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Effect of the Substitution Pattern on the Oxidation of the Isoxazolidine Moiety in Bi- and Tricyclic Compounds

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Abstract: The N-benzylated bicyclic compounds **5** were converted to C-phenyl nitrones **6** by highly regioselective oxidative opening of the isoxazolidine ring with MCPBA. One or both of the isoxazolidine rings of compound **8** were opened in the same way affording a mixture of compounds **9** and **10**. Compounds **13a** and **b** were formed by oxidation of N-methylated bicyclic compounds **11a and b**, respectively, with MCPBA, while **11c** was decomposed under these conditions. A mixture of **15** and **16** was isolated after oxidation of the tricyclic compound **14**, whereas oxidation of the diasteromeric **17** provided the oxime **19** as the single product. The reason for the different course of the oxidation is discussed. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Nitrones, Bicyclic heterocyclic compounds, Isoxazolidines, Stereocontrol

Introduction

Isoxazolidines which are easily accessible by 1,3-dipolar cycloaddition of nitrones with alkenes may be cleaved either by reduction or by oxidation [1]. Oxidation mostly performed with m-chloroperbenzoic acid (MCPBA) generates again a nitrone function. In principle, two regioisomeric nitrones may be formed [2]. Frequently, however, ring opening proceeds with high regioselectivity [2,3]. Thus, the combination of 1,3-dipolar cycloaddition with oxidative cleavage of the resulting isoxazolidine ring has a high synthetic potential [3,4]. In particular, cyclic nitrones have been used for this reaction sequence. The nitrones formed by oxidative cleavage may again undergo a 1,3-dipolar cycloaddition reaction (second generation nitrone cycloaddition) and even a third generation process [5] is possible in favorable cases.

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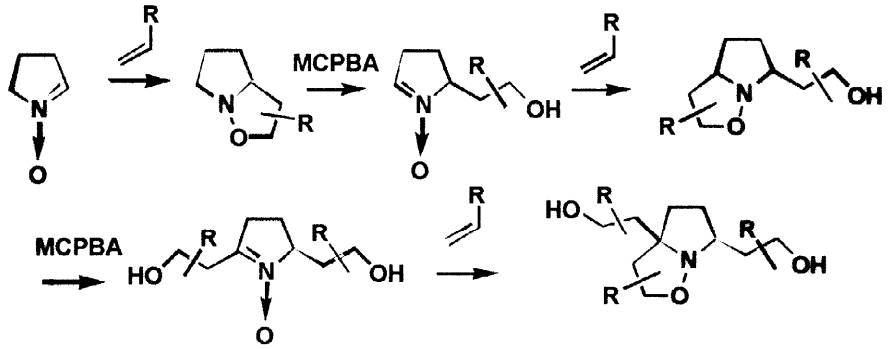
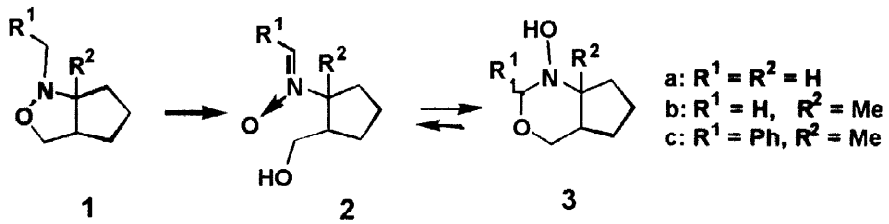


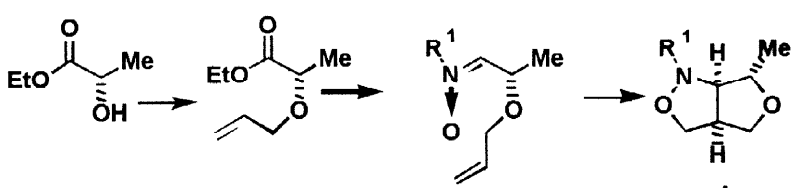
Le Bel et al. [6] studied the oxidation of 3-oxa-2-azabicyclo[3.3.0]octanes **1** and related compounds formed by intramolecular cycloaddition of the corresponding nitrones. With these compounds the oxidation proceeded with high regioselectivity to give nitrones **2** [7] which underwent an addition of the hydroxy group to the nitrone double bond affording 2-hydroxy-4-oxa-2-azabicyclo[4.3.0]nonanes **3**. Only nitrone **2c** was found to exist in equilibrium with **3c** [6]. Formation of a regioisomeric ketonitrone in which the double bond is directed to the orginal bridgehead carbon atom by oxidation of nitrones of type **1** (R^2 = H) was only found if the N-substituent was a tert-butyl group [6].

There were some other examples for which the formation of similar compounds with the six-membered N-hydroxytetrahydro-1,3-oxazine moiety was observed [8]. Further oxidation of such compounds **3** is possible to give corresponding cyclic nitrones which were finally hydrolyzed with ring opening.



1 2 3

Starting from enantiopure α-hydroxy esters such as ethyl lactate we prepared enantiopure 3,7-dioxa-2-azabicyclo[3.3.0]octanes **4** [9]. Herein we describe the oxidation of some of such compounds or their racemic mixtures with MCPBA.



