# Synthesis of indole substituted dihydro- and tetrahydro-isoxazoles *via* 1,3-dipolar cycloadditions of *C*-(1-methylindol-2-yl)-*N*-methylnitrone with unsaturated carbonyl derivatives and a study of their acid-induced intramolecular cyclizations

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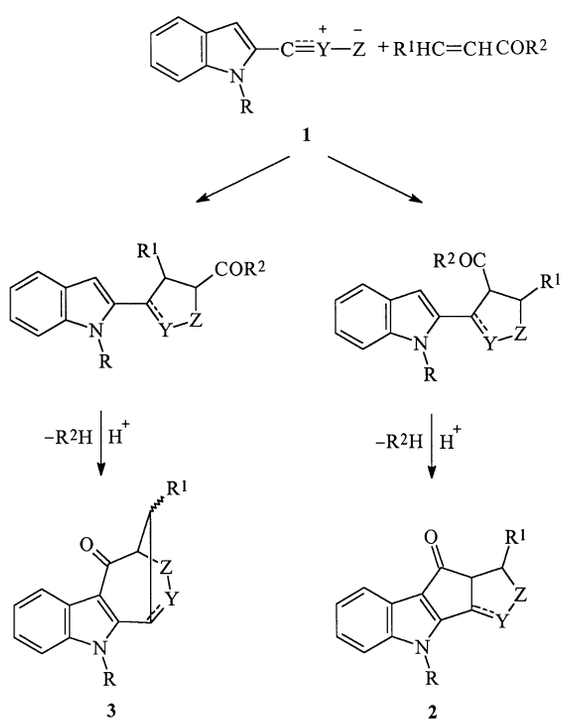
***C*-(1-Methylindol-2-yl)-*N*-methylnitrone 4 reacts with carbonyl-substituted dipolarophiles to afford the isoxazolidines 6–9 and the 3,4-dihydroisoxazole 10 in high yields and with low to moderate regio- and stereo-selectivity. The indolyl-isoxazolidines 6a–c,e,f bearing a 5-methoxycarbonyl or a 5-carboxy substituent in a *cis* relationship to the 3-indolyl group undergo acid-induced intramolecular acylation to afford the bridged indole derivatives 11a–d. The acid-induced intramolecular cyclization products of the isoxazolidines 7a,b that lack a *cis* 5-methoxycarbonyl substituent or the isoxazolidines 8c,f that have no 5-methoxycarbonyl substituent are the enamine (⟸ imine) 12 and/or the diketone 13 depending on the reaction conditions. The spectral elucidation of the products is discussed and mechanistic schemes to explain the formation of the products are suggested. An X-ray structure determination has been carried out on product 11a.**

Since the indole nucleus is present in a large number of naturally occurring as well as biologically active molecules, indole derivatives are of considerable contemporary interest and importance. An important group of alkaloids containing the cyclopenta[*b*]indole unit are such compounds and include the known antioxidants indeno[1,2-*b*]indoles,[1] a large number of tremorgenic mycotoxins[2] (penitrems, janthitrems, lolitrems, paxilline, paspaline, *etc*.) as well as the monoterpenoid alkaloid yeuhchukene[2a,3] noted for its strong antiimplantation activity in rats and mice. Moreover, iboga alkaloid analogues[4] as well as the alkaloid ervitsine[5] and indole alkaloids of the macroline–ajmaline–sarpagine family,[6] possessing a bridged aza-cycloalka[*b*]indole substructure, have long been at the forefront of synthetic endeavour because both of their diverse biological properties and of their structural complexity.

The Pictet–Spengler and Bischler–Napieralski reactions along with some related cyclizations, involving intramolecular acylation of appropriately substituted indoles, constitute undoubtedly one of the most powerful tools for the construction of the polycyclic systems of most indole alkaloids.

In connection with our studies[7a,b] directed towards the synthesis of polycyclic fused [*b*]indoles, we planned the 1,3-dipolar cycloadditions of unsaturated carbonyl derivatives to indol-2-yl 1,3-dipoles of type **1** with subsequent acid-induced cyclization of the products either to the cyclopenta[*b*]indole derivatives **2** or to the bridged heterocyclic compounds **3** (Scheme 1) depending on the position of the carbonyl substituent. Indol-2-yl 1,3-dipoles have earlier been employed in intramolecular cycloadditions which opened up a new route to mitomycin related pyrroloindoles.[8]




**Scheme 1**

## Results and discussion

We have recently reported[9] the participation of 1-methyl- and 1,3-dimethyl-indol-2-yl nitrile oxides, prepared *in situ* from the corresponding indolyl aldoximes and sodium hypochlorite, in 1,3-dipolar cycloadditions with the above mentioned

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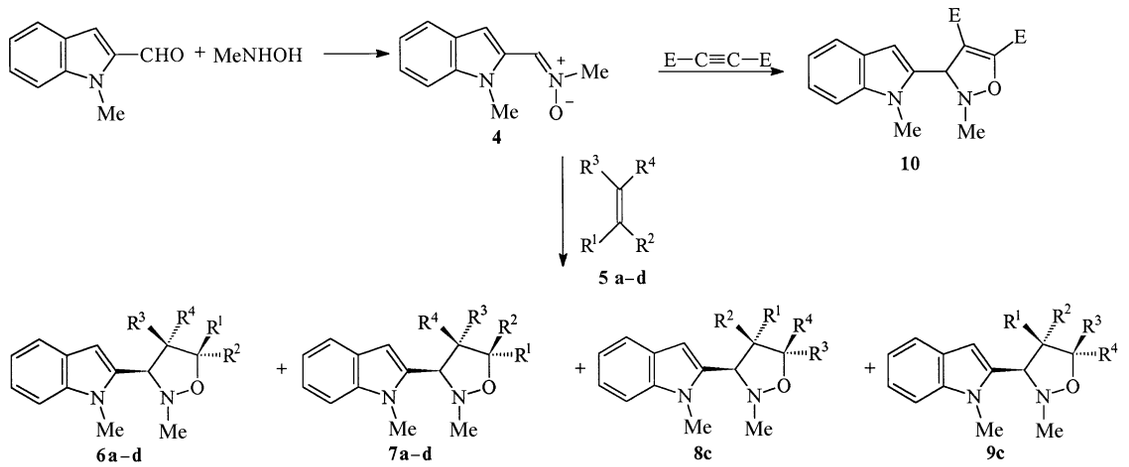



**a** $R^1 = R^4 = CO_2Me$, $R^2 = R^3 = H$
**b** $R^1 = R^3 = CO_2Me$, $R^2 = R^4 = H$
**c** $R^1 = CO_2Me$, $R^2 = R^3 = R^4 = H$
**d** $R^1$—$R^3$ = CON(Me)CO, $R^2 = R^4 = H$
E = $CO_2$Me

**Scheme 2**

dipolarophiles to give interesting carbonyl-substituted 2-(isoxazol-3-yl)indole and 3-(isoxazol-3-yl)indolin-2-one derivatives. However, this reaction route was not considered as a promising pathway for further transformations since in all cases the 3-unsubstituted derivatives suitable for intramolecular acylations were accompanied with the 3-chloro substituted by-products which were formed under the reaction conditions employed for the *in situ* formation of indolyl nitrile oxides. So, we have chosen to prepare and study the 1,3-dipolar cycloadditions of *C*-(1-methylindol-2-yl)-*N*-methylnitrone **4**. Nitrones are stable dipoles and can be prepared and handled separately without the contamination of by-products. Furthermore, the isoxazolidine ring lacking the C=N double bond has a greater flexibility than the dihydroisoxazole ring and appears more suitable for an intramolecular closing up of its carbonyl substituents as shown from molecular models.

The *C*-(1-methylindol-2-yl)-*N*-methylnitrone **4** was prepared from the 1-methylindole-2-carbaldehyde by treatment with *N*-methylhydroxylamine. From its $^1$H NMR spectrum only one stereoisomer was detected, probably the *Z*, as it is the preferred isomer for most of the aldonitrones.[10] The reaction of the nitrone **4** with the alkenes **5** or with dimethyl acetylenedicarboxylate (DMAD) afforded the expected isoxazolidines **6**–**9** or 3,4-dihydroisoxazole **10** (Scheme 2), respectively, in high yields (70–90%). The reaction of methyl acrylate **5c** was carried out in the absence of solvent, with the alkene in excess, whereas the reactions of the other alkenes **5a**,**b**,**d** were performed in refluxing benzene or toluene, with a nitrone : alkene ratio of 1 : 1.1. The reaction mixture in benzene was kept at room temperature, this proving to be the optimum for DMAD, since the cycloaddition product **10** was somewhat unstable at reflux. Even at room temperature when kept in chloroform solution, compound **10** was converted quantitatively into 1-methylindole-2-carbaldehyde and unidentified products.

