Synthesis and Spectral Properties of Some *N*-(2-Benzimidazoyl)-α-aminoesters and their *N*-Oxides

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Received May 7, 1986

A series of new *N*-(2-benzimidazol)(*S*)-α-aminoesters and the respective *N*-oxides have been prepared, and their spectral data discussed. The CD spectra of the *aliphatic* and *aromatic* amino ester derivatives of either series show sign reversal for the observed Cotton effect (CE) band. This chiroptical behaviour was rationalized as due to differences in conformational isomerism.

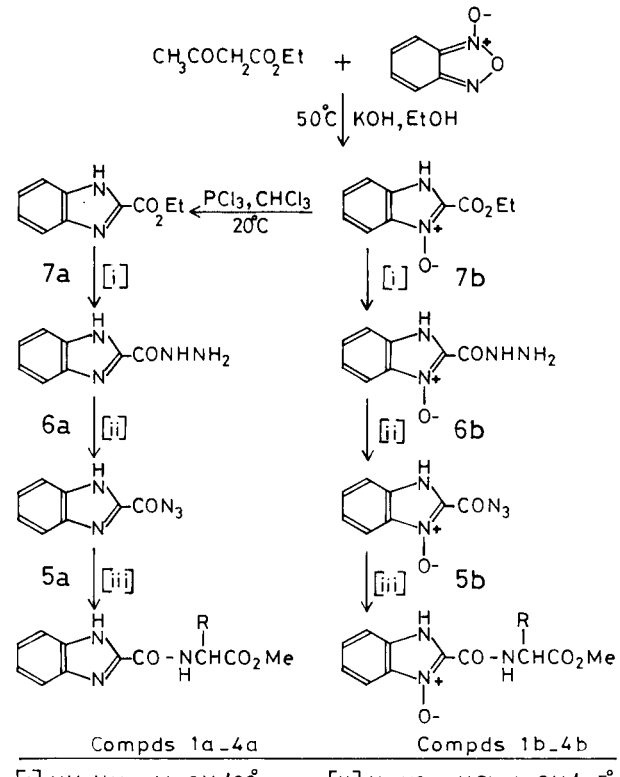
J. Heterocyclic Chem., **24**, 165 (1987).

Benzimidazoles, both natural and synthetic, have received considerable interest as they possess marked physiological activity [1,2]. A number of benzimidazoles are of commercial importance as pharmaceuticals, veterinary anthelmintics, and fungicides [2]. Recently, several amino acid-, and peptide-benzimidazole derivatives have been synthesized and found to possess herbicidal activity [3]. As part of our program directed towards the study of heterocycles with chiral biomolecules [4-6], we wish to report here on some new *N*-(2-benzimidazoyl)-α-aminoesters **1a-4a** and the respective *N*-oxides **1b-4b**. To our knowledge, the achiral *N*-(6-nitro-2-benzimidazoyl)glycine *N*-oxide is the only compound of relevance to the title series so far reported [7]. This compound resulted from a slow conversion of peptides containing 2,4-dinitrophenylglycine as the *N*-terminal moiety at *p*H 8.3-9.6 and 37° [7].

Compounds **1-4** have been prepared *via* interaction of the particular (*S*)-α-aminoester hydrochloride with 2-benzimidazoyl azide (**5a**) or its *N*-oxide (**5b**) (Scheme I and Table I). The latter azides were obtained from the respective ethyl benzimidazole-2-carboxylate (**7a** or **7b**) by hydrazinolysis [8,9], and subsequent treatment of the resulting hydrazides (**6a,6b**) with nitrous acid. Compound **7b** was prepared by the reaction of benzofuroxan [10] with ethyl acetoacetate in ethanolic potassium hydroxide at 50° [11,12]. This reaction condition was reported to favor the formation of the benzimidazole *N*-oxide derivative **7b** rather than the quinoxaline di-*N*-oxide ring system normally obtained under milder basic conditions at ambient temperature. Plausible mechanistic pathways to either heterocycle have been proposed [11,12]. Compound **7a** was obtained by the deoxygenation of **7b** using phosphorus trichloride [13].

