Selenium Dioxide Oxidation of Tetrahydro-β-carboline Derivatives

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The oxidation of some tetrahydro-β-carboline derivatives with selenium dioxide led to the formation of 1,4-dihydro or fully aromatic β-carbolines, depending on the nature and the number of substituents at 1 position. The oxidation of 2-acetyl derivatives followed a different course and the products originated by the attack at C-1 of the ring C of the tetrahydro-β-carboline were obtained.

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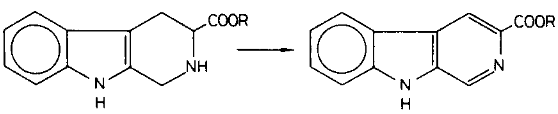
Recent researches have shown that methyl and ethyl β-carboline-3-carboxylate are strong inhibitors of the specific binding of benzodiazepines to its brain receptors *in vitro*, and are antagonists of some of the pharmacological effects of benzodiazepines *in vivo* [1-3]. The key step in their preparation was the dehydrogenation of the corresponding tetrahydro-β-carboline esters (Scheme 1). The above dehydrogenation carried out by sulfur in refluxing xylene [4] or with chloranil in tetrachloroethane [5] or with Pd/C in boiling cumene [6] gave low yields. A better method, but rather cumbersome, was the dehydrogenation with lead tetraacetate in glacial acetic acid, followed by separation of methyl β-carboline-3-carboxylate as the hydrogen oxalate from the reaction mixture [7].

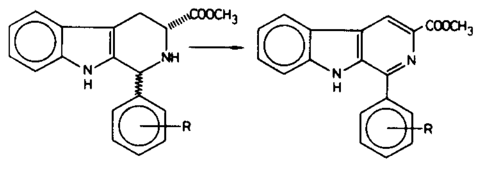


I a-c   II a-c

a: R = $-CH_3$; b: R = $-C_2H_5$; c: R = $-nC_3H_7$

The selenium dioxide oxidation of some tetrahydro-β-carbolines has been recently reported [8], so we subjected the tetrahydro compounds **I** to treatment with the latter oxidizing agent, in order to obtain the related β-carboline esters **II**. These compounds were obtained in good yields, and this method proved to be superior to the use of other oxidizers, so that it can be employed very effectively to provide gram quantities of pharmacologically interesting β-carboline-3-carboxylic acid esters.

The oxidation of the corresponding 1-alkyl derivatives has not been investigated by us because Cain and co-workers [8] reported that the oxidation of 1-ethyl-3-(methoxycarbonyl)tetrahydro-β-carboline produces a mixture of four compounds. In contrast, the 1-aryl-3-(methoxycarbonyl)tetrahydro-β-carbolines **III** were dehydrogenated in the above oxidation conditions to give again the fully aromatic compounds **IV** in good to excellent yields (Scheme 2).



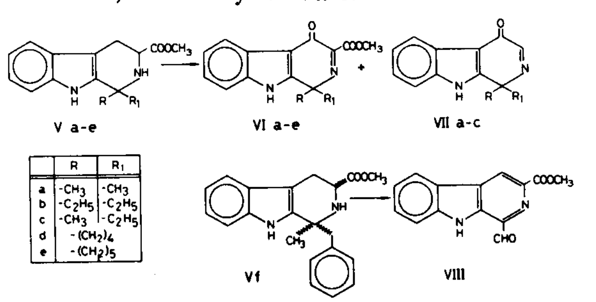
III a-f   IV a-f

	R
a	H
b	2-Cl
c	4-Cl
d	4-F
e	$4-OCH_3$
f	$3,4-OCH_3$

Scheme 2

When two substituents at 1-position were present, the selenium-oxidation followed a different course, probably because the double substitution prevents the oxidative attack to C-1 and the aromatization of ring C of tetrahydro-β-carbolines results prohibited.

Actually, the 1,1-disubstituted compounds **Va-e**, by treatment with selenium dioxide in the above reported conditions (Scheme 3), gave a 50-70% yield of the 3-(methoxycarbonyl)-1,4-dihydro-4-oxo-β-carbolines **VIa-e** together with about 10% yield of the corresponding decarboxylated ketones, exclusively for **Va-c**.



