RuO_4-Mediated oxidation of *N*-benzylated tertiary amines. 2. Regioselectivity for *N*,*N*-dimethyl- and *N*,*N*-diethylbenzylamine as substrates

Horia Petride,* Oana Costan, Constantin Drăghici, Cristina Florea, and Aurica Petride

Centrul de Chimie Organică "Costin D. Nenitzescu", Spl. Independenței 202B, P.O. Box 15-254, RO-060111 Bucharest, Romania
E-mail: hpetride@cco.ro

Dedicated to Professor Alexandru T. Balaban on his 75th birthday

(received 08 Nov 04; accepted 08 Jan 05; published on the web 19 Jan 05)

Abstract

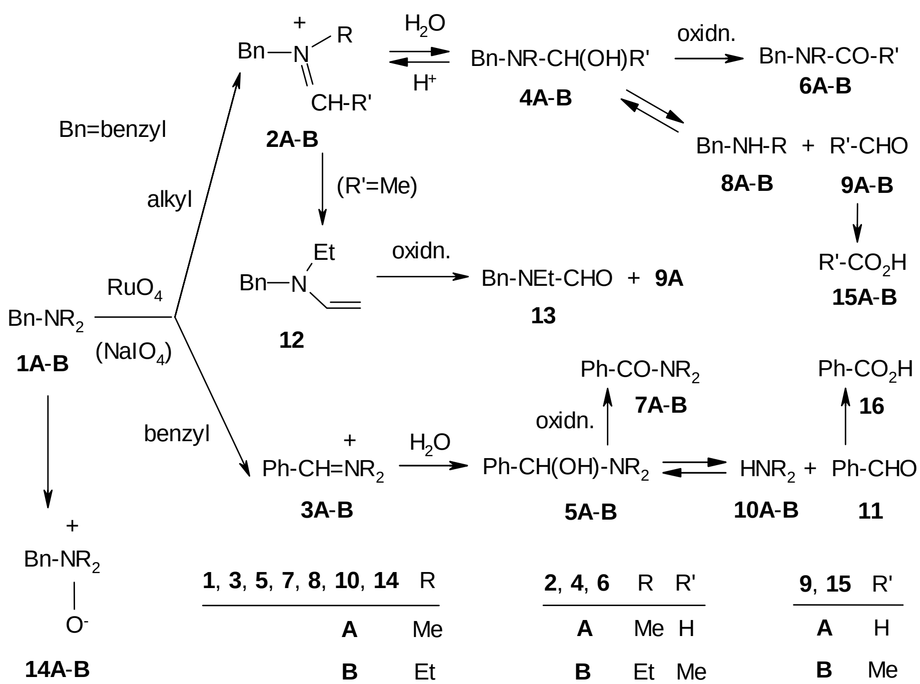
N,*N*-Dimethyl- (**1A**) and *N*,*N*-diethylbenzylamine (**1B**) underwent RuO_4-mediated oxidation by attack at both types of (*N*-α)C-H bonds (i.e., alkyl and benzyl) to yield the corresponding *N*-alkyl-*N*-benzylamides [and *N*-methyl- (**8A**) or *N*-ethylbenzylamine (**8B**), resp.] and benzaldehyde (and *N*,*N*-dialkylbenzamides), respectively. Oxidation of **8A**-**B** occurred also, as well as their reaction with formaldehyde or acetaldehyde, respectively, equally formed during the oxidation of **1A**-**B** or **8A**-**B**. Initial formation of the iminium cations from **1A**-**B** was proved by their capture as nitriles. The statistically corrected alkyl/benzyl regioselectivity of the oxidation reaction was 4.1 for **1A** and 2.1 for **1B**. Comparison with the results obtained on *N*-benzylpiperidine showed that RuO_4 does not discriminate axial and equatorial CH bonds in the piperidine ring. The *N*-α-C· carbon-centered radical and the amine cation radical seem not to be involved as precursors of the iminium cations.

Keywords: Oxidation, ruthenium tetraoxide, tertiary amines, iminium cations, regioselectivity

Introduction

In a previous paper[1] we studied the RuO_4-mediated oxidation[2] of some *N*-benzylated cycloalkylamines and found that the attack occurs at both types of *N*-α-methylene positions,[3] i.e., endocyclic and exocyclic (benzylic). Proof of the incursion of the corresponding iminium cations as intermediates came from their capture as nitriles in the presence of cyanide anion (cyano trapping). Deprotonation of the endocyclic iminium cation to the respective cyclic enamine was observed too in the absence of cyanide. The statistically corrected regioselectivity (endocyclic/exocyclic) experienced by the mentioned substrates varied from 0.8 (morpholine derivative) to 2.1 (piperidine compound). Our results were highly different from those found in the literature. For instance, Bettoni *et al.*[3a] have claimed the *unique* formation of endocyclic attack-derived compounds when starting from *N*-benzylpiperidine.

In the six-membered cycloalkylamines the endocyclic hydrogens are of two types (i.e., axial and equatorial) and this could influence, almost in principle, the regioselectivity. No such stereoelectronic constraints exist in the similar acyclic derivatives. Consequently, we decided to study the RuO_4-mediated oxidation of *N*,*N*-dimethyl- (**1A**) and *N*,*N*-diethylbenzylamine (**1B**) and the respective results are presented in this paper.



Scheme 1

By analogy with the previously studied compounds,[1] the tertiary amines **1A-B** could follow the transformations depicted in Scheme 1. Thus, two types of iminium cation might result in the first step, that is **2A-B** (alkyl attack) and **3A-B** (benzyl attack). These species are trapped by water and the resulting hemiaminals (**4A-B** and **5A-B**, resp.) could undergo oxidation to the corresponding amides (**6A-B** and **7A-B**, resp.), but also cleavage to amine+aldehyde equimolecular mixtures. For instance, **4A-B** would give the corresponding secondary benzylamines **8A-B** and the aliphatic aldehydes **9A-B**; similarly, **5A-B** could be cleaved to the secondary aliphatic amines **10A-B** and benzaldehyde (**11**). In the case of **2B**, which possesses an (*N*-β)C-H bond, deprotonation to the enamine **12** could also occur; oxidative cleavage of the C=C double bond in **12** would give[4] an equimolecular mixture of formamide **13** and formaldehyde (**9A**). As observed previously,[1] small amounts of the *N*-oxides **14A-B** might also result from **1A-B**. Finally, partial oxidation of the aldehydes **9A-B** and **11** to the corresponding acids **15A-B** and **16**, respectively, can be also envisaged.