The cycloaddition of dimethyl fumarate **5a** in refluxing toluene was found to be highly diastereoselective affording the diastereoisomers **6a** and **7a** in a relative ratio of 10 : 1. However, a lower reaction temperature (reflux in benzene) afforded the cycloadducts **6a** and **7a** in a relative ratio of 1.4 : 1. The relative ratio of the cycloadducts **7b** : **6b** isolated from the reaction of **5b** was found to be 2.7 : 1 in refluxing benzene and 3.6 : 1 in refluxing toluene. Structural assignments for the adducts **6a**,**b** and **7a**,**b** were based on their $^1$H NMR signals (300 MHz), which for the 4-, 5-$CO_2CH_3$ protons of **7a** and **6b** appear at $\delta$ 3.11 (br), 3.75 and $\delta$ 3.11, 3.76, respectively. Signals at $\delta$ 3.11 are in both cases ascribed to the 4-$CO_2CH_3$ protons which are shielded by the vicinal indolyl group in a *cis* configuration; molecular models confirm these geometrical considerations. Similar shielding has been suggested[11] for analogous systems. Upfield signals for the $CO_2CH_3$ protons are not present in the $^1$H NMR spectra of isomers **6a** ($\delta$ 3.73, 3.87) and **7b** ($\delta$ 3.66, 3.78) where the 4-$CO_2CH_3$ groups are *trans* to the indolyl group. It is worth mentioning that there is some broadening of the $^1$H and $^{13}$C NMR signals for compounds **6a**,**b**, **7a**,**b** as well as for the other isolated isoxazolidines **6**–**9**, when the spectra were recorded at 25 °C on a 300 MHz spectrometer. This broadening can be attributed to dynamic effects arising from the slow inversion of the nitrone nitrogen atom, as recorded in the literature[12,13] for other isoxazolidines. Similar dynamic effects are absent in the $^1$H NMR spectra recorded at 80 MHz.

The stereoselectivity of the reactions of **4** with **5a** and **5b** resulting from a study of the transition states[14] seems to be in accord with that observed. In the case of **5a**, where the secondary orbital interactions are thought to affect both of the transition states similarly, steric factors are expected to predominate and lead to preferential formation of the cycloadduct **6a** with an *endo*- substituent at the less crowded C-4 position. In the case of **5b**, the observed stereoselectivity is smaller as a result of competing steric factors and secondary orbital interactions. Thus, the major isomer **7b** resulting from a less crowded *endo* transition state is favoured by steric factors whereas the minor isomer **6b** resulting from an *exo* transition state is favoured by secondary orbital interactions developing between the p-orbitals of the indolyl moiety and those of the carbonyl substituents. Secondary orbital interactions involving the orbitals of the nitrone nitrogen and those of the alkene substituents, which are also possible in the *endo* transition state, have in several cases been considered to be ineffective[12] or to have a destabilizing effect.[15] In both cases when the reaction is carried out at higher temperatures the ratio of the thermodynamically more stable isomers **6a** and **7b** is increased.

Two stereoisomers, **7d** and **6d**, were also isolated from the reaction of *N*-methylmaleimide **5d** in a relative ratio 0.45 : 1 (reflux in benzene) or 0.5 : 1 (reflux in toluene). In this case the structural assignment, not obvious from the observed proton chemical shifts, was supported by NOE experiments. Thus, saturation of the frequency of 3′-H of the minor product **7d** causes 12% and 11% increase of the signal intensity of 4-H and 5-H respectively, whereas saturation of the frequency of 4-H and 5-H causes 16% and 17% increase of the signal intensity of

3′-H respectively. With the major isomer **6d** no significant increases are observed upon saturation of the corresponding frequencies. These increments are indicative of a *cis* arrangement of the indole ring and the 4-H in the minor product **7d** and a *trans* arrangement in the major product **6d**. The observed stereoselectivity which is reversed in relation to that of the reaction with dimethyl maleate is in accordance with the predictions from the transition state consideration. *N*-Methylmaleimide **5d** is sterically less demanding than dimethyl maleate, whereas the situation governing the secondary orbital interactions in the transition state of the reaction of **5d** is supposed to be similar to that with dimethyl maleate. Thus, a decrease in the *endo*:*exo* (**7d**:**6d**) ratio is expected[12] for *N*-methylmaleimide compared with dimethyl maleate. Since the relative ratio of products **7d**:**6d** was 0.64:1 in refluxing xylene the *endo* product **7d** is thermodynamically more stable.

The reaction with the monosubstituted alkene **5c** showed poor regio- and stereo-selectivity affording four cycloadducts, the isoxazolidines **6c**, **7c**, **8c**, **9c** in ~3:1.3:2.1:1 relative ratio as was estimated for three of them (**6c**, **7c**, **9c**) from the integrals of the $^1$H NMR spectrum of their mixture. The isoxazolidine **8c** was isolated in a pure state after chromatographic separation of the reaction mixture, whereas **6c** was largely separated from its mixture with **7c** and **9c** by crystallization. However, the cycloadducts **7c** and **9c** were not separated. The structures of the isolated regio-isomers **6c** and **8c** were assigned on the basis of their 3-H, 4-H and 5-H chemical shifts, in analogy with other similar compounds.[10,16] Thus, in the $^1$H NMR spectrum of **6c** recorded at 55 °C (300 MHz), peaks for the 4-, 3- and 5-H appear at $\delta$ 2.82, 4.22 and 4.79 respectively, instead of $\delta$ 3.70, 4.24 and 4.36 for compound **8c**. Of diagnostic importance for the assignment of the above structures are also the resonances of C-3, C-4 and C-5, which appear at $\delta$ 64.5, 39.2 and 75.3, respectively, in the spectrum of compound **6c** but at $\delta$ 68.5, 54.7 and 68.8 in the spectrum of compound **8c**. The *trans* arrangement of the methoxycarbonyl and indolyl groups in **8c** was established from the resonance of the methoxy protons which appears at $\delta$ 3.71 indicating that they lie far from the shielding region of the aromatic ring (in comparison with the spectra of compounds **6a**, **7b**). Besides, the presence of shielded methoxy protons ($\delta$ 3.08) is apparent in the spectrum of the mixture of **6c**, **7c** and **9c**. As for the configuration of **6c**, although it cannot easily be established from the $^1$H NMR data, it has been confirmed by the results of acid-induced cyclizations attempted with this compound as well as with some other isoxazolidines of the type **6**–**8** that are reported below.

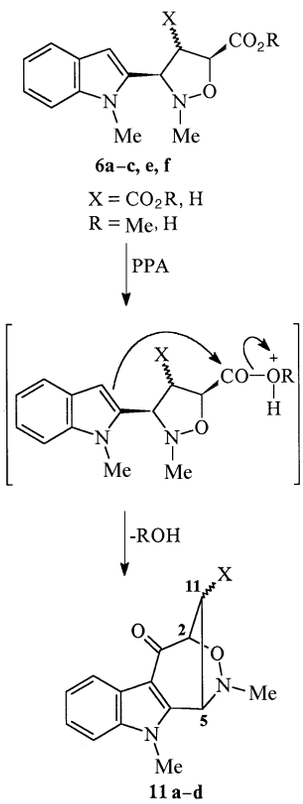
For the acid-induced cyclizations of the cycloaddition products (according to Scheme 1) several conditions were tested (hydrochloric acid, sulfuric acid, boron trifluoride–diethyl ether, polyphosphoric acid with a wide range of temperatures and solvents). Since in many cases nucleophilic attack of the 3-indole position is easier with acid carbonyls,[17] some of the methoxycarbonyl substituted cycloaddition products (**6a,c**, **8c**) were hydrolysed to the corresponding acids (**6e,f**, **8f**) [eqn. (1)] the cyclization of which was also attempted; there were no significant differences in reactivity. Finally, the intramolecular cyclizations were effected with polyphosphoric acid (PPA) in either refluxing dichloromethane or toluene; they proceeded successfully with the isoxazolidines **6**–**8**, especially those bearing a methoxycarbonyl substituent (**6a**–**c**, **7a,b**, **8c**) as well as with the products of their alkaline hydrolysis (**6e,f**, **8f**). No attempt was made with the dihydroisoxazole **10** because of its lability in solution; the imides derived from cycloadditions of **5d** were less reactive.

