Sodium Periodate Oxidation of Tetrahydro-β-carboline Derivatives [1]

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The oxidation of some 3-(methoxy- and ethoxycarbonyl)tetrahydro-β-carboline derivatives with sodium periodate led to the formation of 1,4-benzodiazonine derivatives or fully aromatic β-carbolines depending on both nature and number of substituents at 1-position.

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Compounds containing the β-carboline structure have recently aroused remarkable interest in neuropharmacology. Indeed several β-carboline-3-carboxylates have been shown to possess high affinity for benzodiazepine-binding brain proteins [2].

As a result of the continuing interest in the chemistry of the β-carbolines and as a further development of our previous work on the selenium-oxidation of tetrahydro-β-carboline nucleus [3], it seemed interesting to investigate the action of sodium periodate on some methyl and ethyl tetrahydro-β-carboline-3-carboxylates.

Sodium periodate has been used to oxidize with decarboxylation tetrahydro-β-carboline-3-carboxylic acid to β-carboline [4]. Since the esterification would avoid the decarboxylation resulting from sodium periodate treatment, we tried the latter oxidizing agent in the case of some 3-(methoxy- and ethoxycarbonyl)tetrahydro-β-carbolines **1**, in order to obtain the related β-carboline esters.

However we observed that the course of sodium periodate oxidation in aqueous methanol of compounds **1** depended on the nature of the substituents at the 1-position (Scheme 1). So, when R_1 = H and R_2 = H, alkyl or cycloalkyl group, by cleavage of the indole double bond, the 5-(methoxy- and ethoxycarbonyl)-1,3-dihydro-2*H*-1,4-benzodiazonin-2-ones **2** were formed. Compounds **1f,g** afforded **2f,g** also together with the 3-(methoxycarbonyl)-β-carbolines **4f,g**, in an approximate ratio of 1:1.

Scheme 1

	R	R_1	R_2
a	$-CH_3$	H	H
b	$-C_2H_5$	H	H
c	$-CH_3$	H	$-CH_3$
d	$-C_2H_5$	H	$-CH_3$
e	$-CH_3$	H	$-C_2H_5$
f	$-CH_3$	H	$-C_6H_{11}$
g	$-CH_3$	H	
h	$-CH_3$	$-CH_3$	$-CH_3$
i	$-C_2H_5$	$-CH_3$	$-CH_3$
j	$-CH_3$	$-C_2H_5$	$-C_2H_5$
k	$-CH_3$	$-(CH_2)_5-$	
l	$-CH_3$	Ph	H
m	$-CH_3$	$-COOCH_3$	H

