.9), 202(48.8).
10b	E	~320(+0.50),290(+0.95),244(+2.30), 227(-2.35), 214(+1.12).	320(6.9), 241(32.8), 203(39.1).
11a	E	~335(+0.30), ~320(+0.32),286(+0.38), 240(+2.40), 215(+0.90), 201(-2.20).	320(7.1), 242(35.3), 203(40.1).
	E/KOH	319(+1.19), 242(+2.19), 217(+0.91), ~200(-ve).	322(6.7), 241(35.9), 200(63.1).
11b	E	320(+0.44), 290(+0.55), 241(+2.90), 227(-1.00), 215(+0.44).	320(6.8), 241(33.5), 203(39.3).
12a	E	308(-2.75), 255sh(-2.79),243(-11.25), 226(+19.40), 205(-3.29).	320(7.0), 242(35.7), 203(46.5).
	E/KOH	308(-2.50), 242(-10.95), 226(+17.03),	321(6.8), 241(36.7), 200(82.4).
12b	E	308(-2.21),257sh(-0.84), 243(-7.76), 223(+15.57), 207(-1.90), 197(+1.70).	320(7.0), 242(35.1), 203(46.8).
13a	E	342(-0.27), 309(-1.59), 242(-4.92), 223(+8.77), 197(+4.0).	320(6.4), 242(31.9), 203(43.0).
	E/KOH	305(-1.52), 242(-4.52), 223(+8.96).	321(5.7), 242(30.5), 202(47.8).
13b	E	311(-1.50),257sh(-0.62), 243(-5.74), 222(+6.08).	320(6.7), 242(32.8), 203(44.4).
14a	E	305(-1.75), 242(-10.62), 227(+13.72), 216(-7.62), 193(-8.0).	321(6.3), 290(8.1), 281(8.7), 274(8.4), 242(32.9), 220(47.6), 203(55.8).
	E/KOH	308(-1.88), 241(-14.86), 227(+23.19), 214(-3.18).	323(6.4), 291(8.1), 283(8.7), 275(8.3), 241(32.1), 222(46.5), 201(62.5).
14b	E	306(-2.0), 257sh(-0.70), 242(-8.72), 227(+9.28), 216(-8.59).	321(6.8), 290(8.8), 282(9.3), 274(8.9), 242(35.1), 220(50.5), 203(58.4).

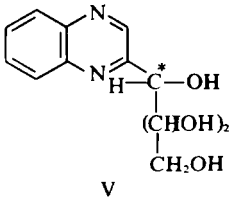
Abbreviations used: A: Acetonitrile, E: Ethanol, E/KOH: Ethanolic KOH (1%), sh=shoulder.

two resolved enantiomeric doublets for the chiral methine proton, after the addition of the indicated [(tfc)$_3$Eu]/[substrate] molar ratio. However, the NMR spectrum of the L-**12b** (Fig. 1(b)) shows only one singlet and one doublet for the methyl ester and the chiral methine protons respectively after the addition of almost the same [(tfc)$_3$Eu]/[substrate] ratio. These results indicate that L-**12b** is optically pure. The use of (tfc)$_3$Eu for optishift–NMR studies on DL-**5b** and L-**5b** resulted in an unacceptable level of signal broadening which did not allow optical purity to be performed directly on these dioxide derivatives. Further stereochemical results of optishift–NMR studies on these compounds are in progress, and the results will be communicated separately.

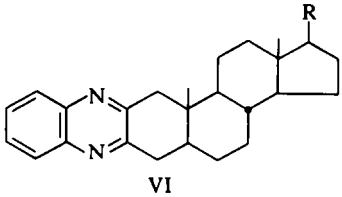
UV spectra. Several authors studied the electronic spectra of quinoxalines,[9] where three major bands, ascribed to $\pi \rightarrow \pi^*$ transitions, are usually observed around 320, 240 and 205 nm. Similar bands were observed for compounds IV in this study (Table 2). The expected $n \rightarrow \pi^*$ band around 340 nm could not be clearly observed, because it is masked under the more intense band at 320 nm.