**6a, 6c, 8c** $\xrightarrow[\text{MeOH}]{\text{KOH}}$ **6e, 6f, 8f** (respectively) (1)

**e:** $R^1 = R^4 = CO_2H$, $R^2 = R^3 = H$

**f:** $R^1 = CO_2H$, $R^2 = R^3 = R^4 = H$

As illustrated in Scheme 1, bridged indole derivatives of type **3** are expected to result from isoxazolidines bearing an electrophilic centre ($CO_2CH_3$, $CO_2H$ group) and having a favourable *cis* configuration with respect to the indole ring, whereas cyclopenta[*b*]indoles **2** are expected to result from isoxazolidines bearing a *cis* substituent at the 4-position. In fact, all of the cycloadducts bearing a *cis* substituent at the 5- position underwent acid-induced attack of the indole 3- nucleophilic centre quite easily, at relatively low temperature (refluxing dichloromethane) to afford the fused bicyclic products **11** (Scheme 3) in




**11a** X = $CO_2Me$ (*exo*–orientated to indole)
**b** X = $CO_2Me$ (*endo*–orientated to indole)
**c** X = $CO_2H$ (*exo*–orientated to indole)
**d** X = H

**Scheme 3**

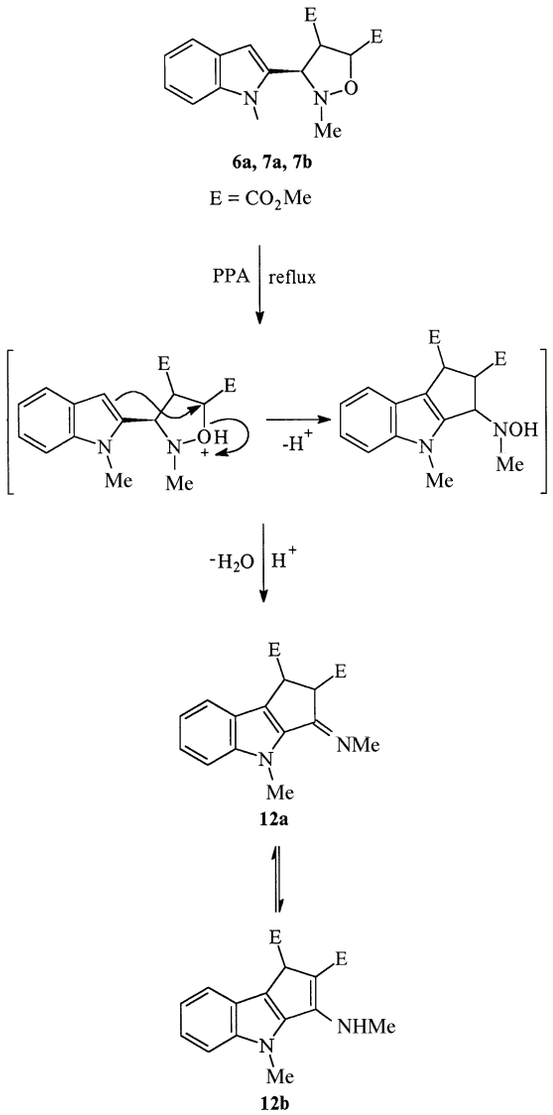
moderate yields (43–57%). In contrast, the isoxazolidine **7a** bearing a 4-*cis* substituent failed to give any product of type **2**, whereas the isoxazolidine **6b** having a favourable *cis* substituent at both the 4- and 5- positions gave only the bridged product **11**.

In general, where formation of product **11** is not expected because of the absence of a 5-methoxycarbonyl substituent in a *cis* relationship to the indolyl group, *i.e.* compounds **7a,b**, the enamine (⟍⟋ imine) **12** was isolated in low yields (10–29%) upon treatment of such compounds with PPA in refluxing dichloromethane (Scheme 4). The imine **12** was also obtained in low yield (15%) from the reaction of **6a** under the same reaction conditions along with the main product **11a**.

The isoxazolidines **7a,b** mentioned above as well as those from which the 5-carbonyl substituent lacks completely, *i.e.* **8c,f**, afforded the diketone **13** in 18–55% yield (in some cases along with small amounts of compound **12**) when treated with PPA (Scheme 5) at higher temperatures (refluxing toluene). Smaller amounts of the diketone **13** were also obtained from the reaction of **8c** conducted in refluxing dichloromethane (yield 10%).

The assignment of structure to products **11** was based on spectral and analytical evidence. The molecular ion peak in their mass spectra suggests the loss of one molecule of

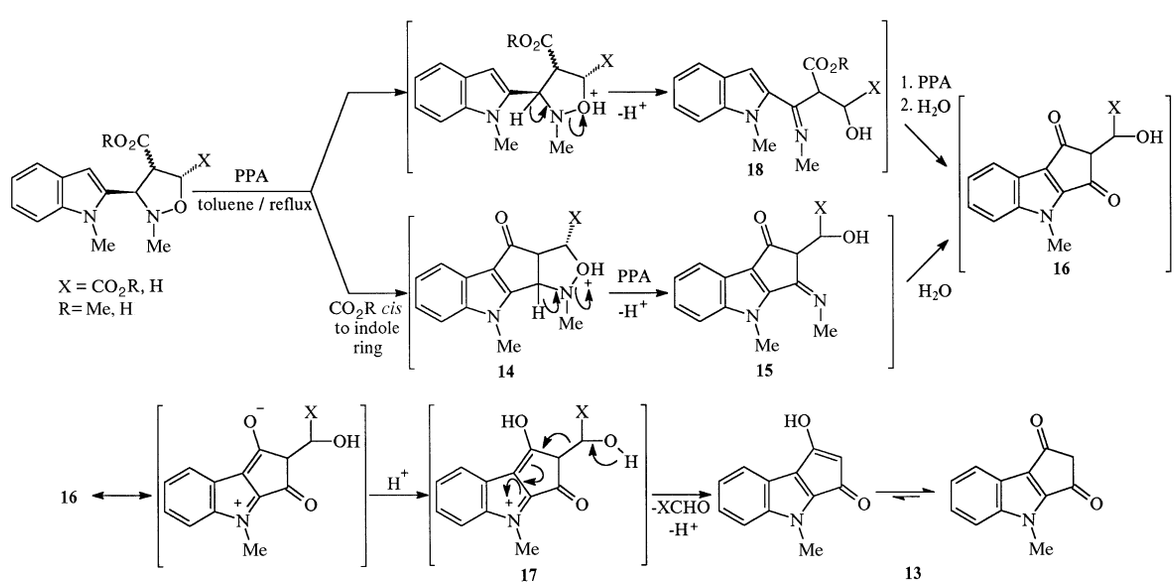
methanol (for **6a,b,c**) or water (for **6e,f**). In their IR spectra, besides the carbonyl absorption for the $CO_2CH_3$ ($\nu$/cm$^{-1}$ 1725, 1730 for **11a**, **11b**, respectively) or $CO_2H$ ($\nu$/cm$^{-1}$ 1710 for **11e**) they show absorption for a conjugative carbonyl ($\nu$/cm$^{-1}$ 1640–1650). The presence of a ketonic carbonyl is also indicated in




