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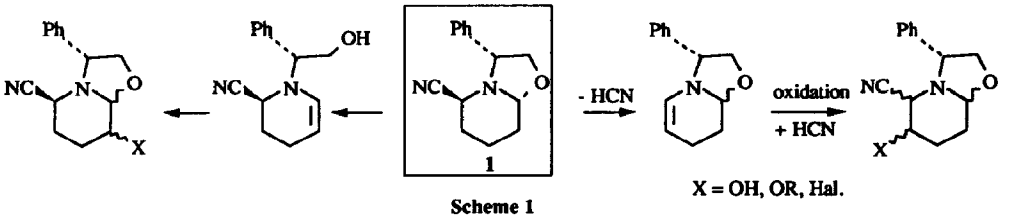
Anodic Oxidation of the N-Cyanomethyl-Oxazolidine System: Regioselective Chlorination α to the N,O-Acetal Function.

Thierry Martens[a], Florence Souquet[a] and Jacques Royer[b]*

[a] Laboratoire de chimie Analytique et d'Électrochimie, associé au CNRS, Université René Descartes, Faculté de Pharmacie, 4, avenue de l'Observatoire, 75782 Paris cedex 06.
[b] Institut de chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette.

Abstract : The anodic oxidation of the N-cyanomethyl-oxazolidine system in acetonitrile at a platinum electrode, in the presence of a mixture of chloride and bromide ions, regioselectively affords the corresponding monochloro- or dichloro- products α to the N,O-acetal function in goods yields.

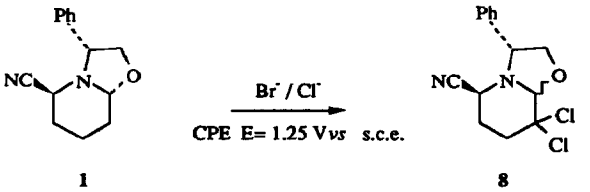
2-cyano-6-oxazolopiperidine **1** can be considered as an asymmetric synthetic equivalent of 1,4-dihydropyridine.[1] Several syntheses of piperidine alkaloids[2] have been achieved from **1**, mainly by exploiting the reactivity at the α-aminonitrile and α'-aminoether centers of this chiral synthon. In contrast, few reactions at the β or β' centers corresponding to the enamine reactivity, have been described.[3] In order to develop this latter reactivity further we postulated that the potential enamine function of **1** could be oxidized to give substitution β to nitrogen according to the following sequence (scheme 1):



Scheme 1

The electrochemical oxidation of enamines has already been reported[4,5] and the above sequence appears valid. Nevertheless most reports[6,7] on electrochemical processes deal with oxidation of enecarbamates rather than enamines. Furthermore, as compound **1** represents a potential double enamine, a regiochemical problem arises. The antiplanar arrangement of the cyano group and the nitrogen lone pair in **1**[1] would favor the initial removal of HCN according to Scheme 1.

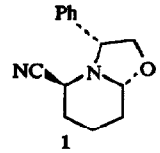
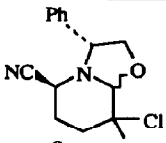
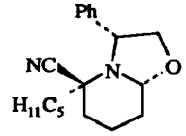
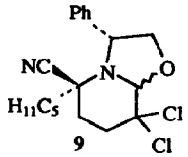
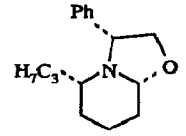
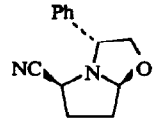
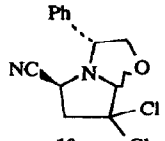
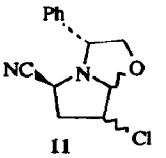
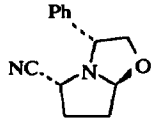
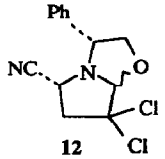
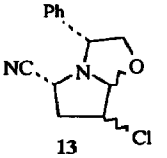
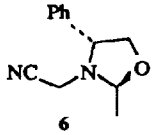
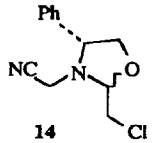
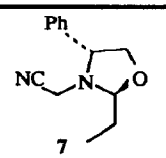
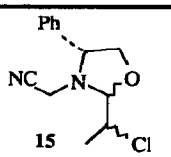
The controlled potential electrolysis (CPE) of **1** (E = 1.25 V *vs.* s.c.e.) at a platinum electrode in acetonitrile, using a chloride-bromide ion mixture as reactant[8] and lithium perchlorate as supporting electrolyte, leads to the corresponding dichloroderivative **8**[9] in excellent yield (see scheme 2 and Table). Unexpectedly, oxidation occurs only at the C-5 position[10] (scheme 2).



