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4,5-Dihydro-1,2,4-triazin-6-ones Condensed with Heterocycles. Part 1: Synthesis and Spectral Properties of Chiral 4,5-dihydro-6-oxo-1,2,4-triazino[4,5-b] 1,2,3,4-tetrahydro-β-carbolines†

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A novel series of 4,5-dihydro-6-oxo-1,2,4-triazino[4,5-b] 1,2,3,4-tetrahydro-β-carboline (**5**) have been prepared *via* direct interaction between methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate (**3**) and the appropriate hydrazonoyl chloride (**4**) in presence of triethylamine.

INTRODUCTION

Recently we have described[1] a convenient synthetic route to 4,5-dihydro-1,2,4-triazin-6-ones, involving reaction of α-amino esters with hydrazonoyl chlorides (precursors of nitrile imines, the reactive 1,3-dipolar species). This method permitted direct synthesis of 4,5-dihydro-1,2,4-triazine-6-ones as part of spiro ring systems, or condensed with heterocyclic systems (such as pyrrolidine, piperidine, 1,2,3,4-tetrahydroisoquinoline and indoline).[1]

1,2,4-Triazines condensed with various heterocycles (such as indoles, benzimidazoles, quinolines, isoquinolines, pyrimidines, azepines and 1,4-benzdiazepines) were described in the literature.[2] Examples of 1,2,4-triazine-6-ones and their 4,5-dihydro analogues, condensed with a few heterocycles, such as pyrazole[3] and indole,[4] have also been reported.

β-Carboline is present in Harmala alkaloids.[4] This system, particularly in its 1,2,3,4-tetrahydro form, occurs frequently in the indole alkaloid series,[4] and there are literally hundreds of monoterpenoid-derived indole alkaloids containing this unit as part of their skeleton.[5] The 3,4-dihydro-β-carboline unit and its 1,2,3,4-tetrahydro form also occur as congeners of Ipecac alkaloids.[5] 4,5-Dihydro-1,2,4-triazine-6-ones, condensed with 1,2,3,4-tetrahydro-β-carbline are, however, not described in the literature. We now report on the synthesis of selected set of these fused heterocycles, namely, 4,5-dihydro-6-oxo-1,2,4-triazino-[4,5-b] 1,2,3,4-tetrahydro-β-carbolines (**5**) (*cf.* Scheme-1).

EXPERIMENTAL

Melting points were determined on an electrothermal Mel-Temp apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer 577 autoscan spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were performed on a 300

†IUPAC nomenclature: 6,7,12,12a-tetrahydro-1,2,4-triazino[4′,5′:1,6]pyrido[3,4-b]indol-1(2H)ones.

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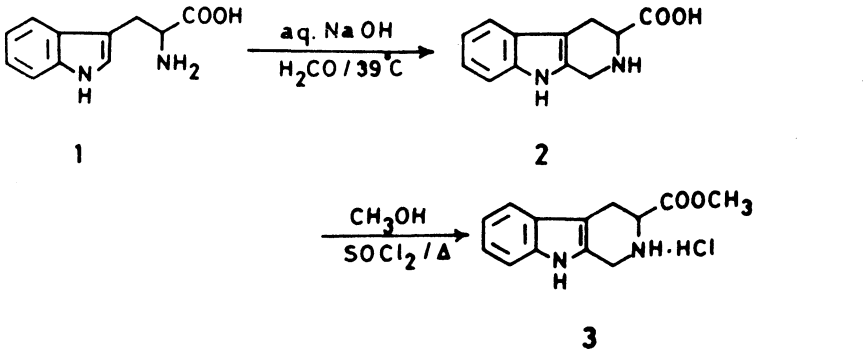
Scheme-I



No.	R	Ar
4a / 5a	CH_3	p-(Cl)C_6H_4
4b / 5b	CH_3	p-(Br)C_6H_4
4c / 5c	CH_3	p-(CN)C_6H_4
4d / 5d	OCH_3	C_6H_4
4e / 5e	OCH_3	p-(F)C_6H_4

MHz Bruker AM instrument for solutions in $CDCl_3$ at 21°C, using TMS as an internal reference. Mass spectra were obtained using a Finnigan MAT 731 spectrometer at 70 eV. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Elemental analyses were carried out by M.H.W. Laboratories at Phoenix, Arizona, USA.

L-Tryptophan (biochemical grade) was purchased from Aldrich, and was used as received. The N-arylhydrazonoyl chlorides (**4a**)[6], (**4b**)[7], (**4c**)[1], and (**4d**),[8] used in this study, were prepared following literature procedures.

