1,3-Dipolar Cycloaddition Reactions of Nitrones with Vinylacetic Olefins in the Racemic Series and Synthesis of δ-Lactams *via* Isoxazolidines

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A study of the cycloaddition behavior of a series of esters and nitriles α-chloro- and α-hydroxyvinylacetic dipolarophiles with *C*-aryl-*N*-alkylnitrones has been carried out. Regiospecific cycloadditions are observed; the reactions lead to a mixture of 5-substituted isoxazolidines either *erythro* or *threo*, wherever the nitrone is involved. We report the synthesis of some δ-lactams in which isoxazolidines are used as latent synthons.

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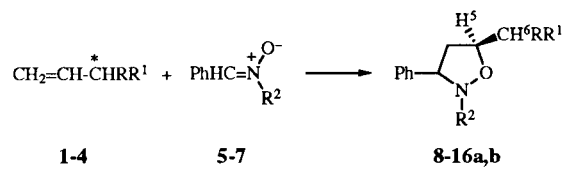
New methods of constructing the β-lactam ring continue to be of interest in connection with the synthesis of analogues of the naturally occuring antibiotics such as penicillin or nocardicine [1]. Different approaches by rearrangement or hydrogenolysis of isoxazolidines obtained by cycloaddition of nitrones with various alkenes are known [2], but only a few reports deal with the synthesis of δ-lactams by 1,3-dipolar cycloaddition [3]. Moreover because of their great importance as active agents, a considerable number of methods have been developed for the synthesis of polyhydroxylated piperidines and pyrrolidines which have been shown to be glycosidase inhibitors [4]. For example, Fleet [5] has shown that D-Mannonolactam is a powerful inhibitor of rat epididymal α-mannosidase and of apricot β-glucosidase [6]. Other δ-lactams have been used as intermediates in the synthesis of stereoisomers of castanospermine [7a] including the natural product 6-epicastanospermine [7b]. Common to all these methods is the involvement of an expensive protecting group technique which consequently requires a large number of reaction steps and thus leads to low overall yields.

This paper illustrates the potential of isoxazolidines as starting materials for the synthesis of a wide range of polyhydroxylated piperidones, which could provide an extensive class of powerful and specific glycosidase inhibitors as polyhydroxylated piperidines [8]. We utilized nitrone-olefin cycloaddition as the key feature in the synthesis of analogues of Mannonolactam and we reported a simple synthesis of dihydroxypiperidone and piperidione: easily accessible isoxazolidines are converted in two steps into δ-lactams. The key step of this approach involves a reductive cleavage of an isoxazolidine ring to give a β-hydroxy-γ-aminoester which undergoes subsequent cyclization *via* the carbomethoxy and amino groups.

Our intention was to synthesize new chiral isoxazolidines *via* 1,3-dipolar cycloaddition of nitrones with various chiral dipolarophiles possessing geminal electron-withdrawing (CN or CO_2Me) and electron-donating (Cl, OH) substituents. We have examined the reaction of methyl 2-chlorobut-3-enoate **1** with *C*-phenyl-*N*-methylnitrone **5**, *C,N*-diphenylnitrone **6** and *C*-phenyl-*N*-*tert*-butylnitrone **7**, methyl 2-hydroxybut-3-enoate **2**, 2-chlorobut-3-enenitrile **3** and 2-hydroxybut-3-enenitrile **4** and studied the regio- and stereochemical aspects. The cycloadditions, performed according to conventional methods by refluxing a benzene solution of dipolarophile with the nitrone, afforded a mixture of 5-substituted isoxazolidine stereoisomers **a,b**, that never have been separated where **a** is the major product. Scheme 1 and Table 1 summarize our results [9].

