SOME 3-CARBOXAMIDES OF β-CARBOLINE AND TETRAHYDRO-β-CARBOLINE

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Abstract - A series of tetrahydro-β-carboline-3-carboxamides (L- and D-series) was made by the interaction of the respective amine with the appropriate methyl tetrahydro-β-carboline-3-carboxylate. The β-carboline-3-carboxamides were prepared by a similar route from methyl β-carboline-3-carboxylate or by aromatization of the respective tetrahydro-β-carboline-3-carboxamide. The diastereomers of N-sec-butyl tetrahydro-β-carboline-3-carboxamide (L- and D-series) were separated by chromatography.

The studies by Braestrup and co-workers in 1979, which suggested that ethyl β-carboline-3-carboxylate may be an endogenous ligand for the benzodiazepine receptor in the mammalian central nervous system[1-3], created considerable interest in biogenically active β-carbolines and tetrahydro-β-carbolines. Subsequent studies which indicated that ethyl β-carboline-3-carboxylate was probably an artifact, formed from the endogenous factor, during the extraction and isolation procedure[4,5], have intensified research directed towards identifying the endogenous ligand; towards the use of β-carbolines as probes for studying the benzodiazepine receptor; and towards identifying lead compounds for developing new therapeutic agents.

Recent research has shown that both ethyl β-carboline-3-carboxylate and 3-(hydroxymethyl)-β-carboline are antagonists of some of the pharmacological effects of benzodiazepines *in vivo*[6-10]. A very recent publication described the preparation of a series of β-carboline and tetrahydro-β-carboline esters[11]. Behavioral studies with these compounds suggested that they were antagonists of benzodiazepines *in vivo*[11]. These studies also showed that an important factor in determining the affinity of the 3-substituted β-carboline for the benzodiazepine receptor site is the presence of a carbonyl moiety at the C-3 position; the C-3 esters, the C-3 aldehyde and the C-3 acetyl derivatives all proved to be much more effective than the corresponding C-3 primary and secondary alcohols[11].

This paper describes the synthesis and physical properties of various D- and L-tetrahydro-β-carboline-3-carboxamides and β-carboline-3-carboxamides, which were prepared to study their

binding to rat brain benzodiazepine receptor sites. Preliminary results from these binding studies have been reported[12-13].

The β-carboline esters were the most active compounds in the series studied by Skolnick and co-workers[11]. They have a short duration of pharmacological action[7,11], probably because of relatively rapid hydrolysis to the less potent β-carboline-3-carboxylic acid. The amides while possessing the important activity requirement of a C-3-carbonyl function, would also be expected to be longer acting *in vivo* because of increased stability to hydrolysis.

The route used for the preparation of the tetrahydro-β-carboline-3-carboxamides (D- and L-series), 5, and the β-carboline-3-carboxamides, 6, is summarized in Scheme 1; while the physical data on the compounds prepared are included in Tables 1 (tetrahydro-β-carboline-3-carboxamides-L-series); 2 (tetrahydro-β-carboline-3-carboxamides-D-series); 3 (β-carboline-3-carboxamides); and 4 (3-*sec*-butylcarboxamides).

