On the Reactivity of (−)-(R)-Carvone and (−)-4aα,7α,7aβ-Nepetalactone: Synthesis of New Heterocycles

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The 1,3-dipolar cycloaddition of 4-chlorobenzonitrile oxide to the unsaturated system of (−)-(R)-carvone occurred exclusively at C(8) to give a new isoxazoline derivative. This derivative reacts with NH_2OH to yield a new heterocycle, observed for the first time. On the other hand, the addition of 4-chlorobenzonitrile oxide to the unsaturated lactone (−)-4aα,7α,7aβ-nepetalactone gave, in a good yield, also a new heterocycle, again obtained for the first time. The terpenoid (−)-(R)-carvone and iridoid (−)-4aα,7α,7aβ-nepetalactone were isolated from Moroccan species *Mentha viridis* (L.) and *Nepeta tuberosa* (L.), respectively. The new heterocycles obtained were identified by combination of chromatographic and spectroscopic methods.

1. Introduction. – 1,3-Dipolar cycloaddition of nitrile oxides to unsaturated systems as (−)-(R)-carvone (**I**; for antimicrobial action, see [1–3]) and (−)-4aα,7α,7aβ-nepetalactone (**II**; referred to as therapeutic molecule [4–10]) is a convenient method to prepare isoxazoline derivatives. The reactivity of the dipolarophile in our case is activated by a ketone function in **I** and a lactone function in **II**.
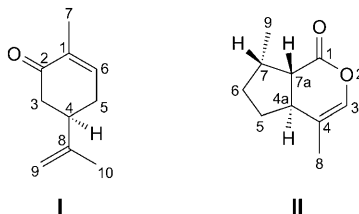

Our review of the literature on (−)-(R)-carvone revealed that the reactivity of nitrile oxides is regioselective, strongly dependent on the substituents. In general, all substituents in the dipolarophile (relative to H) strongly accelerate 1,3-dipolar cycloadditions [11]. Indeed, *Shiue et al.* have shown in 1976 that the addition of

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acetonitrile oxide at C(8)=C(9) of dipentene (=1-methyl-4-(1-methylethenyl)cyclo-hexene; **1**) gave the dihydroisoxazole derivatives **2a** and **2b**, but no adduct **3** (*Scheme 1*). The same dipole underwent addition to carvone (**4a**; enantiomer not specified) at both C=C bonds to give a mixture of dihydroisoxazole derivatives **5a** and **6a**. Benzonitrile oxide, however, gave the analogous carvone derivatives **5b** and **5c**, respectively, without contamination of the isomers **6b** or **6c** [11–14].

Scheme 1
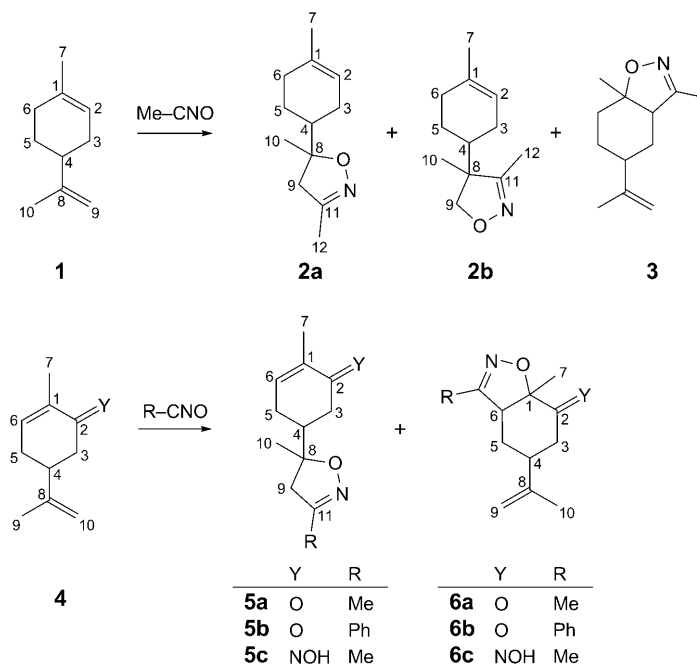
We note here that the addition of the benzonitrile oxide was carried out after oximation of the carvone **4a**. It is completely the opposite in our case, since we added $NH_2OH \cdot HCl$ to the **5b** equivalent after having synthesized it, using 4-chlorobenzoni-trile oxide instead of benzonitrile oxide (see *Schemes 2* and *3*).

In the case of iridoid **II**, the work encountered in the literature is mostly on organic synthesis or pharmacological activity [15–18]. To our knowledge, no study of 1,3-dipolar cycloaddition on the molecule **II** has been described previously.