The azide method, employed for amide bond formation of compounds **1-4**, is expected to avoid recemization. This was ascertained by the chiral lanthanide shift reagent (LSR)-pmr technique [14] on compound **4a** as a model. The criterion used for optical purity determination was the ester methyl protons' signal. This signal was resolved into two enantiotopic signals in the (*R,S*) compound **4a**

Scheme I



R	Me	$CHMe_2$	$PhCH_2$	Ph
No	1	2	3	4

after the addition of $(tfc)_3Eu$ (molar ratio [LSR]/[substrate] ≤ 0.163), but no such splitting was observed for the (*S*)-compound **4a** up to 0.50 molar ratio.

PMR Spectra.

The aromatic protons in the benzimidazole ring of compounds **1a-4a** belong to A_2B_2 systems [15] and appear as two multiplets (7.6-7.9 and 7.1-7.5). The amide N-H appears as a doublet centered at 8.3 ppm ($J_{CH\text{-}NH}$ = 8 Hz), while the imidazole N-H appears as a broad singlet at ~

Table I

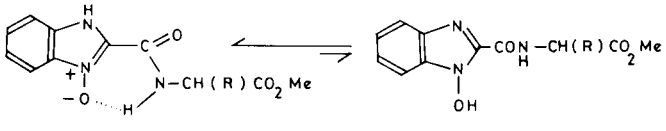
Physical Data for Compounds **1-4**

No.	Yield (%)	Mp °C	$[\alpha]_D^{30}$	Formula (Mol Wt)	Analyses (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
(*S*)-**1a**	36	156-157	+47.4°	$C_{12}H_{13}N_3O_3$ (247.3)	58.29	5.30	17.00	57.85	5.42	16.58
(*S*)-**2a**	26	142-143	+30.0°	$C_{14}H_{17}N_3O_3$ (275.3)	61.08	6.22	15.26	60.80	6.24	15.22
(*S*)-**3a**	27	88-90	−67.3°	$C_{16}H_{17}N_3O_3$ (323.4)	66.89	5.30	13.00	66.33	5.34	12.85
(*S*)-**4a**	35	186-188	+30.6°	$C_{17}H_{15}N_3O_3$ (309.3)	66.00	4.89	13.59	65.51	4.90	13.42
(*RS*)-**4a**	30	210-211	—	$C_{17}H_{15}N_3O_3$ (309.3)	66.00	4.89	13.59	65.84	4.88	13.60
(*S*)-**1b**	15	163-164	+55.6°	$C_{12}H_{13}N_3O_4$ (263.3)	54.75	4.98	15.96	54.50	5.20	15.83
(*S*)-**2b**	27	192-193	+30.4°	$C_{14}H_{17}N_3O_4$ (291.3)	57.72	5.88	14.43	57.31	5.98	14.19
(*S*)-**3b**	22	93-96	−33.1°	$C_{16}H_{17}N_3O_4$ (339.4)	63.70	5.03	12.38	63.28	5.21	12.10
(*S*)-**4b**	18	193-194	+15.2°	$C_{17}H_{15}N_3O_4$ (325.3)	62.76	4.65	12.92	62.48	4.84	13.13

12.2 ppm. The aromatic protons of the *N*-oxygenated compounds **1b-4b** appear as two multiplets in the ratio 1:3 (7.8-8.3 and 7.3-7.6 ppm); the imidazole N-H appears at 10.1 ppm.

The *N*-oxygenated benzimidazoles are reported to exist in a tautomeric equilibrium between the *N*-hydroxy and the *N*-oxide forms (A ⇌ B) [16]. In this study, compounds **1b-4b** seem to exist predominantly as the *N*-oxide form (A) (Scheme 2). This is supported by the pmr spectra showing that the doublet of the amide proton appears at a lower field (11.3 ppm) compared to that of the non-oxygenated system (8.3 ppm). Also, the rate of the amide N-H exchange with deuterium oxide is extremely slow in **1b-4b** compared to **1a-4a**, suggesting that the N-H amide is strongly intramolecular hydrogen-bonded to the *N*-oxide oxygen (form A).