V a-e   VI a-e   VII a-c   Vf   VIII

	R	R₁
a	$-CH_3$	$-CH_3$
b	$-C_2H_5$	$-C_2H_5$
c	$-CH_3$	$-C_2H_5$
d	$-(CH_2)_4$	
e	$-(CH_2)_5$	

Scheme 3

These results confirm that the preferential oxidative attack in the selenium oxidations occurs at the benzylic-type positions, as extensively reported in the literature [9].

Table 1

Compound N°	Yield %	Mp (°C)	Recrystallized from	Molecular Formula	Analysis % Calcd./Found C	H	N
IIa	66	258-260 [a]	1-propanol	$C_{13}H_{10}N_2O_2$	69.01	4.46	12.38
					68.86	4.19	12.30
Acetylderivative **XIIb**	90	201-203	chloroform-*n*-hexane	$C_{15}H_{12}N_2O_3$	67.15	4.51	10.44
					67.33	4.44	10.22
IIb	72	231-233 [b]	1-propanol	$C_{14}H_{12}N_2O_2$	69.99	5.03	11.66
					70.24	5.11	11.45
Acetylderivative	86	159-161	ethanol	$C_{16}H_{14}N_4O_3$	68.07	5.00	9.92
					67.92	5.03	10.08
IIc	65	185-188 [c]	1-propanol	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02
					70.65	5.48	10.92
Acetylderivative	90	112-113	1-propanol	$C_{17}H_{16}N_2O_3$	68.90	5.44	9.45
					68.71	5.32	9.44
IVa	84	257-260 [d]	methanol	$C_{19}H_{14}N_2O_2$	75.48	4.67	9.27
					75.39	4.37	9.19
IVb	81	284-286	methanol	$C_{19}H_{13}ClN_2O_2$	67.76	3.89	8.32
					67.91	3.96	8.29
IVc	79	288-291	methanol	$C_{19}H_{13}ClN_2O_2$	67.76	3.89	8.32
					67.57	4.00	7.96
IVd	88	278-281	methanol	$C_{19}H_{13}FN_2O_2$	71.24	4.09	8.74
					71.15	3.88	8.79
IVe	77	229-231	methanol	$C_{20}H_{16}N_2O_3$	72.28	4.85	8.43
					72.42	4.66	8.45
IVf	86	238-241	methanol	$C_{21}H_{18}N_2O_4$	69.60	5.00	7.73
					69.38	5.15	7.62
Va	86	201-203	benzene	$C_{13}H_{18}N_2O_2$	69.74	7.02	10.85
					69.89	6.85	10.72
Vb	74	157-159	benzene	$C_{17}H_{22}N_2O_2$	71.30	7.74	9.78
					71.36	7.96	9.47
Vc	68	124-130 [e]	benzene-*n*-hexane	$C_{16}H_{20}N_2O_2$	70.56	7.32	10.29
					70.78	7.40	10.35
Vd	59	134-136	benzene-*n*-hexane	$C_{17}H_{20}N_2O_2$	71.80	7.09	9.85
					71.94	7.19	9.62
Ve	64	173-175	benzene	$C_{18}H_{22}N_2O_2$	72.45	7.43	9.39
					72.70	7.68	9.38
Vf	52	154-158 [e]	benzene	$C_{21}H_{22}N_2O_2$	75.42	6.63	8.38
					75.41	6.93	8.30
VIa	47	218-222	benzene	$C_{15}H_{14}N_2O_3$	66.65	5.22	10.37
					66.41	5.14	10.38
VIb	60	195-197	benzene-*n*-hexane	$C_{17}H_{18}N_2O_3$	68.44	6.08	9.39
					68.41	6.09	9.44

Table 1 (continued)