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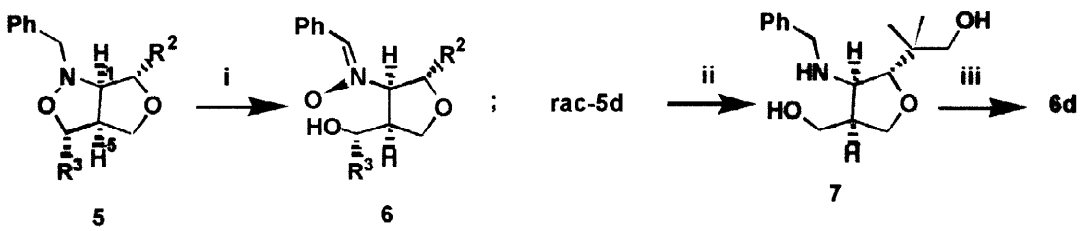
Results and Discussion

Oxidation of the N-benzyl-3,7-dioxa-2-azabicyclo[3.3.0]octanes **5a-d** with MCPBA in dichloromethane at -5°C afforded nitrones **6a-d** in approximately 75% yield after purification by chromatography. Nitrones **6** were formed diastereomerically pure. **6a-c** were obtained as optically active compounds that must be enantiopure, because the educts **5a-c** possessing at least three stereogenic centers were also enantiopure. On the contrary, compound **5d** was used as racemic mixture. The racemic compound **6d** was also prepared on an alternative way from **5d** by a reduction-oxidation sequence. Thus catalytic reduction of **5d** yielded the β-aminoalcohol **7**, which was subsequently oxidized by hydrogen peroxide and sodium tungstate [10] to give **6d**.



i, MCPBA, CH_2Cl_2, -5°C, ii, H_2, $Pd(OH)_2/C$, iii, H_2O_2, Na_2WO_4

	R^2	R^3
a	Bz	H
b	Me	Ph
c	Ph	Ph
d	(DL)$HOCH_2(Me)_2C$	H

There was no indication for the formation of a ketonitrone by abstraction of the proton at the bridgehead position 1 instead of the benzylic proton by the oxidation reaction of all compounds **5**. The constitution of compounds **6** was determined, in particular, by their ^1H and ^{13}C NMR spectra. In addition X-ray analyses of compounds **6a** and **6d** were performed [11]. In Figures 1-3 crystal structure projection of compounds **5d** [9a], **6d** and **7** [9a] are represented for comparison. They reveal interesting features. In **5d** two molecules are connected by an intermolecular hydrogen bond between the OH groups (1-hydroxy-2-methyl-prop-2-yl) of two different molecules. In addition, the H atom of one of these groups, however, forms an intramolecuar hydrogen bond to the N atom (Fig 1). For nitrone **6d** three different types of intermolecular hydrogen bonds were found: a. between the 1-hydroxy-2-methyl-prop-2-yl group and the O atom of the nitrone group (H8-O19A), b. between the hydroxymethyl groups of two molecules (H 212-O212c), c. between the H atom of the

hydroxymethyl group and the O atom of the 1-hydroxy-2-methyl-prop-2-yl group (H211-O8B)(Fig 2). Finally, in compound 7 two intramolecular hydrogen bonds, viz., $[C(CH_3)_2CH_2O....H....NCH_2Ph$ and $PhCH_2N....H....O\text{-}CH_2\text{-}C(4)]$ and one intermolecular hydrogen bond $[C(4)\text{-}CH_2O....H....O\text{-}CH_2(CH_3)_2C]$ exist.

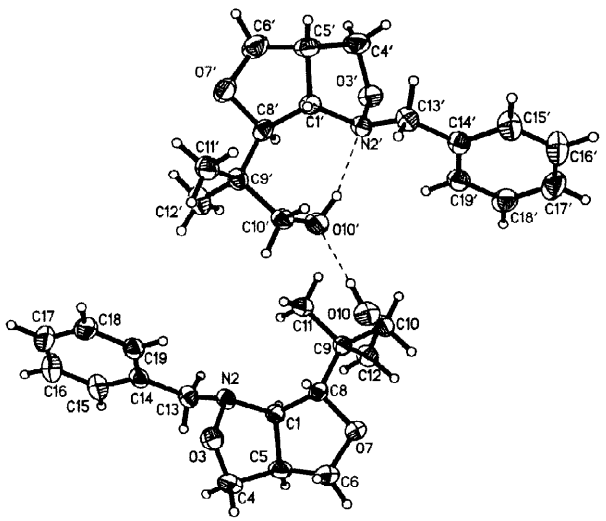


Figure 1: ORTEP drawing of **5d;**

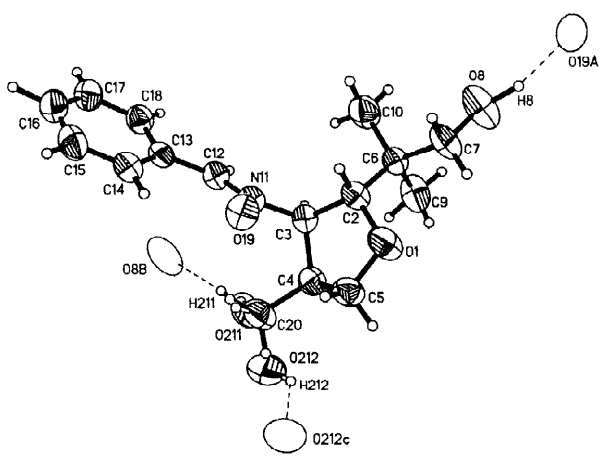


Figure 2: ORTEP drawing of **6d;** According to b and c the two possible confirmations of the hydroxymethyl group are depicted, Selected bond lengths [A]:O1-C5 1.420(3), O1-C2 1.423(3), C2-C6 1.537(3), C2-C3 1.540(3), C3-N11 1.487(3), C3-C4 1.533(4), C4-C20 1.514(4), C4-C5 1.520(4); Selected bond angles [°]: C5-O1-C2 109.9(2), O1-C2-C6 109.7(2), O1-C2-C3 106.5(2), C6-C2-C3 115.6(2), N11-C3-C4 111.8(2), N11-C3-C2 110.8(2), C4-C3-C2 104.1(2), C20-C4-C5 115.7(3), C20-C4-C3 115.8(2), C5-C4-C3 102.8(2), O1-C5-C4 104.6(2).

