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Chemical Studies on Drug Metabolism: Oxidation with Ruthenium Tetroxide of Some Medicinal Alicyclic *N*-Methylamines

Roberto Perrone*, Giuseppe Carbonara and Vincenzo Tortorella

Dipartimento Farmaco – Chimico, Università degli Studi, Via Amendola 173, I-70126 Bari, Italy
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Oxidation with ruthenium tetroxide of alicyclic *N*-methylamines, such as nicotine **(1)**, *trans*-phendimetrazine **(2)**, tropacocaine **(3)** and pempidine **(4)**, leads to the *N*-demethylated, N-formyl and, where possible, lactam derivatives. Only from pempidine the *N*-oxide was obtained. All products obtained by this procedure are metabolites of compounds **1, 2, 3** and **4**.

Chemische Studien zum Arzneimittelmetabolismus: Oxidation einiger N-methylierter alicyclischer medizinisch verwendeter Amine mit Rutheniumtetroxid

Die Oxidation einiger N-methylierter alicyclischer Amine mit Rutheniumtetroxid, wie Nicotin **(1)**, *trans*-Phendimetrazin **(2)**, Tropacocain **(3)** und Pempidin **(4)**, ergaben die entsprechenden N-demethylierten, N-Formyl- und, soweit möglich, Lactamderivate. Nur bei der Oxidation von Pempidin wurde das N-Oxid erhalten. Alle bei diesem Oxidationsverfahren erhaltenen Verbindungen sind in vivo Metabolite der Verbindungen **1, 2, 3** und **4**.

In previous studies on cyclic aliphatic amines such as N-benzyl and N-benzoyl substituted piperidines, pyrrolidines and morpholines, we had observed that oxidation with ruthenium tetroxide was highly regioselective because only the carbon atom next to the heteroatom was affected[1,2].

In this paper we are considering the behaviour of N-methyl derivatives of cyclic aliphatic amines when oxidated with ruthenium tetroxide in order to see whether, together with other α-Coxidation compounds, N-demethylated products can be obtained.

Since this type of endo- and exo-cyclic regioselective α-Coxidation is one of the most important in-vivo metabolic pathways for drugs bearing aminic or ethereal functions[3,4], we thought it would be interesting, to try this type of oxidative procedure on N-methyl alicyclic amines of pharmaceutical interest in order to evaluate the possibility of using this oxidative method as a fast and simple way to obtain some metabolites of a certain drug by a chemical method.

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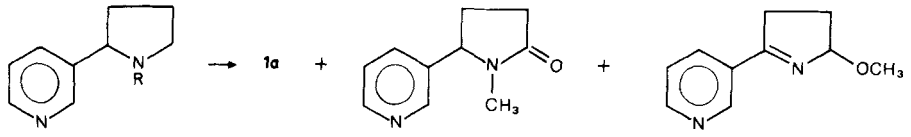
In this paper nicotine **(1)**, *trans*-phendimetrazine **(2)**, tropacocaine **(3)** and pempidine **(4)** are considered.

The principle metabolic pathway for these type of compounds is an α-C-oxidation leading to the corresponding N-demethylated derivatives and, for compound **1** and **2**, the corresponding lactams too[5,6].

Oxidation of nicotine **(1)**, (scheme 1), with ruthenium tetroxide afforded nornicotine **(1a)**, 3-cotinine **(1b)**, which both are very important metabolites of nicotine and a 3-myosmine derivative, 3-(3,4-dihydro-2-methoxy-2*H*-pyrrol-5-yl) pyridine **(1c)**.

Scheme 1



1: R = CH_3 **1b** **1c**

1a: R = H

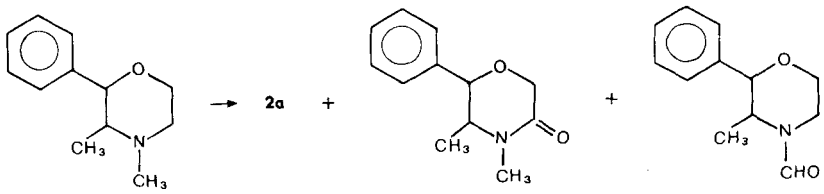
The structures of **1a** and **1b** were determined by comparison of the MS[7] and NMR spectral data with those reported[8,9]. Since the values of the optical activity were found to be identical to those reported, racemization did not occur during ruthenium tetroxide oxidation.