Scheme I

Tetrahydro-β-Carboline and β-Carboline Carboxamides

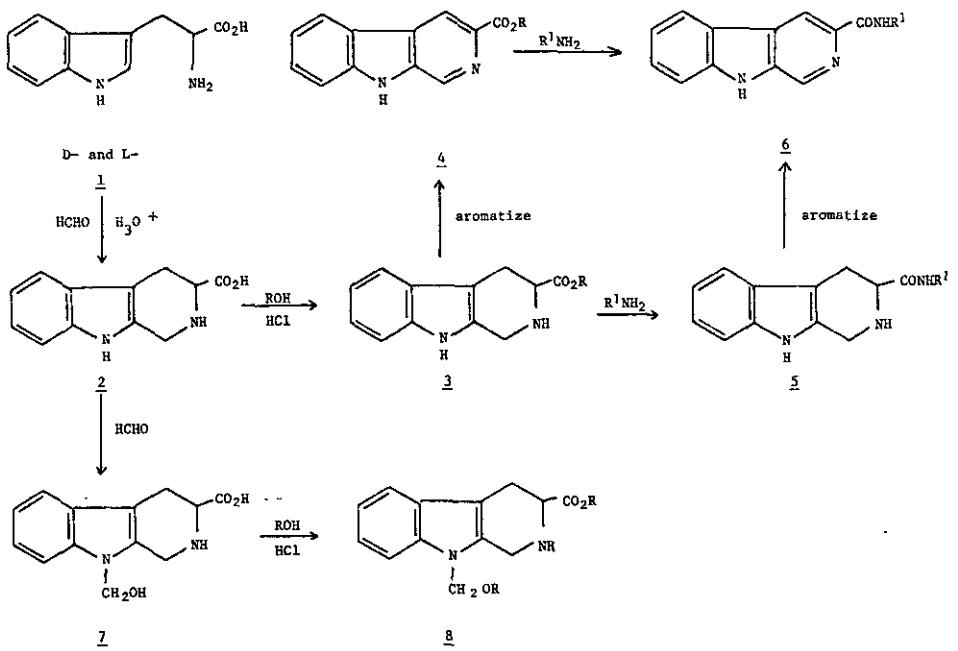
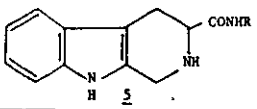


TABLE 1. TETRAHYDRO-β-CARBOLINE-3-CARBOXAMIDES (L-SERIES)



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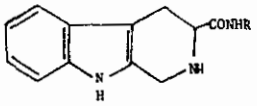
No	R	mp °C	$[\alpha]_D$	Prepn Conditions			Yield %	Elemental Calcd			Analysis Found		
				Solvent	Temp	Time		C	H	N	C	H	N
5a	H	235-236 dec	-162.8°	Amine	R.T.	18 h	80	66.96	6.09	19.52	66.66	6.15	19.59
5b	CH_3	268-270	-122.4°	Amine	R.T.	18 h	70	68.10	6.59	18.33	67.70	6.75	17.90
5c	C_2H_5	228-230	-127.8°	Amine	R.T.	18 h	90	69.11	7.04	17.27	69.03	6.95	17.21
5d	n-C_3H_7	219-220 dec	-123.0°	Amine	R.T.	18 h	90	70.01	7.44	16.33	69.87	7.54	16.15
5e	i-C_3H_7	230dec	-108.6°	Amine	R.T.	72 h	90	70.01	7.44	16.33	69.77	7.51	16.30
5f	n-C_4H_9	215-217	-111.06°	Amine	R.T.	18 h	95	70.82	7.80	15.48	70.56	7.76	15.27
5g	sec-C_4H_9	212dec	-122.76°	Amine	Reflux	4 days	50	70.82	7.80	15.48	70.58	7.78	15.28
5h	n-C_5H_{11}	175dec	-108.55°	Amine	R.T.	24 h	90	71.55	8.12	14.72	71.17	8.12	14.66
5i	n-C_6H_{13}	181dec	-99.84°	Amine	50°C	24 h	60	72.21	8.45	14.03	71.88	8.49	13.77
5j	n-C_7H_{15}	187-188	-97.35°	Dioxane Amine (2eq)	R.T.	18 h	75	72.81	8.68	13.41	72.87	8.64	13.40
5k	n-C_8H_{17}	179-180	-90.9°	Dioxane Amine (2eq)	R.T.	18 h	70	73.36	8.93	12.83	73.26	9.01	12.87
5l	n-C_9H_{19}	168-169	-85.7°	Amine	R.T.	48 h	70	73.86	9.15	12.30	73.97	9.16	12.25
5m	n-$C_{10}H_{21}$	151-153	-83.47°	Amine	R.T.	48 h	70	74.32	9.36	11.81	74.31	9.38	11.76
5n	n-$C_{11}H_{23}$	150-152	-81.52°	Amine	50°C	48 h	65	74.61	9.72	11.35	74.48	9.37	11.29
5o	n-$C_{12}H_{25}$	148-150	-79.39°	Amine	50°C	48 h	60	75.15	9.72	10.95	74.84	9.85	10.96
5p	$-(CH_2)_2-$	194-195	-88.4°	Amine	85°C	18 h	65	75.21	6.63	13.16	75.04	6.49	13.13
5q		269 dec	-116°	Amine	R.T.	48 h	75	72.06	7.47	14.83	71.90	7.64	14.63
5r		242 dec	-106.45°	Amine	R.T.	48 h	45	71.61	7.84	13.92	71.85	7.67	13.84*
5s	$-CH_2CH(CH_3)_2$	215 dec	-100.6°	Amine	Reflux	48 h	60	70.82	7.80	15.49	70.56	7.87	15.38
5t	$-CH(CH_3)CH(CH_3)_2$	203-205	-102.27°	Amine	Reflux	48 h	60	71.55	8.12	14.72	71.49	8.21	14.67

