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ANODIC OXIDATION OF TETRAHYDRO-β-CARBOLINE DERIVATIVES: FORMAL OXIDATION OF PROTONATED TERTIARY AMINES

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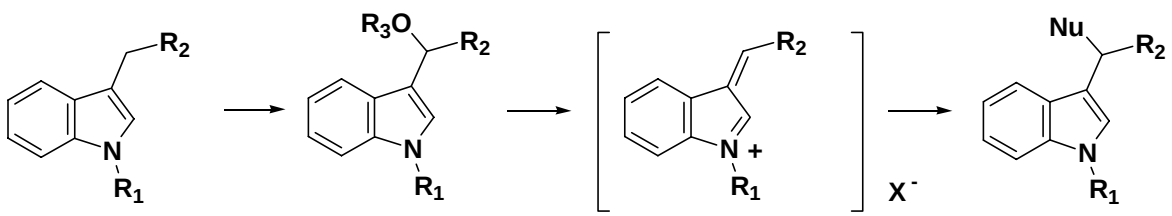
Abstract – A study of the anodic oxidation of indolic compounds in the tetrahydro-β-carboline series is described. Methoxylation at the α position of the C-3 indole ring was observed furnishing a convenient access to variously substituted products at that position. Nevertheless, this oxidation reaction was not general and very slight structural variation led to different chemical behavior corresponding to a formal oxidation of protonated tertiary amines.

INTRODUCTION

Oxidation of indolic compounds such as **1**, at the α position of the C-3 of the heteroaromatic nucleus to lead to hydroxy- and alkoxyindole derivatives (**2**) (Scheme 1) appears as a quite interesting reaction. Indeed, compounds (**2**) are suitable intermediates to access to variously substituted products (**4**) through the formation of an imine or iminium ion (**3**) (by Lewis acid treatment for example) as illustrated in Scheme 1. Such a strategy was recognized for years[1-2] but not so frequently used. It was found useful, however, in the synthesis of different alkaloid families including aspidosperma,[3] strychnos[4] or quite recently sarpagine-ajmaline [5-7] by the formation of a C-N or C-O bond but also in the synthesis of bis-indolic structures [8,9] by formation of a C-C bond.



1 **2** **3** **4**

Scheme 1

The oxidation step necessary to transform **1** into **2** is not an easy process and, may be, can explain that the above strategy has only a limited number of applications.

Several reagents (DDQ [10,11] or selenium dioxide[12,13]) were reported to allow oxidation at such a position but to give the carbonyl derivatives. To the best of our knowledge only a few examples of controlled oxidation α of the indolic C-3 were reported with DDQ[5,8] or through a multistep sequence.[14] If the indole ring bears a chain (or ring) at C-2, the regioselectivity of the oxidation to carbonyl[10,12,] or hydroxy- (or alkoxy-) derivatives[15, 16] was not always observed and mixtures were obtained with oxidation α to the C-2 of the indole ring as by-product.[16]

We were thus interested to investigate this oxidation reaction through anodic oxidation which should be more selective and allow a controlled oxidation and more generally permit a better understanding of the reaction.[17] We were particularly interested in oxidation of tetrahydrocarboline and related type compounds. Furthermore due to the presence of a basic nitrogen, such compounds are sensitive to oxidation at this atom.

