Chiroptical Properties of Some *N*-5(6)Benzofuroxanoyl-L-α-Amino Acids and Esters (1)

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The CD spectra of a series of *N*-5(6)benzofuroxanoyl-L-α-amino acids and esters reveal, in ethanol and acetonitrile, cotton effect (CE) bands around 365, 320, 265 and 223 nm. It was found that the signs of the CE maxima, located at longest and shortest wavelengths, were both positive for the L-*aliphatic* series, whereas these bands display sign inversion in the CD spectra of the L-*aromatic* counterparts. This chiroptical behaviour might be attributed to conformational differences. Nmr spectral data give support to this assumption. Mass spectral fragmentations of these compounds are discussed.

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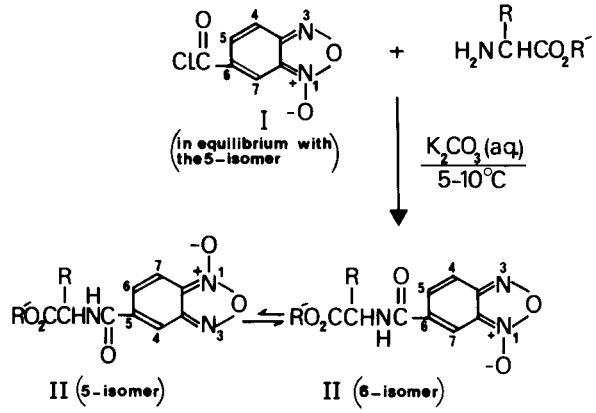
Introduction.

Benzofuroxan (benzofurazan *N*-oxide) serves, *via* its reactions with nucelophiles, as a convenient precursor towards the synthesis of various biologically interesting heteroaromatic *N*-oxides (2). The structure and chemistry of benzofuroxans also raised considerable interest (2,3). As yet, the optical properties of the benzofuroxan chromophore in dissymmetric environment have not been investigated (4). Such studies are desirable as they might lead to stereochemical (configurational and/or conformational) correlations. The present work describes the chiroptical properties of a new series of *N*-5(6)-benzofuroxanoyl-α-amino and esters (**II**, Scheme 1) using the circular dichroism (CD) technique.

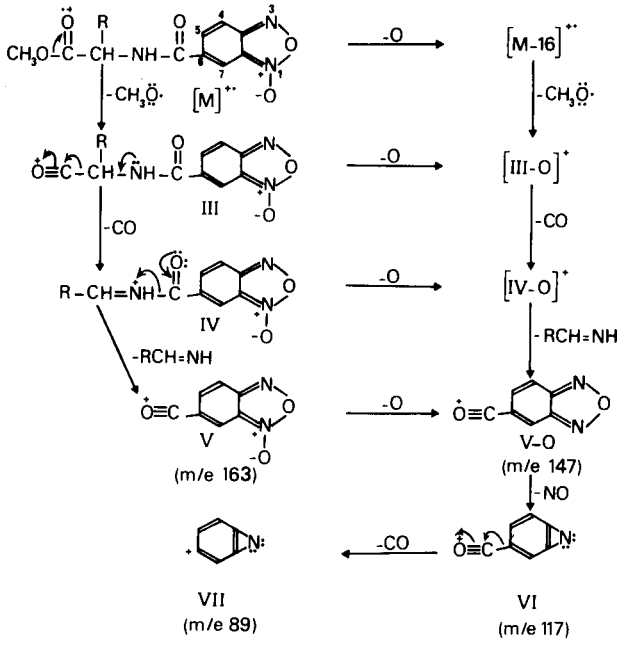
Scheme 1



No.	R	No.	R
1	H	4	$CH_2CH(CH_3)_2$
2	CH_3	5	CH_2Ph
3	$CH(CH_3)_2$		

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

Scheme 2



Synthesis.