*This compound (5r) analysed repeatedly as the hydrate (1/4 H_2O). Confirmation of structure was obtained by mass spectrometry.

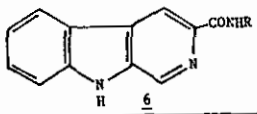
TABLE 2. TETRAHYDRO-β-CARBOLINE-3-CARBOXAMIDES (D-SERIES)



No.	R	mp °C	$[\alpha]_D$	Prepn Conditions: Solvent	Temp	Time	Yield %	Elemental Calcd: C	H	N	Analysis Found: C	H	N
5u	H	235-240-dec	+156.8°	Same as L-Series			80	66.96	6.09	19.52	66.88	6.19	19.53
5v	$-CH_3$	270 dec	+111.13°		"		65	68.10	6.59	18.33	67.95	6.69	18.04
5w	$-C_2H_5$	227-228-dec	+115.05°		"		80	69.11	7.04	17.27	68.76	7.05	17.27
5x	n-C_3H_7	219-220-dec	+131.4°		"		85	70.01	7.44	16.33	69.73	7.52	16.17
5y	$-CH(C_2H_5)_2$	203-204	+107.53°		"		50	70.41	8.00	14.50	70.61	8.06	14.54*
5z	$-CH(CH_3)C_3H_7$	208 dec	-		"		50	70.41	8.12	14.50	70.75	7.99	14.45*
5aa	sec-C_4H_9	210 dec	+110.49°		"		45	70.82	7.80	15.48	70.64	7.62	15.13

*These compounds (5y,5z) analyzed repeatedly as hydrates (1/4 H_2O). Confirmation of structures was obtained by mass spectrometry.

TABLE 3. β-CARBOLINE-3-CARBOXAMIDES



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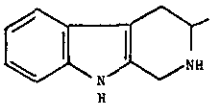
No.	R	mp °C	Prepn Conditions: Solvent	Temp	Time	Yield %	Elemental Calcd: C	H	N	Analysis Found: C	H	N
6a	H	320 dec	Amine	R.T.	18 h	80	68.24	42.29	19.89	68.06	4.31	19.90
6b	CH_3	265 dec	Amine	R.T.	18 h	80	69.32	4.92	18.65	68.80	4.98	18.43
6c	C_2H_5	247-249 dec	Amine	R.T.	18 h	45	70.28	5.48	17.56	69.84	5.52	17.56
6d	n-C_3H_7	242 dec	Amine	R.T.	72 h	50	71.13	5.97	16.59	70.67	6.02	16.49
6e	i-C_3H_7	225-226	Amine	Reflux	72 h	60	71.13	5.97	16.59	70.76	6.05	16.55
6f	n-C_4H_9	229-230	Amine	R.T.	24 h	80	71.89	6.41	15.72	71.73	6.25	15.75
6g	sec-C_4H_9	196°	Benzene*	R.T.	24 h	70	71.89	6.41	15.72	71.74	6.40	15.41
6h	n-C_5H_{11}	189-190	Amine	40°	48 h	70	72.57	6.81	14.93	72.62	7.10	14.91
6i	$-(CH_2)_2$	205 dec	Benzene*	R.T.	48 h	50	76.17	5.43	13.31	76.14	5.41	13.04
6j	$-CH(CH_3)CH(CH_3)_2$	185-186 dec	Benzene*	R.T.	48 h	50	75.57	6.81	14.94	72.55	6.89	14.79
6k	$-CH_2CH(CH_3)_2$	210-211	Amine	R.T.	48 h	50	71.89	6.41	15.72	71.78	6.57	15.63
6l	$-CH(C_2H_5)_2$	183-184	Benzene*	R.T.	24 h	60	72.57	6.81	14.94	72.54	6.88	14.85
6m	$-CH(CH_3)C_3H_7$	198-199	Benzene*	R.T.	24 h	60	72.57	6.81	14.94	72.58	6.76	14.95

* These compounds were prepared by oxidation of the appropriate tetrahydro-β-carboline with MnO_2.