1 **8**

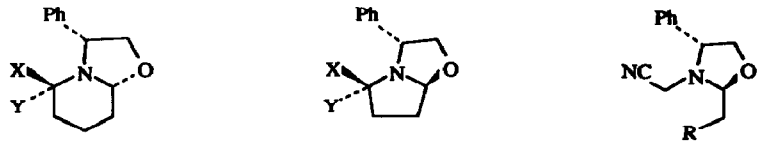
Scheme 2

Table: Controlled potential electrolysis[a] of oxazolidine derivatives **1** to **7** using chloride-bromide ion mixture

Reactant 0.5 mmol	Cl^-/Br^- [b] (mmol)	Isolated chorinated products	Yield[c] %	Epimeric ratio[d]
 **1**	1.5 / 0.15	 **8**	95	65:35
 **2**	1.5 / 0.15	 **9**	22	65:35
 **3**	1.5 / 0.15		0 [e]	
 **4**	1.5 / 0.15 2.0 / 0.20	 **10**  **11**	40(**10**)[13]; 38(**11**) 73(**10**)[13]; 17(**11**)	90:10
 **5**	1.5 / 0.15 2.0 / 0.20	 **12**  **13**	17 (**12**); 27 (**13**) 40 (**12**); 35 (**13**)	60:40
 **6**	0.8 / 0.15	 **14**	70	70:30
 **7**	1.0 / 0.15	 **15**	57	60:40

[a]In acetonitrile at a platinum electrode (E = 1.25 V *vs* s.c.e.), with lithium perchlorate as supporting electrolyte; [b] amount of tetraethylammonium chloride / tetraethylammonium bromide; [c] yield of isolated compounds; [d] all the dichlorosubstituted products are obtained as a mixture of diastereoisomers (epimerization occurs at the oxazolidine center); [e] 25% of starting material was recovered.

We extend this study to the preparative anodic oxidation of oxazolopiperidine analogues **2** and **3**[2], oxazolopyrrolidines **4** and **5**[11] and oxazolidines **6** and **7**[12], which all contain the same N-cyanomethyl-oxazolidine system (scheme 3).



1 X = CN, Y = H
2 X = CN, Y = pentyl
3 X = H, Y = propyl

4 X = CN, Y = H
5 X = H, Y = CN

6 R = H
7 R = CH_3

Scheme 3

From the data (table), it is clear that the chloride-bromide reagent mixture is useful for the regioselective chlorination in the studied series; acceptable yields are obtained for all oxidations except for **3**. Moreover, this chlorination takes place solely α to the N,O-acetal function.

Several points should be underlined: (a) all the chlorinated products are obtained as mixtures of epimeric oxazolidines; (b) using **1** as a starting material the dichlorosubstituted compound **8** is afforded in a nearly quantitative yield; (c) only poor yield is observed using the alkylated analog **2** as the starting material; (d) in the absence of the cyano group (**3**), the controlled potential electrolytic behavior differs markedly and no chlorosubstituted derivatives are obtained; (e) the stereochemical configuration of the cyano group influences the efficiency of the chlorination, as different product yields are obtained from **4** and **5** in the oxazolopyrrolidine series. These results indicate that the cyano group plays a prominent role in this electrochemical reaction even though the chlorination takes place regioselectively α to the N,O-acetal function. With these two compounds **4** and **5**, the electrochemical reaction leads to a mixture of the monochloro- and dichloro- derivatives **13** in roughly same ratio.

In the acyclic series, the monochlorinated compounds **14**[14] or **15** constitute the sole isolated products. While this oxidation appears to be a general process for the N-cyanomethyl-oxazolidine system, the effectiveness of the dichlorination decreases according to the sequence piperidine > pyrrolidine > acyclic series. Nevertheless, significantly increased yields of **11** and **13** are obtained when the reaction mixture is supplemented with chloride-bromide ions in a 2.00 / 0.20 mmol ratio.