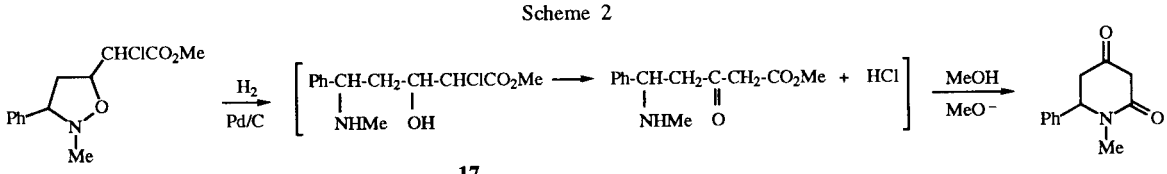
Scheme 1



1-4 **5-7** **8-16a,b**

For example the reaction of *C*-phenyl-*N*-methylnitrone **5** with methyl 2-chlorobut-3-enoate 1 gave a mixture of two isoxazolidine diastereoisomers **8a,b**. The structural proofs are based on the spectroscopic ^1H (300 MHz, perdeuteriobenzene) and ^{13}C nmr results. The presence of two doublets at 3.34 ppm and 3.29 ppm (1H) due to the C-6 proton shows the presence of two stereoisomers, their presence is confirmed by the number of signals in the ^{13}C nmr spectrum. We calculated the ratio of the stereoisomers from the relative intensities of both signals. The spectrum of ^1H nmr of isoxazolidines **8a,b** reveals the presence of two multiplets near 2.22-2.60 ppm (2H) attributed to the 4-methylene protons characterizing a 5-

Scheme 2



Scheme 3

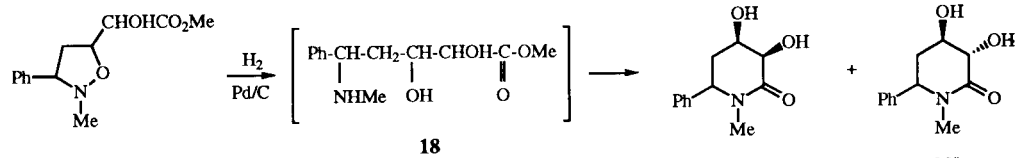


Table 1

1-16	R^1	R	R^2	isoxazolidines a/b
1	Cl	CO_2Me	-	-
2	OH	CO_2Me	-	-
3	Cl	CN	-	-
4	OH	CN	-	-
5	-	-	Me	-
6	-	-	Ph	-
7	-	-	tBu	-
8a,b	Cl	CO_2Me	Me	75/25
9a,b	Cl	CO_2Me	Ph	70/30
10a,b	Cl	CO_2Me	tBu	75/25
11a,b	OH	CO_2Me	Me	85/15
12a,b	OH	CO_2Me	Ph	55/45
13a,b	Cl	CN	Me	75/25
14a,b	Cl	CN	Ph	70/30
15a,b	OH	CN	Me	65/35
16a,b	OH	CN	Ph	65/35

substituted isoxazolidine; the 4-substituted regioisomers would exhibit signals for the 5-methylene protons near 4.50 ppm. The irradiation of the C-3 proton (1H) at 3.25 ppm of isoxazolidines **8a,b** permits confirmation of the structure previously ascribed: a change occurs in the two multiplets at 2.54 ppm and 2.27 ppm attributed to 4-methylene protons, no change of the other signals has been detected. To account for the formation of the two cycloadducts **8a,b** we can assume that nitrone having a fixed configuration (as a rule, *Z*-nitrones are more stable and show a higher reactivity than their *E* counterparts) we obtained the two isomers *erythro* and *threo* due to the carbon atom introduced by the chiral olefin. Configurations of C-3, C-5 and C-6 protons cannot be made rigorously on the basis of chemical shift values and vicinal coupling constants. The composition of the mixture **a,b** of cycloadducts is usually variable, according to the substitution pattern of both the nitrone and the dipolarophile. The elemental analyses, ^1H and ^{13}C-nmr spectra of all compounds are compatible with the given structures, which have been confirmed further by hydrogenation.