TABLE 4 sec-BUTYLAMIDES

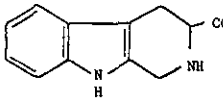
L-Series



5g

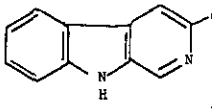
	mp	$[\alpha]_D$
Isomer mixture	212° dec	-122.76°
*separated isomers: upper band (tlc)	215° dec	-129.9°
*separated isomers: lower band (tlc)	229° dec	-101.56°

D-series



5aa

	mp	$[\alpha]_D$
Isomer mixture	210° dec	+110.49°
*separated isomers: upper band (tlc)	215° dec	+117.24°
*separated isomers: lower band (tlc)	229° dec	+ 97.65°



6g

	mp	$[\alpha]_D$
Isomer mixture	196°	0°
*From upper band of 5g (Table 1) or 5aa (Table 2)	200°	- 16.97°
*From lower band of 5g or 5aa (Table 2)	200°	+ 22.60°

*See experimental

The preparation of the D- and L-tetrahydro-β-carboline-3-carboxylic acids, 2, utilized the well-known Pictet-Spengler reaction[14], starting with D- and L-tryptophan, 1, respectively; and the procedure of Jacobs and Craig[15]. The tetrahydro-β-carboline-3-carboxylic acids, 2, thus prepared were then converted to the respective D- and L-methyl tetrahydro-β-carboline-3-carboxylates, 3, by refluxing with methanol containing hydrogen chloride.

In initial experiments following the procedure of Jacobs and Craig[15], a mixture of the desired ester, methyl tetrahydro-β-carboline-3-carboxylate, 3, and methyl 9-methoxymethyl-tetrahydro-β-carboline-3-carboxylate, 8, was obtained. The mixture was separated by flash column chromatography. This procedure of Jacobs and Craig was modified, mainly by controlling the stoichiometry of the reaction, to optimize the yield of 2 and hence 3.

The various tetrahydro-β-carboline-3-carboxamides (D- and L-series), 5, were obtained by treating the methyl esters, 3, with the appropriate amine. In most cases the amine was used as reactant and solvent; if the amine was relatively volatile, the reaction was carried out in a pressure vessel. The progress of the reaction was monitored by thin layer chromatography, and when complete, the reaction mixture was concentrated. The amide then usually crystallized from solution and was isolated by filtration.

In addition to the chiral center at C-3, the tetrahydro-β-carboline-3-carboxamides 5g, 5t, 5z and 5aa, also possess an additional chiral center in the amide substituent. The benzodiazepine receptor binding activity of the sec-butylamides, 5g and 5aa, was significant[16], and hence the diastereomers of these compounds were separated by thick layer chromatography (see Table 4). The benzodiazepine receptor binding activities of the separated diastereomers were appreciably different[16]. Oxidation of the separated diastereomers, as described below, produced the respective optical isomers of the β-carboline-3-sec-butylamide 6g (see Table 4).

The β-carboline-3-carboxamides, 6, were made by the two routes illustrated in scheme 1. The tetrahydro-β-carboline-3-carboxamides, 5, were oxidized directly to the β-carboline-3-carboxamides, 6. Methods that were investigated for this oxidation included the use of palladium on charcoal; reflux in a suitable solvent in the presence of air; and the use of manganese dioxide. In our studies, the best method, suitable for small scale (50 mg) and larger scale (up to 5g) reactions, was to react the compound with freshly prepared manganese dioxide in a solvent such as benzene.