**Scheme 4**

the $^{13}$C NMR spectra of compounds **11** ($\delta$ 187.1–189.3). Loss of methanol from **6a**, **6b** and **6c** is also evident from the absence of a signal for one of the $OCH_3$ groups in the $^1$H NMR of their cyclization products **11a**, **11b** and **11d** respectively, whilst the position of the intramolecular junction in **11** is indicated by the lack of a characteristic upfield signal ($\delta$ ~6.50) for the indole 3-H. The proposed stereochemistry of compounds **11** is supported by the chemical shifts of the 11-H and the 11-$CO_2CH_3$ groups. Thus, the protons of the *endo* $CO_2CH_3$ group of **11b** exhibit considerable diamagnetic shielding (0.25 ppm) in comparison with those of **11a** (the result of shielding by the indole group), whilst there is considerable deshielding (0.80 ppm) of the 11-H of **11b** in comparison with that of **11a**. Noteworthy features in the $^1$H NMR spectra of compounds **11** are also the signals for the 2-, 5- and 11-H which in combination with the chemical shifts for the $OCH_3$ groups are illustrative of their stereochemical nature. Thus, in the spectrum of compound **11a**, three singlets are found at $\delta$ 3.41, 4.91 and 5.11 for 11-H, 5-H and 2-H respectively, whereas the corresponding peaks in the spectrum of **11c** in DMSO are at $\delta$ 3.79, 4.58 and 5.34. The absence of coupling between these neighbouring protons is understandable from molecular models of **11a,c** which clearly demonstrate that, with an *exo* (to the indole ring) $CO_2CH_3$ or $CO_2H$ substituent, the dihedral angles between the carbon bonds with 11-H and 5-H or 2-H are almost 90°. In the case of an *endo* substituent, the corresponding dihedral angles seem to be <90°, with the expected coupling observable in the $^1$H NMR spectrum of **11b** [$\delta$ 4.21 (dd, *J* 4.3, 5.8) for the 11-H, 4.76 (d, *J* 5.8) for the 5-H and 5.04 (d, *J* 4.3) for the 2-H]. Coupling of 2-H and 5-H with only one 11-H is also observed in the spectrum of **11d** [2.89 (ddd, *J* 4.0, 5.6, 11.3) for 11-H *exo*-orientated to the indole ring, 4.62 (d, *J* 5.6) for 5-H and 4.79 (d, *J* 4.0) for 2-H]. The *endo*-orientated 11-H of **11d** gives only the *gem* coupling at $\delta$ 2.56 (d, *J* 11.3) thus illustrating its structural similarity with **11a–c** and, by induction, the stereochemistry of the isoxazolidine **6c** ($CO_2CH_3$ and indolyl groups in *cis* arrangement) from which it is formed. Another remarkable feature in the $^1$H NMR of **11d** measured at ambient temperature is the differential broadening of some signals, probably as a result of inversion of the pyramidal nitrogen between two differentially populated conformations. At higher temperature (55 °C) differences are observed. The ddd signal at $\delta$ 2.89 becomes sharper whereas the doublets for the 2-H and 5-H tend to coalesce.

Finally, the configuration of the bicyclic products **11** has been unambigously confirmed by the results of a crystallographic X-ray analysis carried out on **11a.** The molecular structure and numbering scheme of **11a** is shown in Fig. 1. In fact,




**Scheme 5**

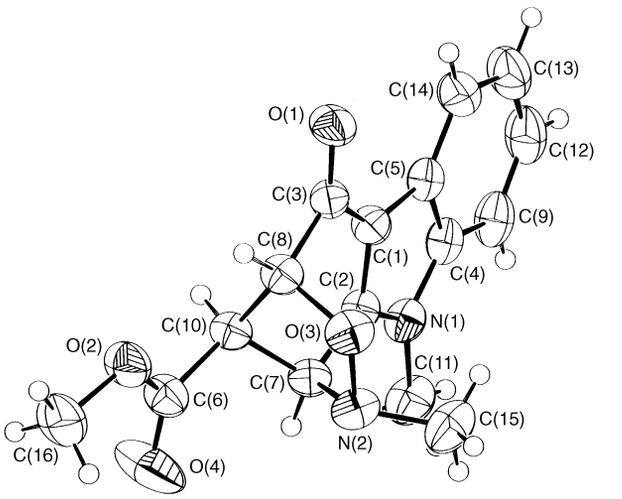



**Fig. 1** A projection of the molecular structure of compound **11a** showing the atomic numbering scheme. Thermal displacement parameters are drawn at 50% probability level.

**Table 1** Selected bond lengths (Å) and angles (deg) for **11a**

| | | | |
|---|---|---|---|
| O(1)–C(3) | 1.241(3) | O(2)–C(6) | 1.338(3) |
| O(2)–C(16) | 1.473(3) | O(3)–C(8) | 1.456(3) |
| O(3)–N(2) | 1.501(3) | C(1)–C(2) | 1.399(3) |
| C(1)–C(3) | 1.462(3) | C(1)–C(5) | 1.464(3) |
| N(1)–C(2) | 1.381(3) | N(1)–C(4) | 1.412(3) |
| N(1)–C(11) | 1.467(3) | C(2)–C(7) | 1.517(3) |
| N(2)–C(15) | 1.471(3) | N(2)–C(7) | 1.504(3) |
| C(3)–C(8) | 1.548(3) | C(4)–C(5) | 1.429(3) |
| C(6)–O(4) | 1.209(3) | C(6)–C(10) | 1.538(3) |
| C(7)–C(10) | 1.540(3) | C(8)–C(10) | 1.542(3) |
| | | | |
| C(6)–O(2)–C(16) | 117.0(2) | C(8)–O(3)–N(2) | 107.63(14) |
| C(2)–C(1)–C(3) | 119.3(2) | C(2)–C(1)–C(5) | 107.5(2) |
| C(3)–C(1)–C(5) | 133.2(2) | C(2)–N(1)–C(4) | 108.7(2) |
| C(2)–N(1)–C(11) | 126.7(2) | C(4)–N(1)–C(11) | 124.6(2) |
| N(1)–C(2)–C(1) | 109.7(2) | N(1)–C(2)–C(7) | 127.6(2) |
| C(1)–C(2)–C(7) | 122.7(2) | C(15)–N(2)–O(3) | 105.4(2) |
| C(15)–N(2)–C(7) | 115.3(2) | O(3)–N(2)–C(7) | 103.6(2) |
| O(1)–C(3)–C(1) | 125.6(2) | O(1)–C(3)–C(8) | 121.4(2) |
| C(1)–C(3)–C(8) | 113.0(2) | N(1)–C(4)–C(5) | 108.5(2) |
| C(4)–C(5)–C(1) | 105.6(2) | O(4)–C(6)–O(2) | 123.3(2) |
| O(4)–C(6)–C(10) | 124.0(2) | O(2)–C(6)–C(10) | 112.7(2) |
| N(2)–C(7)–C(2) | 113.8(2) | N(2)–C(7)–C(10) | 99.1(2) |
| C(2)–C(7)–C(10) | 107.0(2) | O(3)–C(8)–C(10) | 103.8(2) |
| O(3)–C(8)–C(3) | 107.2(2) | C(10)–C(8)–C(3) | 111.5(2) |
| C(6)–C(10)–C(7) | 111.8(2) | C(6)–C(10)–C(8) | 115.1(2) |
| C(7)–C(10)–C(8) | 98.5(2) | | |

the dihedral angles H(11)–C(11)–C(5)–H(5) and H(11)–C(11)–C(2)–H(2) for the *endo* 11-H have been as 75.22 and 83.09°, respectively. The corresponding dihedral angles for the *exo* 11-substituent of **11a** are 47.92 and 42.55° respectively.

The intramolecular acylation products **11** have been shown to be sensitive to alkali treatment, so that an attempt to convert **11a** into **11c** by alkaline hydrolysis of the methoxycarbonyl group resulted in decomposition of the compound.

The molecular ion peak in the MS spectrum of compound **12** confirms the abstraction of one molecule of water from the starting material **7a,b**, while its $^1$H NMR spectrum suggests the presence of all the methoxy groups that existed in the starting material and the absence of a 3-H on the indole ring ($\delta$ ~6.50). The potential tautomerism **12a** ⟵ **12b** can also be recognized from the $^1$H and $^{13}$C NMR spectra. Thus, in the $^{13}$C NMR spectrum, 11 signals are present for the aliphatic carbons whilst there are 5 signals (158.1, 167.6, 170.8, 171.6 and 172.4) corresponding to one C=N and four C=O (ester) carbons. Furthermore, in the aliphatic region of the $^1$H NMR spectrum measured at ambient temperature there are two groups of peaks corresponding to the tautomers **12a** and **12b** (estimated ratio 1:1.5). The chemical shifts at $\delta$ 3.42, 3.75, 3.78, 3.97, 4.42 and 4.78 are assigned to the minor isomer whilst the signals at 3.35 (d), 3.70, 3.75, 3.98 and 4.56 are assigned to the major isomer. At higher temperature (55 °C) the ratio of **12a**:**12b** is almost reversed (1.4:1) consistent with a temperature dependent equilibrium.

The insert in Scheme 4 shows a reasonable mechanistic interpretation for the formation of **12**. Protonation of the isoxazolidine oxygen atom induced by PPA makes the neighbouring C-5 atom electrophilic. Subsequent attack of the nucleophilic C-3 atom of the indole ring accompanied by the isoxazolidine ring opening and loss of water gives **12**.