It is well known that cleavage of the N-O bond of 2,3-diphenyl-substituted isoxazolidinic derivatives provokes loss of aniline. We choose to hydrogenate 2-methylisoxazolidines possessing a carbomethoxy group because we wanted to obtain lactams.

Hydrogenolysis of Isoxazolidines **8a,b**.

The mixture of diastereoisomeric isoxazolidines **8a,b** in the ratio 75/25 underwent facile cleavage on catalytic hydrogenolysis in the presence of 10% palladium-charcoal catalyst to afford the aminoalcohol **17** containing the desired carbomethoxy group for the transformation into δ-lactam. The reaction of sodium methylate with the crude product of hydrogenolysis which was not purified leads to the piperidione **19** resulting from the cyclization of the amino group with the carbomethoxy group (Scheme 2).

The structure of **19** was assigned on the basis of its nmr spectral data. The spectrum of ^{13}C-nmr shows two signals at 200.4 and 171.2 ppm characterizing respectively the carbon of ketone and amide groups.

Hydrogenolysis of Isoxazolidines **11a,b**.

Hydrogenation of the mixture of diastereoisomeric isoxazolidines **11a,b** in the ratio 85/15 in methanol in the presence of 10% palladium-charcoal gave an aminoalcohol **18** which spontaneously rearranged into lactams **20a,b** in the same ratio (85/15) which have been separated (Scheme 3).

The structure and the relative configuration of these products can be deduced from nmr spectral data. The ^1H-nmr spectra of diastereoisomers **20a** and **20b** differ substantially: the 3-H and 4-H of the compound **20a** has a smaller coupling constant ($J_{3,4} = J_{a,e} = 2.56$ Hz) than **20b** ($J_{3,4} = J_{a,a} = 9.18$ Hz). The configuration of these lactams **20a** and **20b** permits us to establish that isoxazolidines **11a** and **11b** have respectively 5,6-*syn* and *anti* configurations. It is well known that allylic alcohols affording a similar five-membered ring, according to Houk's concept

[10], give *syn* products as major compounds, the *syn/anti* ratio depending on alkene substitution [1c].

Conclusion.

In conclusion, we have shown that the 1,3-dipolar cycloaddition of nitrones with several racemic vinylacetic derivatives results in the production of stereoisomeric 5-substituted isoxazolidines in high yield: with racemic vinylacetic esters, a reduction cleavage of the isoxazolidinic ring leads to a β-hydroxy-γ-aminoester which undergoes a subsequent cyclization between the carbomethoxy and amino groups. The limited number of studies on compounds with a chloro [10b], cyano or ester substituents produced at the stereocenter do not allow any generalization about the effect of substituents on the stereochemical outcome of such cycloadditions. New methods of constructing the six-membered lactam ring continue to be of interest in connection with the synthesis of analogues of natural products such as glycosidases inhibitors. Advantages of this approach to δ-lactams are the low number of steps, excellent stability and the easy accessibility. It should open a practical route to a number of other polyhydroxylated compounds.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer 241 spectrometer. The ^1H and ^{13}C nmr spectra were determined on a Brüker MLS spectrometer operating at 300.13 MHz and 75.5 MHz. Chemical shifts are reported in ppm downfield from tetramethylsilane (δ). Silica column chromatography was performed with Merck silica gel 60 (70-230 mesh) or silica gel (35-70 mesh) for flash chromatography. Elemental analyses were performed by the Department of Analyses of Vernaison (France).

Starting dipolarophiles **1-4** and dipoles **5-7** were prepared according to known methods [11a-d,12] respectively.

General Procedure for the Synthesis of Isoxazolidines **8-16**.

A solution of nitrone (0.01 mole) and olefin (0.01 mole) in benzene (50 ml) was heated and stirred at reflux for the requisite time. The solvent was evaporated and the crude product was purified by chromatography on silica gel with hexane/ethyl acetate 80/20 as the eluant.