An alternate route to the β-carboline-3-carboxamides, 6, was to aromatize methyl tetrahydro-β-carboline-3-carboxylate, 3, to methyl β-carboline-3-carboxylate, 4. For this reaction also, manganese dioxide was found to be the most satisfactory agent. The methyl β-carboline-3-carboxylate, 4, was then reacted with the respective amine (used as solvent and reagent) as described above for the preparation of the tetrahydro-β-carboline-3-carboxamides, to produce the β-carboline-3-carboxamides, 6. These reactions of the amines with methyl β-carboline-3-carboxylate, 4, were appreciably slower than the reactions of the same amines with methyl tetrahydro-β-carboline-3-carboxylate, 3.

While these reactions proceeded well with primary amines, attempts to prepare amides from secondary amines using this approach, were unsuccessful, only starting materials being recovered.

The purity of the prepared compounds was determined by HPLC before the compounds were subjected to biological evaluation. Only those compounds with a purity of better than 95% were tested. The details of the HPLC method of analysis are included in the experimental section.

EXPERIMENTAL

Melting points were taken on a Thomas Hoover "UniMelt" capillary melting point apparatus, and are uncorrected. Optical rotations were measured in methanol (concentration 10 mg/ml) using a PERKIN ELMER model 241 automatic recording polarimeter.

D- and L-Tryptophan were obtained from Chemalog, Chemical Dynamics Corp., New Jersey, U.S.A. The various amines used were obtained from Aldrich Chemical Co., Milwaukee, U.S.A. The activated manganese dioxide used for the oxidations was prepared by the method of Pratt and McGovern[17].

HPLC of β-carbolines and tetrahydro-β-carbolines

A Waters Associates Liquid Chromatograph equipped with the following modules: U6K Injector, 6000A Solvent Delivery System, 440 Absorbance Detector, (Waters Associates, Milford, Mass.), a FS 970 L.C. Fluormeter (Schoeffel Instrument Corp., Westwood, N.J.), a 3390A Integrator (Hewlett-Packard, Mississauga, Ontario), and a Recordall Series 5000 Potentiometric Recorder (Fisher Scientific Ltd., Montreal, PQ.) was used. The chromatographic procedures were as follows: Hexyl sodium sulfate (Eastman Kodak Co.) was dissolved in glacial acetic acid to give a stock solution such that when 20 ml were diluted to 1 liter the ion-pairing mobile phase was 0.005 M with respect to hexyl sulfate. For the separation of the tetrahydro-β-carbolineamides, the mobile phase was 0.005 M hexyl sulfate in 40:60 methanol:water containing 2.0 percent acetic acid and a 55:45 methanol:water mixture with the ion-pairing agent was used to separate the aromatic β-carboline-3-carboxamides. The flow rate was 1 ml/min. The chromatographic column was a Brownlee C2-10A column 4.6 mm id x 25 cm (Brownlee Labs Inc., Santa Clara, CA) which was protected by a Whatman guard column containing Co:Pell ODS (Whatman Inc., Clifton, NJ). The column effluent was passed through the 440 absorbance detector set at 254 nm and then through the FS 970 fluormeter, excitation wavelength 264 nm, 340 emission filter. The signal from the absorbance detector was recorded by one pen of the Recordall recorder and by the 3390A integrator. The signal from the fluorescence detector was recorded by the other pen of the Recordall recorder.

SYNTHETIC PROCEDURES

Representative examples are described.

Methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate, 3, and methyl 9-methoxymethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate, 8.

Tryptophan (10 g, 0.049 mole) was dissolved in a mixture of sulfuric acid (50 ml) and water (160 ml), and formalin (50 ml of a 37% solution, ca. 0.6 mole) was added in one portion to the stirred solution, when a tan colored precipitate separated. After stirring at room temperature for 1.5 h, ammonium hydroxide solution (16ml of a 14.8 normal solution) was added. The reaction mixture was stirred overnight at room temperature, after which it was filtered and the off-white solid washed with ice-water and dried giving 11.9 g of a yellow powder. The crude product was used as such in the esterification reaction.

The solid was suspended in methanol (300 ml) and dry hydrogen chloride bubbled through the stirred mixture, until the compound dissolved. The solution was then heated under reflux overnight. The methanol was removed, the resulting solid stirred with saturated aqueous sodium bicarbonate (150 ml) and extracted (twice) with ethyl acetate (150 ml). The combined ethyl acetate layers were dried over magnesium sulfate, filtered, and concentrated, to give 10 g of a pale yellow foam.