The UV spectra of quinoxaline-1,4-dioxides are sensitive to solvent polarity.[1,9g,10] Kubota and Miyazaki [10a] studied the UV spectra of several heterocyclic N-Oxides and showed that the $\pi \rightarrow \pi^*$ bands (especially those located at longest wavelengths) experience an increasing blue-shift with increased solvent polarity, in contrast to the behaviour of other aromatic $\pi \rightarrow \pi^*$ transitions. This has been attributed to specific hydrogen bonding to the N-oxide oxygen atoms.[10a] In acetonitrile, the dioxides III showed two weak maxima around 393 and 380 nm, and three strong bands at about 268, 230 and 205 nm (Table 2). The two bands at longest wavelengths experience blue-shifts in ethanol, in agreement with Kubota's findings. The band around 230 nm is red-shifted in ethanol, while the other bands at 268 and 205 nm appear at almost the same position. However, their intensities increase with increased solvent polarity.

CD spectra. Previous CD and ORD data on the quinoxaline and on the quinoxaline-1,4-dioxide chromophores are limited to a few cases. Chilton and Krahn[11] studied the ORD of some polyhydroxy quinoxaline derivatives V. Cotton effect (CE) bands were observed at 315, 242 and 231 nm whose signs are determined by the absolute configuration at the chiral center directly bound to the chromophore (C*-3 of the original sugar).[11a] The stereochemistry at the other more distant asymmetric carbons influence only the magnitude of these CE bands. The ORD curve of the steroidal quinoxaline VI (R=OAc) revealed a CE band around 326 nm and another one which was characterized by its first extrema at 255 nm.[12] The unusual shape of this ORD curve also suggested the presence of two CE bands of opposite signs situated at shorter wavelengths. The dioxide analogue of VI (R=C_8H_{17}) was reported to give a positive CE around 395 nm.[12]



V



VI

The main features of the CD spectra of N - (3 - methyl - 2 - quinoxaloyl) - L - α - *aliphatic* amino acid and ester - 1,4 - dioxides III (**1–4**) are similar to those of the L-α-*aromatic* amino acid and ester series III (**5–7**, Table 2, Fig. 2). Both series display, in acetonitrile, CE bands around 370 (weak, − ve),325 (weak, + ve), 268 (strong, + ve), 230 (strong, + ve) and 205 nm. A weak + ve CE at about 395 was also observed in the CD spectra of a number of these compounds. Similar CE bands are observed in ethanol solutions.

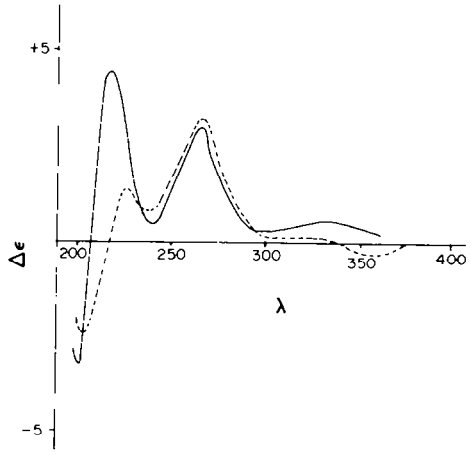


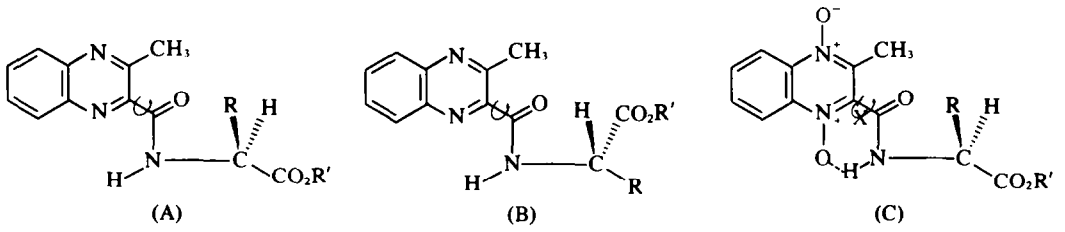
Fig. 2. CD Curves of **2b** (------), and **7b** (———) in acetonitrile.

