# 1,3-Dipolar Cycloaddition Reactions of 1-Methyl- and 1,3-Dimethylindol-2-yl Nitrile Oxides [1]



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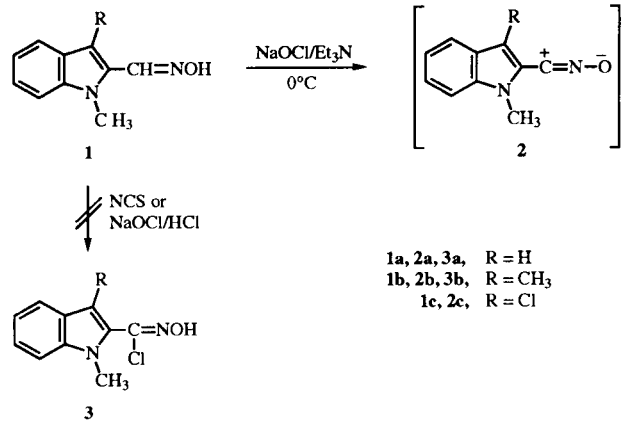
Received February 29, 1996

**Dedicated to the memory of Professor N. E. Alexandrou**

Reactions of the *in situ* prepared 1-methylindol-2-yl nitrile oxide (**2a**) with dipolarophiles lead to isoxazolines **5** and isoxazoles **8** and to their chloro-derivatives **6** and **9** in good yields. Analogous reactions of the 1,3-dimethylindol-2-yl nitrile oxide (**2b**) give the isoxazolines **10** and the isoxazoles **12** as main products as well as their oxidation products **11** and **13** in low yields. The mechanism of the reactions and the spectral elucidation of the cycloadducts are discussed.

*J. Heterocyclic Chem.*, **33**, 563 (1996).

In connection with our previous work [2-4] on the synthesis of indole derivatives we studied the 1,3-dipolar cycloaddition reactions of indol-2-yl nitrile oxides with the aim to synthesize 3-indol-2-yl isoxazolines. 2-Substituted indoles are pharmacologically important compounds and are useful intermediates for the synthesis of many indole alkaloids and biologically active substances [5-7]. On the other hand dihydro- and tetrahydroisoxazoles have been proven useful synthons because of their ready reductive cleavage and susceptibility to ring transformations [8,9]. Therefore we chose to investigate 1,3-dipolar cycloaddition reactions of indol-2-yl nitrile oxides as a route to the synthesis of 2-substituted indoles. To the best of our knowledge indol-2-yl 1,3-dipoles have been used as intermediates only in intramolecular cycloaddition strategies for the synthesis of fused indole derivatives [10-13].