Scheme 1 might be correct if the indicated reaction products are inert against further transformation. As will be shown in the following, this was not the case especially because the secondary amines **8A-B** underwent oxidation and other reactions by themselves.

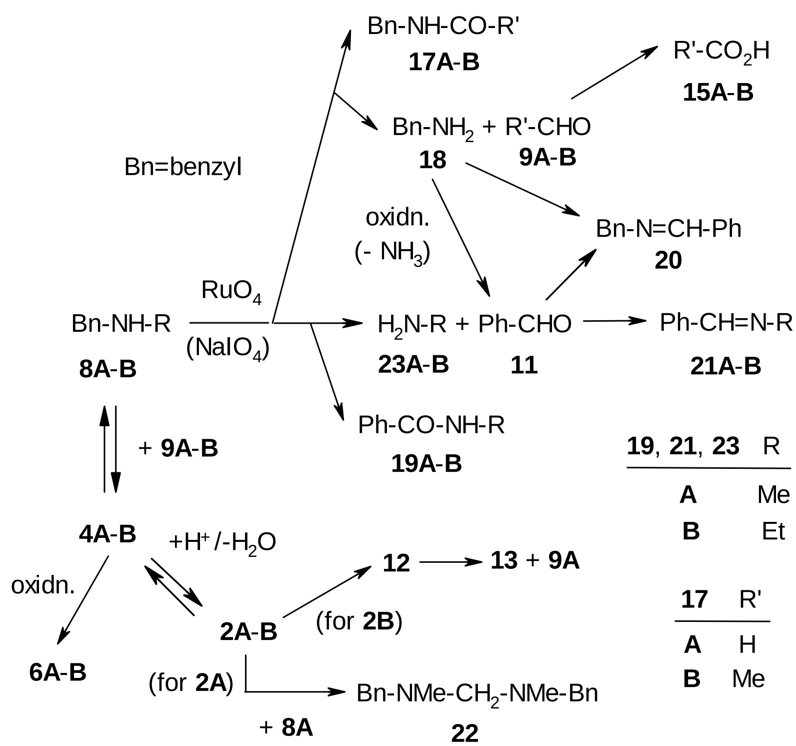
Results and Discussion

Oxidation of **1A-B** by RuO_4 (generated *in situ* from catalytic RuO_2 and $NaIO_4$ in excess), either without or in the presence of NaCN, was performed in the same conditions as before.[1] The identified reaction products and the corresponding yields are shown in Table 1 (entries 1-4). To understand better the behaviour of **1A-B**, several control experiments were performed also and the respective results are partly listed in Table 1 (entries 5-11). In all reactions, benzaldehyde (**11**) was accompanied by small amounts of benzoic acid (**16**), whose yield was added to that experimentally found for **11**. Accordingly, the yield of **11** in Table 1 means actually that of the **11**+**16** sum. The identification of the various reaction products was achieved by ^{1}H- and ^{13}C-NMR and also by GLC, but only ^{1}H-NMR spectroscopy was used for quantification. The spectral NMR features of all compounds of interest are presented in Tables 2 and 3 (see Experimental Section).

A. Oxidation by RuO_4 (+$NaIO_4$)

As can be seen in Table 1 (entries 1 and 2), in the absence of NaCN, the tertiary amines **1A-B** were oxidized by RuO_4 to several compounds, many of them coming clearly from the secondary amines **8A-B** (formulae in Scheme 2). Thus, apart from the expected reaction products (Scheme 1: **6A**, **7A**, **8A**, **11**, **14A**), the amine **1A** gave also **17A** (traces), **18**, **19A** (traces), **20**, **21A**, and **22** (Scheme 2). Analogously, **1B** yielded both expected (Scheme 1: **6B**, **7B**, **8B**, **11**, **13**, **14B**) and unexpected (Scheme 2: **17B**, **18**, **19B**, **20**, **21B**) reaction products. Dimer **22** could be formed by the alkylation of **8A** with **2A**. A similar compound was not observed in the reaction mixture of **1B**, meaning that the reaction **2B**+**8B** was unlikely, probably because of steric reasons and/or the competition with the deprotonation **2B** → **12**.

Before going into details, we can rule out the intervention of **14A-B** as reactive intermediates in entries 1 and 2, respectively. An example is offered in entry 5 for the oxidation of **14B** itself and this should be compared with the results of entry 2. Analogously to our previous findings,[1] the *N*-oxide **14B** was far more resistant than the corresponding amine (see the substrate conversions in column 2). Moreover, its reaction products covered only some of those shown by the oxidation of **1B** and resulted in very different relative yields. The *N*-oxide **14A** behaved similarly (reaction not shown in Table 1).



Scheme 2

The origin of **17A-B**, **18**, **19A-B**, **20**, and **21A-B** in entries 1 and 2 should be the oxidation of **8A-B**. Although the RuO_4-oxidation mechanism of secondary amines **8A-B** is unknown and its elucidation is out of the scope of this paper, some considerations on it are necessary. We imagined as a working hypothesis the upper part of Scheme 2. Thus, the functionalization at the alkyl site might give **17A-B** and **18**+**9A-B**. Analogous reaction at the benzyl site would yield **19A-B** and **11**+**23A-B**. It is well known that benzaldehyde reacts easily with primary amines to give the corresponding Schiff bases, thus explaining the formation of **20** and **21A-B**. Obviously, other pathways are possible. For instance, we do not exclude the direct formation of **21A-B**, followed by its partial hydrolysis to **11**+**23A-B** (not depicted in Scheme 2). At the same time, the oxidation of benzylamine (**18**) itself might give a mixture of **11** and **20**. Whatever would be the real steps involved, it is clear that some benzaldehyde could result from the oxidation of **8A-B**, either directly or *via* **18** (or from **21A-B**). In other words, the yields of **11** in entries 1 and 2 seems to be the sum of contributions due to both tertiary (**1A-B**) and secondary (**8A-B**) amines oxidation.