N-5(6)benzofuroxanoyl-α-amino acids (**1a-5a**) were prepared by direct interaction between 5(6)benzofuroxanoyl chloride (**I**) (5) and the appropriate amino acid in aqueous potassium carbonate. The corresponding methyl esters **1b-5b** were obtained either by esterification of the parent acids **1a-5a** with diazomethane or, more conveniently, by direct benzofuroxanoylation of the particular amino ester hydrochloride (Scheme 1). Under these quite mild reaction conditions, the center of chirality was unaffected and compounds **2-5** were optically pure (>95%). This is inferred from previous results establishing that aroylation (quinoxaloylation and pyraxinoylation) of the

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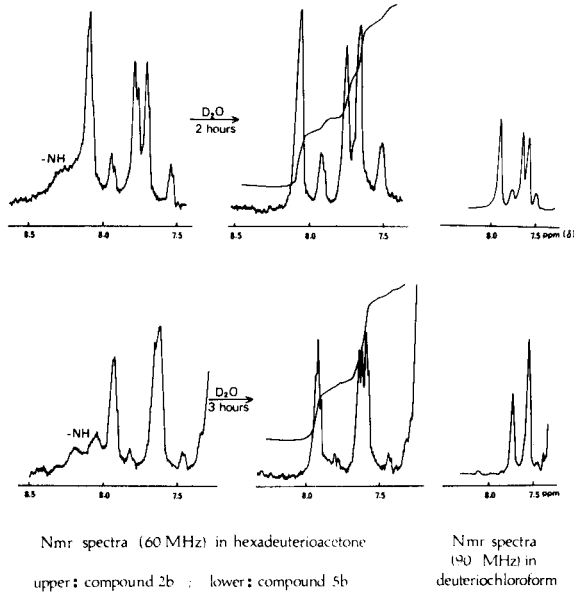
Table 1

Physical Data for Compounds **1-5**

No.	Yield (%)	M.p. °C	$[\alpha]_D^{20}$ C, ~1	Formula	Analyses (%) Calcd. C	H	N	Found C	H	N
1a	75	142 (c)		$C_9H_7N_3O_5$	45.58	2.97	17.72	45.59	3.01	17.49
1b	70	120 (c)		$C_{10}H_9N_3O_5$	47.81	3.61	16.73	47.82	3.67	16.71
L-2a	83	158 (d)	+170.5°	$C_{10}H_9N_3O_5$	47.81	3.61	16.73	47.50	3.62	16.73
L-2b	75	119 (e)	+ 90.1°	$C_{11}H_{11}N_3O_5$	49.81	4.18	15.84	49.68	4.19	15.81
L-3a	88	173 (c)	+162.5°	$C_{12}H_{13}N_3O_5$	51.61	4.69	15.05	51.43	4.62	15.00
L-3b	76	78 (c)	+ 98.2°	$C_{13}H_{15}N_3O_5$	53.24	5.16	14.33	53.62	5.26	14.21
L-4a	80	167 (c)	+151.3°	$C_{13}H_{15}N_3O_5$	53.24	5.16	14.33	53.18	5.09	14.30
L-4b	68	76 (c)	+ 87.4°	$C_{14}H_{17}N_3O_5$	54.72	5.58	13.67	54.66	5.52	13.61
L-5a	93	173 (c)	−168.8°	$C_{16}H_{13}N_3O_5$	58.71	4.00	12.84	58.40	4.02	12.93
DL-5a	92	178 (c)		$C_{16}H_{13}N_3O_5$	58.71	4.00	12.84	58.51	4.02	12.68
L-5b	80	133 (c)	+116.5°	$C_{17}H_{15}N_3O_5$	59.82	4.43	12.31	59.78	4.43	12.42
DL-5b	80	122 (c)		$C_{17}H_{15}N_3O_5$	59.82	4.43	12.31	59.80	4.45	12.30

(c) Crystallized from chloroform + petroleum ether (b.p. 40-60°). (d) Crystallized from water (softens at 122°). (e) Crystallized from chloroform + diethyl ether.