2. Results. – 2.1. *Fomation of* **I$_a$**. (−)-(*R*)-Carvone (**I**) was isolated from *Mentha viridis* (L.), a plant cultivated in Morocco. It was identified by combination of chromatographic and spectroscopic methods. This compound alone represents 70% of the essential oil of the plant.

Addition of 4-chlorobenzonitrile oxide to (−)-(*R*)-carvone was conducted in $CHCl_3$ with stirring at 0°. The addition has affected only the C(8)=C(9) bond to give isoxazoline **I$_a$** (*Scheme 2*).

Scheme 2
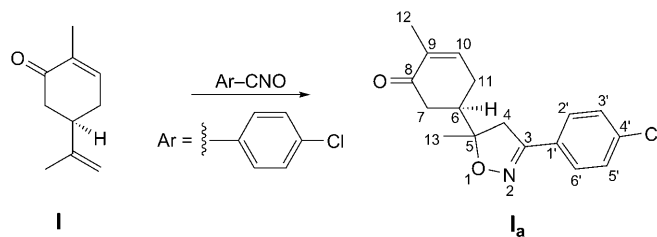
2.1.1. *Reaction of* **I**$_a$ *with NH*$_2$*OH · HCl.* We have studied the chemical behavior of isoxazoline derivative **I**$_a$ towards NH$_2$OH · HCl. The reaction mixture was stirred at room temperature in EtOH/NaOH. Thereby, derivative **I**$_b$ was formed as major compound, accompanied by traces of oxime **I**$_c$ (*Scheme 3*). The formation of **I**$_b$ indicates the binucleophilic character of H$_2$N–OH, as we have already reported in [19].

Scheme 3
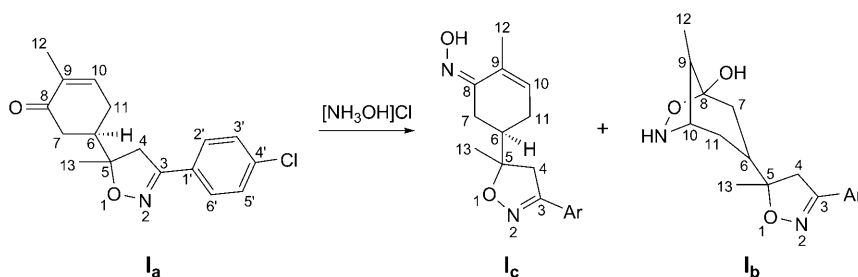
2.2. *Formation of* **III**. The essential oil obtained by steam distillation contains 80% of iridoid **II**. We isolated **II** from the oil by filtration after having induced its crystallization. The spectroscopic data agreed well with those in the literature [4–7].

To synthesize new molecules starting from **II** for pharmacodynamic applications, or having some interesting olfactory properties, we have added 4-chlorobenzonitrile oxide to 4aα,7α,7aβ-nepetalactone **II**. The reaction took place in the presence of *Javel* water with stirring at 0° for 48 h. We obtained a new compound, III, with heterocyclic structure **III** (*Scheme 4*).

Scheme 4
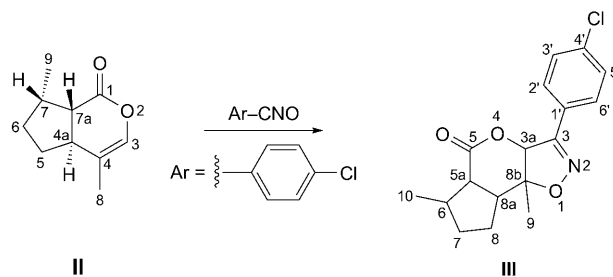
Experimental Part

1. *Preparation of* **I$_a$**. In a 200-ml *Erlenmeyer* flask, equipped with a Br$_2$ funnel, were introduced 1.00 g of (−)-(*R*)-carvone (6.66 mmol) and 1.03 g of 4-chlorobenzaldehyde oxime in CHCl$_3$ (30 ml). The soln. was stirred at 0° for 4 h, while 25 ml of *Javel* water (NaOCl) were added dropwise. The mixture was stirred at r.t. for 48 h (the progress of the reaction was followed by TLC). The aq. phase was washed with CH$_2$Cl$_2$ (50 ml), and the combined org. phases were dried (Na$_2$SO$_4$) and evaporated to dryness. The oily residue was taken up with Et$_2$O (25 ml). A white solid appeared, which was isolated by filtration.