Table 1. Oxidation with the $RuO_4/NaIO_4$ system

Entry	Substrate (conv.)[a,b]	Conds.[c]	Reaction products (yields)[b,d]	*RS*[e]
Tertiary amines **1A-B**				
1.	**1A** (76)	*A*	**6A** (16.5), **7A** (2), **8A** (17), **11** (19), **14A** (1), **17A** (tr), **18** (4), **19A** (tr), **20** (1), **21A** (1.5), **22** (35)	
2.	**1B** (94)	*A*	**6B** (12.5), **7B** (1.5), **8B** (40), **11** (26), **13** (5.5), **14B** (0.5), **17B** (tr), **18** (2.5), **19B** (1), **20** (1), **21B** (3)	
3.	**1A** (74)	*B*	**6A** (2), **8A** (3), **11** (0.5), **24A** (87), **25A** (7)	4.1
4.	**1B** (90)	*B*	**6B** (1.5), **8B** (1), **11** (0.5), **13** (0.5), **24B** (77), **25B** (19)	2.1
Control experiments [f]				
5.	**14B** (8)	*A*	**1B** (19.5), **6B** (12.5), **7B** (13), **11** (34.5), **13** (17)	
6.	**8A** (75)	*A*	**6A** (4.5), **11** (41), **17A** (tr), **18** (10.5), **19A** (1), **20** (8), **21A** (10), **22** (16)	
7.	**8B** (50)	*A*	**6B** (2.5), **11** (44), **13** (6), **17B** (tr), **18** (6), **19B** (0.5), **20** (5), **21B** (13.5)	
8.	**8A** (55)	*C*	**6A** (9), **11** (39), **17A** (tr), **18** (10), **19A** (0.5), **20** (7), **21A** (8), **22** (15)	
9.	**8A** (75)	*C*	**6A** (12), **11** (21.5), **17A** (tr), **18** (7.5), **19A** (0.5), **20** (4), **21A** (5), **22** (45)	
10.	**8B** (55)	*C*	**6B** (7), **11** (35.5), **13** (17.5), **17B** (tr), **18** (4.5), **19B** (0.5), **20** (3), **21B** (10)	
11.	**18** (50)	*A*	**11** (65), **20** (30)	

[a] Substrate conversion (%) calculated with respect to its initial amount. [b] All figures were corrected for the work-up loss. [c] Reaction conditions (substrate = 1 mmol): *A* – $RuO_2/NaIO_4/CCl_4/H_2O$ = 10/4/10/10 (mg/mmol/mL/mL); *B* - $RuO_2/NaIO_4/NaCN/CCl_4/H_2O$ = 10/4/4/10/20 (mg/mmol/mmol/mL/mL); *C* – as in *A*, but HCO_2H (0.25 mmol; entry 8), CH_2O (0.2 mmol; entry 9), or CH_3CHO (0.2 mmol; entry 10) was added too. [d] Yields (%) calculated with respect to the reacted substrate and reaction stoichiometry; tr means traces (< 0.5%). The value of **11** refers to the **11**+**16** sum. [e] For the calculation of *R*egio*S*electivity (alkyl/benzyl) see text. [f] Compounds **6A-B**, **7A-B**, **13**, **17A-B**, and **19A-B** are all stable in reaction conditions *A* or *B*, but **14A-B** only in *B*.

Control experiments performed with the secondary amines **8A-B** (entries 6 and 7, respectively) showed their transformation into **11**+**17-21** mixtures, in accord with the discussed part of Scheme 2, but also to **6A-B**, **13**, and **22**. Consequently, the same arrays of compounds (except **7A-B** and **14A-B**) were obtained whatever the starting amine, i.e., secondary (**8A-B**) or tertiary (**1A-B**). The formation of **6A-B**, **13**, and **22** from **8A-B** is highly intriguing. At first sight, this might be ascribed to a partial transformation of **8A-B** into **1A-B**, even **7A-B** and **14A-B** are lacking (hypothesis A). Indeed, their absence could be due to undetectable, very small amounts, as suggested by the relative yields quoted in entries 1 and 2. Alternatively, the products' identity in entries 1 and 6 (or 2 and 7) could be due to some common intermediates, without formation of **1A**-**B** as such from **8A**-**B** (hypothesis B). If hypothesis A is correct, **6A**, **7A**, and **22** in entry 1, on one hand, and **6B**, **7B**, and **13** in entry 2, on the other hand, should derive only from **1A**-**B**, respectively, just because some of **8A**-**B** gave back **1A**-**B**. If hypothesis B is acting, it is conceivable that the yields of the mentioned products are the sum of contributions belonging to **1A**+**8A** (entry 1) and **1B**+**8B** (entry 2). We will analyze below the consequences of these two hypotheses.

According to Scheme 1, some aliphatic aldehydes (**9A** from **1A**; **9A**-**B** from **1B**) accompany the formation of **8A**-**B** and **13** when starting from **1A**-**B**. Along with them, discrete amounts of the corresponding acids **15A**-**B** could be present also, as indicated by the partial oxidation of **11** to **16** found experimentally. This means that the secondary amines **8A**-**B**, formed from **1A**-**B**, were actually in the presence of all these aliphatic aldehydes and acids. It is known[5] that **8A** reacts really with formaldehyde (**9A**) *and* formic acid (**15A**) to give mainly the tertiary amine **1A**, by the consecutive reactions [a]-[c]:

[a] **8A**+**9A** $\leftrightarrow$ **4A**,

[b] **4A**+H^+ $\leftrightarrow$ **2A**+H_2O,

[c] **2A**+**15A** $\rightarrow$ **1A**+CO_2.

The reaction goes on even with a molar deficit of **9A** *vs.* **8A**, but **15A** must be in excess. This sequence suggests that the inverse transformation of **8A** into **1A** could be possible in the reaction conditions of entry 1. Extension of [a]-[c] to the case of **1B** (entry 2) seems logical only for the reactions **8B**+**9A**-**B** $\leftrightarrow$ **4A**-**B** and **4A**-**B**+H^+ $\leftrightarrow$ **2A**-**B**+H_2O. Indeed, the subsequent transformation of **2B** into **1B** is unlikely because acetic acid (**15B**) can not be oxidized similarly to formic acid (**15A**) as in reaction [c]. On the contrary, the [c]-like step **2B**+**15A** could occur and generates an unsymmetrical amine, i.e., *N*-ethyl-*N*-methylbenzylamine (**1C**). However, compound **1C** (and/or its oxidation products)[6] has been never detected as an outcome of **1B** or **8B** (entry 2 or 7, resp.). Therefore, **8B** can not be a source for **1B** (and/or **1C**). On the other hand, because **6A** and **13** have been really obtained[7] by direct formylation of **8A**-**B**, respectively, with **15A**, this new route might be also possible during the RuO_4-oxidation of **8A**-**B**. To test these suppositions several control experiments were performed and the respective results are presented below.