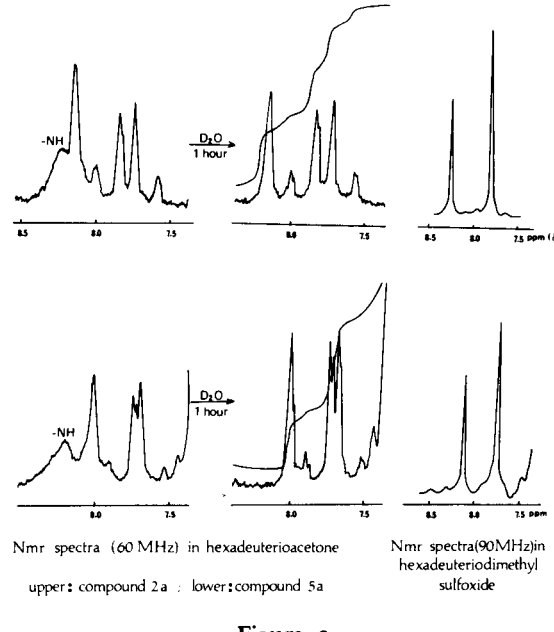


Nmr spectra (60 MHz) in hexadeuterioacetone

upper: compound 2b ; lower: compound 5b

Nmr spectra (90 MHz) in deuteriochloroform

Figure 1



Nmr spectra (60 MHz) in hexadeuterioacetone

upper: compound 2a ; lower: compound 5a

Nmr spectra (90MHz) in hexadeuteriodimethyl sulfoxide

Figure 2

amino function, under identical conditions, resulted in no detectable racemization (6).

Isomerization.

It is well-known that 5-substituted benzofuroxans in solution are in rapid equilibrium with the 6-substituted isomers at room temperature (7,8). Low temperature Nmr studies on 5(6)-chlorobenzofuroxan showed that the 5-chloro isomer predominates over the 6-chloro isomer (8), in agreement with previous X-ray results which established the exclusive existance of the 5-chloro isomer in the solid phase (9). On the other hand, low temperature nmr studies demonstrated that 6-carboxybenzofuroxan (as well as the corresponding ethyl ester) predominates over the corresponding 5-isomer (8). Mesomeric conjugative ability between the 5(6)-carbonyl (in these amide, acid and ester BFO's) and the *N*-oxide group (acting as an electron donor) is best allowed in the 6-isomer.

The multiplicity-splitting pattern of the three protons (belonging to the BFO-moiety) in the Nmr spectra (at room temperature in acetone d_6) of 5(6)-carboxamido-BFO-s, **1-5**, resembles very closely that of the 5(6)carboxy-BFO, but is different from that of 5(6)-chloro-BFO. This suggests that the isomeric equilibrium in **1-5** is similar to that of