For compound **13**, the spectral and analytical data are in good agreement with the proposed structure. Absorptions at 1670 and 1715 cm$^{-1}$ in the IR spectrum agree with the presence of the two carbonyl groups, whereas the frequencies of the absorptions agree with that of analogous fused oxocyclopenta-[*b*]indoles.[2a] The ketonic nature of the carbonyls is further confirmed by the signals at $\delta$ 188.6 and 188.9 in the $^{13}$C NMR spectrum. Furthermore, the structure is supported by the molecular ion peak as well as by the signals at $\delta$ 3.47 and 4.07 for the methylenic and *N*-methyl protons in the $^1$H NMR spectrum, where the absence of a 3-H in the indole ring is also noted.

For the formation of compound **13** a mechanistic scheme involving the formation of an intermediate **14** (Scheme 5) through intramolecular acylation is suggested for cases where the 4-methoxycarbonyl substituent is *cis* to the indolyl group. Acid-induced opening of the isoxazolidine ring and hydrolysis of the imine **15** so produced, which may be favoured in the high temperature where the reaction is performed, leads to the formation of **16**, the protonated form of which is converted into **13** by abstraction of XCHO (X = $CO_2CH_3$, $CO_2H$, H); however, such a fragment has not been detected in the complex reaction mixture. A scheme involving initial acid-induced opening of the isoxazolidine ring **18** followed by intramolecular acylation and hydrolysis of the imine group is more probable for formation of the intermediate **16**, especially for cases where the lack of a 4-carbonyl substituent *cis* to an indolyl group cannot lead to initial intramolecular acylation.

In conclusion, the 1,3-dipolar cycloaddition products of *C*-(1-methylindol-2-yl)-*N*-methylnitrone with carbonyl substituted dipolarophiles can easily undergo intramolecular cyclization induced by acid treatment to afford a variety of interesting fused [*b*]indoles. The cyclization products depend principally on the stereochemistry of the initial isoxazolidine and have an important potentiality as precursors to other polycyclic indole derivatives due to their functionality.

## Experimental

Mps are uncorrected and were determined on a Kofler hot-stage microscope. IR spectra were recorded on a Perkin-Elmer 297 spectrometer. $^1$H NMR spectra were recorded at 300 MHz on a Bruker 300 AM spectrometer and $^{13}$C NMR spectra at 75.5 MHz on the same spectrometer and are quoted relative to tetramethylsilane as internal reference, in deuteriochloroform solutions, unless otherwise stated. *J* Values are given in Hz. Mass spectra were determined on a VG-250 spectrometer with ionization energy maintained at 70 eV. Microanalyses were performed on a Perkin-Elmer 240B element analyser. Column chromatography was carried out on Merck Kieselgel (particle size 0.063–0.200 mm) and solvents were distilled before use. Light petroleum refers to the fraction of bp 40–60 °C.

1-Methylindole-2-carbaldehyde was prepared by formylation of 1-methylindole according to a literature method.[18]

### *C*-(1-Methylindol-2-yl)-*N*-methylnitrone 4

A solution of *N*-methylhydroxylamine hydrochloride (564 mg, 6.75 mmol) and sodium carbonate (476 mg, 4.5 mmol) in water

(1 ml) was added to a solution of 1-methylindole-2-carbaldehyde (477 mg, 3 mmol) in ethanol (3 ml) and the mixture was stirred at room temperature for 3 h. Ethanol was removed under reduced pressure and the residue was extracted with benzene (3 × 10 ml). The organic layer was washed with brine, dried ($Na_2SO_4$) and evaporated. Trituration of the residue with diethyl ether gave crystals of the nitrone **1** (354 mg, 63%), mp 161–163 °C (from dichloromethane–diethyl ether) (Found: C, 70.16; H, 6.40; N, 14.60. Calc. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1595 (C=N) and 1185 (N→O); $\delta_H$ 3.76 (3 H, s, 1-$CH_3$), 3.95 [3 H, s, N(O)$CH_3$], 7.07–7.17 (1 H, m, 5-H), 7.28–7.34 (2 H, m, 6-, 7-H), 7.59 (1 H, s, 3-H), 7.70 (1 H, d, *J* 8, 4-H) and 8.19 (1 H, s, CH=N→O); $\delta_C$ 29.7 (1-$CH_3$), 53.8 [N(O)$CH_3$], 107.9 and 109.0 (C-3, C-7), 120.1 (C-5), 122.2 (C-4), 124.1 (C-6), 125.3, 127.4 and 129.7 (CHN→O, C-3a, C-2) and 138.1 (C-7a); *m/z* 188 ($M^+$, 100), 171 (71), 144 (49), 130 (43), 115 (37), 89 (34) and 77 (27).

### 1,3-Dipolar cycloadditions

**General procedure.** The nitrone **4** (188 mg, 1 mmol) and the dipolarophile **5** (1.1 mmol) were dissolved in benzene or toluene (2 ml); in the case of methyl acrylate, the solvent was the dipolarophile itself, used in excess (3 ml). The solution was refluxed until the consumption of the starting materials (2–3 h), monitored by TLC. After evaporation of the reaction mixture the residue was separated by column chromatography, using mixtures of light petroleum–ethyl acetate (1.5:1→7:1) as the eluent. Because of the instability of the cycloaddition product **10** at elevated temperatures, higher yields were achieved when a benzene solution of the reactants was kept at room temperature for 18 h. Subsequently, benzene was removed by evaporation *in vacuo*, at room temperature.

**Reaction of 4 with 5a.** From the column chromatography (eluent: light petroleum–ethyl acetate, 7:1) there were obtained in order of elution: (a) (3*S**,4*R**,5*R**)-4,5-bis(methoxycarbonyl)-2-methyl-3-(1′-methylindol-2′-yl)isoxazolidine **6a** (149 mg, 45% in benzene or 266 mg, 80% in toluene) as an oil (Found: C, 61.46; H, 6.09; N, 8.24. Calc. for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43%); $\nu_{max}$(neat)/cm$^{-1}$ 1730 (C=O); $\delta_H$ 2.68 (3 H, br, 2-$CH_3$), 3.73, 3.82 and 3.87 (9 H, three s, 5-$CO_2CH_3$, 1′-$CH_3$, 4-$CO_2CH_3$), 4.13 (2 H, br, 3-H, 4-H), 4.93 (1 H, br, 5-H), 6.57 (1 H, s, 3′-H), 7.11 (1 H, t, Σ*J* 14.8, 5′-H), 7.24 (1 H, t, Σ*J* 15.2, 6′-H), 7.32 (1 H, d, *J* 8.2, 7′-H) and 7.58 (1 H, d, *J* 7.8, 4′-H); $\delta_C$ 30.4 (1′-$CH_3$, indole), 42.9 (2-$CH_3$), 52.6 and 52.8 (two $OCH_3$), 57.6 (C-4), 69.8 (C-3), 77.4 (C-5), 102.9 (C-3′), 109.1 (C-7′), 119.6 (C-5′), 120.6 (C-4′), 121.9 (C-6′), 127.2 (C-3′a), 133.6 (C-2′), 138.2 (C-7′a), 171.2 and 171.3 (two C=O, ester); *m/z* 332 ($M^+$, 83), 188 (88), 171 (100), 156 (29), 144 (36), 130 (21), 113 (17) and 59 (12); (*b*) (3*S**,4*S**,5*S**)-4,5-bis(methoxycarbonyl)-2-methyl-3-(1′-methylindol-2′-yl)isoxazolidine **7a** (106 mg, 32% in benzene or 27 mg, 8% in toluene), mp 116–118 °C (from dichloromethane–diethyl ether) (Found: C, 61.54; H, 6.20; N, 8.49. Calc. for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1730 (C=O); $\delta_H$ 2.82 (3 H, br, 2-$CH_3$), 3.11 (3 H, br, 4-$CO_2CH_3$), 3.75 and 3.84 (6 H, two s, 5-$CO_2CH_3$, 1′-$CH_3$), 3.70–3.93 (1 H, br, hidden, 4-H), 4.19 (1 H, br, 3-H), 5.27 (1 H, d, *J* 6.7, 5-H), 6.44 (1 H, s, 3′-H), 7.08 (1 H, t, Σ*J* 14.7, 5′-H), 7.21 (1 H, t, Σ*J* 15.2, 6′-H), 7.32 (1 H, d, *J* 8.3, 7′-H) and 7.57 (1 H, d, *J* 7.8, 4′-H); $\delta_C$ 30.1 (1′-$CH_3$), 43.8 (br, 2-$CH_3$), 52.1 and 52.7 (two $OCH_3$), 56.3 (C-4), 68.3 (C-3), 77.1 (C-5), 101.1 (C-3′), 108.9 (C-7′), 119.7 (C-5′), 120.8 (C-4′), 121.8 (C-6′), 127.4 (C-3′a), 133.4 (C-2′), 137.7 (C-7′a), 169.3 and 169.6 (br) (two C=O, ester); *m/z* 332 ($M^+$, 77), 188 (88), 171 (100), 156 (34), 144 (54), 130 (36), 113 (89), 85 (64) and 59 (49).