6-Carbomethoxy-6-chloro-2*N*-methyl-3-phenylisoxazolidine **8**.

The reaction of *C*-phenyl-*N*-methylnitrone **5** with methyl 2-chlorobut-3-enoate **1** was carried out under reflux for 5 days. The crude product was purified to yield 2.2 g (82%) of two isomers in the ratio **8a/8b** = 75/25 as a colorless oil; ir (nujol): of the mixture υ, 1755 (CO_2Me) cm^{-1}; ^1H-nmr (perdeuteriobenzene); **8a** δ 2.39 (s, 3H, NMe), 2.60-2.22 (m, 2H, H-4, J_{gem} = 13.3, $J_{4,5}$ = 4.9, $J_{4',5}$ = 8.2), 3.25 (dd, 1H, H-3, $J_{3,4}$ = 7.2, $J_{3,4'}$ = 9.5), 3.34 (d, 1H, H-6, $J_{6,5}$ = 4.8), 3,42 (s, 3H, OMe), 4.75-4.59 (m, 1H, H-5), 7.55-7.20 (m, 5H, Ph); **8b** δ 2.38 (s, 3H, NMe), 3.29 (d, 1H, H-6, $J_{6,5}$ = 7.24), 3.41 (s, 3H, OMe), 4.78-4.55 (m, 1H, H-5); ^{13}C-nmr (deuteriochloroform); **8a** δ 41.8 (NMe), 43.3 (C-4), 53.2 (OMe), 57.6 (C-6), 72.4 (C-3), 76.9 (C-5), 127.8-128.2-128.5-138.2 (Ph), 168.2 (CO_2); **8b** δ 42.3 (NMe), 43.0 (C-4), 58.3 (C-6), 72.7 (C-3), 77.2 (C-5).

Anal. Calcd. for $C_{13}H_{16}ClNO_3$: C, 57.89; H, 5.98; Cl, 13.14. Found: C, 58.15; H, 5.93; Cl, 13.10.

6-Carbomethoxy-6-chloro-2,3-diphenylisoxazolidine **9**.

The reaction of *C,N*-diphenylnitrone **6** with methyl 2-chlorobut-3-enoate **1** was carried out under reflux for 5 days. The crude product was purified and gave 2.48 g (75%) of two isomers in the ratio **9a/9b** = 70/30 as a colorless oil; ir (nujol): of the mixture υ 1755 (CO_2Me) cm^{-1}; ^1H-nmr (perdeuteriobenzene): **9a** δ 2.45-2.35 (m, 1H, H-4', J_{gem} = 16.1, $J_{4,5}$ = 7.1, $J_{4',5}$ = 10.3), 2.55-2.50 (m, 1H, H-4,), 3.45 (s, 3H, OMe), 4.21 (d, 1H, H-6, $J_{6,5}$ = 7.3), 4.51 (t, 1H, H-3, $J_{3,4}$ = 6.48), 4.80-4.65 (m, 1H, H-5), 7.40-6.80 (m, 5H, Ph); **9b** δ 2.45-2.20 (m, 1H, H-4', J_{gem} = 16.1, $J_{4,5}$ = 7.1, $J_{4',5}$ = 10.3); 2.68-2.49 (m, 1H, H-4), 3.35 (s, 3H, OMe), 4.30 (d, 1H, H-6, $J_{6,5}$ = 9.0), 4.38 (t, 1H, H-3, $J_{3,4}$ = 7.76); ^{13}C-nmr (deuteriochloroform): **9a** δ 41.9 (C-4), 53.2 (OMe), 56.4 (C-6), 66.9 (C-3), 78.3 (C-5), 114.9-115.3-115.7-116.0-122.5-122.7-122.9-126.5-126.6-127.0-127.8-128.7-128.8-140.3-141.0-150.5 (Ph), 168.3 (CO_2); **9b** δ 42.8 (C-4), 53.2 (OMe), 56.3 (C-6), 70.2 (C-3), 77.8 (C-5).