The structure of **1c** was established on the ground of instrumental analysis data; its MS spectrum shows a M^+ molecular peak at 176 m/e and together with a few other fragments, a base peak at 118 m/e. This type of fragmentation, especially the peak at 118 m/e, is reported[7] to be characteristic for 3- and 4-myosmine. Its IR spectrum shows a very strong peak at 1670 cm^{-1} due to an enaminic function. Furthermore in the ^{1}H-NMR spectrum we found a singlet at $\delta = 3.0$ ppm characteristic of a methyl ether group and a triplet at 3.7 ppm, due to a hydrogen atom in α-position to the nitrogen, which became a doublet when the multiplet at 2.6 ppm of one of the two hydrogen atoms on C-3 was irradiated.

Finally compound **1c** did not show optical activity at any wavelength proving that the chiral center in nicotine has been destroyed.

Oxidation of *trans*-phendimetrazine **(2)** with ruthenium tetroxide afforded *trans*-phenmetrazine **(2a)** and *trans*-2-phenyl-3,4-dimethyl-5-morpholinone **(2b)**, the two principle metabolites of *trans*-phendimetrazine, together with *trans*-N-formyl-phenmetrazine **(2c)** (scheme 2).

Scheme 2



2: R = CH_3 **2b** **2c**

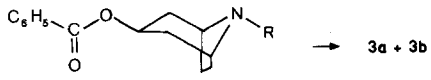
2a: R = H

MS and NMR spectral data of **2a** and **2b** are identical to those reported[10,11].

The NMR spectrum of compound **2c** shows a singlet at $\delta = 8.35$ ppm, which is typical of a formyl-hydrogen and the signal of the nitrogen methyl group is missing. In addition on acidic hydrolysis of **2c** with HCl dil. phenmetrazine was obtained. Reaction of the latter with formic acid and acetic anhydride leads to the corresponding N-formyl derivative **2c**. Its NMR spectrum is identical with the one obtained from compound **2c** present in the oxidation mixture of **2**.

Oxidation of tropacocaine **(3)** with ruthenium tetroxide gave the corresponding N-demethylated compound nor-tropacocaine **(3a)** and N-formyl-nor-tropacocaine **(3b)** (scheme 3). Compound **3a** presents the spectroscopic characteristics reported in literature[12]. The structure of the N-formyl derivative **(3b)** was established, as for **2c**, comparing its NMR spectrum with the one obtained from the N-formylation product of **3a**.

Scheme 3



3: R = CH_3
3a: R = H
3b: R = CHO

Oxidation of 1,2,2-6,6-pentamethyl piperidine **(4)** gave a mixture of products consisting of the N-demethylated product, 2,2-6,6-tetramethyl piperidine**(4a)**,N-formyl derivative **(4b)** and 2,2,6,6-tetramethyl piperidine-N-oxide **(4c)** known to possess ganglioplegical activity[13] (scheme 4).

Scheme 4

4: R = CH_3
4a: R = H
4b: R = CHO

4c

Compound **4a** has been identified by comparison with the commercial product; compound **4b** is identical to the one obtained by N-formylation of **4a**. The presence of compound **4c** among the reaction products was hypothesised because, unlike the reactions reported above, in this case the oxidation mixture, analysed by ESR, showed a triplet 1:1:1 with a coupling constant a_N of 1575G, characteristic of the N-oxide derivative of 2,2-6,6-tetramethyl piperidine[14]. In addition, compound **4c** shows chemical-physical properties as reported in the lit.[15].

Experimental Part

MP: Büchi capillary apparatus, uncorr. *Elementary analyses*: Hewlett-Packard Model 185 C.H.N. Analyzer, laboratory for Microanalysis of Istituto di Chimica Farmaceutica of University of Bari, Italy.