Oxidation of **8A** was repeated in identical conditions as those of entry 6, but some formic acid (entry 8) or formaldehyde (entry 9) was added from the beginning of the reaction. In the former case, only the relative yield of **6A** was raised (by a factor of two), which represents a disappointingly low molar consumption of about 6% of the extra **15A**.[8] The relative yields of other reaction products were little influenced, including that of **22**. At the same time, the substrate conversion dropped from 75% (entry 6) to 55%, probably because **8A** has been subtracted to oxidation by protonation. Consequently, in our conditions, little (if any) formamide **6A** might result by direct formylation of **8A** with **15A**. In the case of entry 9, the yields of **6A** and **22** were three times higher with respect to those of entry 6, counting for more than 80% of **9A** introduced;[8] obviously, the yields of the other reaction products were reduced consequently, but their relative ratios remained unaffected. The substrate conversion was also the same. Because **9A** was in excess, some raise in the **15A** concentration could be envisaged too on passing from entry 6 to 9. This should cause a marked decrease of the substrate conversion, which does not fit our experimental results. This means that the aforementioned variation of yields can be ascribed mainly to the extra **9A** influence. Accordingly, formaldehyde (**9A**) participated really in the formation of *both* **6A** and **22**. Moreover, because the yields of **6A** and **22** varied in an identical manner, an intermediate giving both **6A** and **22** seems to be involved.

We repeated also the oxidation of **8B** in the presence of added acetaldehyde (entry 10) and found higher yields of **6B** and **13** (*each* by a factor of 3) with respect to those of entry 7; this represents a molar consumption of 46% of the added **9B**.[8] Consequently, acetaldehyde played for **8B** a role similar to that of formaldehyde to **8A**. To the difference of the effect of added formic acid (entry 8), initial addition of acetic acid in the reaction mixture of **8B** (reaction not shown in Table 1) caused only a smaller substrate conversion; the yields of the various reaction products remained unchanged, within the experimental errors. Finally, we checked the oxidation of benzylamine (**18**) and found its transformation into an **11**+**20** mixture, as expected (entry 11).

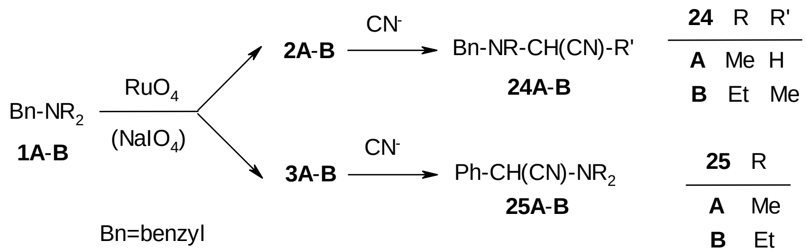
We never detected **1A** in the experiments of entries 6, 8, or 9. Taking into consideration the identical substrate conversion in entries 1, 6 and 9 and the identical relative yields of **6A** and **22** in entries 6 and 9, a detectable amount of **1A** should be present in entry 9 if hypothesis A was acting. Consequently, the absence of **1A** and the aforementioned considerations favor the hypothesis B. The same seems to be true also for **8B**.

With all these facts in mind we are now able to rationalize the transformation of **8A** into **6A**+**22** and of **8B** into **6B**+**13** as shown in the lower left corner of Scheme 2. Condensation of **8A-B** with **9A-B** gives **4A-B**, which will suffer oxidation to **6A-B** and formal dehydration to **2A-B**. The latter reaction could be assisted by the acids **15A-B** and/or **16**. Cation **2A** alkylates the starting amine **8A** to yield the dimer **22**, but **2B** prefers to give an equimolecular mixture of formamide **13** and formaldehyde (**9A**), *via* deprotonation to **12**. When **9A-B** are in excess (entries 9 and 10, resp.), the equilibria **9A-B**+**8A-B** ↔ **4A-B** are pushed more to the right, thus explaining the *identical* increase of the yields belonging to **6A**+**22** and **6B**+**13**, respectively. The steps showing the transformation of **8A-B** into **4A-B** and **2A-B**, depicted in Scheme 2, are practically the inverse pathways invoked in Scheme 1. Actually, this was the reason for which these reactions have been written as equilibria. Even resulting from different reactions, the species **2A-B** and **4A-B** are common intermediates in the oxidation of both secondary (i.e., **8A-B**) and tertiary amines (i.e., **1A-B**). The formation of the same reaction products (i.e., **6A-B**, **13**, **22**) in these two cases now finds an explanation.

B. Regioselectivity and cyano trapping

In order to calculate the alkyl/benzyl regioselectivity of the **1A-B** oxidation we need to know the yields of all compounds derived from **2A-B** and **3A-B** (Schemes 1 and 2). According to Section

A, the compounds **17A-B**, **18**, **19A-B**, **20**, and **21A-B** originate all from **8A-B** and therefore are **2A-B**-derived species. At the same time, the yields of **6A-B**, **13**, and **22** quoted in entries 1 and 2 are the sums of those deriving from RuO_4+**1A-B** (Scheme 1) and the ones originating from **8A-B**+**9A-B** (Scheme 2). This does not influence the regioselectivity calculation because **6A-B**, **13**, **22** and **8A-B** originate all from the initially formed **2A-B**. However, benzaldehyde (**11**) results from both **3A-B** (Scheme 1) and **2A-B**, *via* **8A-B** (Scheme 2). Separate contributions can not be calculated because the corresponding kinetic data are not known. Moreover, the total amount of **11** is also unknown, because, apart from the quantifiable consumption to yield **20**, it is not clear if **21A-B** are initial reaction products or the results of the **11**+**23A-B** reaction. This means that the regioselectivity can not be calculated using the data from entries 1 and 2. On the contrary, the calculation became possible for the reactions performed in the presence of NaCN, as discussed below.