In contrast, the CD spectra of the quinoxaline derivatives of *aliphatic* L-α-amino acids and esters IV (**9–11**) are enantiomorphic to those of the L-α-aromatic amino acid series IV (**12–14**) in the solvents studies (Table 2, Fig. 3). The phenomenon of enantiomorphic CD spectra has been observed for the furoyl and pyridinium derivatives of L-alanine and L-phenylalanine acids, methyl esters and alcohols.[13]

The differences in the chiroptical behaviour between the quinoxalines IV and the corresponding quinoxaline - 1,4 - dioxides III may be explained on the following basis: The quinoxaline derivatives of aliphatic L-α-amino acids may exist in a conformational equilibrium A $\rightleftharpoons$ B in which conformation A predominates. However, in the L-α-aromatic series, conformation B predominates. The corresponding quinoxaline - 1,4 - dioxide derivatives III would have a conformational equilibrium that is the same for both L-aliphatic and L-aromatic series, and in which conformation C predominates.

Evidence in support of these conformations is obtained from the analysis of the proton NMR spectra (Table 3). It can be seen that there is an upfield shift (~ 0.20–0.31 ppm) of the C_3–CH_3 signal in the aromatic amino acid and ester derivatives of quinoxaline - 1,4 - dioxide III (**6a–8a, 6b** and **7b**) compared to the chemical shift of this C_3–CH_3 signal in the aliphatic analogues III (**1a–4a, 2b–4b**). This shielding effect might be explained on the basis of the intramolecularly hydrogen bonded conformation C in which the aromatic moiety of the aromatic amino acid is

Conformations A, B and C



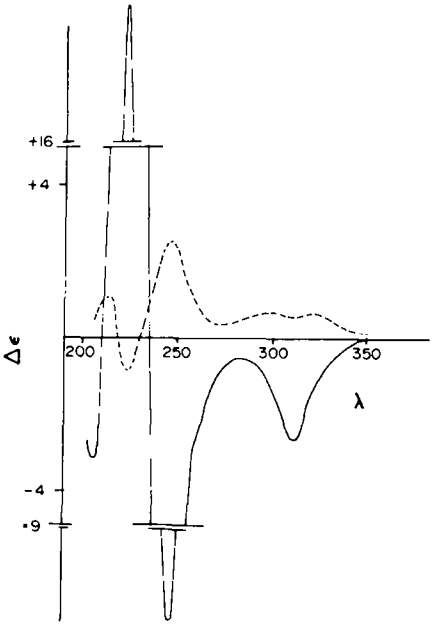


Fig. 3. CD Curves of **9a** (-----), and **12a** (———) in ethanol.

Table 3.* Chemical shifts of C_3–CH_3 protons in quinoxaline dioxides (III) and quinoxalines (IV)

III		IV	
No	δ(ppm)	No	δ(ppm)
2b	2.63	9b	2.96
3b	2.60	10b	2.97
4b	2.62	11b	2.97
6b	2.43	13b	2.93
7b	2.41	14b	2.91
1a	2.55		
2a	2.53	9a	2.66
3a	2.52	10a	2.68
4a	2.52	11a	2.68
6a	2.22	13a	2.65
7a	2.28	14a	2.63
8a	2.28		

* Solvents used: $CDCl_3$ for the esters (2b–14b); $SO(CD_3)_2$ for the acids (1a – 14a).

in close proximity to the quinoxaline - 1,4 - dioxide ring. Such conformation brings the C_3–CH_3 protons under the influence of the ring current of the aromatic group, leading to an upfield shift of these protons. The existence of intramolecular hydrogen bonding in related heterocyclic N-oxide derivatives has been demonstrated from IR studies by Szafran.[14] The stability of these conformations is probably enhanced by the partial double bond character in the CO–NH bond so that rotation in C is more restricted than in A or B.