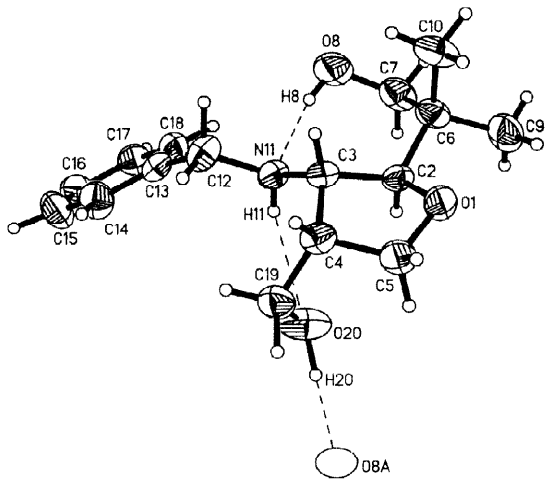


Figure 3: ORTEP drawing of **7;**

In Table 1 the torsional angles of compound **6d** formed by the protons of the tetrahydrofuran ring are given along with the ^{1}H NMR coupling constants J_{calcd} derived from these angles by the Karplus equation. Since these J values agree well with those determined from the spectrum, it could be assumed that the conformation of compound **6d** in solution is very similar to that in solid state [12a].

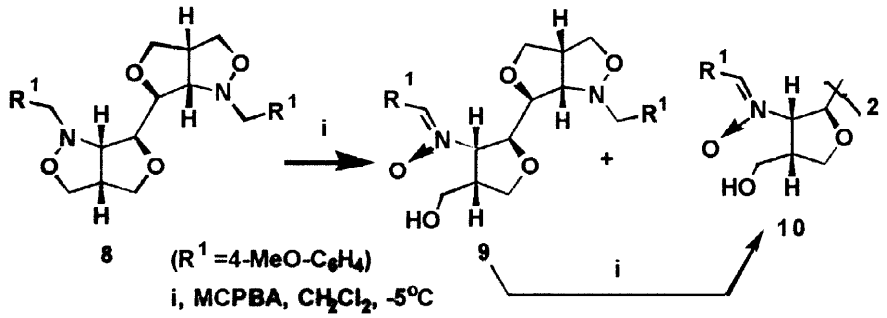
Table 1
Selected torsional angles of compound **6d** and comparison of ^{1}H NMR coupling constants J(Hz) with theoretical values calculated from the torsional angles with the aid of the Karplus equation[a]

Selected J values between the protons	(°)	J_{cacld}	J_{found}
3/4	31	6.0	7.3
4/5	-38	5.0	3.5
4/5'	-160	8.1	6.3
2/3	115	1.4	1.8

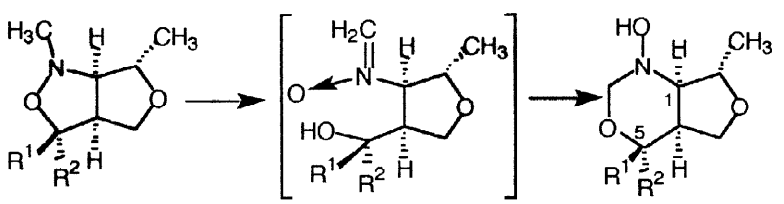
[a]-Ref [12b], Calculated with the aid of the Karplus equation $^3J = 8.5\cos^2\phi$-0.28 for 0° to 90° and $^3J = 9.5\cos^2\phi$-0.28 for 90°-180°.

Oxidation of the enantiopure compound **8** [9a] with MCPBA under the same conditions yielded two products which could be separated by chromatography. One of them was the expected dinitrone **10**, the ^{1}H and ^{13}C spectra of which showed a single set of signals for the tetrahydrofuran part, the nitrone group and the hydroxymethyl group. The second compound was identified as nitrone **9** formed by oxidative cleavage of only one of the bicyclic moieties.

In particular, the appearance of a ^{1}H NMR signal of the nitrone group along with those of the benzyl group as well as two different sets of signals for the 4-methoxyphenyl group are indicative for its structure. Compound **9** could be converted to **10** by an additional oxidation with MCPBA, however, the oxidation was again incomplete yielding only 60% of compound **10** together with unchanged educt **9** even with an excess of two equivalents of MCPBA.



In contrast to the N-benzyl-substituted bicyclic compounds **5**, oxidation of the N-methyl-substituted compounds **11a,b** [9a,13] with MCPBA at -5°C afforded 2-hydroxy-4,8-dioxa-2-azabicyclo[4.3.0]nonanes **13a,b** in accordance with the results of Le Bel [6] and others [15] who oxidized similar bicyclic compounds. Of course, compounds **13** must be formed via nitrones **12** which underwent subsequently a Michael-type addition of the hydroxy group to the nitrone group. In this way, racemic **13a** and enantiopure **13b** were formed in 55% and 65% yield, respectively. However, neither **12c** nor **13c** could be isolated after oxidation of **11c** [14] under identical conditions. Instead, a complex mixture of unidentified products presumably formed by decomposition of either **12c** or **13c** was found in this case. Obviously, the reaction course is strongly effected by the substitution pattern of compounds **11**.