Scheme II

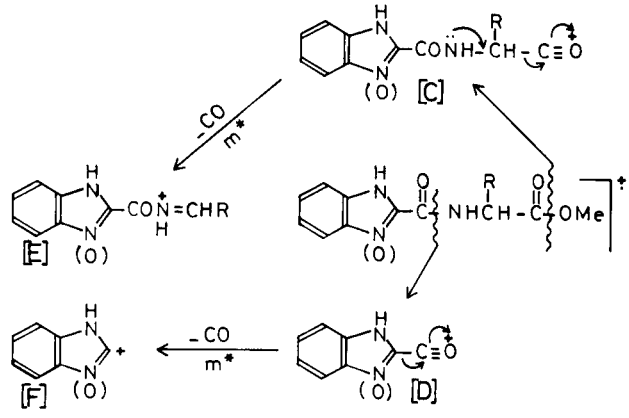


(A) (B)

Mass Spectra.

The mass spectra of the benzimidazole derivatives **1a-4a** show the correct molecular ion. As expected, the primary fission of the molecular ion occurs at the ester carbonyl or the amide carbonyl giving rise to the acylium ions $[C]^+$ and $[D]^+$, respectively. Expulsion of carbon monoxide from these ions produces the corresponding iminium ions $[E]^+$ and $[F]^+$, respectively, of which the former ion is the base peak (Scheme III). The MS of the *N*-oxygenated analogues **1b-4b** exhibit, besides ions [C-F] and their *N*-oxygenated analogues, the characteristics M-17 ions (due to the loss of OH radical from $[M^{+\cdot}]$) as the base peak. The M-16 ion (arising *via* extrusion of oxygen atom from $[M]^{+\cdot}$) is also observed, but is of low intensity. This behaviour is in accord with the intramolecularly hydrogen-bonded form (A), and is comparable to the MS behaviour of structurally related quinoxaline *N*-oxides [5]. Noteworthy is that, in benzimidazole *N*-oxides lacking intramolecular hydrogen bonding, the M-16 peak predominates over the M-17 [17].

Scheme III



The benzimidazole nucleus $[D]^+$ breaks down further to produce ions C_6H_4N (m/e 90) and C_5H_3 (m/e 53) *via* successive expulsion of two molecules of HCN, a mode that has been previously documented [18].

UV Spectra.

The uv spectra of the benzimidazoyl derivatives **1a-4a** exhibit, in ethanol and acetonitrile, strong absorption bands at about 290 and 230 nm ascribed to $\pi \rightarrow \pi^*$ transitions (Table II, Figure I). This is in agreement with literature data on the uv spectra of benzimidazoles having comparable electron-withdrawing substituents in the 2-position [19]. The $n \rightarrow \pi^*$ transition band around 315 nm is masked under the rising tail of the intense band at 290 nm.