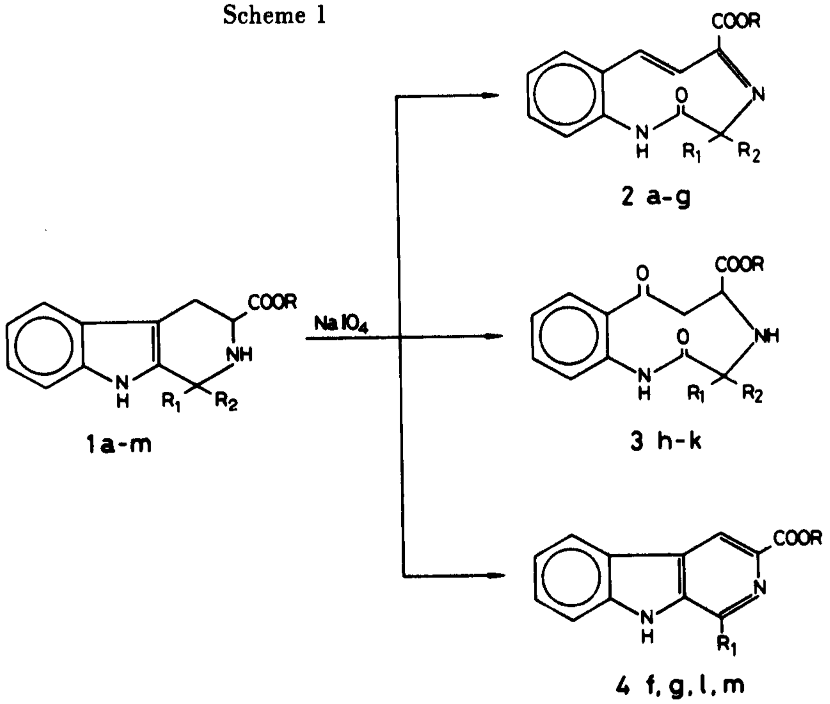

Table 1

Compound No.	Yields %	Mp (°C)	Recrystallized from	Molecular formula	Analysis %					
					Calcd.			Found		
					C	H	N	C	H	N
1i	89	133-135	benzene	$C_{16}H_{20}N_2O_2$	70.56	7.40	10.29	70.69	7.57	10.29
2a	42	178-180	methanol	$C_{13}H_{12}N_2O_3$	63.92	4.95	11.47	63.72	5.07	11.49
2b	48	163-165	methanol	$C_{14}H_{14}N_2O_3$	65.10	5.46	10.82	65.19	5.46	10.86
2c	50	197-200	methanol	$C_{14}H_{14}N_2O_3$	65.10	5.46	10.82	65.28	5.69	11.09
2d	48	178-180	methanol	$C_{15}H_{16}N_2O_3$	66.16	5.92	10.29	66.22	5.82	10.25
2e	55	185-187	methanol	$C_{15}H_{16}N_2O_3$	66.16	5.92	10.29	66.13	5.79	10.07
2f	28	177-180	benzene	$C_{19}H_{22}N_2O_3$	69.92	6.79	8.58	70.11	7.02	8.34
2g	22	87-89	*n*-hexane	$C_{19}H_{20}N_2O_3$	70.35	6.22	8.64	70.52	6.06	8.50
3h	62	164-166	benzene	$C_{15}H_{18}N_2O_4$	62.05	6.25	9.65	62.28	6.20	9.77
3i	60	139-141	benzene	$C_{16}H_{20}N_2O_4$	63.14	6.59	9.21	63.38	6.73	9.19
3j	68	158-160	benzene	$C_{17}H_{22}N_2O_4$	64.13	6.97	8.80	63.92	7.00	8.56
3k	74	168-170	benzene	$C_{18}H_{22}N_2O_4$	65.44	6.71	8.48	65.47	6.66	8.20
4f	34	280-282	ethyl acetate	$C_{19}H_{20}N_2O_2$	74.00	6.54	9.09	73.88	6.82	9.02
4g	30	262-264	ethyl acetate	$C_{19}H_{18}N_2O_2$	74.49	5.92	9.15	74.38	5.77	9.05
4l	68	258-260 [a]	methanol	$C_{19}H_{14}N_2O_2$	75.48	4.67	9.27	75.36	4.55	9.22
4m	75	242-244	methanol	$C_{15}H_{12}N_2O_4$	63.38	4.26	10.02	63.21	4.24	9.86

[a] Lit [8] mp 254-255°.

The oxidation of compounds **1h-k** containing two alkyl substituents at the 1-position followed a different course and 5-(methoxy- and ethoxycarbonyl)-2,3,4,5,6,7-hexahydro-1*H*-1,4-benzodiazonine-2,7-diones **3h-k** were obtained.

Finally compounds **1l** (R_1 = phenyl and R_2 = H and **1m** (R_1 = methoxycarbonyl and R_2 = H), under the same oxidation conditions, gave the related β-carbolines **4l,m**.

It is noteworthy that the sodium periodate oxidation accompanied by cleavage of the indole double bond did seem to require in ring C of the tetrahydro-β-carbolines the presence of the unsubstituted NH group at the 2-position and the presence of the ester group at the 3-position: indeed attempts to oxidize 2-acetyltetrahydro-β-carboline [5] and 2-benzyl-3-(methoxycarbonyl)tetrahydro-β-carboline [6] were unsuccessful.

The structure of compounds **2** and **3** was supported by elemental analyses and by nmr and mass spectra.

Compounds **2** showed the following nmr spectral data (deuteriochloroform): a broad signal between δ 9.85 and 9.30 for the amide NH proton and two doublets in the range of 7.60-7.53 and 6.45-6.37 (J = 16 Hz), both integrating for 1 H, representing *trans* H-6 and H-7. Particularly compound **2a** exhibited a two proton sharp singlet at δ 4.23 (in **2b** it appeared at 4.33) for the methylene at the 3-position, while in **2c,d** the methine at the same position gave a quartet at 3.85 and in **2e** and a triplet at 3.44, affording indirect evidence that the double bond is positioned between C-6 and C-7.