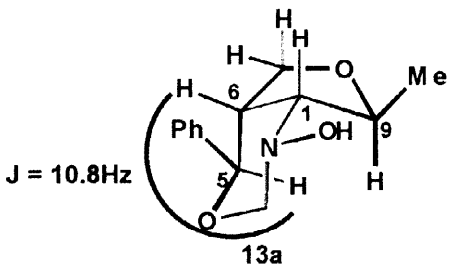


	R^1	R^2
a	H	Ph
b	Ph	Ph
c	H	H

11 **12** **13**

The substitution pattern of **13a** and **b** influences also the conformation of the molecules as the ^{1}H NMR coupling constants reveal. Thus, the six-membered ring of **13a** is forced in a chair-conformation (Fig 4) with the large phenyl group in a favorable equatorial position so that the protons 5-H and 6-H occupy a *trans*-axial position ($J_{5/6}$ =10.8Hz). In this way, the *cis*-annulated five-membered ring adopts a conformation as depicted in Figure 4 bringing

protons 1-H and 9-H also in a *quasi trans*-axial relationship ($J_{1/9}$=8.5 Hz), whereas the angles between protons 6-H and 7-H as well as between 6-H and 7-H' are somewhere between 0 and 90° ($J_{6/7}$, = 5.3 Hz, $J_{6/7'}$ = 1.2 Hz). By the second phenyl group at position 5 in compound **13b**, however, this directing effect is lost so that the six-membered ring exists in a reversed conformation (Fig 5) in which the axial phenyl group points away from the annulated five-membered ring. The latter is now orientated in a way that brings protons 1-H and 9-H in an approximately perpendicular position ($J_{1/9}$< 1 Hz). Thus, protons 7-H and 7-H' are brought in positions relative to 6-H that give rise to relatively large coupling constants ($J_{6/7}$ =7.5 *cis*, $J_{6/7'}$ =11.2Hz, *trans*) (Figure 5) [16].



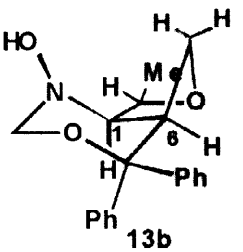
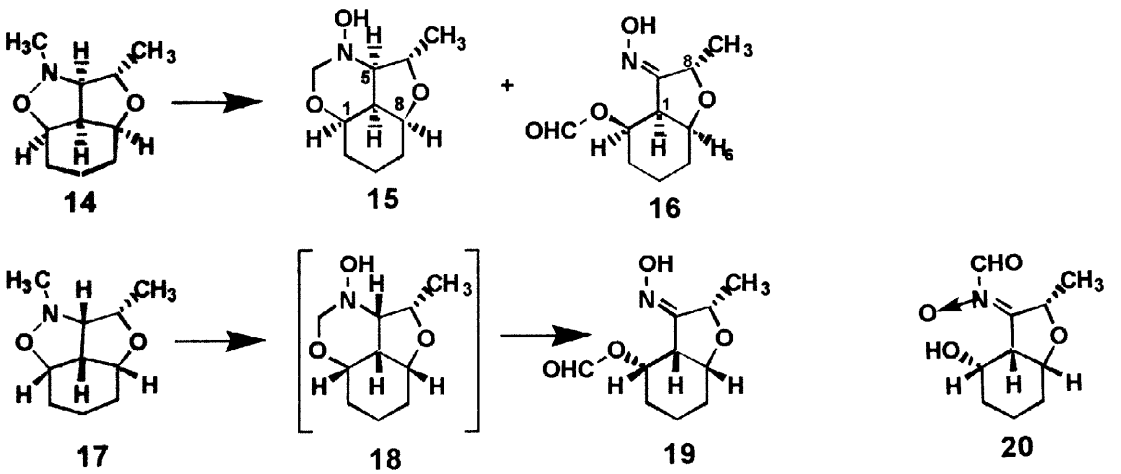


Figure 4 **Figure 5**

These results were confirmed by a calculation based on CHEM 3D program by which the lowest energy conformations for the two compounds were determined [17].

That the course of the oxidative conversion of the isoxazolidine ring with MCPBA is largely effected by the structural features is shown by the oxidation of the tricyclic compounds **14** and **17** [18].



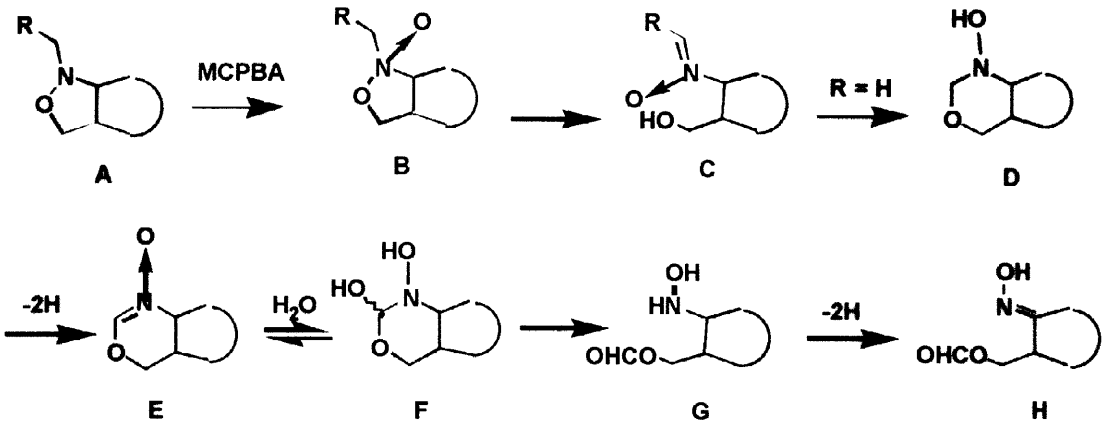
Thus, oxidation of **14** with one equivalent of MCPBA at -5°C yielded an inseparable mixture of compounds **15** and **16** (in the ratio of 2:1) together with a small amount of an unidentified product in a total yield of 25% while approximately 65% of the educt was

recovered. Enhancing the amount of MCPBA to 1.6 equivalents resulted in 40% conversion to these compounds in approximately the same ratio. Under the same conditions using 1.2 equivalents of MCPBA the tricyclic compound **17** afforded oxime **19** as single product in 40% yield, remaining approximately 60% of **17** unchanged [19].