With regard to the mechanistic pathway, it is noteworthy that: (a) no bromosubstituted products have been isolated, although the presence of bromide ions is obligatory for the success of this chlorination; these facts lead us to suppose that bromide ions, which are added in small amount, behave as a mediator in this electrochemical oxidation; (b) a coulometric value of 4.0 ± 0.1 is found for the number of electrons involved in the disubstitution (2.0 ± 0.1 for the monosubstitution) of one molecule of **1** to **7**. At the electrode potential used for these electrolyses, Cl^- ions are oxidized by one electron and we found that all oxazolidine derivatives are also oxidized by only one electron. The observed results can be explained by a radical coupling process but voltametric investigations are now in progress in our laboratory in order to provide a better understanding of this reaction.

From a synthetic point of view, this electrochemical chlorination may find applications in the synthesis of piperidine or pyrrolidine products substituted at the β position to the nitrogen.

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1) Guerrier, L.; Royer, J.; Grierson, D.S.; Husson, H.-P., *J. Am. Chem. Soc.*, **1983**, *105*, 7754-7755.

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9) A typical procedure is as follows: 2-cyano-6-oxazolopiperidine **1** (0.114g; 5.10^{-4}mol) is dissolved in dry acetonitrile (MeCN, 200 mL) containing lithium perchlorate (1.06g; 10^{-2}mol) or lithium fluoroborate (0.94g; 10^{-2}mol) as supporting electrolyte. Tetraethylammonium bromide (0.031g; 1.5 10^{-4} mol) and tetraethylammonium chloride (0.250g; 1.5 10^{-3}mol) are added. The resulting solution is oxidized, at a platinum electrode (E = 1.25 V *vs.* s.c.e.), under nitrogen, at 5°C, using a two compartment cell. After exhaustive electrolysis, MeCN is distilled off and the residue is diluted in dichloromethane (50 mL) and washed with water (2x50 mL). The organic layer is dried over sodium sulfate and evaporated, yielding **8** as white crystals (0,141g; 95% yield, two epimers in a 65:35 ratio, not separated): m.p. 84-85 °C; MS m/z: 297, 299, 301; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.70-2.90 (m, 4 H, CH_2-3 and CH_2-4): 3.87 (m, 2H, H-2 and H-8): 4.07 (m, 1H, H-9); 4.40 (t, 1H, H-8): 4.45 (s, major epimer, H-6): 4.58 (s, minor epimer, H-6); 7.40 (m, 5 H, ar): ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 26.6, 26.8 ($\underline{C}H_2$-3): 39.9, 41.2 ($\underline{C}H_2$-4): 45.8, 46.1 ($\underline{C}$H-2): 63.5, 63.7 ($\underline{C}$H-9): 73.7, 74.0 ($\underline{C}H_2$-8): 85.8 ($\underline{C}Cl_2$-5): 93.8, 94.3 ($\underline{C}$H-6): 114.9 ($\underline{C}$N): 127.8, 129.0, 129.1, 135.1 (ar).

10) Bromide oxidation of **2** has been shown to furnish a lactam: Liénard, P.; Varéa, T.; Quirion, J.-C.; Husson, H.-P., *Synlett.*, **1994**, 143-144.

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13) 2-cyano-4,4-dichloro-5-oxazolopyrrolidine **10** is isolated as white crystals (two epimers in a 90:10 ratio, not separated) : m.p.112-116 °C; MS m/z: 283, 285, 287; ^{1}H NMR (CDCl3, 300 MHz) δ (ppm): 3.10-3.30 (m, 2 H, CH_2-3): 4.00 (m, 2H): 4.35 (m, 1H); 4.60 (m, 1H): 5.35 (s, major epimer, H-5): 5.55 (s, minor epimer, H-5); 7.40 (m, 5 H, ar): ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 49.4 ($\underline{C}H_2$-3): 52.1 ($\underline{C}$H-2): 69.0 ($\underline{C}H_2$-7): 86.0 ($\underline{C}Cl_2$-4): 102.8 ($\underline{C}$H-5): 118.0 ($\underline{C}$N): 126.3, 128.2, 128.8, 137.6 (ar).

14) 2-chloromethyl-3-cyanomethyl-4-phenyl-oxazolidine **14** is isolated as an oil, (two epimers in a 70:30 ratio, not separated); MS m/z: 237, 239; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.70 (d, 2 H, CH_2Cl): 3.50-3.60 (m, 3H): 4.15-4.35 (m, 2H); 4.80 (t, 1H, H-6); 7.40 (m,5 H, ar): ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 33.8 ($\underline{C}H_2CN$): 37.5, 45.0 ($\underline{C}H_2Cl$): 73.4, 73.5 ($\underline{C}H_2$-5): 92.8 ($\underline{C}$H-4): 113.9 ($\underline{C}$N): 127.7, 129.0, 129.1, 136.9 (ar).

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