

Salim S. Sabri*, Mustafa M. El-Abadelah and Hani A. Yasin

Department of Chemistry, Faculty of Science, University of Jordan,
 Amman, Jordan

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A series of new *N*-(2-benzimidazolyl)(*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.

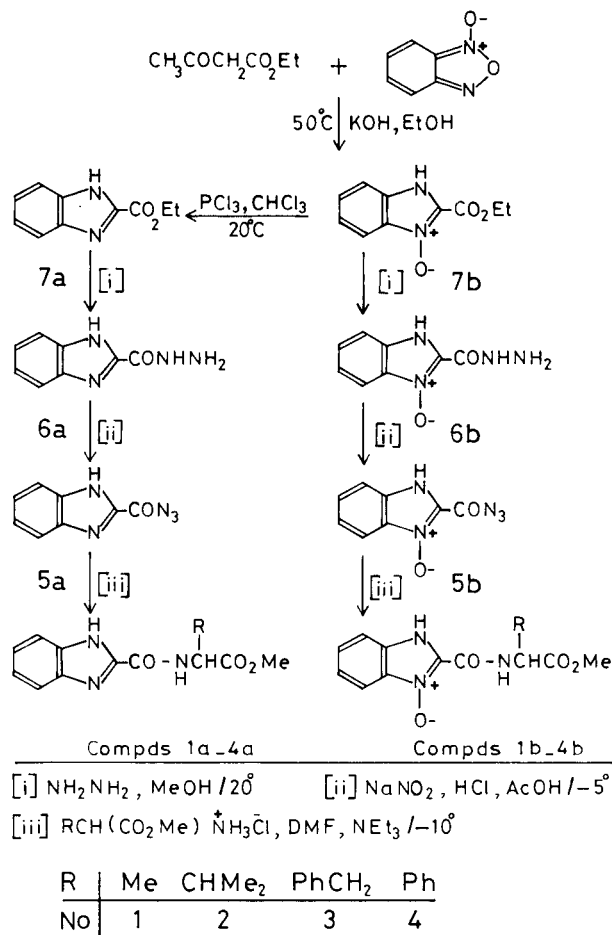
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Benzimidazoles, both natural and synthetic, have received considerable interest as they possess marked physiological activity [1,2]. A number of benzimidazoles are of commercial importance as pharmaceuticals, veterinary anthelmintics, and fungicides [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-benzimidazolyl)- α -aminoesters **1a-4a** and the respective *N*-oxides **1b-4b**. To our knowledge, the achiral *N*-(6-nitro-2-benzimidazolyl)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 pH 8.3-9.6 and 37° [7].

Compounds **1-4** have been prepared *via* interaction of the particular (*S*)- α -aminoester hydrochloride with 2-benzimidazolyl 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 racemization. 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



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 A₂B₂ 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-NH} = 8 Hz), while the imidazole N-H appears as a broad singlet at ~

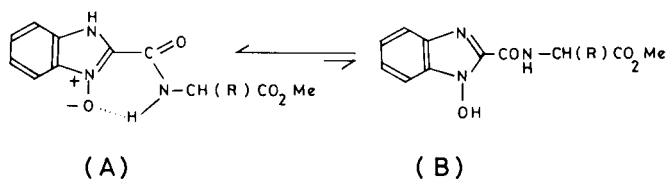
Table I
Physical Data for Compounds 1-4

No.	Yield (%)	Mp °C	[α] _D ²⁰	Formula (Mol Wt)	Analyses (%)					
					C	Calcd. H	N	C	Found H	N
(S)-1a	36	156-157	+47.4°	C ₁₂ H ₁₃ N ₃ O 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 ₃ O ₃ (275.3)	61.08	6.22	15.26	60.80	6.24	15.22
(S)-3a	27	88-90	-67.3°	C ₁₈ H ₁₇ N ₃ O 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 ₃ O 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 ₃ O 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 ₃ O 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 ₃ O ₄ (291.3)	57.72	5.88	14.43	57.31	5.98	14.19
(S)-3b	22	93-96	-33.1°	C ₁₈ H ₁₇ N ₃ O 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 ₃ O 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 ($A \rightleftharpoons B$) [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