The NMR data of **15** are in accordance with those of compound **13**. The most important features of the NMR spectra of compounds **16** and **19** are the splitting of the 1-H signal by only two protons (triplets at δ 3.50 ppm and 3.22 ppm, respectively) and the splitting of the 8-H signal by only three protons (quartets at δ 4.78 ppm and 4.28 ppm, respectively) indicating the absence of a proton at 9-position, as well as the appearance of ^{13}C signals (off-resonance decoupled) which are characteristic for an oxime group (singlets at δ 166.1 ppm and 160.2 ppm, respectively) and a formyl group (doublets at δ 176.7 and 165.6 ppm, respectively). In addition, the structure of **19** was confirmed by elemental analysis and mass spectrum. The alternative structure **20** which would also be in agreement with these data is rather improbable, since such N-acylnitrones were shown to be extremely reactive being strongly acylating agents [20]. Even if they would be formed in any way, they are expected to undergo spontaneously an intramolecular acylation to give **19**.

As a result of our studies we can summarize that compounds **5** and **8** (**A**: R=Ar) are oxidized by MCPBA to give the C-arylnitrones **6** and **9/10**, respectively (**A**→**B**→**C**: R=Ar) (see schematic representation on next page). These nitrones are stabilized by the aryl group at the α-position and thus prevented from further conversion.

Nitrones with a methylene group (**C**: R=H) arising from oxidation of N-methyl compounds (**11,14,17**) are far more reactive and undergo spontaneously an intramolecular Michael-type addition affording cyclic hydroxylamines of type **D** possessing a tetrahydro-1,3-oxazine moiety [21]. Such hydroxylamines are susceptible to further dehydrogenation with formation of nitrones **E** [22] followed by further conversion. In principle, oxidation of hydroxylamines (**D**→**E**) is thought to proceed more easily than oxidation of an amino group such as in compounds of type **A** (**A**→**B**) [23]. Thus, a competition between the two oxidation reactions is expected. However, the dehydrogenation process (**D**→**E**) seems to depend strongly on the substitution pattern as is indicated by the different behavior of the educts.



Since compounds **13a,b** formed by oxidation of **11a, b** respectively, could be isolated in moderate yields in contrast to the oxidation of **11c** which provided only decomposition products, it must be assumed that **13a** (R^1 = H, R^2 = Ph) and **13b** (R^1 = R^2 = Ph) exist in a respective conformation in which dehydrogenation of the molecule (**D→E**) is more difficult compared to the oxidation of the starting compounds **11a** and **b**, respectively (**A→B**) [6]. Obviously, this is not true for the assumed intermediate **13c** arising from **11c**. The less-substituted **13c** is conformationally more flexible and thus can adopt a conformation in which oxidation is easier.

The situation is quite unequivocal with compounds **14** and **17**. Oxidation of **14** with 1 or 1.6 equivalents of MCPBA afforded 25% or 40% of products (mainly **15** = **D** and **16** = **H**), respectively, leaving a large amount of **14** unchanged. Here the dehydrogenation steps **D→E** and **G→H** compete successfully with the oxidative conversion **A→B** in consumption of the oxidant [24]. This means that the additional third ring component either makes the oxidation **A→B** more difficult or facilitates the dehydrogenation **D→E** or does both together, as compared to **11a,b/13a,b**. The effect is even stronger in the oxidation of **17** yielding 40% of **19** as the single product along with approximately 60% of starting material with 1.2 equivalents of MCPBA. The conformation of the starting compound **17** is known from an X-ray analysis as well as from ^{1}H NMR data [18]. Thus, it is known that the N atom of **17** is better shielded against the attack of MCPBA by the endocyclic methyl group at C-5 (**A→B**) compared to the situation in **14**, the shape of which is very similar but where the methyl group is exocyclic, pointing away from the free electron pair of the N atom.

Such a shielding effect would play a less important role in the dehydrogenation of **18** (**D→E**), because now this process occurs more at the outer sphere of the molecule. If one

assumes that the conformation of **15** and **18** is not very different [25], the methyl group of **18** would destabilize the molecule more, compared to that of the diastereomer **15**. In this way **18** is more destabilized and thus its oxidation followed by further conversion (**D→E→F→G**) with relief of internal strain should be facilitated. The destabilization can be understood as follows. The ^{1}H NMR coupling constant $J_{5II/6II}$ of **15** was found to be <1Hz (see Experimental part). Thus, the torsional angle between 5-H and 6-H should be approximately 90° with the consequence that the methyl group at C-6 is close to the proton 5-H as is depicted in the Newman projection (Fig 6). In the diastereomeric compound **18** with the inverted position of the N atom and 5-H the methyl group is located close to the N atom (Fig 6) giving rise to a stronger destabilization by torsional strain.

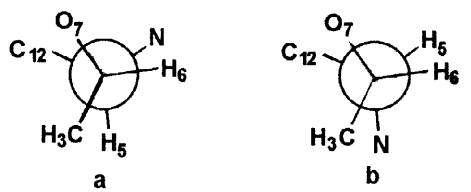


Figure 6. Newman projections of the conformation at C-5 and C-6 of compounds **15a** and **18b**

Thus both effects, the better shielding of the N atom of **17** as well as a stronger destabilization of the intermediate **18**, are a reasonable explanation for the result that in the oxidation of **17**, only compound **19** but not the intermediate **18** was isolated, whereas in the oxidation of **14** a mixture of **15** and **16** was formed.