RESULTS AND DISCUSSION

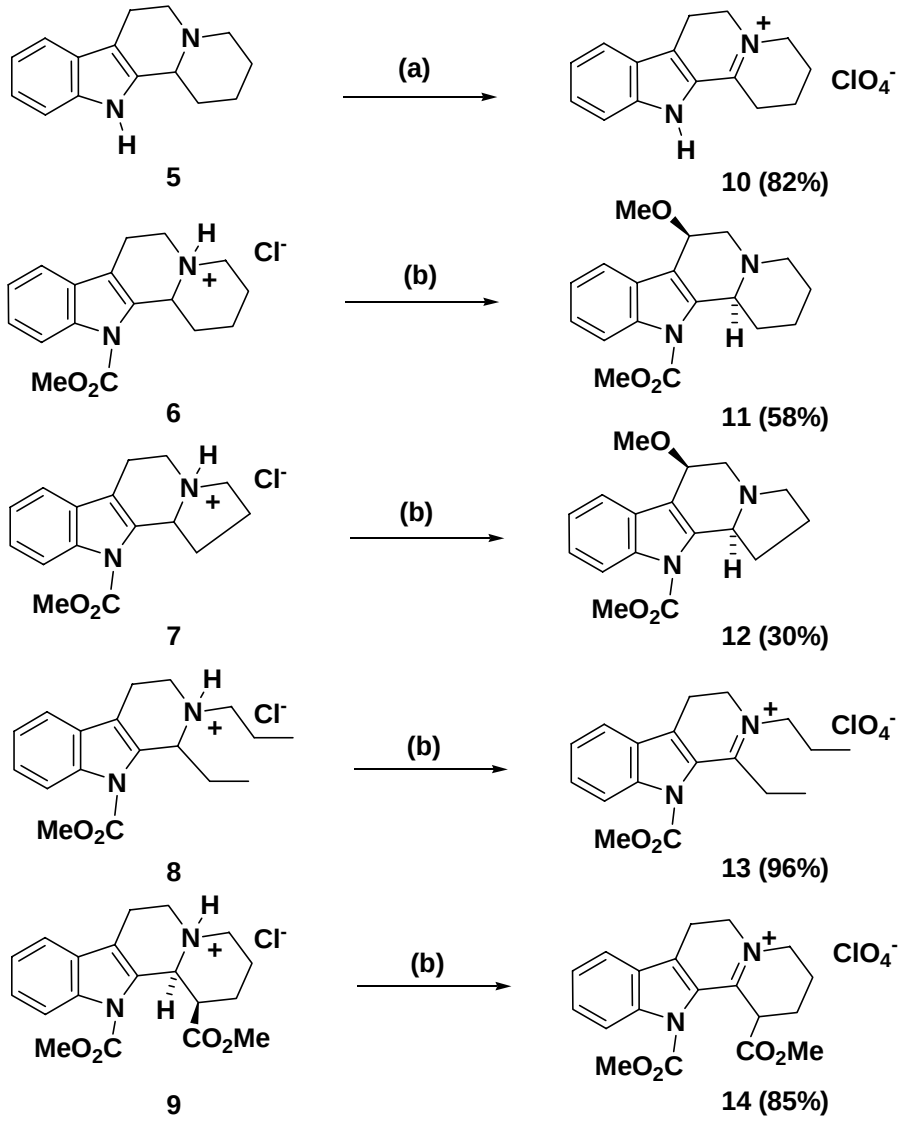
We envisioned to investigate the anodic oxidation of compounds (**5-9**) (Scheme 2) for which we thought that a simple combination of protection of each nitrogen present in the structure should solve the regioselectivity problem. As a matter of fact, it is well established that tertiary amines are much more easily oxidized than carbamates.[18] On the other hand, protonation of amine function protects the nitrogen atom against any oxidation. This is clearly shown by voltammetry study of compounds (**5**) and (**6**). Compound (**5**) exhibits two anodic peaks at respectively 1.0 and 1.2 V ecs while compound (**6**) exhibits two signals at 1.0 and 1.6 V ecs. In this latter case, the anodic peak at 1.0 V ecs disappeared by addition of one equivalent of hydrochloric acid.

With the aim of preparing alkoxy or hydroxy derivatives of type (**2**), we reasoned that anodic oxidation of indolic compounds with a carbamate function at the indole nitrogen and in an acidic medium will allow us to attain our goal. Furthermore, the presence of the carbamate would furnish, after oxidation, a more reactive *N*-acyliminium intermediate.

As expected, in the absence of added acid, the anodic oxidation of unprotected product (**5**) furnished the iminium perchlorate (**10**)[19] as the only product of the reaction which could be isolated in good yield (82%).

Then, compound (**6**) where the indolic nitrogen was protected as a carbamate was oxidized in methanol at a controlled potential of 1.6 V ecs in the presence of 1.5 equivalent of HCl.[20] A mixture of dimethoxylated product (**15**)[21] (45%) and methoxylated derivative (**11**)[21](13%) was first obtained.