1,2,3,4-Tetrahydro-β-carboline-3-carboxylic acid (2)[8]

The title compound was prepared by the following procedure as reported by Harvey *et al.*[9]: *L*-Tryptophan (10.2 g, 0.05 mol) was dissolved in 500 mL of 0.1 N aqueous sodium hydroxide containing 6 mL (0.075 mol) of 40% aqueous formalin. The resulting solution was incubated at 39°C for 72 h. The reaction

mixture was then neutralized with 4 mL of glacial acetic acid, the separated solid was filtered and recrystallised from water to give 6.0 g of (**2**). Yield: 56%; m.p. 305-306°C (Lit.[9] m.p. 306°C).

Methyl 1,2,3,4-Tetrahydro-β-carboline-3-carboxylate hydrochloride (3)

Thionyl chloride (25 mL) was dropwise added to a suspension of the acid **2** (21.6 g, 0.1 mol) in absolute methanol (100 mL) at –2 to 0°C, with vigorous stirring. Thereafter, the reaction mixture was heated under reflux for 1–2 h. The solvent was then evaporated *in vacuo*, and the residue was recrystallised from methanol/diethyl ether to give 18.2 g of (**3**). Yield: 72% m.p. 280–281°C. Mol. formula $C_{13}H_{14}N_2O_2Cl$; Mol. weight 265.72; Found: C, 58.51; H, 5.22; N, 10.35%. Calcd.: C, 58.76; H, 5.31; N, 10.54.

Mol. Formula $C_{13}H_{14}N_2O_2Cl$/Found		C, 58.51	H, 5.22	N, 10.35%
(Mol. Weight 265.72)	/(Calcd)	58.76	5.31	10.54

4,5-Dihydro-6-oxo-1,2,4-triazino[4,5-b] 1,2,3,4-tetrahydro-β-carbolines (5a–e)

A solution of the methyl ester hydrochloride 3 (2.5 g, 0.01 mol) in methanol (25 mL) was added to a solution of the appropriate hydrazonoyl chloride (0.012 mol) in chloroform (25 mL). To this stirred reaction mixture, cooled in an ice-bath, was dropwise added triethylamine (0.05 mol). The reaction temperature was then allowed to rise slowly to room temperature, and stirring was continued for 4–6 h.. The organic solvent was then evaporated under reduced pressure, the residual solid product was filtered, washed with water and recrystallized from methanol. Further purification of the crystalline products (**5**) was achieved on preparative TLC plates, using Merck Silica gel 60 HF_{254} as the adsorbent, and $CDCl_3$ as the eluent. The physical and analytical data of the title compounds **5a–e** are provided in Table-1.

TABLE-1
CHARACTERIZATON DATA OF THE SYNTHESISED COMPOUNDS

Compd. No.	Mole. Formula (Mol. Weight)	Yield (%)	m.p.* (°C)	$[\alpha]_D^{20}$†	Analysis, found (Calcd) %		
					C	H	N
5a	$C_{21}H_{17}N_4O_2Cl$ (392.5)	58	184	–741°	64.10 (64.21)	4.60 (4.36)	13.98 (14.26)
5b	$C_{21}H_{17}N_4O_2Br$ (437)	72	198	–501°	57.71 (57.68)	4.16 (3.92)	12.54 (12.81)
5c	$C_{22}H_{17}N_5O_2$ (383)	40	248	–489°	68.64 (68.92)	4.71 (4.47)	17.98 (18.27)
5d	$C_{21}H_{17}N_4O_3$ (374)	51	214	–528°	67.12 (67.37)	5.03 (4.85)	14.68 (14.96)
5e	$C_{21}H_{17}N_4O_3F$ (392)	55	218	–454°	63.97 (64.28)	4.55 (4.36)	14.03 (14.28)

*All compounds were crystallised from methanol.
†Solvent: $CHCl_3$(c *ca.* 0.5–1% wt./vol.).

RESULTS AND DISCUSSION

The title compounds (**5a–e**) are prepared *via* one-pot reaction between methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate (**3**) and the appropriate hydrazonoyl chloride (**4**) in the presence of triethylamine (Scheme-I). 1,2,3,4-Tetrahydro-β-carboline-3-carboxylic acid (**2**) was prepared *via* the Mannich reaction from L-tryptophane and H—CHO following the procedure of Harvey *et al.*[9] Compound **2** was converted to the corresponding methyl ester hydrochloride **3** by treatment with thionyl chloride/methanol, following a reported procedure[10] for esterification of related α-amino acids. Physical and analytical data of compounds **5a–e** are shown in Table-1.