Flash chromatography of 6 g of the crude product on silica gel using 5% methanol in chloroform as eluant gave 1.3 g of methyl 9-methoxymethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate, 8, as a thick oil; nmr (CDCl): s, 3.00, m, 3H; 3.20, s, 3H; 3.79, s, 3H; 4.15, m, 2H; 5.23, s, 2H; 7.28, m, 5H; followed by 4.0 g of methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate, 3, mp 186-187°C[11,18].

(L- or D-) Methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate, 3.

The procedure described above was modified to give essentially pure methyl ester 3. Tryptophan (L- or D-isomer, 10.2 g, 0.05 mole) was dissolved in sulfuric acid (50 ml of a normal solution, 0.05 mole) and diluted with water (150 ml). Formalin (5 ml of a 37% solution, ca. 0.06 mole) was added in one lot and the resulting turbid mixture stirred for about 2 h, after which aqueous ammonia (16 ml of 14.8 normal solution) was added. The mixture was stirred overnight, cooled in an ice-bath, and then filtered. The resulting white solid was washed with ice-water and dried to give 10.3 g of a solid. This solid was stirred in methanol (300 ml) and dry hydrogen chloride bubbled through until solution was complete. The resulting solution was heated under reflux overnight and the methanol removed on a rotary evaporator. The resulting solid was stirred with ethyl acetate and aqueous sodium bicarbonate as described in the previous experiment and the organic layer separated. The aqueous layer was extracted (twice) with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to give 11 g of a white solid. This solid was chromatographed on silica gel using 5% methanol in chloroform as eluant, when 10.45 g (85%) of the desired methyl ester, mp 185-187°C[11,18] was obtained.

Both isomers (L- and D-tryptophan) gave approximately the same yield of the isomeric products.

(L- or D-) N-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide, 5b and 5v.

A mixture of L-methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate, 3 (500 mg) and methylamine (10 ml) was stirred for 24 h in a sealed pressure flask, kept at ambient temperature. The methylamine was then allowed to evaporate slowly, when the desired methylamide began to crystallize. When the volume had reached approximately 3 ml, the reaction mixture was filtered and the resulting solid washed well with ice-cold ether, and then dried when 350 mg of the desired product with the properties summarized for 5b in Table 1, was obtained.

The D-N-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide, 5v, was prepared in a similar way from D-methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate, and had the physical properties summarized in Table 2.

L-N-n-Hexyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide, 5i.

A mixture of L-methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate, 3 (500 mg) and n-hexylamine (5

ml) was heated in an oil-bath kept at 50°C for a period of 24 h. The resultant solution was concentrated to a small volume (about 2 ml) on a rotary evaporator when the amide crystallized. The amide was filtered, washed with ether, and dried, and 340 mg of the desired compound with the properties summarized for 5i in Table 1, was obtained.

L-N-n-Octyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide, 5g and 5aa.

A mixture of L-methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate, 3 (500 mg, 0.002 mole), dioxane (anhydrous 5 ml) and n-octylamine (0.55 g, 0.004 mole) was stirred at room temperature in a nitrogen atmosphere for 18 h. The mixture was then concentrated to a small volume (1 ml) and the amide that crystallized was filtered, washed with ice cold ether and dried to give 0.32 g of the n-octylamide with the properties summarized for 5k in Table 1.

(L- and D-) N-sec-butyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide, 5g.

A mixture of L-methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate, 3 (2g, 0.008 mole) and sec-butylamine (20 ml, bp 63°C) was heated under reflux in a nitrogen atmosphere for 4 days, keeping the volume constant by the addition of sec-butylamine as required. The reaction mixture was concentrated to about 1 ml and cooled in an ice-bath when the amide crystallized and was filtered. The resulting solid was washed with ether and dried to give 1.05 g of a white powder which was purified and the diastereomers separated as described below.

The corresponding C_3-D-isomer was made from D-methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate by the same procedure.

Separation of diastereomers of 5g.