Compound **3h** showed a broad amide NH signal at δ 9.23, a multiplet at 3.98 (partially overlapped by the singlet of the methyl ester signal; in **3i** it clearly appeared at 3.95) assigned to the C-5 methine group, an apparent triplet at 3.00 due to the C-6 methylene group and a broad amine NH signal at 2.75.

The mass spectra were in agreement with the proposed structures. So, for example, the mass fragmentation pattern of the most significant compounds **2a** and **3h** were as follows: **2a**, m/z (%) 244 (M^+, 50), 216 (23), 199 (19), 185 (100), 184 (20), 167 (33), 156 (25); **3h**, m/z (%) 262 (M^+ - 28, 10), 205 (21), 146 (75), 142 (100), 129 (47), 120 (60), 92 (20).

EXPERIMENTAL

Melting points are uncorrected, the ^{1}H nmr spectra were determined on a T-60 Varian spectrometer with TMS as the internal standard. Electron ionization mass spectra were obtained on a LKB 2091 apparatus. Column chromatographic separations were accomplished on Merck silica gel (70-230 mesh). The drying agent was sodium sulfate. Yields, crystallization solvents, melting points and microanalytical data for all the new compounds described herein are reported in Table 1.

3-(Methoxy- and ethoxycarbonyl)tetrahydro-β-carbolines **1**.

Compounds **1a,b** [7], **1c** [8], **1d** [9], **1e** [10], **1f,l** [11] and **1h,j,k** [3] were synthetized according to the methods described in the literature. Compound **1g** was prepared by a Pictet-Splenger condensation between L-trypthophan methyl ester and 1,2,5,6-tetrahydrobenzaldehyde in refluxing toluene for 24 hours with a Dean-Stark trap to remove water. Compounds **1i,m** were obtained from the corresponding acids [12] by esterification in methanolic or ethanolic hydrogen chloride and converted into free bases. Compounds **1c**, **1d**, **1e**, **1f**, **1g**, **1l** and **1m** were employed as a mixture of *cis/trans* isomers and the new compounds **1g** and **1m** are not reported in Table 1.

Sodium Periodate Oxidation of Compounds **1**: 5-(Methoxy- and ethoxycarbonyl)-1,3-dihydro-2*H*-1,4-benzodiazonin-2-ones **2a-g**, 5-(Methoxy- and ethoxycarbonyl)-2,3,4,5,6,7-hexahydro-1*H*-1,4-benzodiazonine-2,7-diones **3h-k** and 3-(Methoxycarbonyl)-β-carbolines **4f,g,l,m**.

A solution of each compound **1** (0.02 mole) in methanol (250 ml) was added to a stirred solution of sodium periodate (17 g, 0.08 mole) in water (130 ml). The mixture was allowed to stir for 20 hours at room temperature for **1a-e** or refluxed for 4 hours for **1f-m**. The reaction was monitored by tlc, and stopped when starting material was disappeared. Then water (600 ml) was added and the mixture extracted with dichloromethane (3 x 200 ml). The solvent was evaporated and the residue was treated in a different way.

In the case of the oxidation of **1a-k** the residue was purified by chromatography on a silica gel column by eluting with ethyl acetate for (**1a-d**) or an ethyl acetate/*n*-hexane (1:1) mixture for **1e-k**. Compounds **2a-e** and **3h-k** were isolated and then crystallized. Compounds **4f,g** were eluted first followed by **2f,g**: both were recrystallized to give pure samples.

In the case of the oxidation of **1l,m** the residue was directly recrystallized to give pure **4l,m**.

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REFERENCES AND NOTES

[1] A preliminary account of this work was presented as a poster communication at the French-Italian Joint Meeting on Medicinal Chemistry - Piza, September 22-26, 1987.

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[6] This compound was obtained in 72% yield by reaction of 3-(methoxycarbonyl)tetrahydro-β-carboline with benzyl bromide and sodium hydrogen carbonate in refluxing methanol for 20 hours, mp 138-140°, from benzene-hexane.

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