Table 2

CD and Uv Spectral Data of the L-Derivative **1-5**

No.	Solvent	CD λ max (Δε)	Uv λ max (ε × 10^{-3})
2a	E	365 (+0.11), 3.08 (+0.15), 265 (−0.88) 255 (+5.78).	366 (6.6), 332 sh (3.0), 315 sh (2.2), 265 sh (3.2), 223 (26.4).
	A	363 (+0.18), 328 (+0.35), 310 (+0.58) 267 (−0.28), 225 (+6.32).	365 (8.1), 332 sh (3.9), 315 sh (2.7), 266 sh (3.1), 222 (31.4).
2b	E	365 (+0.16), 332 (+0.13), 308 (+0.33), 267 (−1.13), 224 (+6.94).	365 (7.1), 333 sh (3.5), 315 sh (2.9), 265 sh (3.3), 223 (28.8).
	A	362 (+0.16), 328 (+0.32), 311 (+0.53), 269 (−0.34), 224 (+6.22).	364 (7.7), 332 sh (3.8), 315 sh (3.1), 265 sh (3.1), 222 (29.4).
3a	E	330 (+0.06), 310 (+0.06), 266 (−0.51), 227 (+3.87).	365 (7.8), 334 sh (4.0), 315 sh (3.4), 264 sh (3.9), 223 (29.3).
	A	363 (+0.07), 327 (+0.40), 315 (+0.63), 301 (+0.55), 226 (+5.10).	364 (7.5), 332 sh (3.7), 315 sh (2.9), 265 sh (2.9), 222 (29.0).
3b	E	365 (+0.05), 310 (+0.14), 265 (−0.51), 226 (+3.84)	365 (7.5), 333 sh (3.8), 315 sh (3.1), 265 sh (3.9), 223 (27.8).
	A	363 (+0.15), 328 (+0.34), 311 (+0.60), 225 (+4.81).	364 (7.6), 332 sh (3.8), 315 sh (2.9), 265 sh (3.2), 222 (29.8).
4a	E	325 (+0.10), 308 (+0.20), 266 (−0.96), 225 (+4.29).	366 (5.0), 333 sh (3.2), 315 sh (2.5), 266 sh (3.7), 223 (26.9).
	A	364 (+ve), 326 (+0.30), 310 (+0.57), 267 (−0.33), 223 (+5.35).	365 (6.6), 332 sh (3.1), 315 sh (2.4), 265 sh (2.2), 222 (24.7).
4b	E	326 (+0.10), 308 (+0.26), 265 (−0.90), 223 (+4.11)	366 (6.2), 334 sh (3.0), 315 sh (2.3), 265 sh (3.5), 223 (25.3).
	A	365 (+ve), 326 (+0.30), 310 (+0.57), 267 (−0.33), 223 (+5.35).	365 (6.6), 332 sh (3.1), 315 sh (2.4), 265 sh (2.2), 222 (24.7).
5a	E	364 (−0.45), 303 (+0.05), 266 (−0.60), 223 (−13.75), 205 (+ve).	365 (7.1), 333 sh (3.3), 315 sh (2.5), 265 sh (3.9), 333 (28.7).
	A	363 (−0.35), 306 (+0.43), 265 (−0.28), 222 (−13.10), 205 (+ve).	365 (7.7), 333 sh (3.9), 315 sh (3.2), 265 sh (3.2), 222 (29.9).
5b	E	365 (−0.32), 307 (+0.07), 266 (−0.94) 224 (−14.66).	365 (7.8), 332 sh (3.9), 315 sh (3.2) 264 sh (4.0), 222 (29.4).
	A	363 (−0.40), 306 (+0.34), 261 (−0.38) 223 (−13.62)	365 (8.0), 332 sh (4.1), 315 sh (3.2), 265 sh (2.9), 221 (31.0).
1a	E		366 (6.4), 333 sh (3.0), 315 sh (2.1), 265 sh (3.3), 224 (26.0).
	A		364 (6.4), 331 sh (2.9), 315 sh (2.1), 265 sh (2.9), 222 (27.4).
1b	E		367 (7.2), 334 sh (3.4), 315 sh (2.4), 265 sh (3.4), 222 (28.2).
	A		364 (7.3), 332 sh (3.5), 315 sh (2.4), 270 sh (2.9), 222 (30.6).

A = Acetonitrile; E = 95% Ethyl alcohol; sh = Shoulder.

5(6)carboxy-BFO in which the 6-isomer predominates. However, a main difference between the aliphatic series (**1a-4a** and **1b-4b**) and the aromatic analogues (**5a** and **5b**) lies in the value for the peak at lowest field (belonging to the BFO-moiety). This peak experiences an upfield shift (0.15 ppm in **5b**; 0.20 ppm in **5a**) compared to an invariant position in the corresonding aliphatics (8.10 ppm for **1b-4b**; 8.15 for **1a-4a**). Comparable differences are also observed in hexadeuteriodimethyl sulfoxide and in deuteriochloroform (Figures 1 and 2). This is probably due to an allowed interaction between the phenyl ring and the benzofuroxan moiety in **5a** and **5b**, and leads to the observed shielding (ring current) effect.

Mass Spectra.