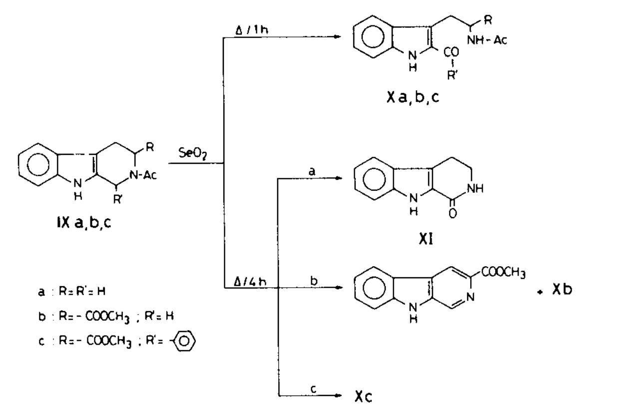
Compound No.	Yield %	Mp (°C)	Recrystallized from	Molecular Formula	Analysis % Calcd./Found C	H	N
VIc	54	171-173	benzene	$C_{16}H_{16}N_2O_3$	67.59 67.50	5.67 5.69	9.85 9.58
VId	66	242-246	ethyl acetate-*n*-hexane	$C_{17}H_{16}N_2O_3$	68.90 69.11	5.44 5.48	9.45 9.24
VIe	72	277-280	ethyl acetate-*n*-hexane	$C_{18}H_{18}N_2O_3$	69.66 69.42	5.85 5.83	9.03 8.87
VIIa	10	295-299	ethyl acetate	$C_{13}H_{12}N_2O$	73.56 73.31	5.70 5.48	13.20 13.08
VIIb	8	264-266	ethyl acetate	$C_{15}H_{16}N_2O$	74.97 74.82	6.71 6.76	11.66 11.13
VIIc	12	233-235	ethyl acetate	$C_{14}H_{14}N_2O$	74.31 74.14	6.24 6.29	12.38 12.29
VIII	48	244-246	benzene	$C_{14}H_{10}N_2O_3$	66.13 66.21	3.96 4.08	11.02 10.76
IXb	86	183-186	methanol	$C_{15}H_{16}N_2O_3$	66.16 66.01	5.92 6.01	10.29 10.17
IXc *cis*	85	199-202	ethyl acetate	$C_{21}H_{20}N_2O_3$	72.39 72.11	5.79 5.86	8.04 7.94
IXc *trans*	92	226-229	methanol	$C_{21}H_{20}N_2O_3$	72.39 72.32	5.79 5.91	8.04 8.11
Xa	44	165-167	methanol	$C_{13}H_{14}N_2O_2$	67.81 67.59	6.13 6.01	12.17 12.19
Xb	52	193-195	methanol	$C_{15}H_{16}N_2O_4$	62.25 62.49	5.60 5.60	9.58 9.72
Xc	78	181-183	isopropanol-*n*-hexane	$C_{21}H_{20}N_2O_4$	69.21 69.39	5.53 5.73	7.69 7.47
XI	68	189-190 [f]	methanol	$C_{11}H_{10}N_2O$	70.95 70.70	5.41 5.47	15.05 15.15
XIIa	24	123-125	benzene	$C_{13}H_{10}N_2O$	74.27 74.39	4.79 4.78	13.33 13.50
XIII	54	153-155	benzene	$C_{17}H_{16}N_2O_4$	65.37 65.17	5.16 5.20	8.97 8.80
XIV	66	214-217	methanol	$C_{15}H_{14}N_2O_3$	66.65 66.60	5.12 5.29	10.37 10.28
XV	67	151-153	isopropanol-*n*-hexane	$C_{25}H_{24}N_2O_6$	66.95 67.10	5.39 5.47	6.25 6.28

[a] Lit [7] mp 261-262°. [b] Lit [7] mp 231-232°. [c] Lit [7] mp 187-188°. [d] Lit [5] mp 254-255°. [e] Employed as a mixture of diastereomers. [f] Lit [13] mp 189-190°.

Moreover, the oxidation of the compound **V** (R = CH_3, R_1 = $CH_2C_6H_5$) in a diastereoisomeric mixture (1*R*, 3*S* and 1*S*, 3*S*) provided a 48% yield of 1-formyl-3-(methoxycarbonyl)-β-carboline **VIII** - probably through the oxidation of the benzylic moiety affording benzaldehyde - then the aromatization of ring C and finally the oxidation of the C-1 methyl to formyl group.