**Reaction of 4 with 5b.** The following compounds were obtained in order of elution (eluent: light petroleum–ethyl acetate, 3:2): (a) (3S*,4R*,5S*)-4,5-*bis*(*methoxycarbonyl*)-2-*methyl*-3-(1′-*methylindol*-2′-*yl*)*isoxazolidine* **7b** (226 mg, 68% in benzene or 240 mg, 72% in toluene), mp 103–105 °C (from dichloromethane–diethyl ether) (Found: C, 61.58; H, 6.11; N, 8.50. Calc. for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1752 and 1725 (C=O); $\delta_H$ 2.76 (3 H, br, 2-$CH_3$), 3.66, 3.78 and 3.82 (9 H, three s, 4-$CO_2CH_3$, 1′-$CH_3$, 5-$CO_2CH_3$), 3.55–4.08 (1 H, br, hidden, 4-H), 4.28 (1 H, br, 3-H), 5.04 (1 H, br, 5-H), 6.56 (1 H, s, 3′-H), 7.11 (1 H, t, Σ*J* 14.8, 5′-H), 7.23 (1 H, t, Σ*J* 15.0, 6′-H), 7.32 (1 H, d, *J* 8, 7′-H) and 7.58 (1 H, d, *J* 7.8, 4′-H); $\delta_C$ 30.5 (1′-$CH_3$), 43.8 (br, 2-$CH_3$), 52.6 (two $OCH_3$), 58.8 (br, C-4), 69.8 (br, C-3), 77.1 (C-5), 102.3 (br, C-3′), 109.3 (C-7′), 119.9 (C-5′), 120.7 (C-4′), 122.2 (C-6′), 127.3 (C-3′a), 134.1 (br, C-2′), 138.3 (C-7′a), 168.8 and 170.2 (two C=O, ester); *m/z* 332 ($M^+$, 84), 286 (30), 226 (85), 188 (48), 171 (100), 156 (66), 144 (72), 130 (59), 113 (69), 89 (46) and 59 (69). (b) (3S*,4S*,5R*)-4,5-*Bis*(*methoxycarbonyl*)-2-*methyl*-3-(1′-*methylindol*-2′-*yl*)*isoxazolidine* **6b** (83 mg, 25% in benzene or 67 mg, 20% in toluene), mp 161–163 °C (from dichloromethane–diethyl ether) (Found: C, 61.47; H, 6.12; N, 8.45. Calc. for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1760 and 1735 (C=O); $\delta_H$ 2.85 (3 H, s, 2-$CH_3$), 3.11 (3 H, s, 4-$CO_2CH_3$), 3.76 and 3.78 (6 H, two s, 5-$CO_2CH_3$, 1′-$CH_3$), 4.20 (2 H, br, 3-, 4-H), 4.96 (1 H, br, 5-H), 6.50 (1 H, s, 3′-H), 7.07 (1 H, t, Σ*J* 14.8, 5′-H), 7.20 (1 H, t, Σ*J* 15.2, 6′-H), 7.31 (1 H, d, *J* 8.1, 7′-H) and 7.53 (1 H, d, *J* 7.8, 4′-H); $\delta_C$ 29.9 (1′-$CH_3$), 44.0 (2-$CH_3$), 51.8 and 52.2 (two $OCH_3$), 56.5 (C-4), 68.8 (C-3), 75.5 (C-5), 101.4 (C-3′), 108.8 (C-7′), 119.6 (C-5′), 120.7 (C-4′), 121.7 (C-6′), 127.3 (C-3′a), 132.2 (C-2′), 137.6 (C-7′a), 168.4 and 170.3 (two C=O, ester); *m/z* 332 ($M^+$, 50), 286 (10), 226 (61), 188 (41), 171 (100), 156 (21), 144 (32), 130 (19), 113 (22), 89 (7) and 59 (20).

**Reaction of 4 with 5c.** (3S*,4S*)-4-*Methoxycarbonyl*-2-*methyl*-3-(1′-*methylindol*-2′-*yl*)*isoxazolidine* **8c** was eluted (light petroleum–ethyl acetate 7:1 as eluent) first (69 mg, 25%) as an oil (Found: C, 65.61; H, 6.79; N, 9.98. Calc. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21%); $\nu_{max}$(neat)/cm$^{-1}$ 1730 (C=O); $\delta_H$(55 °C) 2.60 (3 H, br s, 2-$CH_3$), 3.70 (1 H, hidden, 4-H), 3.71 and 3.83 (6 H, two s, $CO_2CH_3$, 1′-$CH_3$), 4.24 and 4.36 (3 H, two overlapped multiplets, 3-H, 5-H), 6.55 (1 H, s, 3′-H), 7.08 (1 H, t, Σ*J* 14.8, 5′-H), 7.21 (1 H, t, Σ*J* 15.1, 6′-H), 7.30 (1 H, d, *J* 8.1, 7′-H) and 7.56 (1 H, d, *J* 7.8, 4′-H). Signals at $\delta$ 2.60, 3.70 and 4.24, 4.36 are broadened and appear at $\delta$ 2.29, 2.66 (both broad), 3.66 and 4.10–4.44, respectively, when the spectrum is measured at 25 °C; $\delta_C$(55 °C) 30.5 (1′-$CH_3$), 42.4 (br, 2-$CH_3$), 52.5 ($OCH_3$), 54.7 (br, C-4), 68.5 (br, C-3), 68.8 (C-5), 102.0 (C-3′), 109.2 (C-7′), 119.8 (C-5′), 120.6 (C-4′), 122.0 (C-6′), 127.4 (C-3′a), 138.3 (C-7′a) and 172.6 (C=O). The C-2′ signal was not visible; *m/z* 274 ($M^+$, 100), 243 (7), 228 (49), 216 (12), 188 (65), 171 (84), 156 (25), 144 (34), 130 (15), 115 (9) and 89 (10). A mixture of (3S*,5R*)-5-*methoxycarbonyl*-2-*methyl*-3-(1′-*methylindol*-2′-*yl*)*isoxazolidine* **6c**, (3S*,5S*)-5-*methoxycarbonyl*-2-*methyl*-3-(1′-*methylindol*-2′-*yl*)*isoxazolidine* **7c** and (3S*,4R*)-4-*methoxycarbonyl*-2-*methyl*-3-(1′-*methylindol*-2′-*yl*)*isoxazolidine* **9c** was eluted second (173 mg, 63% total yield), in 3:1.3:1 relative ratio (NMR integration); $\delta_H$ 2.74 (br), 2.82 (br), 2.95 (m), 3.08 (s), 3.75 (s), 3.80 (s), 3.81 (s), 3.82 (s), 4.04 (m), 4.24 (t, Σ*J* 17.2), 4.50 (t, Σ*J* 15.8), 4.71 (t, Σ*J* 15.3), 4.81 (br), 6.45 (s), 6.48 (s), 7.03–7.15 (m), 7.15–7.26 (m), 7.26–7.34 (m) and 7.53–7.60 (m). Compound **6c** crystallized upon trituration with dichloromethane–diethyl ether and was filtered off, mp 105–107 °C (from dichloromethane–diethyl ether) (Found: C, 65.53; H, 6.71; N, 10.11. Calc. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1740 (C=O); $\delta_H$(55 °C) 2.64 (3 H, br, 2-$CH_3$), 2.82 (2 H, m, 4-H), 3.79 and 3.80 (6 H, two s, $CO_2CH_3$, 1′-$CH_3$), 4.22 (1 H, br, 3-H), 4.79 (1 H, t, Σ*J* 14.4, 5-H), 6.47 (1 H, s, 3′-H), 7.08 (1 H, t, Σ*J* 14.8, 5′-H), 7.20 (1 H, t, Σ*J* 15.1, 6′-H), 7.28 (1 H, d, *J* 8.2, 7′-H) and 7.55 (1 H, d, *J* 7.9, 4′-H). Peaks at $\delta$ 2.64 and 4.22 broaden and appear at $\delta$ 2.31 and 4.03, respectively, in the spectrum measured at 25 °C; $\delta_C$(55 °C) 30.4 (1′-$CH_3$), 39.2 (br, C-4), 43.0 (br, 2-$CH_3$), 52.3 ($OCH_3$), 64.5 (br, C-3), 75.3 (C-5), 101.3 (C-3′), 109.0 (C-7′), 119.7 (C-5′), 120.6 (C-4′), 121.9 (C-6′), 127.5 (C-3′a), 138.4

(C-7′a) and 171.4 (C=O). A signal for the C-2′ was not detected; *m/z* 274 ($M^+$, 100), 228 (42), 215 (15), 188 (31), 171 (33), 168 (53), 158 (34), 144(37), 130 (22), 115 (14) and 89 (13).