The spectra of the esters **1b-5b** show the correct molecular ions. The general fragmentation modes involve primary cleavage of the molecular ion at the ester and amide bonds giving rise, successively, to the acylium III, the aldiminium IV, and the benzofuroxanoylium V, ions (Scheme 2). Loss of an oxygen atom from the molecular ion, under electron impact, is also a favoured process (10) and leads to the corresponding $[M-16]^{+}$ ion. The latter ion then generates, by similar fragmentation pattern as for $[M]^{+}$, the *N*-deoxygenated fragment ions III-O, IV-O and V-O. Alternatively, these ions could originate from ions

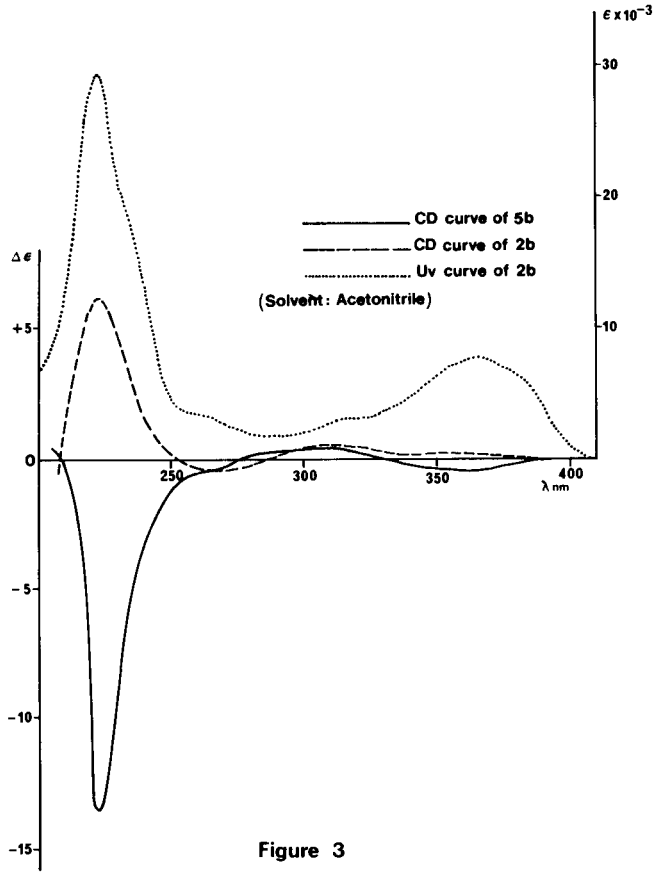


Figure 3

III, IV, and V, respectively, *via* the loss of the *N*-oxide oxygen (Scheme 2). Electron impact-induced expulsion of nitrogen monoxide from benzofurazans has been reported as an important path (11). This process is also prominant for the benzofurazanoylium V-O ion, producing ion VI which then extrudes carbon monoxide to yield ion VII (Scheme 2).

Uv Spectra.

The electronic absorption spectra of the acids **(1a-5a)** and esters **(1b-5b)** show, in acetonitrile and ethanol, an intense high energy band around 222 nm, and a weaker low energy band around 365 nm. The latter band appears to be a composite of at least two bands that are strongly overlapping, typical of the benzofuroxan chromophore (3). These electronic transitions are probably of $\pi \rightarrow \pi^*$ origin. Medium energy bands of low intensity appear as shoulders or inflection in the uv spectra around 330, 315 and 265 nm (Table 2, Figure 3).

CD Spectra.