It is important to note that the acetylation of the nitrogen atom in 2-position of the above tetrahydro-β-carbolines does not allow the aromatization of ring-C, consequently the oxidative attack at C-1 results in a cleavage of the C-N bond with the formation of carbonyl derivatives.

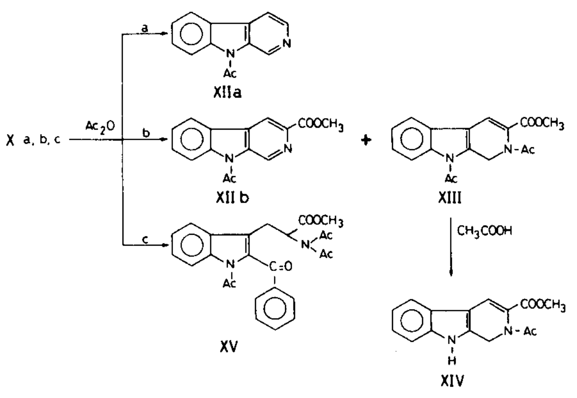
Particularly, 2-acetyl-1,2,3,4-tetrahydro-β-carbolines **IXa-c**, by reacting with selenium dioxide in refluxing dioxane for 1 hour, produced the formyl derivatives **Xa,b** and the benzoyl derivative **Xc**, respectively (Scheme 4). Moreover, by prolonging heating for 4 hours **IXa** was transformed into 1,2,3,4-tetrahydro-1-oxo-β-carboline **XI**; **IXb** afforded a mixture of the fully aromatic β-carboline **IIa** and the formyl derivative **Xb** while *cis* and *trans* diastereoisomers of **IXc** [10] gave a 64% yield of **Xc**; that is the same compound obtained in the 1 hour oxidation reaction.



Scheme 4

As was clearly shown by tlc-monitoring, compounds **XI** and **IIa** were formed through the intermediates **Xa** and **Xb** respectively when the reaction was carried out on pure **Xa,b** for 4 hours in the same conditions of the above selenium-oxidation.

Interesting information was obtained in the attempt to prepare *N*-acetyl derivatives of the compounds **Xa-c** by refluxing with acetic anhydride (Scheme 5). Thus, **Xa** provided the 9-acetyl-β-carboline **XIIa** in 24% yield, while **Xb** gave a mixture of 9-acetyl-3-(methoxycarbonyl)-β-carboline **XIIb** and 2,9-diacetyl-3-(methoxycarbonyl)-1,2-dihydro-β-carboline **XIII**, in a ratio of 1:2, the latter was then 9-deacetylated in boiling 30% acetic acid to give compound **XIV**. Finally, the benzoyl derivative **Xc** afforded a 67% yield of methyl 3-(1-acetyl-2-benzoylindol-3-yl)-2-diacetylaminopropionate **XV**.



Scheme 5

EXPERIMENTAL

Melting points were determined on a Köfler hot stage apparatus and are uncorrected. The [1]H-nmr spectra were determined on a T-60 Varian spectrometer with TMS as an internal standard. Column chromatographic separations were accomplished on Merck silica gel (70-230 mesh); Merck silica gel plates were also used. The drying agent was sodium sulfate. Yields, crystallization solvents, melting points and microanalytical data for all the compounds described herein are reported in Table 1. The ir and nmr spectral data of the described compounds are in agreement with the assigned structures and nmr data are reported only for the most significant compounds.

1,2,3,4-Tetrahydro-3-(methoxycarbonyl)-βcarbolines **Ia-c** and **IIIa-f**.

The synthesis of methyl, ethyl and *n*-propyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylates **Ia-c** [7], *cis* and *trans* 3-(methoxycarbonyl)-1-phenyl-1,2,3,4-tetrahydro-β-carboline **IIIa** [6] has been reported elsewhere. Compounds **IIIb-f** were prepared in 80-90% yields by Pictet-Splenger condensation of L-tryptophan methyl ester with aromatic aldehydes in refluxing toluene for 20 hours (Dean-Stark trap to remove water). Since the chirality at position 1 and 3 of ring C is destroyed by conversion to β-carbolines, no attempt was made to separate the diastereoisomers, and their crude mixture was used in the oxidation.