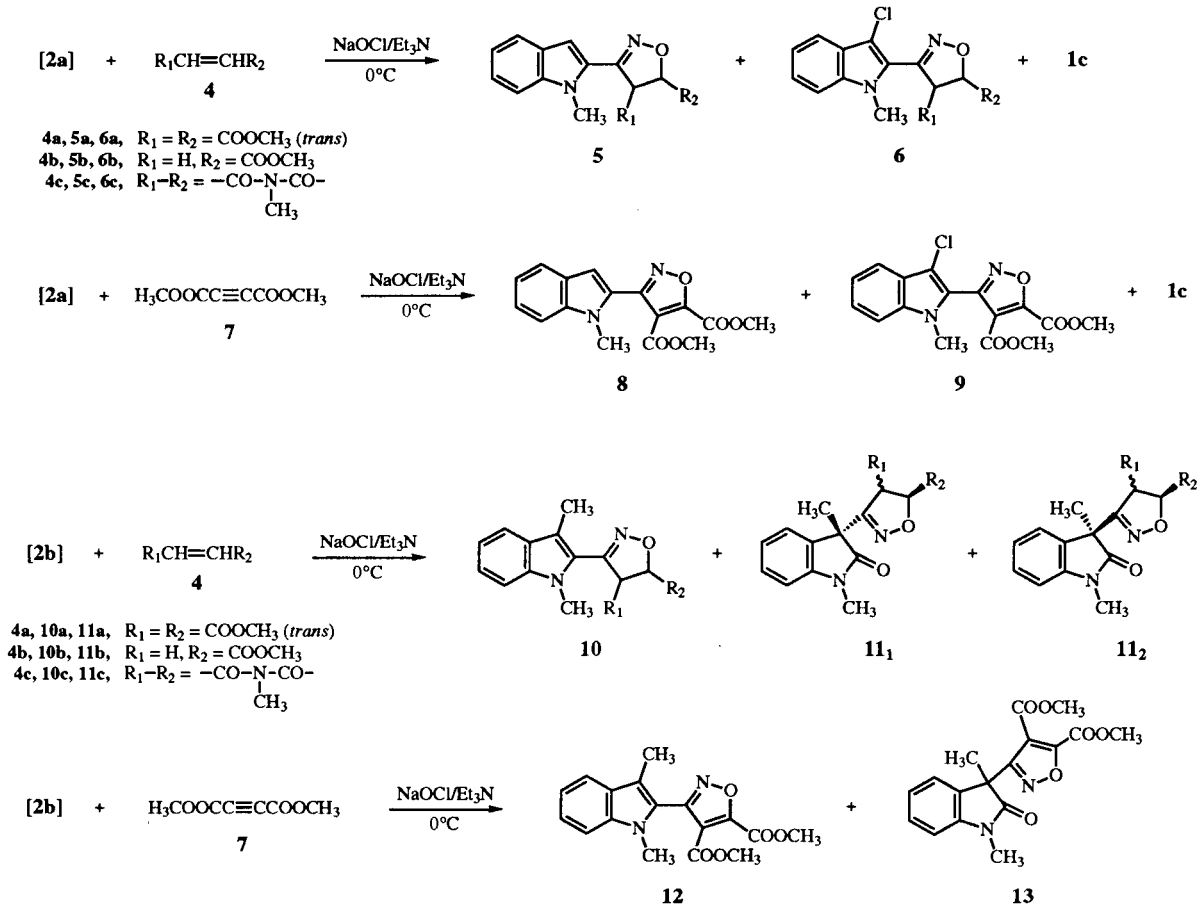



## Results and Discussion.

The nitrile oxides **2a** and **2b** were formed *in situ* from the corresponding aldoximes **1a** and **1b** upon treatment with sodium hypochlorite. The aldoximes **1a** and **1b** were prepared from the corresponding aldehydes and they were isolated: **1b** as one stereoisomer, probably the *E*-form, whereas **1a** as a mixture of two stereoisomers, in a ratio 2.5:1. The *E*-form is attributed to the isolated **1b**, since the *Z*-isomer is highly stereochemically hindered as it comes from molecular models. The reactions were carried out in methylene chloride solutions in the presence of dipolarophiles at 0°. Attempts to prepare and isolate the corresponding chloro-oximes **3a** and **3b** in a former stage, using the common chlorination procedures (sodium hypochlorite/hydrochloric acid or *N*-chlorosuccinimide), were unsuccessful.

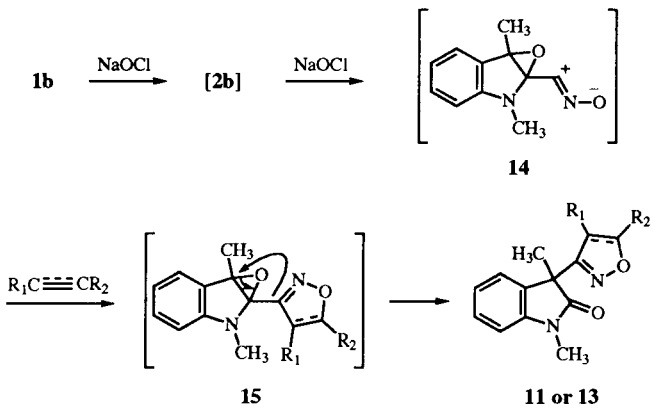
Reactions of the aldoxime **1a** with the alkenes **4** and the alkyne **7** gave the expected cycloaddition products **5** and **8** accompanied by their chloro-derivatives **6** and **9** in good yields (total yield of non chlorinated and chlorinated cycloadducts 60-80%). In all cases, the chloro-oxime **1c** was also isolated as a side product in yields 5-20%. The relative ratio of non chlorinated to chlorinated cycloadducts, which varies slightly with the dipolarophile used (~1.3-1.4:1), depends on the reaction conditions. The use of sodium hypochlorite in excess increases the yield of chlorinated cycloadducts, whereas the use of smaller quantities of sodium hypochlorite lowers the total yield of the reaction. The chlorinated cycloadducts **6** and **9** are probably formed by cycloaddition of the intermediate chloro-nitrile oxide **2c** to the dipolarophiles used. Indeed, treatment of the isolated chloro-oxime **1c** with sodium hypochlorite in the presence of acetylene dicarboxylate **7** gave the cycloadduct **9**. Chlorination of the cycloadducts **5** and **8** does not occur under the applied reaction conditions as it was shown by blank experiments.