The electronic transitions of the benzofuroxan chromophore become dissymmetrically perturbed by the chiral surrounding and give rise to Cotton effect (CE) bands in the CD spectra of Compounds **2-5**. The L-*aliphatic* amino acid series **2a-4a** exhibit, in ethanol and acetonitrile, positive CE bands at *ca.* 365, 320 and 222 nm, and a negative CE band around 265 nm. Similar CD trend is also observed for the corresponding esters **2b-4b** (Table 2 and Figure 3). It is interesting to note that the CD Spectra of the L-*aromatic* counterparts, **5a** and **5b**, are similar, but differ characteristically from those of the L-*aliphatic* series **2-4** in the signs of the CE bands located at longest and shortest wavelengths (365 and 222 nm). Both bands are positive in the L-*aliphatic* series, whereas these bands are negative in the L-*aromatic* counterparts (Figure 3). This phenomenon of *sign reversal* might be the result of differences in conformational isomerism in the different series. It is assumed that the aromatic derivative **5a** (and **5b**) adopts a preferred conformation that allows "interaction" between the phenyl ring (of phenylalanine) and the hetero *N*-oxide ring. This "interaction" is manifested in the nmr spectral data where the peak at lowest field (belonging to the benzofuroxanoyl protons) is upfield shifted in **5** relative to an invariant position for the aliphatic analogues **1-4** (see isomerization section).

EXPERIMENTAL

α-Amino acids and the respective methyl ester hydrochlorides (biochemical grades, Merck) were used as received. Melting points were determined using Büchi 510 apparatus and are uncorrected. Optical rotation measurements were performed in chloroform for the esters **2b-5b**, and in dimethylformamide for the acids **2a-5a** using a Perkin-Elmer 241 polarimeter and a cell of 10 cm pathlength. Nmr spectra were recorded on a Bruker-90 MHz and on JEOL-PMX 60 MHz spectrometers in deuteriochloroform for the esters **1b-5b**, in hexadeuteriodimethyl sulfoxide for the acids **1a-5a**, and in hexadeuterioacetone for **1a-5a** and **1b-5b**, using TMS as an internal reference. Uv spectra were obtained with a Cary-17 spectrometer in cells of 0.1-0.05 cm pathlength. Cd spectra were run on a Jobin-Yuon Dichograph III - Division d'instruments S.A., and on a JASCO J-40C. Concentrations were in the range of 0.1-0.8 mg/ml in spectroscopic grade solvents (Merck). Mass spectra were determined on a Varian CH-5 spectrometer using the direct inlet technique (70 eV; 100 A; temperature of ion source, 200°). Merck Silica Gel ($HF_{254+336}$) was employed in preparative tlc plates (1 mm thickness, 20 × 20 cm) that were used for the purification of the esters **1b-5b** (eluant, chloroform). Microanalyses were performed at the laboratory of Dr. F. Pascher (Bonn).

General Procedures.

N-5(6)Benzofuroxanoyl-α-amino Acids **(1a-5a)** (Table 1).

5(6)Benzofuroxanoyl chloride (0.05 mole) (5) was added portionwise, during 10 minutes, to a stirred solution of the particular amino acid (0.06 mole) in aqueous sodium bicarbonate (10%, 100 ml.) for **1a-3a, 5a**, in aqueous sodium hydroxide (4%, 120 ml.) for **4a**. Stirring was continued at room temperature until a clear yellow solution was obtained (*ca.* 10-15 minutes). The reaction solution was then filtered, and the filtrate was carefully acidified with cold 6*N* hydrochloric acid to *p*H 2-3. The title compounds thus precipitated (cooling and scratching as required) were collected and crystallized from the appropriate solvent.

N-5(6)Benzofuroxanoyl-α-amino Acid Methyl Esters **(1b-5b)** (Table 1).

(i) 5(6)Benzofuroxanoyl chloride (0.02 mole) (5) in dimethylformamide (10 ml.) was added slowly to a stirred cold solution (5°) of the amino ester hydrochloride (0.22 mole) in aqueous sodium carbonate (30%, 100 ml.). The resulting solution was stirred for additional 20 minutes and diluted with cold water (100 ml.). The desired product, thus obtained as yellow buff precipitate, was collected and crystallized.

(ii) The amino acid derivative in question (0.01 mole), covered under ether (40 ml.), was treated at 0-5° with small portions of cold diazomethane etherate until the vigorous evolution of nitrogen ceased. The reaction mixture was then filtered, excess diazomethane in the filtrate was consumed by dropwise addition of glacial acetic acid and the solvents were removed *in vacuo*. The residue was purified on preparative tlc plates. Yields were in the range of 25-35%.

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