1,1-Dialkyl-3-(methoxycarbony)-1,2,3,4-tetrahydro-βcarbolines **Va-f**.

Compound **Va** was prepared from the corresponding acid [11] by esterification in methanolic hydrogen chloride. Compounds **Vb-f** were obtained by dissolving L-tryptophan methyl ester (22 g, 0.1 mole) and different ketones (0.2 mole) in toluene (200 ml). The solution was held at reflux temperature under a reflux condenser equipped with a Dean-Stark trap, until the starting material was not detectable by tlc (about 4 hours). Evaporation of the toluene to dryness gave a crude residue which was crystallized. Compounds **Vc** and **Vf** were employed as a mixture of diastereoisomers.

2-Acetyl-1,2,3,4-tetrahydro-β-carbolines **XIa-c** [12], 9-Acetyl-β-carbolines **XIIb**, and **IIb-c** Acetyl Derivatives.

Compounds **Ia**, **IIa-c** and **IIIa** were acetylated with an excess of acetic anhydride in the presence of pyridine at 80° for 2 hours. The reaction mixture was evaporated and the residue, after water addition, was first made alkaline with diluted ammonium hydroxide, then extracted with chloroform. The solvent was removed *in vacuo* and the residue crystallized.

Selenium Dioxide Oxidation of 1,2,3,4-Tetrahydro-β-carbolines. Methyl, Ethyl, *n*-Propyl β-Carboline-3-carboxylates **IIa-c**, and 1-Aryl-3-(methoxycarbonyl)-β-carbolines **IVa-f**.

A solution of the tetrahydro compounds **Ia-c** or of the mixture of diastereoisomers **IIIa-f** (0.1 mole) in dioxane (200 ml) was treated with selenium dioxide (16.5 g, 0.15 mole), and the reaction mixture was stirred at reflux temperature for several hours until tlc (ethyl acetate) indicated the absence of the starting material. The hot suspension was filtered over Celite to remove the black selenium, then the filtrate was evaporated under reduced pressure. The crude products **IVa-f** were directly crystallized from methanol, while in the case of compounds **IIa-c** the residue was treated with hydrochloric acid (10%, 1 liter) and decolorizing carbon. The resulted suspension was stirred for 2 hours, then filtered. The aqueous solution was basified with concentrated ammonium hydroxide to afford a solid, which was collected, washed with water, and crystallized. The residue obtained from mother liquors evaporation was chromatographed on a silica gel column: additional quantities of **II** were obtained by eluting with ethyl acetate.

Selenium Dioxide Oxidation of 1,1-Dialkyl-3-(methoxycarbonyl)-1,2,3,4--tetrahydro-β-carbolines. 1,1-Dialkyl-3-(methoxycarbonyl)-1,4-dihydro--4-oxo-β-carbolines **VIa-e**, 1,1-Dialkyl-1,4-dihydro-4-oxo-β-carbolines **VIIa-c**, and 1-Formyl-3-(methoxycarbonyl)-β-carboline **VIII**.

Selenium dioxide (1.7 g, 0.015 mole) was added to a solution of **V** (0.01 mole) in dioxane (100 ml) heated at 80°. The reacton mixture was stirred under reflux for 2 hours. The crude mixture was filtered through Celite and the solvent removed. The residue was crystallized to give **VId,e** and **VIII** or more commonly chromatographed on a silica gel column by eluting with an ethyl acetate/*n*-hexane (1:1) mixture to give the compounds **VI** and **VIIa-c**. Generally compounds **VI** were eluted first, followed by **VII**. The benzaldehyde, formed as a by-product in the oxidation of **Vf**, was detected in the reaction mixture by hplc on an octyl bonded-phase column by gradient from acetonitrile-water.

Compond **VIII** shows the following nmr spectral data (hexadeuteriodimethyl sulfoxide): δ 11.90 (broad, N*H*, 1H), 10.30 (s, -C*H*O, 1H), 8.93 (s, =CH-, 1H), 8.20-7.20 (aromatic protons, 4H), 4.05 (s, -CH_3, 3H).