The product (0.5 g) obtained from the previous experiment was dissolved in methanol-methylene chloride 1:1 and applied to six thick layer silica gel plates. These plates were then developed with 7% methanol in methylene chloride, the process of elution being repeated four times, drying the plates after each elution. Three bands (observed under UV light) - the two diastereomers, 5g, and the starting methyl ester, 3 - separated. The two bands corresponding to the diastereomers of the desired product were scraped separately and eluted with methanol/methylene chloride (five times). The combined extracts obtained from extraction of each band were concentrated to give the two separated diastereomers in yields of 150 mg (each isomer).

Oxidation of methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate, 3, using palladium-on-charcoal.

A mixture of methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate (100 mg) and 5% palladium-on-charcoal (100 mg) in dry dioxane (30 ml) was stirred and heated under reflux in an oil-bath maintained at 100°C for a period of 3 days; by which time a tlc on silica gel using 20%

methanol in chloroform, indicated complete reaction. The reaction mixture was filtered and the filtrate concentrated to a small volume. The resulting solid was filtered and dried to give 80 mg of the aromatic ester 4 as a white solid, mp 245°C [Reported mp 245°C[11]; 243°C[19]]

Oxidation of N-n-amyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide, 5h, using air.

A solution of N-n-amyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide (50 mg) in dry dioxane (50 ml) was heated under reflux in a stream of air, for 48 h. The volume was kept constant by the periodic additions of dry dioxane as required. The progress of the reaction was monitored by tlc on silica gel. After about 24 h, the tlc plate showed, in addition to the starting material the appearance of a green fluorescent spot (under UV radiation). Later a further spot (blue under UV radiation) showed. Finally after 48 h, the tlc showed only the presence of the final product, as the blue spot (under UV radiation) on the tlc plate. The reaction solution was treated with charcoal, filtered and concentrated to give 35 mg of the N-n-amyl-β-carboline-3-carboxamide, as a white solid, identical to a sample made from methyl β-carboline-3-carboxylate and n-amylamine, with the properties summarized for 6g in Table 3.

Oxidation of N-ethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide, 5c, using manganese dioxide.

A mixture of N-ethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide (500 mg) in benzene (50 ml) and freshly prepared mangaxide (2 g) was stirred and heated under reflux for 12 h. The progress of the reaction was monitored by tlc. The manganese dioxide was removed by filtration and when most of the benzene was removed on a rotary evaporator, the amide crystallized and was isolated by filtration to give 450 mg of the desired N-ethyl-β-carboline-3-carboxamide, with the properties summarized for 6c in Table 3.

Oxidation of N-sec-butyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide, 5g, using manganese dioxide.

A mixture of N-sec-butyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide, 5g (200 mg of one of the isolated diastereomers - upper band) and manganese dioxide (500 mg) in benzene (50 ml), was stirred and heated under reflux for 10 h, by which time a tlc on the reaction mixture (only one fluorescent spot under UV radiation) showed that the reaction was complete. The mixture was filtered through celite and the celite washed with small amounts of methylene chloride. The combined organic layers were concentrated to a small volume (ca. 2 ml) and the resulting crystals collected by filtration, washed with ether, and dried to give 150 mg of N-sec-butyl-β-carboline-3-carboxamide, 6l, with the properties summarized in Table 3.

Essentially the same results were obtained by repeating this process on the other diastereomer (lower band) of N-sec-butyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide.

N-n-Amyl-β-carboline-3-carboxamide, 6g, from methyl β-carboline-3-carboxylate, 4.

A solution of methyl β-carboline-3-carboxylate 4 (800 mg) in n-amylamine (5 ml, bp 104°C) was stirred and heated in a nitrogen atmosphere, in an oil bath kept at 40°C for 72 h. The reaction mixture was concentrated to small volume on a rotary evaporator, treated with ether and the resulting solid collected by filtration. The solid (700 mg) had the physical characteristics summarized for 6g in Table 3.

ACKNOWLEDGEMENT

This study was financed by the Medical Research Council of Canada, the Alberta Heritage Foundation for Medical Research (AHFMR) and the Alberta Mental Health Research Foundation. T.W. Hall is an AHFMR Fellow.

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Received, 8th August, 1983