It can also be seen from Table 3 that the C_3–CH_3 signal has almost the same δ-value (2.83–2.88 ppm) in the quinoxaline derivatives of aliphatic and aromatic amino acids IV (**9a–11a**, **13a** and **14a**). The corresponding esters IV (**9b–11b**, **13b** and **14b**) show a similar behaviour for the C_3–CH_3 signal (δ = 2.91–2.96 ppm). These data indicate the absence of shielding effect by the aromatic moiety of the aromatic amino acid derivatives IV. It is therefore concluded that the predominant conformation has the aromatic moiety situated away from the quinoxaline ring (conformer B).

The isopropyl methyl groups of valine in several of its derivatives show anisochrony and appear as two doublets in the NMR spectra.[15] This anisochrony is observed in the case of the quinoxaline - 1,4 - dioxide derivative (Fig. 4(a)) but not in the quinoxaline analogue (Fig. 4(b)). Similarly,

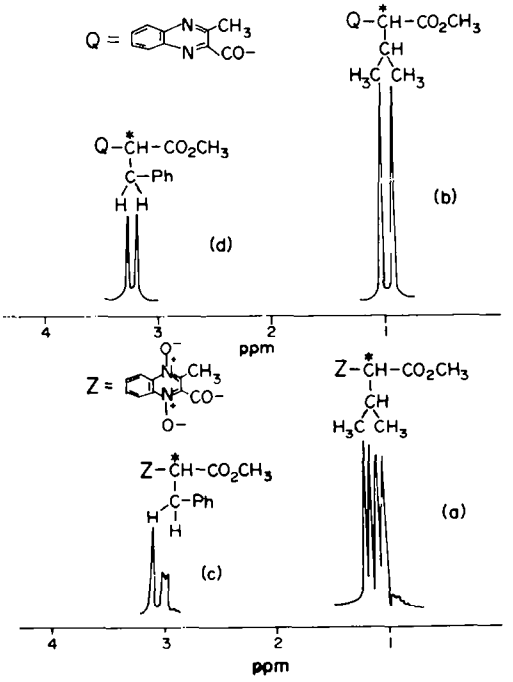
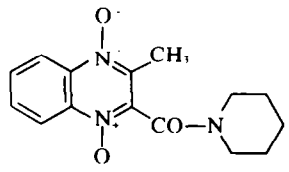


Fig. 4. (a) and (b): The isopropyl methyl proton signals in the valine derivatives; (c) and (d): the benzylic proton signals in **6b** and **13b** respectively.

the benzylic protons of phenylalanine show chemical shift non-equivalence in the quinoxaline - 1,4 - dioxide derivative **6b** (Fig. 4(c)), but not in the corresponding quinoxaline derivative **13b** (Fig. 4(d)). These data indicate that the H-bonded conformation C leads to the increased anisochrony observed for the above mentioned prochiral groups in the dioxide derivatives, III.

The mass spectra (MS) of the quinoxaline - 1,4 - dioxides III (**1b–8b**) display prominant M-17 peak and a less abundant M-16 peak corresponding to the loss of the OH radical and an oxygen atom respectively from the molecular ion. The occurrence of these ions has been observed in the MS of heterocyclic N-Oxides.[16] The M-17 base peak is also present in the MS of both the piperidine derivative VII, and the N_{10}-deuterated analogue of **5b**. No



VII

M-18 peak (M-OD) was observed in the MS of the latter compound. The facts indicate that the hydrogen of the departing OH˙ does not come from the amide N_{10}–H. The hydrogens of the C_3–CH_3 groups are probably the source of the hydrogen in OH˙. The amide bond does not suffer cleavage to any appreciable extent before the loss of one of the N-oxide oxygens from the $[M]^+$.