Reactions of the aldoxime **1b** with the dipolarophiles **4** and **7** also gave the expected cycloadducts **10** and **12** in good yields (55-70%) and the indolinones **11** and **13** as secondary products (8-17%). Indolinones **11** were isolated as an almost equimolar mixture of two diastereoisomers $\mathbf{11}_1$ and $\mathbf{11}_2$. In the case of **11c** the two diastereoisomers were further separated. Indolinones **11** and **13** are oxidation products of the cycloadducts **10** and **12** respectively. The oxidation is more likely to take place before the cycloaddition, since cycloadducts **10** and **12** have been proven stable under the reaction conditions employed. *N*-Substituted indoles are known to be oxidized to




indole-2,3-epoxides, which at room temperature rearrange mainly to indolin-3-ones or indolin-2-ones [14,15]. A possible reaction sequence leading to **11** and **13** is given in Scheme 1. The initially formed nitrile oxide **2b** is further oxidized to **14**. Addition of **14** to the dipolarophiles **4** and **7** results in the cycloadducts **15** which are converted to indolinones **11** or **13**. The selectivity of this conversion to indolin-2-ones is explained in terms of ring opening *via* a carbocation intermediate [14]. In the case of **15** the electronegative isoxazole or isoxazoline ring does not stabilize the cation at C-2 position, so the cation is developed mainly at the more stabilized C-3 benzylic position giving indolin-2-ones. Attempts to isolate some other transformation products of the supposed intermediate nitrile oxide **14** were unsuccessful. Treatment of the oxime **1b** with sodium hypochlorite in the absence of dipolarophiles gave complicated mixtures of unresolved products.

Scheme 1




The structure elucidation of all the isolated new compounds was based on their spectral and analytical data. In the mass spectra all cycloadducts **5**, **6**, **8**, **9**, **10**, **11**, **12**, **13** give molecular ion, which in most of the cases is the base peak. The $^1H$ nmr and $^{13}C$ nmr spectra are also consistent with the proposed structures. So, the indole derivatives **5**, **6**, **8**, **9**, **10** and **12** give the characteristic proton and carbon chemical shifts for the indole and isoxazoline or isoxazole nucleus in accordance with those given in the literature [16-19]. A characteristic feature in the $^1H$ nmr spectra of **5** and **8** which easily differentiates them from their corresponding chloro-derivatives **6** and **9** in their reaction mixtures, is the chemical shift of indole 3-H that appeared as an upfield singlet at δ 6.70-7.26. Another significant difference appears in the 4-H isoxazolyl atom chemical shifts which in the 3-chloro-compounds **6a** and **6c** are

remarkably deshielded, compared with those of **5a** and **5c** (δ 5.41 and 5.48 versus 4.86 and 4.81) whereas that of the corresponding 3-methylindole adducts **10a** and **10c** appear at intermediate chemical shifts (δ 5.09 and 5.15 respectively). Concerning the cycloadducts with methyl acrylate, for which two regioisomeric structures are possible, the isoxazoline proton and carbon chemical shifts are in accordance with the 5-methoxycarbonyl regioisomers **5b**, **6b**, **10b** and **11b**. Thus in all cases, the 4-H and 5-H isoxazoline atoms give the characteristic pattern of an ABX system with the X part in significant higher frequency (X 4.94-5.17 ppm, AB 2.91-3.90 ppm). Also, the chemical shifts of C-4 and C-5 isoxazoline atoms are well differentiated (δ 38.0-41.5 for C-4 and 76.5-77.9 for C-5) as it is expected from analogous substituted isoxazolines [18]. The proposed regioselectivity is in accordance with that usually observed in the reactions of nitrile oxides with acrylates [20]. In the $^1$H nmr and $^{13}$C nmr spectra of indolinones **11** and **13** the chemical shifts of isoxazole hydrogen and carbon atoms are analogous to those of the corresponding indoles **10** and **12**, whereas the indolinone proton and carbon chemical shifts are differentiated and agree with those given for the indolinone ring [14,21]. The assignment of the indolin-2-one structure to the isolated products, instead of the other possible indolin-3-one isomeric structure, was mainly based on the carbonyl carbon chemical shifts. Compounds **11** and **13** show β-lactam carbonyls in the range of 175.4-177.3 ppm (one peak for **13**, two peaks, corresponding to the two diastereoisomers, for **11**). Indolin-3-ones should show benzylic carbonyl in the range of 200 ppm. Furthermore, attempts to obtain some typical carbonyl derivatives, as 2,4-dinitrophenylhydrazones from the indolinone **11c**, were unsuccessful, thus supporting the amide structure. From the above results, intermolecular cycloadditions of indole dipoles emerge as a promising route for the synthesis of indole derivatives. Further transformations of the obtained cycloadducts and reactions with other indole 1,3-dipoles are in progress.