Table II

CD and UV Spectral Data for the (*S*)-Derivatives **1-4**

No.	Solvent [c]	CD [d] λ max (Δε)	UV [d] λ max (ε × 10^{-3})
1a	E	255 (+2.9), 224 (−1.9)	291 (16.2), 230 (16.6)
	A	254 (+2.3), 227 (−2.2)	290 (15.2), 228 (17.1)
2a	E	255 (+2.4), 224 (−1.1)	292 (15.7), 230 (15.5)
	A	255 (+1.5), 230 (−1.2), 215 (+2.2)	290 (14.1), 228 (15.8)
3a	E	310 (+0.3), 268 (−2.3), 218 (+6.6),	292 (16.9), 230 (16.7)
	A	308 (+0.2), 265 (−2.7), 225 sh (+2.4), 215 (+8.7)	290 (15.7), 228 (17.3)
4a	E	312 (+0.1), 270 (−3.4), 220 (+8.6)	292 (15.2), 230 (16.4)
	A	310 (+0.5), 267 (−4.8), 224 (+12.1)	290 (15.7), 228 (17.3)
1b	E	327 (+0.3), 278 (+0.4), 240 (−1.0), 234 (−0.9), 226 (+1.4), 220 (+1.1)	325 sh (4.0), 297 (13.7), 288 (12.1), 228 (24.1)
	A	334 (+0.5), 274 (+0.8), 240 sh (−0.6), 233 (−0.8), 218 (+2.5)	335 (4.2), 298 (12.7), 289 (11.5), 230 (23.9)
2b	E	326 (+0.3), 275 (+0.6), 240 (−0.5), 235 (−0.5), 229 (+0.1)	327 sh (3.8), 298 (16.3), 288 (14.3), 228 (28.0)
	A	333 (+0.2), 273 (+0.7), 240 (−0.5), 232 (−0.4), 220 (+3.6)	334 (4.0), 299 (14.3), 289 (12.6), 230 (27.3)
3b	E	322 (−1.5), 298 (−1.7), 230 (+3.4), 218 (+3.5)	326 sh (3.6), 298 (14.2), 289 (12.6), 228 (27.8)
	A	337 (−1.4), 300 (−0.9), 235 (+2.6), 227 (+2.3), 212 (−1.4)	335 (3.8), 299 (13.0), 289 (11.6), 226 (24.8)
4b	E	325 (−0.3), 276 (−1.3), 232 (+5.2), 219 (+5.4)	328 sh (3.7), 298 (16.0), 288 (15.0), 230 (30.4)
	A	336 (−0.7), 272 (−1.8), 230 (+4.2), 216 (−1.7)	336 (3.9), 297 (14.6), 289 (13.7), 229 (27.8)

[c] A = Acetonitrile, E = Ethanol. [d] sh = Shoulder.

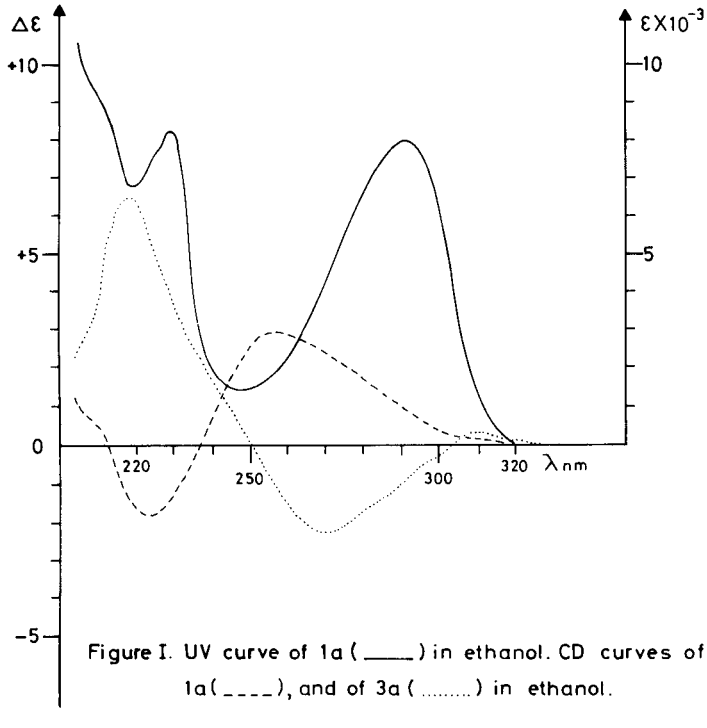
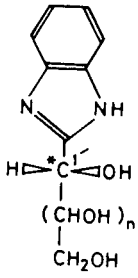


Figure I. UV curve of 1a (____) in ethanol. CD curves of 1a (- - - -), and of 3a (.....) in ethanol.

The uv specta of the *N*-oxygenated analogues **1b-4b** exhibit three strong absorption bands around 300, 290 and 230 nm of $\pi \rightarrow \pi^*$ origin, and a weak band around 330 nm ascribed to $n \rightarrow \pi^*$ transition (Table II).

CD Spectra.