Experimental Section

General. All melting points are uncorrected. Elemental analysis: Division Routine Analytic Section, Fachbereich Chemie, University of Marburg, NMR: Bruker AMX 500, AC 300 and ARC200 using the residues of ^{1}H (δ = 7.24) or of ^{13}C (δ = 77.0) of the solvent $CDCl_3$ as internal standard. J values are expressed in Hz. Unless otherwise stated, the ^{1}H NMR spectra were recorded at 300 MHz, the ^{13}C NMR spectra at 75 MHz in $CDCl_3$, MS: Varian CH 7 (EI), IR: Beckman IR 33 and Bruker IFS 88-FT-IR, Optical rotation: Polarimeter Perkin-Elmer 241, at 589 nm. X-ray: 4-circle diffractometer (Enraf-Nonius CA04), MCPBA is purchased from Merck.

General Procedure for Oxidation using MCPBA.

MCPBA (90% purity, 1.6 mmol) was added to a solution of the bi- or tricyclic compound (1 mmol) in CH_2Cl_2 (20 mL) at -5°C. The reaction mixture was stirred at -5 °C for 2 h. The mixture was then washed successively with solutions of $NaHCO_3$(5%) and $Na_2S_2O_3$ (saturated) and dried with Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on a silicagel column with light petroleum/ethyl acetate 4:1 as eluent.

The oxidation of compound **7** with H_2O_2 and Na_2WO_4 affording **6d** was performed as described by Murahashi et. al, see ref [23].

(*2S,3R,4R*)-(+)-[3-(Benzylideneamino)-2-benzyl-tetrahydrofur-4-yl]-methanol N-oxide (6a). Yield: 72%; $[\alpha]_D^{19}$ = +13.3(c, 0.6, $CHCl_3$); mp. 102-105°C; ^{1}H NMR (500MHz) δ: 2.77(m, 1H, 4-H), 2.83(dd, 1H, C*H*$_2$Ph), 3.00(dd, 1H, C*H*$_2$Ph), 3.60(dd, 1H, 5-H), 3.70(dd, 1H, 5'-H), 4.03(dd, 2H, C*H*$_2$OH), 4.17(dd, 1H, 3-H), 4.75(dq, 1H, 2-H), 7.1-7.36(m, 8H, Ar-H), 8.00-8.08(m, 2H, o-ArH); $J_{2/CH2Ph}$ = 6.5, $J_{2/CH2Ph}$ = 6.8, $J_{3/4}$ = 8.8; $^2J_{CH2OH}$ = 12.0, $J_{4/CHOH}$ = 3.5, $J_{4/CHOH}$ = 5.3, $J_{4/5}$ = 8.4, $J_{4/5'}$ = 9.5, $J_{3/2}$ = 5.3; ^{13}C NMR δ: 40.4(*C*H$_2$Ph), 45.9(C-4), 59.5(C-5), 69.6(*C*H$_2$OH), 80.7(C-3), 81.9(C-2), 127.2-137.7(Ar, CH=N); Anal. Calcd for $C_{19}H_{21}NO_3$ (311.4): C, 73.29; H, 6.80; N, 4.50. Found: C, 73.54; H, 6.43; N, 4.76.

(*αR,2S,3R,4S*)-(+)-α-[3-(Benzylideneamino)-2-methyl-tetrahydrofur-4-yl]-benzyl-alcohol N-oxide (6b). Yield: 71%; $[\alpha]_D^{19}$ = +66.8(c, 1.0, $CHCl_3$); ^{1}H NMR (200MHz) δ: 1.25(d, 3H, CH_3), 2.95(m, 1H, 4-H), 3.62(dd, 1H, 5-H), 3.88(dd, 1H, 5'-H), 4.12(dd, 1H, 3-H), 4.61(dq, 1H, 2-H), 4.75(d,1H, C*H*(OH)Ph) 7.10-7.37(m, 9H, Ar, CH=N), 8.10-8.15 (m, 2H, o-Ar-H); $J_{2/Me}$ = 6.2, $J_{2/3}$ = 3.6, $J_{3/4}$ = 7.7, $J_{4/5}$ = 7.5, $J_{4/5'}$ = 11.1, $J_{5/5'}$ = 8.8, $J_{4/CHPh}$ = 8.3; ^{13}C NMR δ: 21.1(CH_3), 51.2(C-4), 60.8(C-5), 70.4(C-2), 71.4(C-3), 82.3(C-OH),126.1-142.9(Ar, CH=N); Anal. Calcd for $C_{19}H_{21}NO_3$ (311.4): C, 73.29; H, 6.80; N, 4.50. Found: C, 73.43; H, 6.93; N, 4.83.

(*αR,2S,3R,4S*)-(+)-α-[3-(Benzylideneamino)-2-phenyl-tetrahydrofur-4-yl]-benzylalcohol N-oxide (6c). Yield: 70%; $[\alpha]_D^{19}$ = +5.7(c, 0.4, $CHCl_3$); ^{1}H NMR δ: 3.01(m, 1H, 4-H), 3.93(dd, 1H, 5-H), 4.19(dd, 1H, 5'-H), 4.34(dd, 1H, 3-H), 4.89(d, 1H, C*H*(OH)Ph), 5.57(d, 1H, 2-H), 7.23(m, 14H, Ar-H, CH=N), 8.17(m, 2H, ArH), $J_{2/3}$ = 3.6, $J_{3/4}$ = 7.8, $J_{4/CHPh}$ = 8.2,

$J_{4/5}$ = 8.1, $J_{4/5'}$ = 11.1, $J_{5/5'}$ = 8.6; ^{13}C NMR δ: 50.4 (C-4), 70.7(*C*H(OH)Ph), 70.8(C-5), 83.1(C-3), 83.7(C-2), 125.1-137.52(Ar, CH=N); Mass: E(I):373; **Anal. Calcd for $C_{24}H_{23}NO_3$** (373.45): C, 77.19; H, 6.21; N, 3.75. Found: C, 77.36; H, 6.59; N, 3.38.