**Reaction of 4 with 5d.** (3S*,4R*,5S*)-4,5-(N-*Methyldicarboximido*)-2-*methyl*-3-(1′-*methylindol*-2′-*yl*)*isoxazolidine* **7d** was eluted (light petroleum–ethyl acetate, 5:2 as eluent) first (81 mg, 27% in benzene or 90 mg, 30% in toluene or 108 mg, 36% in xylene), mp 203–204 °C (from chloroform–diethyl ether) (Found: C, 64.30; H, 5.72; N, 14.08. Calc. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1700 (C=O); $\delta_C$ 2.47 (3 H, br, 2-$CH_3$), 3.08 [3 H, s, CON($CH_3$)CO], 3.81 (3 H, s, 1′-$CH_3$), 3.85 (1 H, dd, Σ*J* 7.3, 3.0, 4-H), 4.57 (1 H, br, 3-H), 4.98 (1 H, d, *J* 7.1, 5-H), 6.49 (1 H, s, 3′-H), 7.14 (1 H, t, Σ*J* 14.7, 5′-H), 7.26 (1 H, t, Σ*J* 15.2, 6′-H), 7.34 (1 H, d, *J* 8.2, 7′-H) and 7.61 (1 H, d, *J* 7.7, 4′-H); $\delta_C$ 25.2 (N-$CH_3$, imide), 30.1 (1′-$CH_3$), 40.2 (br, 2-$CH_3$), 56.2 (br, C-4), 63.8 (br, C-3), 76.0 (C-5), 102.4 (C-3′), 109.4 (C-7′), 120.0 (C-5′), 120.8 (C-4′), 122.3 (C-6′), 127.2 (C-3′a), 134.0 (br, C-2′), 137.6 (C-7′a) and 175.0 (two C=O); *m/z* 299 ($M^+$, 83), 188 (78), 171 (100), 156 (13), 147 (45), 144 (24), 130 (16), 115 (12) and 89 (9). (3S*,4S*,5R*)-4,5-(N-*Methyldicarboximido*)-2-*methyl*-3-(1′-*methylindol*-2′-*yl*)*isoxazolidine* **6d** was eluted second (179 mg, 60% in benzene or toluene or 167 mg, 56% in xylene), mp 198–200 °C (from chloroform–diethyl ether) (Found: C, 64.11; H, 5.84; N, 14.09. Calc. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1700 (C=O); $\delta_H$ 2.83 and 2.91 [6 H, two s, 2-$CH_3$, CON($CH_3$)CO], 3.81 (3 H, s, 1′-$CH_3$), 3.82 (1 H, dd, *J* 7.3, 8.7, 4-H), 4.07 (1 H, d, *J* 8.7, 3-H), 4.93 (1 H, d, *J* 7.3, 5-H), 6.28 (1 H, s, 3′-H), 7.08 (1 H, t, Σ*J* 14.8, 5′-H), 7.21 (1 H, t, Σ*J* 15.1, 6′-H), 7.33 (1 H, d, *J* 8.2, 7′-H) and 7.54 (1 H, d, *J* 7.9, 4′-H); $\delta_C$ 24.8 (N-$CH_3$, imide), 30.3 (1′-$CH_3$), 43.5 (2-$CH_3$), 53.1 (C-4), 68.7 (C-3), 76.4 (C-5), 100.5 (C-3′), 109.1 (C-7′), 119.8 (C-5′), 120.8 (C-4′), 121.9 (C-6′), 127.4 (C-3′a), 132.6 (C-2′), 138.0 (C-7′a), 172.2 and 175.3 (two C=O); *m/z* 299 ($M^+$, 85), 188 (73), 171 (100), 156 (9), 147 (39), 144 (19), 130 (13), 115 (14) and 89 (8).

**Reaction of 4 with DMAD.** When the reaction was carried out in benzene solution, at room temperature, *dimethyl* 2,3-*dihydro*-2-*methyl*-3-(1′-*methylindol*-2′-*yl*)*isoxazole*-4,5-*dicarboxylate* **10** was obtained (310 mg, 94%) by elution with light petroleum–ethyl acetate (5:1), mp 122–125 °C (decomp.) (from ethyl acetate) (Found: C, 61.49; H, 5.28; N, 8.31. Calc. for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1740 and 1700 (C=O); $\delta_H$ 3.01 (3 H, br, 2-$CH_3$), 3.67, 3.79 and 3.96 (9 H, three s, 5-$CO_2CH_3$, 1′-$CH_3$, 4-$CO_2CH_3$), 5.36 (1 H, br, 3-H), 6.45 (1 H, s, 3′-H), 7.08 (1 H, t, Σ*J* 14.7, 5′-H), 7.22 (1 H, t, Σ*J* 15.2, 6′-H), 7.32 (1 H, d, *J* 8.4, 7′-H) and 7.57 (1 H, d, *J* 7.9, 4′-H); $\delta_C$ 30.1 (1′-$CH_3$), 46.7 (br, 2-$CH_3$), 52.1 and 53.4 (two $OCH_3$), 69.2 (br, C-3), 102.4 (C-3′), 109.2 (C-7′), 119.6 (C-5′), 121.0 (C-4′), 122.1 (C-6′), 127.1 (C-3′a), 138.5 (C-7′a), 152.1 (C-5), 159.2 and 162.5 (two C=O, ester). Signals for C-2′ and C-4 were not detected; *m/z* 330 ($M^+$, 87), 315 (8), 271 (16), 243 (79), 239 (100), 184 (53), 171 (24), 144 (19), 131 (32), 115 (14), 89 (14) and 69 (46).

The yield of **10** was lower (48%) when the reaction was performed in refluxing toluene for 20 min.

### General procedure for the hydrolysis of compounds 6, 8

To a solution of **6** or **8** (1 mmol) in methanol (5 ml) was added a solution of 40% aqueous potassium hydroxide (1.5 ml); the mixture was then refluxed and stirred for 2 h. Methanol was removed *in vacuo* from the mixture and the residue was acidified with 10% hydrochloric acid and then extracted with dichloromethane (3 × 5 ml). The extract was dried ($Na_2SO_4$), and evaporated under reduced pressure to give the hydrolysis product which was further purified by recrystallization.

**Hydrolysis of the isoxazolidine 6a.** (3S*,4R*,5R*)-2-*Methyl*-3-(1′-*methylindol*-2′-*yl*)*isoxazolidine*-4,5-*dicarboxylic acid* **6e** was obtained (268 mg, 88%) from the hydrolysis of **6a**, mp 162–164 °C (from dichloromethane–diethyl ether) (Found: C, 59.11; H, 5.11; N, 9.09. Calc. for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21%), $\nu_{max}$(Nujol)/cm$^{-1}$ 3600–2500 (OH, vbr) and 1725 (C=O); $\delta_H$(DMSO) 2.58 (3 H, s, 2-$CH_3$), 3.76 (3 H, s, 1′-$CH_3$), 3.86 (1 H, br, 4-H), 4.15 (1 H, br, 3-H), 4.85 (1 H, br, 5-H), 6.43 (1 H, s, 3′H), 7.01 (1 H, t, Σ*J* 14.5, 5′-H), 7.14 (1 H, t, Σ*J* 15.0, 6′-H), 7.43 (1 H, d, *J* 8.1, 7′-H), 7.50 (1 H, d, *J* 7.6, 4′-H) and 13.12 (2 H, br s, $CO_2H$); $\delta_C$(DMSO) 30.2 (1′-$CH_3$), 42.8 (br, 2-$CH_3$), 57.9 (br, C-4), 69.0 (br, C-3), 77.1 (br, C-5), 101.5 (C-3′), 109.8 (C-7′), 119.3 (C-5′), 120.1 (C-4′), 121.4 (C-6′), 126.8 (C-3′a), 135.5 (br, C-2′), 137.8 (C-7′a), 172.1 and 172.2 (two $CO_2H$); *m/z* 304 ($M^+$, 8), 188 (26), 171 (96), 156 (100), 144 (26), 130 (42), 115 (21), 103 (13), 89 (23) and 77 (7).