Scheme 3

Similarly to our previous paper,[1] the iminium intermediates **2A-B** and **3A-B**, generated *in situ* from **1A-B**, were efficiently trapped by cyanide anion as the nitriles **24A-B** and **25A-B**, respectively (Scheme 3). Small amounts of benzylamides **6A-B** (and **13** from **1B**), benzaldehyde (**11**), and the respective secondary amine (**8A-B**) resulted also, but at least 94% of the reacted substrate was recovered as nitriles (Table 1, entries 3 and 4, resp.). After optimization, this reaction might be used to prepare the corresponding α-aminoacids.[9] Consequently, the RuO_4/NaCN oxidation of tertiary aliphatic amines could be viewed as a useful, non electrochemical one step-synthesis of α-aminonitriles.[10] The *N*-oxides **14A-B** did not react in these conditions, confirming their non-implication as reactive intermediates in the oxidation of **1A-B**.

These results allowed us to estimate the alkyl/benzyl regioselectivity (*RS*) of the respective oxidation reactions. To calculate *RS*, we must divide the yields' sum of **6A-B**+**8A-B**+**24A-B** (+**13** for **1B**) to that of **11**+**25A-B** (entries 3 and 4). Obviously, these ratios must be corrected statistically, by dividing them by three for **1A**- and by two for **1B**-derived compounds. However, as shown in Section A, benzaldehyde (**11**) originated from **3A-B** *and* from **2A-B**, *via* **8A-B**. Despite this uncertainty, the regioselectivities can be calculated because the yield of **11** is too small to affect significantly the results. The corresponding *RS* values are quoted in the last column of Table 1.

From the regioselectivity point of view, it emerged that in both **1A**-**B** as substrates the alkyl group is the preferred attacked site. At the same time, the methylic C-H bond (as that in **1A**) resulted to be two times more active than a methylenic one (as that in **1B**).

Compound **1B** is structurally more similar than **1A** to the previously studied case[1] of *N*-benzylpiperidine. As mentioned in the Introduction, the last compound presented a regioselectivity of 2.1, that is an identical value to that found now for its acyclic analog **1B**. It results that RuO_4 is a too powerful oxidant to discriminate axial and equatorial C-H bonds in a piperidine ring.

For the amines **1A**-**B**, the reaction course is well described by Schemes 1 and 2 (or 3), but the first step remains still unspecified. Several possibilities might be advanced for the formation of iminium cations, but we cite only three: (i) *h*ydrogen-*a*tom-*t*ransfer (HAT), (ii) *e*lectron-*t*ransfer (ET), or, by analogy with the RuO_4-oxidation of esters,[11] (iii) a concerted mechanism with an S_E2-like transition state. We discovered previously[12] that **1B** undergoes oxidation to **8B** and **11** in *bona fide* HAT or ET conditions with regioselectivities (alkyl/benzyl) of 0.7 and 0.4, respectively. These values are significantly different from that of 2.1 found for **1B** in the present paper. This seems disfavoring a HAT or ET mechanism for the RuO_4-oxidation. However, because the rate-determining step is unknown, only a kinetic study might clarify the real nature of the involved mechanism.[9]

Conclusions

Oxidation by RuO_4 of *N*,*N*-dimethyl- (**1A**) and *N*,*N*-diethylbenzylamine (**1B**) took place at both types of their (*N*-α)C-H bonds, that is alkyl and benzyl, giving initially, on one hand, benzylamides **6A**-**B** (and **13** from **1B** or **22** from **1A**) and the corresponding monoalkylbenzylamines **8A**-**B** and, on the other hand, benzamides **7A**-**B** and benzaldehyde (**11**), respectively. Small amounts of the corresponding *N*-oxides **14A**-**B** were formed too by a side, minor reaction. The first oxidative step was ascribed to the formation of the corresponding iminium cations **2A**-**B** and **3A**-**B**, trapped as nitriles by added NaCN. In these last reaction conditions, the alkyl/benzyl regioselectivity was 4.1 and 2.1 for **1A**-**B**, respectively. Comparison of the regioselectivity values belonging to **1B** and *N*-benzylpiperidine indicated RuO_4 as being a too powerful oxidant, unable to distinguish between axial and equatorial C-H bonds in the latter compound. In the absence of NaCN, the secondary amines **8A**-**B** complicated the reaction outcome of **1A**-**B** by their own oxidation to **11**, benzylamine (**18**), Schiff bases (**20**, **21A**-**B**), traces of *N*-monosubstituted amides (**17A**-**B**, **19A**-**B**), and also to all other compounds written before as originating from **1A**-**B**, unless **7A**-**B** and **14A**-**B**. Formation of these common products was attributed to the reaction of **8A**-**B** with formaldehyde (**9A**) or acetaldehyde (**9B**), generated during the oxidation. Both oxidation of **1A**-**B** (or **8A**-**B**) and the reaction **8A**+**9A** (or **8B**+**9B**) occurred through some common intermediates (i.e., hemiaminals **4A**-**B** and benzyliminium cations **2A**-**B**). The *N*-α-C$^{\cdot}$ carbon-centered radical or the amine cation radical, as requested by a

HAT or ET mechanism, respectively, seemed not to be involved as precursors during the generation of **2A-B**.

Experimental Section

General Procedures. The GLC and NMR apparatuses and procedures were already described.[1] Melting points were taken with a Boetius hot plate and are uncorrected.

Materials. Hydrated ruthenium dioxide, **1A**, **8A-B**, **17A**, **18**, **20**, **21A** (all from Aldrich), and sodium periodate (Merck) were used as purchased. Carbon tetrachloride (Chimopar) was stored over anhydrous Na_2CO_3 and filtered prior to use. Compounds **1B**,[12] **6A-B**,[7] **7A**,[13] **7B**,[14] **13**,[7] **14A**,[15] **17B**,[16] **19A**,[17] **19B**,[14a,18] **21B**,[19] **22**,[20] **24A-B**,[21] **25A**,[22] and **25B**[23] are all known and were synthesized according to the indicated procedures.

***N*,*N*-Diethylbenzylamine *N*-oxide** (**14B**). To a solution of 1.5 g (9.2 mmol) of **1B** in 5 mL of methanol, heated at 50-55°C and stirred, aliquots of 0.15 mL each of hydrogen peroxide (30%) were added every 15 minutes. After the ninth addition (total H_2O_2: 1.35 mL; 13.2 mmol), the stirring was maintained for 3 hours at the same temperature. The reaction mixture was evaporated *in vacuo* and the resulting solid was triturated with ether in order to obtain 1.56 g (yield 86%) of **14B•H₂O** as white crystals melting at 90-92°C after recrystallization from ether/methanol. Calculated (%) for $C_{11}H_{17}NO.H_2O$ (197.28): C, 66.97; H, 9.71; N, 7.10. Found (%): C, 66.94; H, 9.74; N, 7.13. Its NMR spectral characteristics are presented in Tables 2 and 3.