Anal. Calcd. for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; Cl, 10.68; O, 14.47. Found: C, 65.48; H, 5.47; Cl, 10.62; O, 14.47.

6-Carbomethoxy-6-chloro-*N*-*tert*-butyl-3-phenylisoxazolidine **10**.

The reaction of *C*-phenyl-*N*-*tert*-butylnitrone **7** with methyl 2-chlorobut-3-enoate **1** was carried out under reflux for 3 days. The crude product was purified and gave 2.15 g (69%) of two isomers in the ratio **10a/10b** = 75/25 as a colorless oil; ^1H-nmr (deuteriochloroform): **10a** δ 1.10 (s, 9H, *N*-*t*-Bu), 2.33-2.22 (m, 1H, H-4, J_{gem} = 13.1, $J_{4,5}$ = 4.5, $J_{4'5}$ = 8.1), 2.96-2.80 (m, 2H, H-4), 3.81 (s, 3H, OMe), 4.16 (t, 1H, H-3, $J_{3,4}$ = 8.6), 4.47 (d, 1H, H-6, $J_{6,5}$ = 3.1), 4.50-4.35 (m, 1H, H-5), 7.50-7.20 (m, 5H, Ph); **10b** 1.20 (s, 9H, *N*-*t*-Bu), 3.78 (s, 3H, OMe), 4.45 (d, 1H, H-6, $J_{6,5}$ = 5.1); ^{13}C-nmr (deuteriochloroform): **10a** δ 28.5 (Me), 48.1 (C-4), 55.1 (OMe), 59.7 (C-6), 61.32 (*t*-Bu), 66.1 (C-3), 79.2 (C-5), 129.5-129.6-130.9-145.1 (Ph), 171.3 (CO_2) **10b** 47.6 (C-4), 60.5 (C-6), 78.0 (C-5).

Anal. Calcd. for $C_{16}H_{22}ClNO_3$: C, 61.63; H, 7.11; Cl, 11.37; N, 4.49. Found: C, 61.70; H, 7.10; Cl, 11.56; N, 4.68.

6-Carbomethoxy-6-hydroxy-2*N*-methyl-3-phenylisoxazolidine **11**.

The reaction of *C*-phenyl-*N*-methylnitrone **5** with methyl 2-hydroxybut-3-enoate **2** was carried out under reflux for 4 days. The crude product was purified and gave 1.73 g (69%) of two isomers in the ratio **11a/11b** = 85/15 as a colorless oil; ir (nujol): of the mixture υ 1740 (CO_2Me) cm^{-1}: ^1H-nmr (deuteriochloroform): **11a** δ 2.53 (s, 3H, NMe), 2.71-2.59 (m, 1H, H-4'), 2.93-2.80 (m, 1H, H-4, J_{gem} = 12.2, $J_{4,5}$ = 5.3, $J_{4',5}$ = 7.6), 3.51 (t, 1H, H-3, $J_{3,4}$ = 8.4), 4.24 (d, 1H, H-6, $J_{6,5}$ = 2.3), 3.82 (s, 3H, OMe), 4.68-4.58 (m, 1H, H-5), 7.50-7.20 (m, 5H, Ph); **11b** δ 2.56 (s, 3H, NMe), 4.30 (d, 1H, H-6, $J_{6,5}$ = 6.8), 3.80 (s, 3H, OMe); ^{13}C-nmr (deuteriochloroform): **11a** δ 41.3 (NMe), 42.7 (C-4), 52.4 (OMe), 73.9 (C-3), 75.3 (C-6), 76.9 (C-5), 127.9-128.3-128.9-137.1 (Ph), 172.4 (CO_2); **11b** δ 39.4 (NMe), 42.9 (C-4), 52.6 (OMe), 73.6 (C-3), 74.6 (C-6), 77.4 (C-5), 127.8-128.3-128.7-128.9-137.7 (Ph), 171.7 (CO_2).