Anodic oxidation of compounds (5-9)



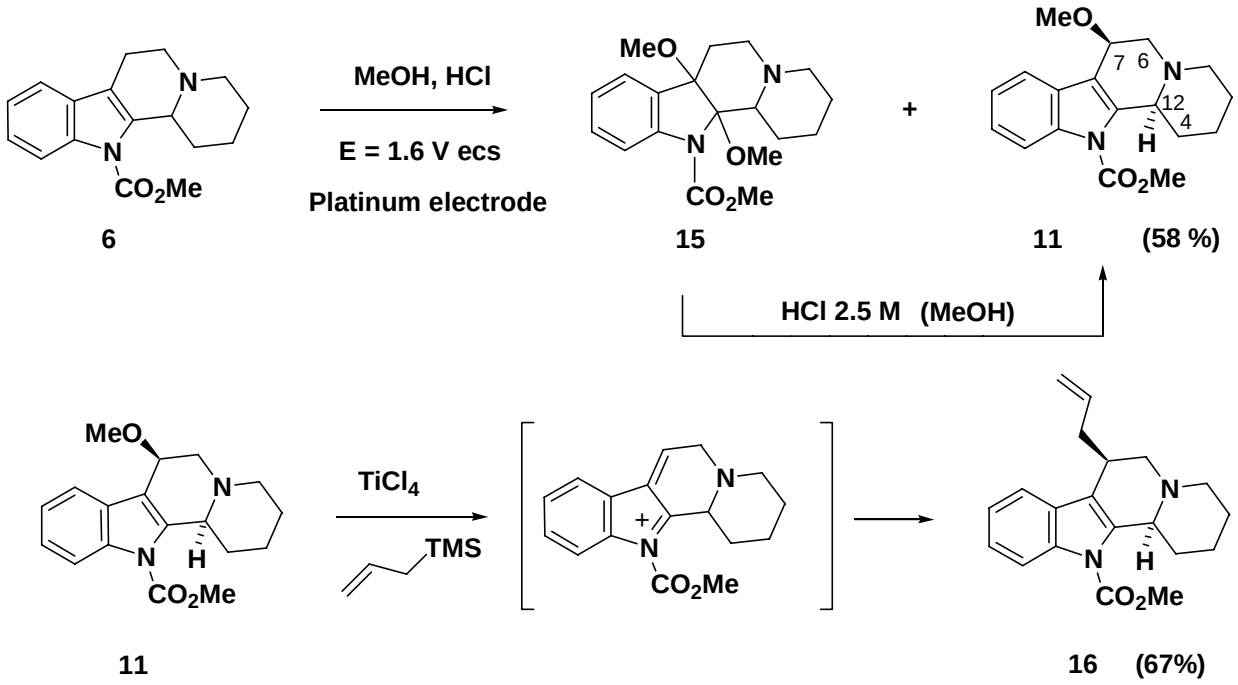
(a): MeCN-H_2O, graphite carbon, CPE, E = 1.0 V sce
(b): MeOH-HCl, platinium, CPE, E = 1.6 V sce

Scheme 2

This mixture was totally transformed through acidic treatment to **11** which was finally obtained in an acceptable 58% yield. The obtention of dimethoxylated compound (**15**) corresponds to the anodic oxidation of enecarbamate derivatives[18] by which nucleophilic group can be introduced at both the α- and β- positions of amines. The oxidation appeared straightforward. Dimethoxy compound (**15**) constitutes an intermediate since it was readily transformed to **11** by methanol elimination probably through iminium ion intermediate (Scheme 3). It is noteworthy that **11** was isolated as an single stereomer. This relative *trans* diaxial configuration of methoxy group at the C7-position and H at C12-position was easily

deduced from the ^{1}H NMR spectrum ($J_{12ax\text{-}4eq}$ = 2 Hz, $J_{12ax\text{-}4ax}$ = 11 Hz and $J_{7eq\text{-}6ax}$ = 4 Hz, $J_{7eq\text{-}6eq}$ = 4Hz).