The *IR, NMR* and *Mass spectra* were determined with a Perkin-Elmer 283 spectrophotometer, a Varian Ha 200 spectrometer (in $CDCl_3$, unless otherwise indicated, chemical shifts (ppm), TMS used as int. ref.), and a Hewlett-Packard GC-MS 5990A spectrometer operating at 70 eV, connected to a Hewlett-Packard 9825A computer. The *gas-chromatographic* determinations were carried out with a Hewlett-Packard 5840A instrument fitted with a flame-ionization detector. Compounds **1, 2** and **4** were obtained from commercial sources and compounds **3** was prepared from 2,2-6,6-tetramethyl-piperidine as described[16].

General procedure for the oxidations with RuO_4 in heterogeneous system

A solution of 0.01 mol amine to be oxidized, in 10 ml CCl_4, was added to a mixture of 100 ml CCl_4 and 100 ml H_2O containing 10 g $NaIO_4$ and $RuO_2 \cdot xH_2O$ in catalytic amounts (0.1 g). The mixture was shaken vigorously. The reaction was followed by TLC of GC, and interrupted when the initial product

Table 1: *Yields and physical data of oxidation-products*

Starting Compound	Time (h) reaction	reaction products	brutto formula[a]	Yield %	R.T (min)
1	6	**1**	$C_{10}H_{14}N_2$	30	0.60[b]
		1a	$C_9H_{12}N_2$	10	0.95[b]
		1b	$C_{10}H_{12}N_2O$	25	5.80[b]
		1c	$C_{10}H_{12}N_2O$	12	8.20[b]
2	7	**2**	$C_{12}H_{17}NO$	15	10.20[c]
		2a	$C_{11}H_{15}NO$	15	11.70[c]
		2b	$C_{12}H_{15}NO_2$	45	6.70[b]
		2c	$C_{12}H_{15}NO_2$	15	8.20[b]
3	3	**3**	$C_{15}H_{19}NO_2$	30	2.15[d]
		3a	$C_{14}H_{17}NO_2$	25	2.32[d]
		3b	$C_{15}H_{17}NO_3$	45	8.67[d]
4	5	**4a**	$C_9H_{19}N$	4	0.74[e]
		4b	$C_{10}H_{19}NO$	41	12.50[e]
		4c	$C_9H_{18}NO$	7	8.30[e]

[a] all the compounds gave satisfactory elemental analyses with deviations of ± 0.3 % from the calcd. values;

[b] on 1 m glass column packed with 3 % OV17 on chromosorb Q oven temp.: isot. 150 °C, N_2 flow rate 60 ml/min.

[c] on 2 m steel column packed with 3 % SP2100 on chromosorb W, oven temp.: isot. 120 °C, N_2 flow rate 30 ml/min.

[d] on 2 m steel column packed with 3 % OV17 on chromosorb W, oven temp.: isot 230 °C, N_2 flow rate 23 ml/min.

[e] same column in b, oven temp.: isot. 70 °C, N_2 flow rate 60 ml/min.

had disappeared. 5 ml of Isp OH was added to the reaction mixture, the phases were separated and analyzed. Yields, physical and spectral data of the oxidised compounds are reported in table 1 and in table 2.