*(5*R*)-5-[3-(4-Chlorophenyl)-4,5-dihydro-5-methyl-1,2-oxazol-5-yl]-2-methylcyclohex-2-en-1-one* (**I$_a$**). Yield 70%. M.p. 166°. IR: 1660, 1620. ^{1}H-NMR (200 MHz, CDCl$_3$): 1.82 (*s*, Me(12)); 1.53 (*s*, Me(13)); 2.32–2.83 (*m*, H–C(6), CH$_2$(7)); 3.09, 3.20 (*AB*, *J* = 16, CH$_2$(4)); 6.76–6.84 (*m*, H–C(10)); 7.41 (*d*, *J* = 9, H–C(3′), H–C(5′)); 7.63 (*d*, *J* = 9, H–C(2′), H–C(6′)). ^{13}C-NMR (50 MHz, CDCl$_3$): 16.06 (C(13)); 23.39 (C(12)); 27.52 (C(4)); 40.01 (C(6)); 44.21 (C(7)); 44.28 (C(11)); 88.82 (C(5)); 128.10 (C(3′), C(5′)); 128.45 (C(4′)); 129.43 (C(2′), C(6′)); 135.95 (C(1′)); 136.41 (C(9)); 144.72 (C(10)); 155.28 (C(3)); 199.12 (C(8)).

2. *Preparation of* **I$_b$** *and* **I$_c$**. In a 200-ml *Erlenmeyer* flask were introduced 3.00 mmol of **I$_a$** (*ca.* 0.93 g), 3.6 mmol of NH$_2$OH · HCl (*ca.* 0.38 g), 3.60 mmol of NaOH (*ca.* 0.15 g), and EtOH (50 ml). The mixture was stirred for 12 h. After removal of EtOH under reduced pressure, the aq. residue was extracted with CH$_2$Cl$_2$ (30 ml). The org. phase was washed with H$_2$O (50 ml), dried (Na$_2$SO$_4$), and concentrated to dryness. Chromatographic and spectroscopic methods evidenced the formation of the major compound **I$_b$** with *ca.* 10% of oxime **I$_c$**.

Data of 3-[3-(4-Chlorophenyl)-4,5-dihydro-5-methyl-1,2-oxazol-5-yl]-8-methyl-6-oxa-7-azabicyclo[3.2.1]octan-5-ol (**I$_b$**). Yield 60%. M.p. 208°. IR: 3230, 3150. ^{1}H-NMR (200 MHz, CDCl$_3$): 1.23 (*s*, Me(13)); 1.25 (*d*, *J* = 8, Me(12)); 1.43–2.09 (*m*, H–C(6), CH$_2$(7), CH$_2$(11)); 1.83 (*m*, H–C(9)); 3.20 (*m*, H–C(10)); 3.47 (*m*, NH); 3.68, 3.79 (*AB*, *J* = 16, CH$_2$(4)); 5.92 (*m*, OH); 7.34 (*d*, *J* = 9, H–C(3′), H–C(5′)); 7.54 (*d*, *J* = 9, H–C(2′), H–C(6′)). ^{13}C-NMR (50 MHz, CDCl$_3$): 17.57 (C(6)); 18.32 (C(7)); 22.88 (C(12)); 23.76 (C(13)); 26.27 (C(4)); 41.69 (C(9)); 43.97 (C(11)); 58.33 (C(10)); 89.22 (C(5)); 127.70 (C(2′), C(6′)); 128.38 (C(3′), C(5′)); 129.36 (C(8)); 132.30 (C(4′)); 135.85 (C(1′)); 156.24 (C(3)).

3. *Preparation of* **III**. In a 200-ml *Erlenmeyer* flask, equipped with a Br$_2$ funnel, were introduced 1.00 g of iridoid **II** (6.024 mmol) and 0.94 g of 4-chlorobenzaldehyde oxime in CHCl$_3$ (30 ml). According to the same procedure as for **I$_a$**, the reaction gave compound **III** in pure form.

*Data of (4a*S*,7*S*,7a*S*)-5,6,7,7a-Tetrahydro-4,7-dimethylcyclopenta[c]pyran-1(4a*H*)-one* (**II**). M.p. 37–39°. [α]$_D^{20}$ = −24.2 (*c* = 6.2, CHCl$_3$). IR (KBr): 1765, 1662, 1140. ^{1}H-NMR (300 MHz, CDCl$_3$): 1.10 (*d*, *J* = 8, Me(9)); 1.71 (*s*, Me(8)); 2.20–2.51 (*m*, CH$_2$(5), CH$_2$(6), H–C(7)); 2.36–2.43 (*m*, H–C(7a), H–C(4a)); 6.23 (*s*, H–C(3)). ^{13}C-NMR (50 MHz, CDCl$_3$): 14.26 (C(8)); 17.66 (C(9)); 26.12 (C(5)); 29.99 (C(6)); 32.02 (C(7)); 37.33 (C(4a)); 49.11 (C(7a)); 120.44 (C(4)); 135.88 (C(3)); 170.21 (C(1)). MS: 166 (24, *M*$^+$), 138 (26), 123 (50), 95 (80), 81 (100).