## EXPERIMENTAL

Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. The ir spectra were obtained with a Perkin-Elmer Model 297 spectrophotometer. The $^{13}$C nmr spectra were recorded on a Bruker AM 300 spectrometer and the $^1$H nmr spectra on the same spectrometer or on a Bruker AW-80 spectrometer, in deuteriochloroform, using tetramethylsilane as internal standard. Mass spectra were measured with a VG TS-250 Model spectrometer, with an ionization energy of 70 eV. Microanalyses were performed with a Perkin-Elmer Model 240B analyzer. Column chromatography was performed over Merck Kieselgel (particle size 0.063-0.200 mm).

Preparation of Starting Materials.

1-Methylindole-2-carbaldehyde and 1,3-dimethylindole-2-carbaldehyde were obtained by formylation of 1-methylindole and 1,3-dimethylindole respectively, according to known procedures [22,23].

The aldehydes were transformed to the corresponding aldoximes by treatment with hydroxylamine hydrochloride. An aqueous solution (2.5 ml) of hydroxylamine hydrochloride (0.54 g, 7.7 mmoles) and sodium carbonate (0.53 g, 5.0 mmoles) was added to an ethanolic solution (10 ml) of the aldehyde (7.0 mmoles) and the reaction mixture was heated under reflux for 30 minutes. After cooling and addition of water the precipitated oxime was collected by filtration and was further purified by recrystallization from diluted ethanol.

1-Methylindole-2-carbaldehyde Oxime (**1a**).

1-Methylindole-2-carbaldehyde gave 0.89 g (73%) of compound **1a** as a mixture of two isomers *E*, *Z* in a ratio 2.5:1, mp 139-147° (from ethanol); ir (nujol): ν 3270, 1620 cm$^{-1}$; $^1$H nmr: δ 9.10 and 7.90 (br s, 1H), [8.27 (s) and 7.71-7.12 (s, hidden), 1H], 7.71-7.12 (m, 4H), [6.76 (s) and 7.71-7.12 (s, hidden), 1H] 3.97 and 3.85 (s, 3H); $^{13}$C nmr: δ 144.3, 139.5, 136.9, 131.1, 127.1, 124.2, 123.7, 122.2, 121.3, 120.2, 120.1, 110.8, 109.5, 107.6, 32.1, 30.0; ms: m/z 174 (100, M$^+$), 157 (44), 156 (20), 142 (13), 131 (33), 130 (66), 115 (10), 89 (38).

*Anal.* Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79, N, 16.08. Found: C, 68.83; H, 5.87; N, 16.11.

1,3-Dimethylindole-2-carbaldehyde Oxime (**1b**).

1,3-Dimethylindole-2-carbaldehyde gave 1.0 g (76%) of compound **1b**, mp 125-127° (from ethanol); ir (nujol): ν 3300, 1620 cm$^{-1}$; $^1$H nmr: δ 8.41 (s, 1H), 7.76 (br s, 1H), 7.58 (d, 1H, J = 7 Hz), 7.29-7.09 (m, 3H), 3.92 (s, 3H), 2.41 (s, 3H); $^{13}$C nmr: δ 143.1, 138.8, 127.6, 127.0, 124.0, 112.5, 119.3, 116.1, 109.3, 32.1, 9.0; ms: m/z 188 (100, M$^+$), 171 (39), 170 (84), 169 (30), 155 (22), 143 (45), 77 (29), 69 (51).

*Anal.* Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.20; H, 6.53; N, 14.86.

General Procedure for the 1,3-Dipolar Cycloaddition Reactions.

A solution of aldoxime **1a** or **1b** (2 mmoles) and the dipolarophile **4** or **7** (2.4 mmoles) in methylene chloride (25 ml) was cooled at 0°. To the vigorously stirred solution commercial bleach (5.3 ml) and triethylamine (six drops) were added. The reaction mixture was allowed to stir at room temperature for 3 hours, then diluted with water and extracted with methylene chloride. The extracts were washed with water, dried over sodium sulfate and then concentrated *in vacuo*. The residue was subjected to column chromatography, using as eluent a mixture of hexane/ethyl acetate (10:1) for the reactions with **1a** or (7:1) for the reactions with **1b**. From the reactions of **1a**, the aldoxime **1c**, the chloro-cycloadducts **6** or **9** and the cycloadducts **5** or **8** were collected, in order of elution. From the reactions of **1b**, the cycloadducts **10** or **12** and the oxidation products **11** or **13** were collected, in order of elution.

3-Chloro-1-methylindole-2-carbaldehyde Oxime (**1c**).