Table 2: *Spectral data*

Compound	IR ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ ppm	Mass spectrum m/e (%)
1a		8.5 (m, 2H, Ar); 7.7 (m, 1H, Ar); 7.2 (m, 1H, Ar); 4.10 (t, 1H, -CH$_2$-N); 3.3–2.9 (m, 2H, -CH$_2$-N); 2.6 (br, 1H, NH, D_2O exchanged); 2.4–1.6 -CH$_2$-CH$_2$-)	M^+148 (20), 147 (40) 120 (40), 119 (100), 70 (80)
1b	1670 (C=O)	8.5 (m, 2H, Ar); 7.6 (m, 1H, Ar); 7.3 (m, 1H, Ar); 4.6 (t, 1H, -CH-N-); 2.7 (s, 3H, CH$_3$); 2.6–2.4 (m, 3H); 1.9 (m, 1H)	M^+176 (50), 119 (10), 118 (20), 98 (100)
1c	1670 (C=N)	8.5 (d, 2H, Ar); 7.6 (m, 1H, Ar); 7.3 (m, 1H, Ar); 3.7 (t, 1H, -CH-N); 3.5 (dt, 2H, -CH$_2$-C=); 3.0 (s, 3H, CH$_3$-O); 2.6 (m, 1H); 2.1 (m, 1H)	M^+176 (80), 119 (30), 118 (100)
2a		7.3 (m, 5H, Ar); 3.9 (d, 1H, -CH-Ar); 3.7 (m, 2H, -CH$_2$-O-); 3.1 (m, -CH-CH$_3$); 2.8 (m, -CH$_2$-N-); 2.0 (br, 1H, NH-, D_2O exchanged); 0.8 (d, 3H, -CH$_3$)	M^+177 (10), 105 (10), 71 (100), 56 (40)
2b	1675 (C=O)	7.4 (s, 5H, Ar); 4.3 (d, 1H, -CH-Ar); 4.2 (s, 2H, -CH$_2$-C=O); 3.6 (d q, 1H, -CH-CH$_3$); 3.0 (s, 3H, CH$_3$-N-); 1.1 (d, 3H, -CH$_3$)	M^+205 (10), 99 (100), 86 (40), 71 (60)
2c	1660 (C=O)	8.3 (s, 1H, -CHO); 7.4 (s, 5H, Ar); 4.3 (d, 1H, -CH-Ar); 4.0 (m, 2H, -CH$_2$-O-); 3.6 (m, 2H, -CH$_2$-N-); 3.0 (m, 1H, -CH-CH$_3$); 1.0(d, 3H, -CH$_3$)	M^+205 (10), 99 (100), 71 (50), 56 (60)
3a		8.1–7.8 (m, 2H, Ar); 7.6–7.3 (m, 3H, Ar), 5.3 (m, 1H, -CH-O-CO); 3.7 (s, 2H, bridgehead H); 2.7 (s, 1H, -NH-, D_2O exchanged); 2.3–1.6 (m, 8H, aliph-CH$_2$-)	
3b	1655 (-CHO) 170 (C=O ester)	8.1 (s, 1H, -CHO); 8.1–7.9 (m, 2H, Ar); 7.6–7.2 (m, 3H, Ar); 5.7–5.1 (m, 1H, -CH-O-CO); 4.7 (broad, 1H, bridgehead H); 4.2 (broad, 1H, bridgehead H); 2.5–1.4 (m, 8H, aliph.-CH$_2$-)	
4b	1675 (C=O)	8.5 (s, 1H, -CHO), 1.6 (s, 6H, 2CH$_3$); 1.5 (s, 6H, 2CH$_3$); 1.4 (s, 6H, aliph.-CH$_2$-).	

Oxidation of **1**: The organic phase was empty. The aqueous phase, alkalized at pH 10, was extracted with $CHCl_3$. The solvent layer was dried over Na_2SO_4. Removal of the solvent by evaporation gave a brown oily residue, which was chromatographed on silica gel. The first elution with $CHCl_3$/MeOH (98:2) gave 1-methyl-5-(3-pyridyl)-2-pyrrolidinone,(3-cotinine; **1b**). The second elution gave 3-(5-methoxy-1-pyrrolin-2yl)pyridine **(1c)**.

The third elution gave a mixture of nicotine **(1)** and another compound. The latter purified by P.T.L., elution with MeOH/CH_3CN (1:1), (Rf of **1** and **1a** was 0.1 and 0.31, resp.) was identified as nor-nicotine **(1a)**.