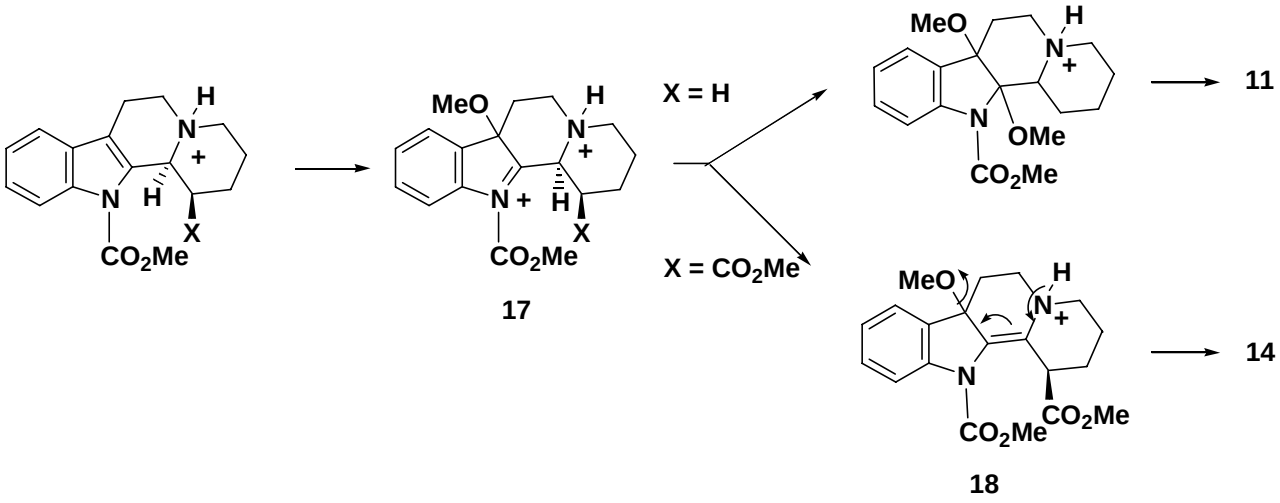
The reactivity of **11** was exemplified by reaction with allyltrimethylsilane in the presence of $TiCl_4$ which furnished allyl derivative (**16**)[21] in 67% yield. Thus the methoxy derivative (**11**) constituted valuable precursor for *N*-acyliminium as amidoalkylation reagents.



Scheme 3

Compound (**7**) was also oxidized to give methoxy derivative (**12**) despite in a rather modest non-optimized 30% yield.

Surprisingly, compounds (**8**) and (**9**)[22] were oxidized to iminiums (**13**)[21] and (**14**)[21] respectively in high yield even in the presence of HCl. The iminium structure of these compounds was readily deduced from their characteristic ^{13}C NMR resonances around 170 ppm.[19c] This result which corresponds to a formal oxidation of a protonated nitrogen deserved to be further examined. Iminiums (**13**) and (**14**) appeared as stable compounds upon which methanol did not add. It is also noteworthy that these iminiums were formed as unique products and no trace of methoxylated derivatives analogous to compounds (**11**) and (**12**) was observed. Thus a completely different electrochemical behavior of compounds (**8**) and (**9**) compared to compounds (**6**) and (**7**) was found. Since a prototropy between the tertiary amine and the enecarbamate function was highy improbable, a possible explanation of the unexpected oxidation of **9** (or **8**) should be a prior oxidation of the enecarbamate to **17** which would give enamide intermediate (**18**) from which methanol elimination furnish stable iminium (**14**) (or **13**)(Scheme 4).



Scheme 4

This reaction corresponds to oxidation α to the C-2 position of the indole nucleus already mentioned (*vide supra*).[16] Further investigations are in progress in our laboratory in order to determine which structural feature are required to induce oxidation α to the C-2 or C-3 indole nucleus.

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17. To the best of our knowledge, anodic oxidation at the α position of the C-3 of the indole nucleus has never been reported; only a few reports are concerned with oxidation of simple indolic compounds (see for example: a) K. Yoshida, *J. Am. Chem. Soc.*, 1977, **99**, 6111. b) A. Berlin, A. Canavesi, G. Schiavon, S. Zecchin, and G. Zotti, *Tetrahedron*, 1996, **52**, 7947).

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19. a) Indoloquinolizidine (**5**) in a 7/1 acetonitrile/water mixture, containing $LiClO_4$ as support electrolyte, was oxidized[23] under nitrogen atmosphere at a graphite carbon electrode (E = 1.0 V ecs). Exhaustive electrolysis (2.2 F / mol), extraction and purification, afforded known **10**[19b]
b) T. Fujii, M. Ohba, and T. Ohashi, *Tetrahedron*, 1993, **49**, 1879.
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20. Anodic oxidation[23] of indoloquinolizidines (**6-9**) was performed using the following general method (method b): indolic compound (2.11 mmol) was dissolved in methanol (80 mL) containing sodium perchlorate (1.0 g; 8.17 mmol) as support electrolyte. A hydrogen chloride (6.5 $mol.L^{-1}$) saturated methanolic solution was added (0.49 mL; 3.17 mmol) and the resulting solution was oxidized at a platinum electrode (E = 1.6 V ecs) under nitrogen. After exhaustive electrolysis (4.8 F / mol) 5 mL of a saturated $NaHCO_3$ solution were added and methanol was distilled off. The residue was extracted with dichloromethane after the addition of water. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The crude product obtained was then purified by flash chromatography (Et_2O/MeOH/NH_4OH; 98/2/0.2).