Compound **1c** was isolated from the reactions of **1a** with **4** and **7**, in yields 5-20%, mp 142-144° (from methylene chloride); ir (nujol): ν 3290, 1620 cm$^{-1}$; $^1$H nmr: δ 8.46 (s, 1H), 7.18-7.64 (m, 5H), 3.97 (s, 3H); $^{13}$C nmr: δ 142.2, 137.9, 126.2, 125.0, 124.9, 120.6, 118.9, 110.1, 109.7, 32.8; ms: m/z 210/208 (100, M$^+$), 193/191 (95).

*Anal.* Calcd. for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43. Found: C, 57.81; H, 4.27; N, 13.28.

3-Chloro-2-[4,5-dihydro-4,5-bis(methoxycarbonyl)isoxazol-3-yl]-1-methylindole (**6a**).

The yield of **6a** was 35%, mp 118-120° (from ethyl ether/hexane); ir (nujol): ν 1755, 1730 $cm^{-1}$; $^1H$ nmr: δ 7.63 (d, 1H, J = 8 Hz), 7.37-7.34 (m, 2H), 7.23-7.17 (m, 1H), 5.47 (d, 1H, J = 4 Hz), 5.41 (d, 1H, J = 4 Hz), 4.00 (s, 3H), 3.87 (s, 3H), 3.73 (s, 3H); $^{13}C$ nmr: δ 168.5, 168.4, 147.7, 137.8, 125.3, 125.2, 122.6, 120.8, 119.1, 110.1, 109.3, 81.2, 57.3, 53.4, 53.3, 33.1; ms: m/z 352/350 (100, $M^+$), 202 (13), 137 (8).

*Anal.* Calcd. for $C_{16}H_{15}ClN_2O_5$: C, 54.79; H, 4.31; N, 7.99. Found: C, 54.69; H, 4.28; N, 8.00.

2-[4,5-Dihydro-4,5-bis(methoxycabonyl)isoxazol-3-yl]-1-methylindole (**5a**).

The yield of **5a** was 45%, mp 116-118° (from ethyl ether); ir (nujol): ν 1760, 1740 $cm^{-1}$; $^1H$ nmr: δ 7.61 (d, 1H, J = 8 Hz), 7.38-7.03 (m, 3H), 6.90 (s, 1H), 5.37 (d, 1H, J = 4.5 Hz), 4.86 (d, 1H, J = 4.5 Hz), 4.04 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H); $^{13}C$ nmr: δ 169.0, 168.5, 148.5, 139.7, 126.6, 126.4, 124.9, 124.4, 121.5, 120.2, 110.0, 80.8, 58.4, 53.3, 53.1, 32.7; ms: m/z 316 (100, $M^+$), 225 (10), 197 (18), 169 (24), 155 (17), 131 (12).

*Anal.* Calcd. for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.73; H, 4.99; N, 8.77.

3-Chloro-2-[4,5-dihydro-5-(methoxycarbonyl)isoxazol-3-yl]-1-methylindole (**6b**).

The yield of **6b** was 35%, mp 145-147° (from methylene chloride/ethyl ether); ir (nujol): ν 1740 $cm^{-1}$; $^1H$ nmr: δ 7.62 (d, 1H, J = 8 Hz), 7.57-7.15 (m, 3H), 5.17 (t, 1H, X part of an ABX system, ΣJ = 18.3 Hz), 4.10-3.90 (m, 2H, AB part of an ABX system), 4.00 (s, 3H), 3.84 (s, 3H); $^{13}C$ nmr: δ 170.5 149.7, 137.8, 125.3, 125.1, 123.1, 120.7, 119.0, 110.0, 109.2, 77.3, 52.8, 41.0, 33.5; ms: m/z 294/292 (100, $M^+$), 235/233 (18), 208/206 (30), 192/190 (20), 178 (38), 123 (24).

*Anal.* Calcd. for $C_{14}H_{13}ClN_2O_3$: C, 57.45; H, 4.48; N, 9.57. Found: C, 57.28; H, 4.38; N, 9.38.

2-[4,5-Dihydro-5-(methoxycarbonyl)isoxazol-3-yl]-1-methylindole (**5b**).

The yield of **5b** was 25%, mp 159-161° (from ethyl ether); ir (nujol): ν 1740 $cm^{-1}$; $^1H$ nmr: δ 7.60 (d, 1H, J = 8 Hz), 7.35-7.09 (m, 3H), 6.70 (s, 1H), 5.10 (dd, 1H, X part of an ABX system, ΣJ = 18.0 Hz), 4.04 (s, 3H), 3.81 (s, 1H), 3.77-3.71 (m, 2H, AB part of an ABX system); $^{13}C$ nmr: δ 170.6, 150.6, 139.7, 127.5, 126.7, 124.2, 121.3, 120.2, 109.7, 107.2, 76.5, 52.8, 40.7, 32.7; ms: m/z 258 (100, $M^+$), 199 (39), 172 (24), 170 (30), 169 (20), 156 (18), 144 (22).