The optical rotatory dispersion (ORD) of some polyhydroxyalkylbenzimidazoles **8** in methanol revealed a Cotton effect (CE) band, centered at 245 nm, whose *positive* sign was correlated with the (*S*)-chirality at C-1′ [20]. The Circular Dichroism spectra of the benzimidazoyl (*S*)-α-*aliphatic* aminoesters **1a,2a** exhibit, in the solvents ethanol and acetonitrile, two CE bands of opposite signs around 255 and 225 nm (positive and negative, respectively) (Table II, Figure I). The former band coincides with a uv minimum, suggesting that the transition is probably magnetic-dipole allowed, but electric-dipole forbidden in the zero order. The CD spectra of the (*S*)-α-*aromatic* amino ester analogues **3a**, **4a** show two CE bands around 268 and 220 nm (negative and positive, respectively). The latter band coincides with a uv minimum and, by virtue of its strength, obscures the transition around 230 nm. The band around 270 nm is probably associated with a $\pi \rightarrow \pi^*$ transition. It is worth noting that both CE bands of the *aromatic* series show sign inversion compared to those of the *aliphatic* counterparts (Table II, Figure I). This phenomenon of sign reversal has been observed for the quinoxaloyl and pyrazinoyl (*S*)-α-*aliphatic/aromatic* amino ester series [4], and is probably the result of differences in relative population of conformational isomers in either series. Arguments along the lines adopted in previous, related work [4,21] apply here also.



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The CD spectra of the *N*-oxygenated benzimidazoyl (*S*)-α-aliphatic aminoesters **1b,2b** exhibit, in ethanol and acetonitrile, two positive CE bands around 330 and 280 nm, and two "double hump" CE bands around 235 and 220 nm (negative and positive, respectively) (Table II). The (*S*)-*aromatic* counterparts **3b,4b** show nearly enantiomorphic CD spectra to those of the (*S*)-*aliphatic* series. This difference in chiroptical behaviour (sign reversal) between the (*S*)-*aliphatic* and (*S*)-*aromatic* pairs might be rationalized, by analogy with series **1a-4a**, as due to differences in conformational isomerism in the different series.

EXPERIMENTAL

(*S*)-α-Amino acid methyl ester hydrochlorides are Biochemical Grades (Fluka) and were used as received. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter in chloroform (c, 1-2) for compounds **1-3**, and in DMF (c, 1-2) for **4a** and **4b**. The pmr spectra were recorded on a Varian T-60A spectrometer in deuteriochloroform with TMS as the internal reference. Mass spectra were obtained on a Varian MAT CH-5 spectrometer, using the direct inlet technique (70eV; temperature of ion source, 200°). The uv spectra were recorded on a Cary-118 spectrophotometer in cells of 0.1-0.01 cm pathlength. The CD spectra were run on a Jasco J-40C instrument; concentrations were in the range 0.1-0.8 mg/ml in spectroscopic grade solvents (Merck). Microanalyses were performed at the Mikroanalytisches Labor-Pascher (Bonn).

General Procedures.

Ethyl 2-Benzimidazolecarboxylate 1-Oxide (**7b**).

This compound was prepared by the reaction of benzofuroxan and ethyl acetoacetate in absolute ethanolic potassium hydroxide at 50°, following literature procedure [11], yield 60% (lit [11] 62%), mp 167-168° (lit [11] 166-167°).

Ethyl 2-Benzimidazolecarboxylate (**7a**).

Phosphorus trichloride (0.15 mole) was slowly added to a stirred solution of **7b** (0.10 mole) in 100 ml of chloroform. The resulting mixture was stirred at room temperature for 15 hours, poured onto 200 ml of ice-cold water, and made alkaline with sodium carbonate. The chloroform layer was separated, and the aqueous layer was extracted with 2 × 50 ml of chloroform. The combined chloroform extracts were evaporated *in vacuo*, and the resulting residue was recrystallized from aqueous ethanol, yield 65%, mp 219-220° (lit [22] 221°).