The structures of these compounds were supported by spectral data. The IR spectra show N—H absorption band in the range ν_{max} 3380–3360 cm^{-1}, a strong band at 1750-1710 cm^{-1} (acetyl/ester ν(C=O)), at 1670–1650 cm^{-1} (lactam ν(C=O)), and at 1630–1600 cm^{-1} ν(C=N).

The electron-impact (EI) mass spectra of compounds **5a–e** display the correct molecular ions in accordance with the suggested molecular formulas. The spectra display prominent peaks at m/z 169, 143 (base peak) and 115 (indole moiety). Compounds **5a–c** also display ions at m/z 239/238, while **5d,e** exhibit low intensity peaks at m/z 255/254. These ions originate *via* successive loss of Ar—NCO and H atom from $M^{+\cdot}$.

The PMR spectral data of compounds **5a–e** are provided in Table-2. The

TABLE-2
PROTON CHEMICAL SHIFTS (δ-VALUES) FOR SELECTED PROTONS OF COMPOUNDS **5a–e** ($CDCl_3$)

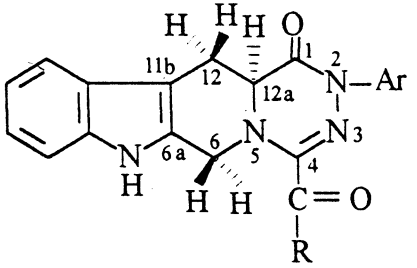
Compound	R		H-12		H-6		H-12a	N—H
5a	CH_3	2.48 (s, 3H)	3.06 (dd, 1H)	3.34 (dd, 1H)	4.45 (d, 1H)	5.70 (d, 1H)	4.37* (2d, 1H)	7.92 (s, 1H)
5b	CH_3	2.48 (s, 3H)	3.06 (dd, 1H)	3.34 (dd, 1H)	4.42 (d, 1H)	5.68 (d, 1H)	4.36* (2d, 1H)	7.94 (s, 1H)
5c	CH_3	2.50 (s, 3H)	3.05 (dd, 1H)	3.35 (dd, 1H)	4.45 (d, 1H)	5.69 (d, 1H)	4.39* (2d, 1H)	7.95 (s, 1H)
5d	OCH_3	3.85 (s, 3H)	3.07 (dd, 1H)	3.37 (dd, 1H)	4.51 (d, 1H)	5.18 (d, 1H)	4.42* (2d, 1H)	7.95 (s, 1H)
5e	OCH_3	3.85 (s, 3H)	3.06 (dd, 1H)	3.35 (dd, 1H)	4, 53 (d, 1H)	5.19 (d, 1H)	4.42* (2d, 1H)	7.94 (s, 1H)

*Center of two doublets.

methine proton at position 12a appears as two doublets in the range δ 4.3–4.4 due to its coupling with the two diastereotopic protons at position 12 ($J \approx 5$ Hz). Correspondingly, the latter H-12 protons apear as two doublets of doublets due to further geminal coupling (J *ca.* 1.4 Hz). The diastereotopic H-6 methylene protons are also mutually coupled to each other (J *ca.* 1.5 Hz) and hence are displayed as two doublets.

The CMR spectral data of compounds **5a–e** are given in Table 3. DEPT experiments were performed to differentiate the different carbons.

TABLE-3
CARBON-13 CHEMICAL SHIFTS (δ-VALUES) FOR SELECTED CARBONS OF THE SYNTHESISED COMPOUNDS **5a–e** ($CDCl_3$)



Compd.	R—C(=O)=		C-1	C-4	C-6	C-6a	C-11b	C-12	C-12a
5a	(CH_3) 27.9	194.7	161.3	142.7	44.0	129.3	106.9	24.8	56.6
5b	(CH_3) 27.9	194.6	161.7	142.7	44.0	129.3	106.8	24.8	56.6
5c	(CH_3) 28.0	194.4	161.8	143.1	44.1	129.1	106.9	24.9	56.7
5d	(OCH_3) 53.3	160.8	161.4	140.1	44.9	128.6	107.3	24.9	56.2
5e	(OCH_3) 53.3	160.9	161.3	139.3	44.9	128.2	107.2	25.0	56.1

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