Antibacterial activity. The quinoxaline - 1,4 - dioxide derivatives III have been tested at Baeyer Farbwerk-Leverkusen (W. Germany) and were found to posses antibacterial activity, typical of quinoxaline - 1,4 - dioxide, but were less potent than others known in this category.

EXPERIMENTAL

L-α-Amine acids and the respective methyl ester hydrochlorides are Biochemical Grades (Merck) and were used as received. M.ps were determined on a Gallenkamp Capillary Melting Point Apparatus and are uncorrected. Optical rotations were taken on a Perkin Elmer 141 polarimeter in a cell of 10 cm path length. NMR spectra were obtained on a Varian A 60 D spectrometer, using TMS as an internal standard. UV spectra were recorded on a Carry 17 spectrometer in a cell of 0.1 cm path length. CD spectra were recorded on a Jobin Yvon Dichrograph III. Concentrations were about 0.1–0.3 mg/ml in cells of 0.02–0.1 cm path length. Mass spectra were determined on a Varian-MAT CH 5 mass spectrometer using the direct inlet technique (at 70 eV, 100 μA, temperature of ion source: 200°). Elemental analyses were performed by Dr. F. Pascher (Bonn).

N - (3 - *Methyl* - 2 - *quinoxaloyl*)L - α - *amino acid* - 1,4 - *dioxides* (III, **1a–8a**). A methanolic soln of the particular compound I[6] (0.1 mole) and II[17] (0.11 mole) was treated with triethylamine (100 ml) and set aside at room temp. for 1–4 days. The solvent was then removed (room temp.), and the brown residue was treated with cold water (100 ml) and filtered. The aqueous filtrate was made acidic (4 N HCl), whereupon the title compounds (**3–8**) were precipitated immediately as yellow solids. However, **1** crystallized out slowly, within 30–60 min, from the acid soln as bright yellow stars, while **2** was formed after 2–4 days as brown granules or discs. On few occasions, **3** was obtained as a brown gummy material which, upon trituration with methanol, yielded the desired solid.

N - (3 - *Methyl* - 2 - *quinoxaloyl*)L - α - *amino acid* - 1,4 - *dioxide methyl esters* (III, **2b–7b**, **9b**). To a soln of I (R'=CH_3, 0.11 mole)[6a,6b,18] in MeOH (40 ml) was added benzofuroxan (0.1 mole) in triethylamine (100 ml). The title compounds were usually crystallized out from the mixture (room temp.) during 1–3 days. The isolation of **3** and **4** was assisted by cooling and scratching of the mixture.

Compounds **2b**, **5b** and **6b** were also obtained in 80–90% yield by the reaction of the respective acids **2a**, **5a**, **6a** with diazomethane etherate.[19]

N - (3 - *Methyl* - 2 - *quinoxaloyl*)L - α - *amino acids* (IV, **9a–14a**). To a boiling soln of the particular dioxide III (**2a–7a**, 0.01 mole) in 60% aqueous EtOH was added slowly, with stirring, a saturated soln of sodium dithionite in hot water until a red coloration persisted.[7] The mixture was further refluxed for 3–6 hr, and then diluted with water (200 ml). The ppt was collected and crystallized from the appropriate solvent. An increase in the yield was achieved by ether extraction of the aqueous filtrate.

N - (3 - *Methyl* - 2 - *quinoxaloyl*)L - α - *amino acid methyl esters* (IV, **9b–14b**). These compounds were obtained in high yields by the reaction of the respective acids **9a–14a** with diaxomethane etherate.

Compounds **12b–14b** were also obtained in moderate yields by sodium dithionite-reduction of the respective 1,4-dioxide methyl ester derivatives **5b–7b**.

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