2-Benzimidazolecarboxylic Acid Hydrazide 1-Oxide (**6b**).

Excess hydrazine hydrate (0.5 mole) was added portionwise at room temperature to a stirred solution of **7b** (0.1 mole) in 100 ml of methanol. The title hydrazide began to precipitate immediately following the addition, and the reaction mixture was stirred for additional 10 minutes. The solid product was collected and recrystallized from aqueous ethanol, yield 90%, mp 305-306°.

Anal. Calcd. for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.16. Found: C, 50.14; H, 4.18; N, 29.10.

2-Benzimidazolecarboxylic Acid Hydrazide (**6a**).

Excess hydrazine hydrate (0.5 mole) was added portionwise at room temperature to a stirred solution of **7a** (0.1 mole) in 100 ml of methanol. The resulting solution was stirred for 1 hour following the addition. The solvents were then removed *in vacuo*, and the residue was crystallized from aqueous ethanol, yield 80% (lit [8] 85%); mp 241-242° (lit [8] 239-240°).

2-Benzimidazolyl Azide 1-Oxide (**5b**).

To a stirred solution of **6b** (0.01 mole) in 12 ml of 2*N*-hydrochloric acid and 2 ml of glacial acetic acid, cooled to −10°, was added dropwise a solution of sodium nitrite (0.012 mole) in 3 ml of water. Stirring was continued for additional 15 minutes at 0° to −10° following the addition. The precipitated yellow azide was then collected, washed with 2 × 5 ml of ice-cold water and dried. A sample of **5b** was purified on preparative tlc plates using Silica Gel as the adsorbent and chloroform as the developing solvent. The title azide **5b** is rather unstable, and starts to decompose as solid at room temperature after 2 days. However, this azide is stable for 7-8 days when stored as solid at −10°, and for 12-14 days when stored as solution in dimethylformamide at −10°, yield 80%, mp 110-111° dec.

Anal. Calcd. for $C_8H_5N_5O_2$: C, 47.29; H, 2.48; N, 34.47. Found: C, 47.21; H, 2.50; N, 34.30.

2-Benzimidazoyl Azide (**5a**).

This compound was prepared from **6a** (0.01 mole) by treatment with sodium nitrite (0.012 mole), following the same experimental conditions described for **5b** above. The instability of title azide **5a** is comparable to that of the *N*-oxygenated analogue **5b** noted above, yield 85%, mp 136-137° dec. A sample of **5a** was purified on preparative tlc plates using Silica Gel as the adsorbent and chloroform as the developing solvent.

Anal. Calcd. for $C_8H_5N_5O$: C, 51.34; H, 2.69; N, 37.42. Found: C, 51.25; H, 2.66; N, 37.29.

N-(2-Benzimidazoyl)-(*S*)-α-Amino Esters **1a-4a**.

To a solution of **5a** (0.01 mole) and the particular (*S*)-α-amino acid methyl ester hydrochloride (0.012 mole) in 40 ml of dimethylformamide, cooled to −10°, was added dropwise triethylamine (0.015 mole). The reaction mixture was stirred at 0-5° for 30 minutes following the addition, and then poured onto 150 ml of ice-cold water. The title compounds were precipitated immediately, collected and recrystallized from aqueous ethanol.

N-(2-Benzimidazoyl)-(*S*)-α-Amino Ester 1-Oxides **1b-4b**.

To a solution of **5b** (0.01 mole) and the appropriate (*S*)-α-amino acid ethyl ester hydrochloride (0.012 mole) in 40 ml of dimethylformamide, cooled to −10°, was added dropwise triethylamine (0.015 mole). The reaction mixture was stirred at 0-5° for 1 hour following the addition, and then poured onto 150 ml of ice-cold water. The resulting aqueous solution was extracted with 3 × 6 ml of chloroform, and the combined chloroform extracts were dried over anhydrous magnesium sulfate. After removal of the solvent *in vacuo*, the resulting oily residue was induced to solidify by trituration with petroleum ether (bp 40-60°). The resulting solid product was collected and recrystallized from aqueous ethanol.

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