21. **15 (**colorless oil): ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.80 (m, 2H), 1.03 (d, 1H, *J* = 15 Hz), 1.2-1.45 (m, 2H), 1.62 (d, 1H, *J* = 15 Hz), 2.23 (dt, 1H, *J* = 5 Hz, *J* = 13 Hz), 2.41 (dt, 1H, *J* = 2 Hz, *J* = 13 Hz), 2.50 (dq, 1H, *J* = 5 Hz, *J* = 12 Hz), 2.86 (dq, 1H, *J* = 3 Hz, *J* = 12 Hz), 2.96 (s, 3H), 3.72 (m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 7.04 (dt, 1H, *J* = 8 Hz, *J* = 1 Hz), 7.17 (dd, 1H, *J* = 8 Hz, *J* = 1 Hz), 7.32 (dt, 1H, *J* = 8 Hz, *J* = 1 Hz), 7.80 (dd, 1H, *J* = 8 Hz, *J* = 1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 18.8, 19.9, 26.0, 29.3, 41.9, 49.5, 52.6, 54.7, 54.7, 64.7, 80.9, 98.8, 114.8, 122.0, 123.0, 127.6, 130.3, 143.2, 153.9. MS (DCI) m/z 347 (MH^+). **11** (colorless oil): ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.40-2.00 (m, 6H), 2.90 (dd, 1H, *J* = 4 Hz, *J* = 12 Hz), 3.12 (m, 2H), 3.35 (dd, 1H, *J* = 4 Hz, *J* = 12 Hz), 3.51 (s, 3H), 4.03 (s, 3H), 4.36 (dd, 1H, *J* = 11 Hz, *J* = 2 Hz), 4.59 (t, 1H, *J* = 4

Hz), 7.25 (m, 2H), 7.60 (d, 1H, *J* = 8 Hz), 8.05 (d,1H, *J* = 8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.3, 25.0, 26.0, 50.1, 53.6, 55.1, 56.3, 57.8, 71.2, 115.6, 116.0, 119.1, 123.2, 124.0, 130.1, 136.3, 140.7, 152.0. MS (DCI) m/z 315 (MH^+). **13** (pale yellow amorphous solid): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.10 (t, *J* = 7 Hz, 3H), 1.30 (t, *J* = 7 Hz, 3H), 2.00 (q, *J* = 7 Hz, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 4.10-4.20 (m, 7H), 7.40 (t, 1H, *J* = 8 Hz), 7.65 (t, 1H, *J* = 8 Hz), 7.70 (d, 1H, *J* = 8 Hz), 8.10 (d, 1H, *J* = 8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 10.6, 12.1, 20.4, 21.9, 26.0, 50.9, 55.3, 57.3, 115.8, 122.2, 124.2, 124.8, 129.2, 131.5, 138.4, 140.8, 151.2, 171.0. **14** (pale yellow amorphous solid): ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.00-2.50 (m, 5H), 3.30(m, 1H), 3.60 (s, 3H), 4.05 (s, 3H), 4.20 (m, 3H), 4.03 (s, 3H), 4.55 (m, 1H), 7.35 (t, 1H, *J* = 8 Hz), 7.60 (t, 1H, *J* = 8 Hz), 7.70 (d, 1H, *J* = 8 Hz), 8.05 (d, 1H, *J* = 8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 19.9, 20.7, 22.8, 45.6, 53.5, 54.2, 55.0, 56.4, 117.1, 124.1, 125.6, 126.1, 128.5, 132.8, 139.4, 140.7, 151.0, 163.0, 169.0. **16** (colorless oil): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.30 (m, 2H), 1.45-1.95 (m, 5H), 2.10 (m, 1H), 2.75 (m, 2H), 3.00-3.15 (m, 3H), 4.00-4.30 (m, 5H), 5.10 (m, 2H), 7.27 (m, 2H)), 7.40 (d, 1H, *J* = 8 Hz), 8.05 (d, 1H, *J* = 8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 25.0, 26.0, 29.3, 37.2, 50.1, 53.6, 55.0, 57.8, 115.6, 116.0 (CH_2 allyl), 116.5, 119.1, 123.3, 124.2, 126.0, 135.7 (CH allyl), 136.5, 137.7, 153.9. MS (DCI) m/z 325 (MH^+).

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