*Anal.* Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.00; H, 5.38; N, 10.79.

2-[4,5-Dihydro-4,5-(*N*-methyldicarboximido)isoxazol-3-yl]-1-methylindole (**5c**).

The yield of **5c** was 45%, mp 229-231° (from methylene chloride/hexane); ir (nujol): ν 1700 $cm^{-1}$; $^1H$ nmr: δ 7.71 (d, 1H, J = 8 Hz), 7.40-7.34 (m, 2H), 7.26 (s, 1H), 7.17-7.12 (m, 1H), 5.45 (d, 1H, J = 9.5 Hz), 4.81 (d, 1H, J = 9.5 Hz), 4.02 (s, 3H), 3.06 (s, 3H); $^{13}C$ nmr: δ 171.8, 170.6, 147.1, 140.1, 126.8, 124.9, 122.1, 120.4, 119.4, 110.6, 109.8, 79.1, 56.5, 31.0, 25.7; ms: m/z 283 (100, $M^+$), 172 (40).

*Anal.* Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.81; H, 4.71; N, 14.91.

3-Chloro-2-[4,5-dihydro-4,5-(*N*-methyldicarboximido)isoxazol-3-yl]-1-methylindole (**6c**).

The yield of **6c** was 35%, mp 182-184° (from methylene chloride/hexane); ir (nujol): ν 1700 $cm^{-1}$; $^1H$ nmr: δ 7.68 (d, 1H, J = 7.8 Hz), 7.40-7.10 (m, 3H), 5.66 (d, 1H, J = 9.5 Hz), 5.48 (d, 1H, J = 9.5 Hz), 3.89 (s, 3H), 3.02 (s, 3H); $^{13}C$ nmr: δ 171.6, 170.2, 146.0, 137.9, 125.6, 125.2, 121.0, 119.3, 110.2, 110.1, 79.6, 54.9, 32.9, 25.5; ms: m/z 319/317 (100, $M^+$), 208/206 (39).

*Anal.* Calcd. for $C_{15}H_{12}ClN_3O_3$: C, 56.70; H, 3.81; N, 13.22. Found: C, 56.81; H, 4.00; N, 13.08.

3-Chloro-2-[4,5-bis(methoxycarbonyl)isoxazol-3-yl]-1-methylindole (**9**).

The yield of **9** was 25%, mp 120-121° (from ethyl ether); ir (nujol): ν 1730 $cm^{-1}$; $^1H$ nmr: δ 7.67 (d, 1H, J = 8 Hz), 7.42-7.21 (m, 3H), 4.05 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H); $^{13}C$ nmr: δ 160.5, 160.3, 156.3, 153.6, 137.8, 124.9, 124.6, 121.2, 120.8, 119.0, 117.1, 110.1, 108.3, 53.6, 53.1, 31.7; ms: m/z 350/348 (100, $M^+$), 313 (16), 232/230 (30), 192/190 (26), 123 (34).

*Anal.* Calcd. for $C_{16}H_{13}ClN_2O_5$: C, 55.11; H, 3.76; N, 8.03. Found: C, 55.01; H, 3.49; N, 8.00.

2-[4,5-Bis(methoxycarbonyl)isoxazol-3-yl]-1-methylindole (**8**).

The yield of **8** was 35%, mp 122-124° (from methylene chloride/ethyl ether); ir (nujol): ν 1740 $cm^{-1}$; $^1H$ nmr: δ 7.65 (d, 1H, J = 8 Hz), 7.40-7.12 (m, 3H), 6.91 (s, 1H), 4.00 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H); $^{13}C$ nmr: δ 161.5, 158.3, 156.2, 154.5, 139.0, 127.1, 125.1, 123.9, 121.6, 120.3, 117.3, 109.9, 106.5, 53.4, 53.3, 32.0; ms: m/z 314 (100, $M^+$), 255 (23), 196 (45), 156 (72), 130 (30).

*Anal.* Calcd. for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.14; H, 4.51; N, 8.79.

2-[4,5-Dihydro-4,5-bis(methoxycarbonyl)isoxazol-3-yl]-1,3-dimethylindole (**10a**).