NMR Spectra. The ^{1}H- and ^{13}C-NMR features of all compounds of interest are collected in Tables 2 and 3, respectively, unless those of **1A**,[24a] **8A**,[24b] **8B**,[24c] **11**,[24d] **16**,[24e] **17A**,[24f] **18**,[24g] and **20**,[24h] as being easily accessible. The ^{1}H- and ^{13}C-NMR chemical shifts are expressed with respect to internal $(CH_3)_4Si$ (0 ppm) and $CDCl_3$ (77 ppm), respectively.

Oxidation by RuO_4 (+$NaIO_4$). The previous procedure[1] was slightly modified as concerning the work-up. To a mixture of CCl_4 (5 mL) and aqueous $NaIO_4$ solution (10 mL, 0.4M) hydrated RuO_2 (10 mg) was added, followed immediately by one mmol of substrate dissolved in 5 mL of CCl_4. In the case of solid **14A-B**, which are insoluble in CCl_4, RuO_2 was added to a CCl_4/aq. $NaIO_4$ (10/10; mL/mL) mixture, followed by the *N*-oxide added as such. In all cases the whole mixture was magnetically stirred for 4-7 hours at room temperature. Aqueous 2.5M NaOH solution (2 mL) was added, the mixture stirred for 15 minutes, filtered, and the layers separated. The filter cake was well triturated with fresh CCl_4 and water and the filtration and separation repeated. The CCl_4- and aqueous layers were combined separately to yield organic (I) and aqueous mixture (II), respectively. A known aliquot of mixture I was freed from solvent (*in vacuo*, max. bath temperature of 50°C) to give the residue Ia. Mixture II was continuously extracted with CH_2Cl_2 and the two layers separated. The organic phase was dried (Na_2SO_4) and the solvent evaporated as before to leave the residue IIa. The remaining aqueous layer was acidified with concentrated HCl and the continuos CH_2Cl_2-extraction repeated. Evaporation of the dried organic layer gave the residue IIb.

Table 2. ^{1}H-NMR data[a]

Compd.	Chemical shifts (δ, ppm, $CDCl_3$)[b]
1B	1.04 (t, *J*=7.1, 6H, CH_3), 2.52 (q, *J*=7.1, 4H, CH_2), 3.57 (s, 2H, Bn).
6A[c]	2.76+2.84 (s+s, 3H, CH_3), 4.39+4.52 (s+s, 2H, Bn), 8.16+8.29 (s+s, 1H, CHO).
6B[c]	1.11+1.13 (t+t, *J*=7.2, 3H, CH_2-C*H_3*), 2.10+2.18 (s+s, 3H, CO-CH_3), 3.26+3.42 (q+q, *J*=7.2, 2H, C*H_2*-CH_3), 4.51+4.59 (s+s, 2H, Bn), 7.15-7.40 (m, 5H, Ph).
7A	2.97+3.10 (br s+br s, 3H+3H, CH_3), 7.38 (s, 5H, Ph).
7B	1.10+1.24 (br s+br s, 3H+3H, CH_3), 3.23+3.53 (br s+br s, 2H+2H, CH_2), 7.38 (s, 5H, Ph).
13[c]	1.05+1.17 (t+t, *J*=7.2, 3H, CH_2-C*H_3*), 3.20+3.28 (q+q, *J*=7.2, 2H, C*H_2*-CH_3), 4.38+4.54 (s+s, 2H, Bn), 7.18-7.40 (m, 5H, Ph), 8.22+8.24 (s+s, 1H, CHO).
14A	3.08 (s, 6H, CH_3), 4.38 (s, 2H, Bn), 7.28 (m, 3H, H_{meta}+H_{para}), 7.41 (d, *J*=7.2, 2H, H_{ortho}).
14B	1.39 (t, *J*=6.4, 6H, CH_3), 3.19 (q, *J*=6.4, 4H, C*H_2*-CH_3), 4.36 (s, 2H, Bn), 7.35-7.45 (m, 3H, H_{meta}+H_{para}), 7.53 (d, *J*=7.5, 2H, H_{ortho}).
17B	1.89 (s, 3H, CH_3), 4.29 (d, $J_{Bn,NH}$=5.8, 2H, Bn), 7.15-7.35 (m, 5H, Ph), 7.85 (br, 1H, NH).
19A	2.98 (d, $J_{CH3,NH}$=4.9, 3H, CH_3), 6.5 (br, 1H, NH), 7.38 (m, 2H, H_{meta}), 7.46 (tt, *J*=7.3 and 1.5, 1H, H_{para}), 7.75 (dd, *J*=8.0 and 1.5, 2H, H_{ortho}).
19B	1.23 (t, *J*=7.3, 3H, CH_3), 3.47 (qd, $J_{CH2,CH3}$=7.3, $J_{CH2,NH}$=1.7, 2H, CH_2), 6.5 (br, 1H, NH), 7.39 (m, 2H, H_{meta}), 7.47 (tt, *J*=7.3 and 1.5, 1H, H_{para}), 7.77 (dd, *J*=8.0 and 1.5, 2H, H_{ortho}).
21A	3.51 (d, *J*=1.7, 3H, CH_3), 7.37-7.43 (m, 3H, H_{meta}+H_{para}), 7.70 (m, 2H, H_{ortho}), 8.27 (q, *J*=1.7, 1H, CH=N).
21B	1.30 (t, *J*=7.3, 3H, CH_3), 3.64 (qd, *J*=7.3 and 1.4, 2H, CH_2), 7.35-7.45 (m, 3H, H_{meta}+H_{para}), 7.72 (m, 2H, H_{ortho}), 8.29 (t, *J*=1.4, 1H, CH=N).
22	2.23 (s, 6H, CH_3), 3.03 (s, 2H, N-CH_2-N), 3.63 (s, 4H, Bn).
24A	2.42 (s, 3H, CH_3), 3.43 (s, 2H, CH_2-CN), 3.59 (s, 2H, Bn), 7.27-7.46 (m, 5H, Ph).
24B	1.12 (t, *J*=7.2, 3H, CH_2-C*H_3*), 1.42 (d, *J*=7.2, 3H, CH-C*H_3*), 2.40-2.52+2.68-2.80 (ABq of q's centered at 2.60 ppm, $J_{CH2,CH3}$=7.2, J_{AB}=13.0, 1H+1H, C*H_2*-CH_3), 3.72 (q, *J*=7.2, 1H, C*H*-CH_3), 3.37+3.95 [d+d (ABq), J_{AB}=14.0, 1H+1H, Bn].
25A	2.31 (s, 6H, CH_3), 4.83 (s, 1H, CH).
25B	1.07 (t, *J*=7.2, 6H, CH_3), 2.46-2.66 (ABq of q's centered at 2.56 ppm, $J_{CH2,CH3}$=7.2, J_{AB}=11.0, 4H, CH_2), 5.02 (s, 1H, CH).