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.36; H, 6.69; N, 5.60.

6-Carbomethoxy-6-hydroxy-2,3-diphenylisoxazolidine **12**.

The reaction of *C,N*-diphenylnitrone **6** with methyl 2-hydroxybut-3-enoate **2** was carried out under reflux for 4 days. The crude product was purified and gave 1.80 g (58%) of two isomers in the ratio **12a/12b** = 55/45 as a colorless oil; ir (nujol): of the mixture υ 1760 (CO_2Me) cm^{-1}; ^{1}H-nmr (deuteriochloroform): **12a** δ 2.75-2.45 (m, 1H, H-4'), 3.02-2.83 (m, 1H, H-4, J_{gem} = 12.0, $J_{4,5}$ = 6.4, $J_{4',5}$ = 7.4), 3.89 (s, 3H, OMe), 4.26 (d, 1H, H-6, $J_{6,5}$ = 2.5), 4.69 (t, 1H, H-3, $J_{3,4}$ = 7.8), 4.78-4.61 (m, 1H, H-5), 7.57-6.90 (m, 5H, Ph); **12b** 4.34 (d, 1H, H-6, $J_{6,5}$ = 3.0); ^{13}C-nmr (deuteriochloroform): **12a** δ 40.9 (C-4), 52.7 (OMe), 69.5 (C-3), 70.7 (C-6), 78.2 (C-5), 121.9-122.3-123.8-126.5-126.9-127.8-128.2-141.0 (Ph), 150.0 (CO_2); **12b** δ 41.1 (C-4), 69.6 (C-3), 71.1 (C-6), 78.4 (C-5).

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.89; H, 6.05; N, 4.78.

6-Chloro-6-cyano-2*N*-Methyl-3-phenylisoxazolidine **13**.

The reaction of *C*-phenyl-*N*-methylnitrone **5** with 2-chlorobut-3-enenitrile **3** was carried out under reflux for 5 days. The crude product was purified and gave 1.30 g (55%) of two isomers in the ratio **13a/13b** =75/25, as a colorless oil; ir (nujol): of the mixture υ 2310 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): **13a** δ 2.65 (s, 3H, NMe), 2.85-2.70 (m, 1H, H-4, J_{gem} = 11.9, $J_{4,5}$ = 5.1, $J_{4',5}$ = 9.1), 3.90-3.65 (m, 1H, H-3, $J_{3,4}$ = 5.6), 4.55-4.45 (m, 1H, H-5), 4.61 (d, 1H, H-6, $J_{6,5}$ = 4.5), 7.60-7.10 (m, 5H, Ph); **13b** 2.68 (s, 3H, NMe), 3.55 (t, 1H, H-3), 4.59 (d, 1H, H-6, $J_{6,5}$ = 4.5);^{13}C-nmr (deuteriochloroform): **13b** δ 42.3 (C-4), 43.4 (NMe), 44.7 (C-6), 75.1 (C-3), 77.3 (C-5); **13a** δ 42.1 (C-4), 43.2 (NMe), 43.7 (C-6), 72.3 (C-3), 76.8 (C-5), 115.5 (CN), 127.9-128.5-129.0-137.6 (Ph).

Anal. Calcd. for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.54; Cl, 14.98; N, 11.86. Found: C, 61.16; H, 5.42; Cl, 14.97; N, 11.84.

6-Chloro-6-cyano-2,3-diphenylisoxazolidine **14**.