(*2RS,3SR,4SR*)-[3-(Benzylideneamino)-2-(1-hydroxy-2-methyl-prop-2-yl)-tetrahydrofur-4-yl]-methanol N-oxide (6d). Yield: 75%; mp. 132-134°C; ^1H NMR δ: 0.86(s, 3H, CH_3), 0.92(s, 3H, CH_3), 2.55(m, 1H, 4-H), 3.33(d, 1H, CH_2OH), 3.48(d, 1H, CH_2OH), 3.68(dd, 1H, 5-H), 3.76(dd, 4H, 5'-H), 4.04(dd, 1H, $C(CH_3)_2CH_2OH$), 4.10(dd, 1H, $C(CH_3)_2CH_2OH$), 4.50(m, 2H, 2-H, 3-H), 7.31-7.41(m, 3H, Ar-H), 7.53(s, 1H, CH=N), 8.20(m, 2H, Ar-H); $^2J_{CH2(Me)2OH}$ = 11.1, $J_{4/5}$ = 3.5, $J_{4/5'}$ = 6.3, $J_{4/CH2OH}$ = 6.8, $J_{4/CH2OH}$ = 8.4, $^2J_{CH2OH}$ = 8.7, $J_{5/5'}$ = 12.1; ^{13}C NMR δ: 19.5(CH_3), 21.2(CH_3), 37.9($C(CH_3)_2$), 46.1(C-4), 58.8(C-5), 69.3(CH-CH_2OH), 70.8($C(CH_3)_2CH_2OH$), 77.2(C-3), 87.2(C-2), 128.2-131.3(Ar), 137.7(CH=N).

(*2S,3S,4S,1'S,5'R,8'S*)-(+)-[3-(p-Methoxybenzylideneamino)-2-{ 2'-(p-methoxybenzyl)-3',7'-dioxa-2'-azabicyclo[3.3.0]oct-8'yl}-tetrahydrofur-4-yl]-methanol N-oxide (9). Yield: 20%; mp. 176-179°C; $[\alpha]_D^{19}$ = +18.3(c, 0.4, $CHCl_3$); ^1H NMR δ: 2.64(m, 1H, 4-H), 3.31(m, 1H, 5'-H), 3.64(s, 3H, OMe), 3.66-3.87(m, 7H), 3.79(s, 3H, OMe), 3.95-4.15(m, 6H), 4.41(bm, 1H, OH), 4.50(dd, 1H), 6.76(d, 2H, Ar-H), 6.86(d, 2H, Ar-H), 7.21(d, 2H, Ar-H), 7.35(s, 1H, CH=N), 8.13(m, 2H, Ar-H); ^{13}C NMR δ: 45.9(C-4), 49.0(C-5'), 55.4(OCH_3), 55.5(OCH_3), 59.4(C-9'), 59.4(C-5), 70.1(CH_2OH), 71.1(C-6'), 73.7(C-4'), 74.1(C-1'), 77.7(C-3), 81.7(C-2), 83.0(C-8'), 114.2(Ar), 130.6(Ar), 131.7(Ar), 137.9(CH=N), 160.0, 162.0(Ar).

(*2S,3S,4S*)-(-)-2,2Bi-[3-{ (p-methoxybenzylideneamino)-tetrahydrofur-4-yl} methanol N-oxide] (10). Yield: 40%; mp. 111-114°C; $[\alpha]_D^{19}$ = -128.9(c, 0.7, $CHCl_3$); ^1H NMR δ: 1.18(t, 2 x 1H, OH), 2.71(m, 2 x 1H, 4-H), 3.67(m, 2 x 2H, 5-H), 3.76(s, 2 x 3H, OMe), 4.08(m, 2 x 2H, CH_2OH), 4.66 (m, 2 x 2H, 2-H,3-H), 6.84(d, 2 x 2H, Ar-H), 7.40(s, 2 x 1H, CH=N), 8.11(d, 2 x 2H, Ar-H); $J_{CH2OH/O-H}$ = 7.2, ^{13}C NMR δ: 45.7(C-4), 55.3(OMe), 59.2(C-5), 70.3(CH_2OH), 77.3(C-3), 80.5(C-2), 113.9(Ar), 122.3(Ar), 131.6(Ar), 138.5(CH=N), 161.9(Ar).

(*1R,5R,6S,9S*)-2-Hydroxy-9-methyl-5-phenyl-4.8-dioxa-2-azabicyclo[4.3.0]nonane (13a). Yield: 55%; mp. 84-87°C; ^{1}H NMR (200MHz) δ: 1.31(d, 3H, CH_3), 2.68(ddd, 1H, 6-H), 3.46(dd, 1H, 1-H), 3.58(dd, 1H, 7-H), 3.71(dd, 1H, 7'-H), 4.06(m, 1H, 9-H), 4.37(d, 1H, 5-H), 4.61(d, 1H, 3-H), 4.75(d, 1H, 3'-H); $J_{1/6}$ = 6.7, $J_{1/9}$ = 8.5, $J_{3/3'}$ = 11.8, $J_{5/6}$ = 10.8, $J_{6/7}$ = 5.3, $J_{6/7'}$ = 1.2, $J_{7/7'}$ = 9.9, $J_{9/CH3}$=6.0; ^{13}C NMR δ: 20.4(CH_3), 39.4(C-6), 68.3(C-7), 72.0(C-1), 73.7(C-9), 79.1(C-5), 82.2(C-3), 125.6-129.0(Ar), 139.8(Ar); Anal. Calcd for $C_{13}H_{17}NO_3$ (235.3): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.43; H, 6.97; N, 6.23.