Selenium Dioxide Oxidation of 2-Acetyl-1,2,3,4-tetrahydro-β-carbolines. 2-Formyl-3-(2-acetylaminoethyl)indole **Xa**, Methyl 2-Acetylamino-3-(2-formylindol-3-yl)propionate **Xb**, Methyl 2-Acetylamino-3-(2-benzoylindol-3-yl)propionate **Xc** and 1,2,3,4-tetrahydro-1-oxo-β-carboline **XI**.

Selenium dioxide (1.5 g) was added to a stirred solution of the acetyl derivatives **IX** (2 g) in dioxane (30 ml) and the reaction mixture was refluxed for 1 hour. After filtration through Celite and removal of the solvent, the residue was chromatographed on silica gel and eluted with ethyl acetate/*n*-hexane (2:1) mixture, to give compounds **Xa-c**.

By refluxing the same reaction mixtures for 4 hours, compound **IXa** gave the 1,2,3,4-tetrahydro-1-oxo-β-carboline **XI** [14] in 68% yield; compound **IXb** afforded a mixture of **Xb** (30% yield) and methyl β-carboline-3-carboxylate **IIa** (13% yield), easily separated by silica gel column chromatography (ethyl acetate); finally compound **IXc** gave the same results obtained in the 1 hour reaction. The above results were confirmed by refluxing for 4 hours the compounds **Xa,b** (1 g) with selenium dioxide (0.8 g) in dioxane (20 ml). Compounds **XI** and **IIa** were obtained in 78 and 85% yields, respectively.

Compound **Xa** shows the following nmr spectral data (hexadeuteriodimethyl sulfoxide): δ 11.50 (broad, indolic N*H*, 1H), 9.93 (s, -C*H*O, 1H), 8.05-6.90 (m, aromatic protons, and amidic N*H*, 5H), 3.60-3.15 (m, -CH_2-CH_2-, 4H), 1.83 (s, -CO-CH_3). Compound **Xb** shows the following nmr spectral data (deuteriochloroform): δ 9.70 (s, -C*H*O, 1H), 9.33 (broad, indolic N*H*, 1H), 7.70-6.95 (m, aromatic protons and amidic N*H*, 5H), 5.25-5.00 (m, =C*H*-, 1H), 3.70 (s, -COOCH_3, 3H), 3.55 (d, -CH_2-, 2H), 2.08 (s, -CO-CH_3, 3H).

Reaction with Acetic Anhydride of Compounds **X**. 9-Acetyl-β-carboline **XIIa**, 9-acetyl-3-(methoxycarbonyl)-β-carboline **XIIb** and 2,9-Diacetyl-3-(methoxycarbonyl)-1,2-dihydro-β-carboline **XIII**, Methyl 3-(1-Acetyl-2-benzoylindol-3-yl)-2-diacetylaminopropionate **XV**.

Each compound **X** (2 g) was boiled in acetic anhydride (20 ml) and pyridine (1 ml) for 2 hours. After cooling, the reaction mixture was diluted with water, made alkaline with potassium carbonate and extracted with chloroform. The solvent was then evaporated and the residue chromatographed on a silica gel column by eluting with ethyl acetate/*n*-hexane (2:1) mixture. Compound **XIII** was eluted first, followed by **XIIb**.

Compound **XIII** shows the following nmr spectral data (deuteriochloroform): δ 7.98-7.22 (m, aromatic protons and =C*H*-, 5H), 5.37 (s, -CH_2, 2H), 3.87 (s, -COOCH_3, 3H), 2.80 (s, 9-CO-C*H*-$_3$, 3H), 2.07 (s, 2-CO-CH_3, 3H).

Compound **XV** shows the following nmr spectral data (deuteriochloroform): δ 8.02-7.20 (m, aromatic protons, 9H), 5.18-4.97 (m, -C*H*=, 1H), 3.70 (s, -COOCH_3, 3H), 3.53 (m, -CH_2-, 2H), 2.48 (s, -CO-CH_3, 3H), 2.10 (s, -CO-CH_3, 6H).

2-Acetyl-3-(methoxycarbonyl)-1,2-dihydro-β-carboline **XIV**.

Compound **XIII** (1 g) was heated under reflux in 30% acetic acid (20 ml) for 6 hours. The solvent was removed and the residue crystallized.

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