Oxidation of **2**: The organic phase was dried over Na_2SO_4. The residue left over after removal of the solvent was chromatographed on silica gel. The first elution with $CHCl_3$/hexane (8:2) gave 4,5-dimethyl-6-phenyl-3-morpholinone **(2b)**. The second elution gave 4-formyl-3-methyl-2-phenyl-morpholine **(2c)** identified by MS and NMR spectra and chemical reactions. **2c** was hydrolysed with 2N-HCl at 100 °C for 30 min. The aqueous phase, alkalized with 2N-NaOH, was extracted with CH_2Cl_2 and gave pure *trans*-phenmetrazine **(2a)**. 0.4 g of the latter was added to a cooled mixture of 10 ml acetic anhydride and 5 ml 97 % formic acid. The reaction mixture was stirred at room temp. for 24 h and then neutralized with NaOH and extracted with CH_2Cl_2. In this way **2c** was obtained again. The aqueous phase, alkalized at pH 10, was extracted with $CHCl_3$. The solvent layer was dried over Na_2SO_4 and evaporated to give a residue, which, analyzed by GC-mass spectrometry (column 2M packed with 3 % SP2100, oven 120 °isot., N_2 30 ml/min) gave two peaks: the starting compound **2**, R.T. = 10.2 min and *trans*-phenmetrazine **(2a)**, R.T. = 11.7 min.

Oxidation of **3**: The solvent layer dried over Na_2SO_4 was evaporated to dryness to give N-formyl-nor-tropococaine **(3b)**. The aqueous phase, after 3 h of reaction time, alkalized at pH 10, was extracted with $CHCl_3$. G.C. analysis of the extract gave two peaks: the starting compound **3**, R.T. = 2.15 and compound with R.T. = 2.32 min. The latter one was identified as nor-tropacocaine **(3a)**. **3a** became the single product by increasing the reaction time to 20 h.

Oxidation of **4**: The solvent layer dried over Na_2SO_4, was evaporated to dryness to give N-formyl-2,2,6,6-tetramethyl-piperidine **(4b)**. The aqueous phase, acidified at pH 1 with 2N-HCl, was extracted with CH_2Cl_2. The solvent layer dried over Na_2SO_4 was evaporated to dryness to give red prisms. Melting point and IR and ESR spectra of the product obtained were identical with those reported in literature[15] for 2,2,6,6-tetramethylpiperidine-N-oxide **(4c)**.

The acid aqueous phase was then alkalized and extracted with CH_2Cl_2. It was dried over Na_2SO_4 and the solvent was evaporated off to give a residue of 2,2,6,6-tetramethylpiperidine **(4a)**.

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Synthese und Eigenschaften von Thiopyrano[4,3,2-de]chinazolinen

Jürgen Dusemund* und Bettina Gruschow**

Institut für Pharmazie der Freien Universität Berlin, Königin-Luise-Str. 2 + 4, 1000 Berlin 33
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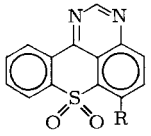
Ausgehend von 5-Aminothiochromonen **5** wurden Thiopyrano[4,3,2-de]chinazoline **11** und ihre S,S-Dioxide **2** synthetisiert. Im Gegensatz zu **2a**, das durch Formamid zu **17** reduziert wurde, reagierte **7a** mit Formamid unter Spaltung des Thiopyron-Ringes zum Chinolon **20**.

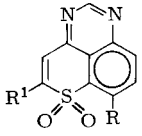
Synthesis and Properties of Thiopyrano[4,3,2-*de*]quinazolines

Starting from the 5-aminothiochromones **5**, the thiopyrano[4,3,2-*de*]quinazolines **11** and their *S,S*-dioxides **2** were prepared. In contrast to **2a**, which was reduced by formamide to give **17**, formamide opened the thiopyranone ring of **7a** to form the quinolone **20**.

Durch Erhitzen von Benzothiopyranochinazolinen **1** mit Formamid wird eine reduktive Spaltung zwischen dem Chinazolin-Ringsystem und der SO_2-Gruppe erzwungen[1,2].



1



2

Uns interessierte, ob diese Reaktion durch den der SO_2-Gruppe benachbarten zweiten Aromaten begünstigt wird. Wir untersuchten daher das Reaktionsverhalten von Thiopyranochinazolinen **2**, deren Synthese wir aus 5-Aminothiochromonen **5** bzw. **7** vorsahen, mit Formamid.

0365-6233/84/0101-0027 $ 02.50/0