The yield of **10a** was 70%, mp 100-102° (from ethyl ether); ir (nujol): ν 1720 $cm^{-1}$; $^1H$ nmr: δ 7.58 (d, 1H, J = 7.6 Hz), 7.38-7.05 (m, 3H), 5.47 (d, 1H, J = 4.6 Hz), 5.09 (d, 1H, J = 4.6 Hz), 3.85 (s, 3H), 3.84 (s, 3H), 3.64 (s, 3H), 2.43 (s, 3H); $^{13}C$ nmr: δ 169.1, 168.0, 148.5, 138.5, 127.8, 123.9, 123.0, 119.5, 119.4, 114.9, 109.6, 81.3, 58.1, 53.2, 53.1, 31.8, 9.7; ms: m/z 330 (100, $M^+$), 271 (11), 243 (19), 211 (88), 186 (38), 183 (50), 169 (58), 144 (35).

*Anal.* Calcd. for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.78; H, 5.38; N, 8.31.

3-[4,5-Dihydro-4,5-bis(methoxycarbonyl)isoxazol-3-yl]-1,3-dimethylindolin-2-one (**11a**).

Compound **11a** was obtained in 8% yield, as an oily mixture of two diastereoisomers, in a ratio 1:1; ir (neat): ν 1740, 1720 $cm^{-1}$; $^1H$ nmr: δ 6.84-7.43 (m, 4H), 5.35 and 5.34 (d, 1H, J = 5.3 and 6.8 Hz), 4.38 and 3.97 (d, 1H, J = 6.8 and 5.3 Hz), 3.82 and 3.76 (s, 3H), 3.67 and 3.28 (s, 3H), 3.21 and 3.10 (s, 3H), 1.72 and 1.61 (s, 3H); $^{13}C$ nmr: δ 176.3, 175.2, 168.8, 168.7, 167.2, 167.1, 153.9, 153.6, 143.2, 143.1, 130.3, 130.1, 129.6, 129.3, 123.9, 123.4, 123.2, 123.1, 108.5, 108.3, 82.1, 81.6, 56.5, 56.3, 53.2, 53.1, 53.0, 52.7, 49.4, 49.0, 26.6, 26.2, 24.8, 23.7; ms: m/z 346 (73, $M^+$), 161 (100).

*Anal.* Calcd. for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.72; H, 5.11; N, 8.13.

2-[4,5-Dihydro-5-(methoxycarbonyl)isoxazol-3-yl]-1,3-dimethylindole (**10b**).

Compound **10b** was obtained in 58% yield, mp 167-168° (from methylene chloride/hexane); ir (nujol): ν 1740 $cm^{-1}$; $^1H$ nmr: δ 7.58 (d, 1H, J = 7.9 Hz), 7.37-7.10 (m, 3H), 5.15 (dd, 1H, X part of an ABX system, ΣJ = 17.9 Hz), 3.93 (s, 3H), 3.83 (s, 3H), 3.91-3.70 (m, 2H, AB part of an ABX system), 2.44 (s, 3H); $^{13}C$ nmr: δ 170.6, 150.7, 138.7, 127.8, 124.2, 124.1, 119.4, 115.0, 109.6, 77.0, 52.8, 41.5, 32.7, 10.3; ms: m/z 272 (100, $M^+$), 213 (33), 183 (18), 169 (33), 144 (7).

*Anal.* Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.23; H, 5.96; N, 10.33.

3-[4,5-Dihydro-5-(methoxycarbonyl)isoxazol-3-yl]-1,3-dimethylindolin-2-one (**11b**).

Compound **11b** was obtained in 17% yield, as an oily mixture of two diastereoisomers in a ratio 1:1; ir (neat): ν 1740, 1710 $cm^{-1}$; $^1H$ nmr: δ 7.37-7.26 (m, 2H), 7.11 (t, 1H, J = 7.5 Hz), 6.89 (d, 1H, J = 8 Hz), 5.06-4.94 (m, 1H), 3.80 and 3.71 (s, 3H), 3.26 and 3.25 (s, 3H), 3.29-2.91 (m, 2H), 1.70 and 1.69 (s, 3H); $^{13}C$ nmr: δ 175.6, 175.5, 170.2, 170.1, 157.4, 157.0, 142.7, 142.6, 130.0, 129.9, 129.0, 128.9, 124.2, 124.0, 123.2, 123.1, 108.5, 108.4, 77.9, 77.8, 52.7, 52.5, 48.9, 48.7, 38.1, 38.0, 26.5, 21.6, 21.3; ms: m/z 288 (35, $M^+$), 160 (100).

*Anal.* Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.61; H, 5.64; N, 9.81.

[4,5-Dihydro-4,5-(*N*-methyldicarboximido)isoxazol-3-yl]-1,3-dimethylindole (**10c**).