The reaction of *C,N*-diphenylnitrone **6** with 2-chlorobut-3-enenitrile **3** was carried out under reflux for 5 days. The crude product was purified and gave 1.52 g (51%) of two isomers in the ratio **14a/14b** = 70/30 as a colorless oil; ir (nujol): of the mixture υ 2250 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): **14a** δ 2.55-2.43 (m, 1H, H-4, J_{gem} = 13.2, $J_{4,5}$ = 4.9, $J_{4',5}$ = 8.25), 3.15-3.01 (m, 1H, H-4), 4.61-4.55 (m, 1H, H-3, $J_{3,4}$ = 7.4), 4.61 (d, 1H, H-6, $J_{6,5}$ = 7.8), 4.82-4.62 (m, 1H, H-5), 7.70-6.95 (m, 5H, Ph); **14b** 2.80-2.69 (m, 1H, H-4'), 2.91-2.81 (m, 1H, H-4), 4.42 (d, 1H, H-6, $J_{6,5}$ = 8.7); ^{13}C-nmr (deuteriochloroform): **14a** δ 43.1 (C-4), 44.1 (C-6), 68.6 (C-3), 77.8 (C-5), 117.9 (CN), 123.9-126.5-127.8-129.1-139.6 (Ph); **14b** 42.3 (C-4), 43.5 (C-6), 68.4 (C-3), 78.7 (C-5), 115.9 (CN).

Anal. Calcd. for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; Cl, 11.87; N, 9.40. Found: C, 67.99; H, 5.05; Cl, 11.63; N, 9.33.

6-Cyano-6-hydroxy-2*N*-Methyl-3-phenylisoxazolidine **15**.

The reaction of *C*-phenyl-*N*-methylnitrone **5** with 2-hydroxybut-3-enenitrile **4** was carried out under reflux for 4 days. The crude product was purified and gave 1.15 g (53%) of two isomers in the ratio **15a/15b** = 65/35 as a colorless oil; ir (nujol): of the mixture υ 2310 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): **15a** 2.52-2.42 (m, 1H, H-4', J_{gem} = 13.6, $J_{4,5}$ = 4.5, $J_{4',5}$ = 8.4), 2.61 (s, 3H, NMe), 3.40-2.90 (m, 1H, H-4), 3.58 (t, 1H, H-3, $J_{3,4}$ = 7.8), 4.52-4.43 (m, 1H, H-5), 4.58 (d, 1H, H-6, $J_{6,5}$ = 3.2), 7.50-7.20 (m, 5H, Ph); **15b** 2.58 (s, 3H, NMe), 2.74-2.64 (m, 1H, H-4), 3.57 (t, 1H, H-3), 4.86 (d, 1H, H-6, $J_{6,5}$ = 3.6); ^{13}C-nmr (deuteriochloroform): **15a** δ 41.1 (C-4), 42.5 (NMe), 66.3 (C-3), 73.7 (C-6), 76.7 (C-5), 118.9 (CN), 127.9-128.8-129.2-136.9 (Ph); **15b** 40.4 (C-4), 65.5 (C-3), 75.2 (C-6), 76.3 (C-5), 117.9 (CN).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.35; H, 6.49; N, 12.48.

6-Cyano-6-hydroxy-2,3-diphenylisoxazolidine **16**.

The reaction of *C,N*-diphenylnitrone **6** with 2-hydroxybut-3-enenitrile **4** was carried out under reflux for 4 days. The crude product was purified and gave 1.73 g (62%) of two isomers in the ratio **16a/16b** = 65/35 as a colorless oil; ir (nujol): of the mixture υ 2310 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): **16a** δ 2.70-2.56 (m, 1H, H-4, J_{gem} = 13.7, $J_{4,5}$ = 6.0, $J_{4',5}$ = 8.5), 2.92-2.81 (m, 1H, H-4'), 4.55 (d, 1H, H-6, $J_{6,5}$ = 3.4), 4.61 (t, 1H, H-3, $J_{3,4}$ = 7.7), 4.75-4.33 (m, 1H, H-5), 7.50-6.90 (m, 5H, Ph), 8.00 (sl, 1H, OH); **16b** 3.07-2.95 (m, 1H, H-4'), 4.53 (d, 1H, H-6, $J_{6,5}$ = 4.7); ^{13}C-nmr (deuteriochloroform): **16a** δ 40.0 (C-4), 63.3 (C-3), 68.9 (C-6), 77.7 (C-5), 116.9 (CN), 122.8-124.1-126.9-128.1-128.5-128.7-128.8-128.9-136.8-149.1 (Ph); **16b** 40.1 (C-4), 63.6 (C-3), 68.5 (C-6), 77.3 (C-5), 117.7 (CN).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.60; H, 5.66; N, 9.99.