(*1R,6S,9S*)-(+)-5,5-Diphenyl-2-hydroxy-9-methyl-4.8-dioxa-2-azabicyclo[4.3.0]nonane (13b). Yield: 65%; mp. 69-72°C; $[\alpha]_D^{19}$ = +185.0(c, 0.3, $CHCl_3$); ^{1}H NMR δ: 1.22(d, 3H, CH_3), 3.10(d, 1H, 1-H), 3.28(t, 1H, 7-H), 3.55(m, 1H, 6-H), 3.73(dd, 1H, 7'-H), 3.93(d, 1H, 3-H), 4.50(q, 1H, 9-H), 4.60(d, 1H, 3'-H); $J_{1/6}$ = 4.8, $J_{1/9}$ <1, $J_{3/3'}$ = 8.0, $J_{6/2}$ = 7.2, $J_{6/7}$ = 7.5, $J_{6/7'}$ = 11.2, J_{9/CH_3}= 6.5; ^{13}C NMR δ: 20.5(CH_3), 43.5(C-6), 68.8(C-7), 69.5(C-1), 78.4(C-5), 79.1(C-9), 80.2(C-3), 124.7-144.4(Ar); Anal. Calcd for $C_{19}H_{21}NO_3$ (311.4): C, 73.29; H, 6.8; N, 4.5. Found: C, 73.12; H, 6.47; N, 4.77.

The products **15** and **16** which appear as single spot in TLC, could not be separated by coloumn chromatography. However, both of them show individual chemical shifts both in ^{1}H NMR and ^{13}C NMR spectra.

(*1R,5R,6S,8S,12R*)-4-Hydroxy-6-methyl-2,7-dioxa-4-azatricyclo[6.3.1.0^{5,12}]dodecane (15). Yield: 26.5%; ^{1}H NMR δ: 1.43(d, 3H, CH_3), 1.5-2.1(m, 6H, cyclohexyl-H), 2.47(m, 1H, 12-H), 3. 09(d, 1H, 5-H), 3.98(d, 1H, 3-H), 4.01(ddd, 1H, 8-H), 4.05(ddd, 1H, 1-H), 4.40(q, 1H, 6-H), 4.60(d, 1H, 3'-H); $J_{1/11}$ = 5.7, $J_{1/11'}$ = 10.2, $J_{1/12}$ = 9.0, $J_{3/3'}$ = 7.7, $J_{5/12}$ = 6.6, $J_{5/6}$ < 1.0, J_{6/CH_3}= 6.6, $J_{8/9}$ = 3.1, $J_{8/9'}$ = 8.0, $J_{8/12}$ = 5.0; ^{13}C NMR δ: 15.0(C-10), 18.7(CH_3), 25.2(C-9), 26.3(C-11), 39.9(C-12), 71.2(C-5), 71.4(C-8), 74.8(C-1), 76.5(C-6), 84.9(C-3); Mass: E(I):199.

(*1S,2R,6S,8S*) 9-(Hydroxyimino-8-methyl-7-oxabicyclo[4.3.0]non-2-yl) formate (16). Yield: 13.5%; ^{1}H NMR (500MHz) δ: 1.13(d, 3H, CH_3), 1.4-1.7(m, 6H, cyclohexyl-H),

3.50(t, 1H, 1-H), 3.83(quintet, 1H, 6-H), 4.21(dt, 1H, 2-H), 4.78(q, 1H, 8-H), 8.0(s, 1H, CHO); $J_{1/2}$ = 6.3, $J_{1/6}$ = 6.3, $J_{2/3}$ = 5.8, $J_{8/CH3}$ = 6.6, $J_{6/5}$ = 4.7, $J_{6/5'}$ = 11.2; ^{13}C NMR δ: 17.8 (CH_3), 19.6 (C-4), 27.6 (C-5), 30.8 (C-3), 46.4 (C-1), 69.9 (C-6), 71.4 (C-8), 77.3 (C-2), 166.1 (C-9), 176.7 (*C*HO).

(*1R,2S,6R,8S*)-(+)-(9-Hydroxyimino-8-methyl-7-oxabicyclo[4.3.0]non-2-yl) formate (19). Yield: 40%; mp. 125-127°C; $[\alpha]_D^{19}$ = +111.5(c, 0.5, $CHCl_3$); ^{1}H NMR δ: 1.3(d, 3H, CH_3), 1.41-2.12(m, 6H, cyclohexyl-H), 3.22(t, 1H, 1-H), 3.91(m, 1H, 6-H), 4.28(q, 1H, 8-H), 5.66(m, 1H, 2-H), 7.9(s, 1H, CHO); $J_{1/2}$ = 5.4, $J_{1/6}$ = 5.4, $J_{8/Me}$= 6.3; ^{13}C NMR δ: 13.5(C-4), 17.5(CH_3), 26.9(C-5), 28.6(C-3), 42.5(C-1), 66.6(C-2), 74.2(C-8), 74.8(C-6), 160.2(C-9), 165.6(*C*HO); Anal. Calcd for $C_{10}H_{15}NO_4$ (213): C, 56.32; H, 7.09; N, 6.56. Found: C, 56.54; H, 6.83; N, 6.85.

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[25] Each other conformation of **18** would give rise to higher internal strain of the molecule as an inspection of molecular models suggests.