[a] Data useful in product identification are listed only. [b] Proton coupling constants (*J*) are given in Hz. Benzylic hydrogens are abbreviated as Bn. [c] Two *E*/*Z* isomers are present; the values of the major one are underlined.

Table 3. ^{13}C-NMR data[a]

Compd.	Chemical shifts (δ, ppm, $CDCl_3$)[b]
1B	11.8 (CH_3), 46.7 (CH_2), 57.5 (Bn), 126.6, 128.1, 128.9, *139.9*.
6A[c]	29.4+34.0 (CH_3), 47.7+53.4 (Bn), 127.3, 127.6, 128.0, 128.2, 128.6, 128.8, *135.7*, *135.9*, 162.5+162.7 (CHO).
6B[c]	12.6+13.5 (CH_2-*C*H_3), 21.3+21.8 (CO-*C*H_3), 40.7+42.3 (*C*H_2-CH_3), 47.6+51.4 (Bn), 126.2, 127.2, 127.9, 128.4, *137.0*, *137.8*, 170.1+170.3 (CO).
7A	35.2+39.5 (br+br, CH_3), 126.9, 128.2, 129.1, *136.3*, 171.5 (CO).
7B	12.9+14.1 (br+br, CH_3), 39.1+43.2 (br+br, CH_2), 126.6 (C_{ortho}), 128.3 (C_{meta}), 129.0 (C_{para}), *137.2*, 171.2 (CO).
13[c]	12.00+14.1 (CH_3), 36.6+41.3 (*C*H_2-CH_3), 44.6+50.6 (Bn), 127.3, 127.8, 127.9, 128.4, 128.6, *136.0*, *136.3*, 162.4 (CHO).
14A	57.0 (CH_3), 75.4 (Bn), 128.6 (C_{meta}), 129.6 (C_{para}), *130.2*, 132.1 (C_{ortho}).
14B	8.4 (CH_3), 58.7 (*C*H_2-CH_3), 63.1 (Bn), 128.5 (C_{meta}), 129.3 (C_{para}), *130.1*, 132.0 (C_{ortho}).
17B	22.6 (CH_3), 43.2 (Bn), 127.0, 127.4, 128.3, *138.15*, 170.3 (CO).
19A	26.8 (CH_3), 126.8, 128.4, 131.3 (C_{para}), *134.5*, 168.3 (CO).
19B	14.8 (CH_3), 34.8 (CH_2), 126.8, 128.4, 131.2 (C_{para}), *134.7*, 167.5 (CO).
21A	48.2 (CH_3), 128.6 (C_{ortho}), 128.9 (C_{meta}), 130.5 (C_{para}), *136.2*, 162.4 (C=N).
21B	16.3 (CH_3), 55.8 (CH_2), 127.9 (C_{ortho}), 128.5 (C_{meta}), 130.4 (C_{para}), *136.3*, 160.4 (C=N).
22	40.4 (CH_3), 59.4 (Bn), 79.7 (N-CH_2-N), 126.7, 128.1, 128.8, *139.6*.
24A	42.2 (CH_3), 44.0 (*C*H_2-CN), 60.0 (Bn), 114.5 (CN), 127.7, 128.5, 128.9, *136.9*.
24B	13.3 (CH_2-*C*H_3), 18.0 (CH-*C*H_3), 45.1 (CH_2), 48.2 (*C*H-CN), 55.4 (Bn), 118.5 (CN), 127.4, 128.5, 128.6, *138.4*.
25A	41.6 (CH_3), 62.9 (CH), 114.9 (CN), *133.7*.
25B	13.2 (CH_3), 44.9 (CH_2), 58.2 (CH), 116.4 (CN), 127.6, 128.4, 128.6, *134.6*.

[a] Data useful in product identification are listed only. [b] Benzylic carbons are abbreviated as Bn. Aromatic *ipso* carbons are quoted in *italics*. [c] Two *E*/*Z* isomers are present; the values of the major one are underlined.

Identification of the various reaction products was mainly performed by ^{1}H- and ^{13}C-NMR spectroscopy using solutions in $CDCl_3$ of residues Ia, IIa, and IIb. Small amounts of unambiguously synthesized or commercial compounds were added into the analyzed sample and the spectra compared. Additionally, GLC was used too to identify the most volatile constituents of mixture I. For this purpose, the mixture I was extracted with aqueous 2.5 M HCl solution, washed with water until neutral, dried over Na_2SO_4 (mixture Ib), and analyzed for non basic constituents. The acidic aqueous layer was basified with NaOH, well extracted with CH_2Cl_2, and the organic layer (mixture Ic) analyzed for basic compounds. Identification was achieved by

GLC peak superposition in the presence of authentic materials. Because the acidic treatment of mixture I destroyed most of **20** and **21A-B** leaving additional **11**, the GLC analysis could not be used for quantitative measurements. Sometimes, the mixtures Ib and Ic were evaporated and the respective residues analyzed by NMR, as before. As an example, the distribution of the identified compounds derived from **1A** was the following: **1A** (unreacted), **6A**, **7A**, **8A**, **11**, **18**, **20**, **21A**, and **22** in mixture I; **6A**, **7A**, **22** (all three in relatively small amounts), **14A**, **17A**, and **19A** in residue IIa; **16** in residue IIb.

Quantification of the reaction products was achieved by ^{1}H-NMR on mixture I and residues Ia, IIa, and IIb (all in $CDCl_3$ as a solvent), in the presence of known amounts of an internal standard (cyclohexane or dichloromethane). Analysis of the more diluted mixture I was indicative only for the main constituents. The amounts of its minor constituents were estimated by the correlation with the analysis of residue Ia (*Note*). In the case of **1A-B** or **8A-B** the mixture I accounted for 75-95% of the recovered materials. Synthetic mixtures of all desired compounds were worked up as before in order to determine the corresponding losses. These results were then used to correct the experimentally found amounts.