*Data of 3-(4-Chlorophenyl)-5a,6,7,8,8a,8b-hexahydro-6,8b-dimethylcyclopenta[4,5]pyrano[2,3-d][1,2]oxazol-5(3a*H*)-one* (**III**). Yield 87%. M.p. 153–154°. IR (KBr): 1757, 1494, 1376, 1015, 837. ^{1}H-NMR (300 MHz, CDCl$_3$): 1.00 (*d*, *J* = 8, Me(10)); 1.55 (*s*, Me(9)); 1.92–2.22 (*m*, H–C(5a), H–C(6), CH$_2$(7), CH$_2$(8), H–C(8a)); 5.56 (*s*, H–C(3a)); 7.35 (*d*, *J* = 10, H–C(2′), H–C(6′)); 7.75 (*d*, *J* = 10, H–C(3′), H–C(5′)). ^{13}C-NMR (50 MHz, CDCl$_3$): 16.42 (C(9)); 21.64 (C(10)); 23.54 (C(7)); 31.53 (C(8)); 32.14 (C(6)); 42.93 (C(8a)); 44.79 (C(5a)); 85.45 (C(3a)); 89.10 (C(8b)); 126.19 (C(4′)); 128.24 (C(3′), C(5′)); 129.22 (C(2′), C(6′)); 136.64 (C(1′)); 154.34 (C(3)); 170.26 (C(5)). MS: 320 (90, [*M* + H]$^+$).

REFERENCES

[1] S. Pattnaik, V. R. Subramanyam, M. Bapaji, C. R. Kole, *Microbios* **1997**, *89*, 39.
[2] S. Lee, R. Tsao, C. Peterson, J. R. Coats, *J. Econ. Entomol.* **1997**, *90*, 883.

[3] J. Wang, M. Froeyen, C. Henrix, C. Andrei, R. Snoeck, E. Lescrinier, E. De Clercq, P. Herdewijn, *Nucleosides, Nucleotides Nucleic Acids* **2001**, *20*, 727.

[4] E. J. Eisenbraun, C. E. Browne, R. L. Irvin-Willis, D. J. McGurk, E. L. Eliel, D. L. Harris, *J. Org. Chem*. **1980**, *45*, 3811.

[5] Y. Takeda, Y. Kiba, T. Masuda, H. Otsuka, M. Tagawa, E. Sezik, E. Yesilada, *Chem. Pharm. Bull*. **1999**, *47*, 1433.

[6] F. Murai, M. Tagawa, H. Inouye, T. Ishida, M. Inoue, *Chem. Pharm. Bull*. **1987**, *35*, 2533.

[7] X. Xie, S. Uesato, H. Inouye, T. Fujita, F. Murai, M. Tagawa, T. Shingu, *Phytochemistry* **1988**, *27*, 469.

[8] J. Bellakhdar, 'La pharmacopée marocaine traditionnelle', Ibis Press, Paris, 1997, pp. 264 – 290.

[9] H. Bouidida, K. Alaoui, Y. Cherrah, S. Fkih-Tetouani, A. Ilidrissi, *Phytothérapie* **2004**, *4*, 120.

[10] H. Bouidida, K. Alaoui, Y. Cherrah, S. Fkih-Tetouani, A. Ilidrissi, *Thérapie* **2006**, *61*, 447.

[11] C.-Y. Shiue, R. G. Lawler, L. B. Clapp, *J. Org. Chem*. **1976**, *41*, 2210.

[12] C.-Y. Shiue, K. P. Park, L. B. Clapp, *J. Org. Chem*. **1970**, *35*, 2063.

[13] G. C. Levy, G. L. Nelson, *J. Am. Chem. Soc*. **1972**, *94*, 4897.

[14] G. Grundman, P. Grunanger, 'Nitrile oxides', Springer-Verlag, New York, 1971, p. 85.

[15] A. Nangia, G. Prasuna, *Tetrahedron* **1996**, *52*, 3435.

[16] P. Callant, P. Storme, E. Van der Eycken, M. Vandewalle, *Tetrahedron Lett*. **1983**, *24*, 5797.

[17] S. Aydin, T. Demir, Y. Öztürk, K. H. C. Başer, *Phytoter. Res*. **1999**, *13*, 20.

[18] S. Aydin, R. Beis, Y. Öztürk, K. H. C. Başer, *J. Pharm. Pharmacol*. **1998**, *50*, 813.

[19] S. Ghoulami, A. Ilidrissi, S. Fkih-Tetouani, *Tetrahedron Lett*. **2001**, *42*, 2107.