General Procedure for Hydrogenolysis.

A mixture of 0.02 mole of isoxazolidine, 100 ml of methanol and 1 g of palladium-charcoal catalyst was shaken in a hydrogen atmosphere until absorption ceased. After filtration and evaporation of the filtrate we purified the crude product by chromatography on silica gel.

N-Methyl-6-phenylpiperidine-2,4-dione **19**.

After hydrogenolysis of isoxazolidines **8a,b**, the crude product was heated in methanol with sodium methylate at reflux for 4 days, the solution was concentrated, and purified by chromatography to yield the piperidione **19** as a colorless oil (49% yield); ^{1}H-nmr (deuteriochloroform): **19** δ 2.55-2.10 (m, 4H, H-3, H-5), 2.80 (s, 3H, NMe), 4.53-4.45 (m, 1H, H-6, $J_{6,5}$ = 8.1, $J_{6,5'}$ = 2.75), 7.50-7.15 (m, 5H, Ph); ^{13}C-nmr (deuteriochloroform): **19** δ 32.3 (C-5), 34.0 (C-3), 37.6 (NMe), 63.7 (C-6), 127.6-128.8-141.5 (Ph), 171.2 (N-C=O), 200.4 (C=O).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.51; H, 6.81; N, 6.84.

3,4-Dihydroxy-*N*-methyl-6-phenylpiperidin-2-one **20**.

After hydrogenolysis of isoxazolidines **11a,b** (85/15), the mixture was shaken 24 hours. Evaporation of the filtrate furnished white crystals, whose purification by chromatography on silica gel provided two compounds **20a** and **20b** in the ratio 85/15 (55%), mp 137°-139°; ^{1}H-nmr (deuteriochloroform): **20a** δ 2.00-1.85 (m, 1H, H-5, $J_{5,6}$ = 5.5, $J_{5,5'}$ = 10.7), 2.55-2.40 (m, 1H, H-5', $J_{5',6}$ = 1.83), 2.75 (s, 3H, NMe), 3.50 (sl, 2H, OH), 4.20 (d, 1H, H-3, $J_{3,4}$ = 2.5), 4.40-4.30 (m, 1H, H-4), 4.70-4.55 (m, 1H, H-6), 7.50-7.15 (m, 5H, Ph); **20b** δ 2.05-1.90 (m, 1H, H-5, $J_{5,6}$ = 5.3, $J_{5,5'}$ = 11.5), 2.50-2.40 (m, 1H, H-5'), 2.70 (s, 3H, NMe), 3.52 (sl, 2H, OH), 4.05-3.90 (dd, 1H, H-4, $J_{4,3}$ = 9.2, $J_{4,5}$ = 1.9), 4.10 (d, 1H, H-3, $J_{3,4}$ = 9.2), 4.45-4.30 (m, 1H, H-6), 7.50-7.15 (m, 5H, Ph); ^{13}C-nmr (deuteriochloroform): **20a** δ 32.7 (C-5), 36.5 (NMe), 61.1 (C-6), 66.0 (C-3 or C-4), 70.2 (C-3

or C-4), 126.7-128.2-129.2-141.3 (Ph), 172.3 (N-C=O); **20b** δ 32.8 (C-5), 38.3 (NMe), 62.0 (C-6), 69.2 (C-3 or C-4), 74.3 (C-3 or C-4), 126.5-128.4-129.3-140.8 (Ph), 171.7 (N-C=O).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: **20a**: C, 65.52; H, 6.77; N, 6.13. Found: **20b**: C, 64.95; H, 6.81; N, 6.18.

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