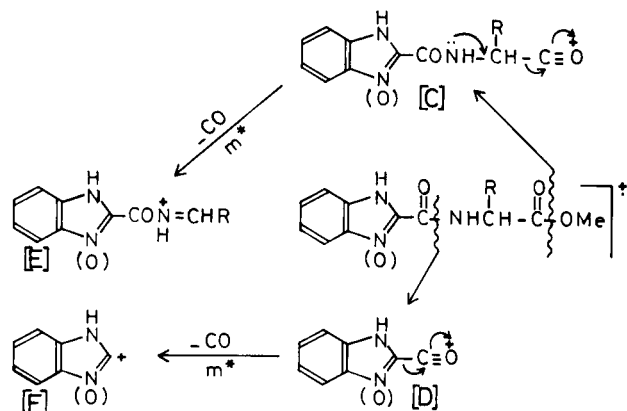


Mass Spectra.

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]⁺) as the base peak. The

M-16 ion (arising *via* extrusion of oxygen atom from [M]⁺) 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 C₆H₄N⁺ (*m/e* 90) and C₅H₃⁺ (*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 benzimidazolyl 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 ($\Delta\epsilon$)	UV [d] λ max ($\epsilon \times 10^{-3}$)
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.

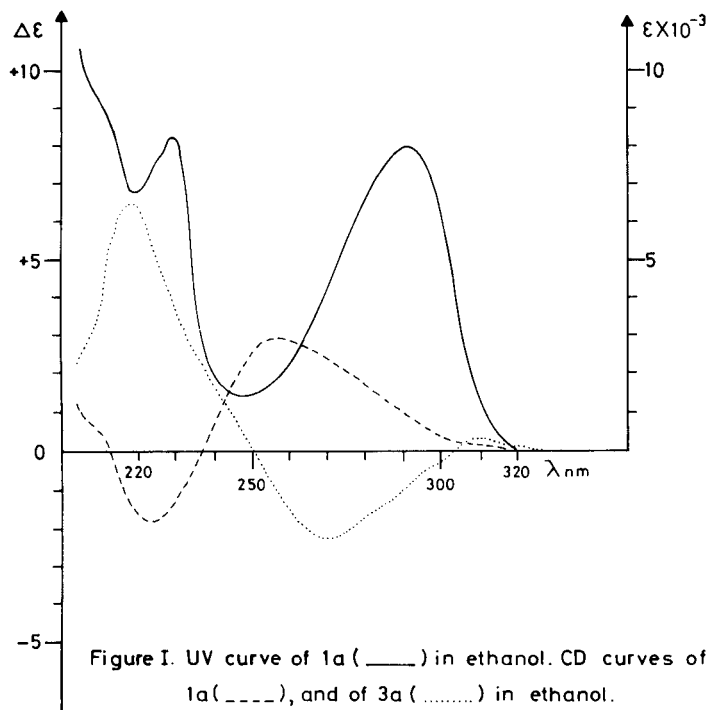
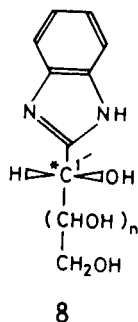


Figure I. UV curve of 1a (—) in ethanol. CD curves of 1a (---), and of 3a (.....) in ethanol.

The uv spectra 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 benzimidazolyl (*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.



The CD spectra of the *N*-oxygenated benzimidazolyl (*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 $\times$ 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 addi-

tion, 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 $\times$ 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 $C_8H_8N_5O_2$: C, 47.29; H, 2.48; N, 34.47. Found: C, 47.21; H, 2.50; N, 34.30.

2-Benzimidazolyl 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 $C_8H_8N_5O$: C, 51.34; H, 2.69; N, 37.42. Found: C, 51.25; H, 2.66; N, 37.29.

N-(2-Benzimidazolyl)-(*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-Benzimidazolyl)-(*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 $\times$ 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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