Compound **10c** was obtained in 55% yield, mp 216-217° (from methylene chloride); ir (nujol): ν 1720 $cm^{-1}$; $^1H$ nmr: δ 7.64 (d, 1H, J = 8.0 Hz), 7.35-7.12 (m, 3H), 5.49 (d, 1H, J = 9.7 Hz), 5.15 (d, 1H, J = 9.7 Hz), 3.86 (s, 3H), 3.03 (s, 3H), 2.62 (s, 3H); $^{13}C$ nmr: δ 172.0, 170.3, 147.1, 139.0, 127.9, 124.6, 122.0, 119.8, 119.6, 116.7, 109.7, 79.3, 55.8, 32.5, 25.5, 10.5; ms: m/z 297 (100, $M^+$), 183 (30), 169 (44).

*Anal.* Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.69; H, 5.13; N, 13.98.

(3*S**)-3-[(4*R**,5*R**)-4,5-dihydro-4,5-(*N*-methyldicarboximido)isoxazol-3-yl]-1,3-dimethylindolin-2-one (**11c$_1$**) and (3*R**)-3-[(4*R**,5*R**)-4,5-dihydro-4,5-(*N*-methyldicarboximido)isoxazol-3-yl]-1,3-dimethylindolin-2-one (**11c$_2$**).

The two diastereoisomers were isolated as colourless crystals; mp 79-81° (from ethyl ether) and 184-186° (from ethyl ether).

The low melting isomer was obtained in 8% yield; ir (nujol): ν 1715 $cm^{-1}$; $^1H$ nmr: δ 7.40-6.97 (m, 4H), 5.32 (d, 1H, J = 9.5 Hz), 3.92 (d, 1H, J = 9.5 Hz), 3.28 (s, 3H), 2.97 (s, 3H), 1.74 (s, 3H); $^{13}C$ nmr: δ 174.8, 171.8, 170.0, 152.8, 143.8, 129.7, 129.6, 123.3, 123.1, 109.2, 80.6, 54.8, 49.4, 26.8, 25.5, 21.9; ms: m/z 313 (100, $M^+$), 161 (70).

*Anal.* Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.34; H, 4.83; N, 13.41. Found: C, 61.32; H, 5.00; N, 13.21.

The high melting isomer was obtained in 7% yield, ir (nujol): ν 1715 $cm^{-1}$; $^1H$ nmr: δ 7.33-6.89 (m, 4H), 5.38 (d, 1H, J = 9.4 Hz), 4.45 (d, 1H, J = 9.4 Hz), 3.35 (s, 3H), 2.64 (s, 3H), 1.77 (s, 3H); $^{13}C$ nmr: δ 176.4, 172.1, 169.6, 153.5, 143.9, 129.7, 129.4, 123.3, 122.9, 108.9, 80.2, 55.0, 48.8, 26.7, 24.9, 23.5; ms: m/z 313 (100, $M^+$), 161 (65).

*Anal.* Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.34; H, 4.83; N, 13.41. Found: C, 61.01; H, 4.92; N, 13.12.

2-[4,5-Bis-(methoxycarbonyl)isoxazol-3-yl]-1,3-dimethylindole (**12**).

Compound **12** was obtained in 62%, mp 125-126° (from ethyl ether); ir (nujol): ν 1730 $cm^{-1}$; $^1H$ nmr: δ 7.62 (d, 1H, J = 7.9 Hz), 7.38-7.13 (m, 3H), 4.05 (s, 3H), 3.78 (s, 3H), 3.66 (s, 3H), 2.26 (s, 3H); $^{13}C$ nmr: δ 160.5, 160.4, 156.6, 155.2, 138.1, 127.8, 123.4, 121.8, 119.6, 119.4, 117.1, 114.4, 109.6, 53.5, 53.0, 31.0, 9.2; ms: m/z 328 (78, $M^+$), 185 (100).

*Anal.* Calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.31; H, 5.01; N, 8.61.

3-[4,5-Bis(methoxycarbonyl)isoxazol-3-yl]-1,3-dimethylindolin-2-one (**13**).

Compound **13** was received in 8% yield, mp 57-60° (from hexane); ir (nujol): ν 1720 $cm^{-1}$; $^1H$ nmr: δ 6.91-7.36 (m, 4H), 3.94 (s, 3H), 3.49 (s, 3H), 3.29 (s, 3H), 1.88 (s, 3H); $^{13}C$ nmr: δ 176.3, 161.1, 160.3, 160.0, 156.4, 143.5, 130.9, 129.1, 124.2, 123.3, 122.9, 108.4, 53.3, 52.5, 48.5, 26.6, 23.0; ms: m/z 344 (30, $M^+$), 160 (100).

*Anal.* Calcd. for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.41; H, 4.70; N, 8.00.

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