Note. The solvent evaporation (i.e., I→Ia) implied uncontrollable losses of **1A-B**, **8A-B**, **11**, and **18** (due to partial evaporation) and partial consumption of **11** and **18** to give additional **20**. Some hydrolysis of **21A-B** occurred too. Correlation of I- and Ia-data was possible because the amounts of **22** (for **1A** or **8A**) and of **6B** (for **1B** or **8B**) were not influenced by evaporation. The yields in Table 1 correspond to their initial amounts.

Cyano trapping. The previously described procedure[1] was followed, but the work-up was identical to the newly proposed one. The acidification and the subsequent steps were performed carefully in a good hood.

Acknowledgements

This work was supported by *Academia Română* and by *Ministerul Educaţiei şi Cercetării* (grant n. 4-232/2004).

References and Notes

1. Part 1: Petride, H.; Drăghici, C.; Florea, C.; Petride, A. *Central Eur. J. Chem.* **2004**, *2*, 302.
2. For a short review on reaction conditions and substrates oxidized by RuO_4 see the Introduction of ref. 1.
3. Only these bonds are attacked in amines. See (a) Bettoni, G.; Franchini, C.; Morlacchi, F.; Tangari, N.; Tortorella, V. *J. Org. Chem.* **1976**, *41*, 2780. (b) Perrone, R.; Bettoni, G.; Tortorella, V. *Synthesis* **1976**, 598. (c) Bettoni, G.; Carbonara G.; Franchini, C.; Tortorella, V. *Tetrahedron* **1981**, *31*, 4159. (d) Tangari, N.; Giovine, M.; Morlacchi, F.; Vetuschi, C.

Gazz. Chim. Ital. **1985**, *115*, 325. (e) Vetuschi, C.; Tangari, N.; Giovine, M.; Franchini, C.; Tortorella, V. *Farmaco* **1992**, *47*, 599.

4. Frunzke, J.; Loschen, C.; Frenking, G. *J. Am. Chem. Soc.* **2004**, *126*, 3642.
5. Pine, S. H.; Sanchez, B. L. *J. Org. Chem.* **1971**, *36*, 829.
6. Along with compounds originating from **8A**-**B**, the oxidation of **1C** gave a complex reaction mixture containing **1C** (unreacted), **6A**, **8A**-**B**, **11**, **13**, *N*-benzyl-*N*-methylacetamide, and *N*-ethyl-*N*-methylbenzamide. We failed to detect the last two compounds and/or **1C** in the reaction mixtures derived from **1B** or **8B**. For sake of simplicity, these results have been not included in Table 1.
7. Lewin, A. H.; Frucht, M.; Chen, K. V. J.; Benedetti E.; Di Blasio, B. *Tetrahedron* **1975**, *31*, 207.
8. The amounts of **6A** in entries 6, 8, and 9 are 0.75*0.045=0.034, 0.05, and 0.09 mmol, respectively. Similarly, **22** is present as 0.75*0.16/2=0.06 and 0.169 mmol in entries 6 and 9, respectively. Accordingly, the raise of **6A** in entry 8 *vs*. 6 is of 0.016 mmol, which counts for a 0.016/0.25=6.4% molar consumption of extra **15A**. On passing from entry 6 to 9, the raise of **6A**+**22** represents 0.165/0.2=82.5% of the molar amount of extra **9A**. Analogously, on passing from entry 7 to 10, the total raise of **6B**+**13** corresponds to a contribution of 0.092/0.2=46% of extra **9B**.
9. Work in progress.
10. Besides other classic routes (i.e., Strecker synthesis), the anodic oxidation of amines to α-aminonitriles is also well documented. See for instance Yang, T.-K.; Yeh, S.-T.; Lay, Y.-Y. *Heterocycles* **1994**, *38*, 1711.
11. Bakke, J. M.; Froehaug, A. E. *J. Phys. Org. Chem.* **1996**, *9*, 310.
12. Bietti, M.; Cuppoletti, A.; Dagostin, C.; Florea, C.; Galli, C.; Petride, H.; Russo Caia, C. *Eur. J. Org. Chem.* **1998**, 2425.
13. Kirsanov, A. V.; Zolotov, Yu. M. *Zh. Obshch. Khim.* **1951**, *21*, 1166.
14. (a) Stenberg, V. I.; Singh S. P.; Narain, N. K. *J. Org. Chem.* **1977**, *42*, 2244. (b) Beak P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.
15. Bather, P. A.; Lindsay Smith, J. R.; Norman, R. O. C. *J. Chem. Soc. (C)* **1971**, 3060.
16. (a) Hartke, K. *Chem. Ber.* **1966**, *99*, 3163. (b) Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1980**, *45*, 105.
17. Cohen, T.; Moran, R. M. Jr.; Sowinski, G. *J. Org. Chem.* **1961**, *26*, 1.
18. Popowski, E. *Z. Chem.* **1975**, *15*, 275.
19. Taylor, K. G.; Chi, M. S.; Clark, M. S., Jr. *J. Org. Chem.* **1976**, *41*, 1131.
20. Boehme, H.; Eiden, F. *Chem. Ber.* **1956**, *89*, 2873.
21. Benarab, A.; Boyé, S.; Savelon, L.; Guillaumet, G. *Tetrahedron Lett.* **1993**, *34*, 7567.
22. (a) Hauser, C. R.; Taylor, H. M.; Ledford, T. G. *J. Am. Chem. Soc.* **1960**, *82*, 1786. (b) Ewing, D. F.; Neilson, D. G. *J. Chem. Soc. (C)* **1966**, 390.

23. (a) Martin, C. F.; Narayanan, V. L. *J. Org. Chem.* **1961**, *26*, 2127. (b) Fabre, C.; Welvart, Z. *Bull. Soc. Chim. France* **1965**, 2620. (c) Jonczyk, A.; Lipiak, D.; Zdrojewski, T. *Tetrahedron* **1990**, *46*, 1025.
24. Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra* Aldrich Chemical Company, Inc., 1993. (a) Vol.2, n. 589A; (b) Vol. 2, n. 581B; (c) Vol. 2, n. 581C. (d) Vol. 2, n. 932B. (e) Vol. 2, n. 1063B. (f) Vol. 2, n. 1359B. (g) Vol. 2, n. 565B. (h) Vol. 3, n. 541C.