**Hydrolysis of the isoxazolidine 6c.** (3S*,5R*)-2-*Methyl*-3-(1′-*methylindol*-2′-*yl*)*isoxazolidine*-5-*carboxylic acid* **6f** was obtained from the hydrolysis of **6c** (231 mg, 89%), mp 147–150 °C (decomp.) (from dichloromethane–diethyl ether) (Found: C, 64.48; H, 6.11; N, 10.60. Calc. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76%); $\nu_{max}$(Nujol)/cm$^{-1}$ 3600–2500 (OH, vbr) and 1705 (C=O); $\delta_H$(DMSO) 2.68 (3 H, br, 2-$CH_3$), 2.82 (2 H, br, 4-H), 3.74 (3 H, s, 1′-$CH_3$), 4.31 (1 H, br, 3-H), 4.65 (1 H, br, 5-H), 6.44 (1 H, s, 3′-H), 7.00 (1 H, t, Σ*J* 14.4, 5′-H), 7.12 (1 H, t, Σ*J* 15.2, 6′-H), 7.41 (1 H, d, *J* 8.1, 7′-H), 7.48 (1 H, d, *J* 7.5, 4′-H) and 12.92 (1 H, br, $CO_2H$); $\delta_C$(DMSO) 30.0 (1′-$CH_3$), 37.7 (br, C-4), 44.6 (br, 2-$CH_3$), 63.8 (br, C-3), 75.5 (br, C-5), 99.4 (br, C-3′), 109.5 (C-7′), 119.1 (C-5′), 120.0 (C-4′), 121.1 (C-6′), 126.8 (C-3′a), 137.6 (C-7′a), 138.2 (br, C-2′) and 172.7 ($CO_2H$); *m/z* 260 ($M^+$, 74), 214 (68), 188 (29), 171 (100), 156 (62), 144 (50), 131 (52), 115 (23) and 89 (21).

**Hydrolysis of the isoxazolidine 8c.** (3S*,4S*)-2-*Methyl*-3-(1′-*methylindol*-2′-*yl*)*isoxazolidine*-4-*carboxylic acid* **8f** was obtained (218 mg, 84%) from the hydrolysis of **8c**, mp 159–161 °C (from dichloromethane–diethyl ether) (Found: C, 64.39; H, 6.11; N, 10.58. Calc. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76%); $\nu_{max}$(Nujol)/cm$^{-1}$ 3500–2300 (OH, vbr) and 1695 (C=O); $\delta_H$ 2.31 and 2.69 (3 H, both br, 2-$CH_3$), 3.66 (1 H, br, 4-H), 3.79 (3 H, s, 1′-$CH_3$), 4.13–4.53 (3 H, overlapped br and multiplet, 5-H and 3-H), 6.57 (1 H, s, 3′-H), 7.09 (1 H, t, Σ*J* 14.5, 5′-H), 7.22 (1 H, t, Σ*J* 14.9, 6′-H), 7.29 (1 H, d, *J* 8.1, 7′-H), 7.55 (1 H, d, *J* 7.7, 4′-H) and 9.44 (1 H, br s, $CO_2H$); $\delta_C$ 30.4 (1′-$CH_3$), 43.2 (br, 2-$CH_3$), 55.2 (br, C-4), 68.6 (br, C-3), 68.8 (C-5), 102.1 (C-3′), 109.2 (C-7′), 119.8 (C-5′), 120.7 (C-4′), 122.1 (C-6′), 127.3 (C-3′a), 135.2 (br, C-7′a), 138.2 (C-2′) and 176.9 ($CO_2H$); *m/z* 260 ($M^+$, 70), 214 (30), 188 (53), 171 (100), 156 (37), 144 (50), 130 (43), 115 (31) and 89 (36).

### General procedure for the reactions of the isoxazolidines 6–8 with PPA

PPA (3 g) was added to a solution of **6** or **7** or **8** (1 mmol) in dry dichloromethane or dry toluene (20 ml) and the mixture was refluxed under argon for 1–24 h. It was then diluted with water (10 ml) and the organic layer was separated. The aqueous layer was extracted repeatedly with dichloromethane (3 × 10 ml) and the combined extracts and organic layer were dried ($Na_2SO_4$) and evaporated. The residue was chromatographed on silica gel using as eluent a mixture of light petroleum–ethyl acetate (5:2) for products **12** or **13** or ethyl acetate for product **11**.

**(2*R**,5*S**,11*R**)-Methyl 4,6-dimethyl-1-oxo-3,4-oxaza-1,2,3,4,5,6-hexahydro-2,5-methanocyclohepta[*b*]indole-11-carboxylate 11a**. This *compound* was obtained (129 mg, 43 %) from the reaction of the isoxazolidine **6a** in dichloromethane (reflux for 3 h), mp 222–224 °C (from dichloromethane–diethyl ether) (Found: C, 64.00; H, 5.57; N, 9.32. Calc. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1725 (C=O, ester) and 1640 (C=O, conjugated); $\delta_H$ 2.23 (3 H, s, 4-$CH_3$), 3.41 (1 H, s, 11-H), 3.77 (3 H, s, $OCH_3$), 3.80 (3 H, s, 6-$CH_3$), 4.91 (1 H, s, 5-H), 5.11 (1 H, s, 2-H), 7.11–7.44 (3 H, m, 7-, 8-, 9-H) and 8.16 (1 H, d, *J* 6.5, 10-H); $\delta_C$ 30.4 (6-$CH_3$), 41.2 (4-$CH_3$,), 52.9 ($OCH_3$), 58.8 and 59.8 (C-5 and C-11), 83.0 (C-2), 110.0 (C-7), 121.8 (C-9), 123.2 (C-10), 123.9 (C-1a), 124.3 (C-8), 138.1 (C-10a), 146.5 (C-6a), 168.5 (C=O, ester) and 189.3 (C=O, ketone);

a signal for C-5a was not detected; *m/z* 300 ($M^+$, 9), 271 (25), 255 (55), 239 (42), 211 (14), 199 (19), 182 (14), 168 (17), 154 (20), 143 (100) and 130 (41).

**(2*R**,5*S**,11*S**)-Methyl 4,6-dimethyl-1-oxo-3,4-oxaza-1,2,3,4,5,6-hexahydro-2,5-methanocyclohepta[*b*]indole-11-carboxylate 11b.** This *compound* was obtained (171 mg, 57%) from the reaction of **6b** in dichloromethane (reflux for 1 h), mp 229–231 °C (decomp.) (from dichloromethane–diethyl ether) (Found: C, 63.69; H, 5.33; N, 9.22. Calc. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1730 (C=O, ester) and 1645 (C=O, conjugated); $\delta_H$ 2.30 (3 H, s, 4-$CH_3$), 3.52 (3 H, s, $OCH_3$), 3.88 (3 H, s, 6-$CH_3$), 4.21 (1 H, dd, *J* 5.8, 4.3, 11-H), 4.76 (1 H, d, *J* 5.8, 5-H), 5.04 (1 H, d, *J* 4.3, 2-H), 7.28–7.90 (3 H, m, 7-, 8-, 9-H) and 8.23 (1 H, d, *J* 6.8, 10-H); $\delta_C$ 30.3 (6-$CH_3$), 41.4 (4-$CH_3$), 52.6 ($OCH_3$), 58.4 and 59.1 (C-5, C-11), 81.7 (C-2), 110.0 (C-7), 122.2 (C-9), 123.1 (C-10), 124.2 (C-8), 138.2 (C-10a), 145.8 (C-6a), 167.5 (C=O, ester) and 187.1 (C=O, ketone); signals for C-1a and C-5a were not detected; *m/z* 300 ($M^+$, 34), 255 (25), 226 (26), 213 (37), 199 (100), 184 (29), 168 (81), 153 (31), 144 (40) and 130 (17).

**(2*R**,5*S**,11*R**)-4,6-Dimethyl-1-oxo-3,4-oxaza-1,2,3,4,5,6-hexahydro-2,5-methanocyclohepta[*b*]indole-11-carboxylic acid 11c.** This *compound* (137 mg, 48%) was obtained from the reaction of **6e** in refluxing dichloromethane (for 3 h), mp 193–195 °C (from methanol–diethyl ether) (Found: C, 62.88; H, 5.00; N, 9.60. Calc. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78%); $\nu_{max}$(Nujol)/cm$^{-1}$ 3600–2200 (O–H, vbr), 1710 (C=O, acid) and 1645 (C=O, conjugated); $\delta_H$(DMSO) 2.17 (3 H, br, 4-$CH_3$), 3.79 (1 H, s, 11-H), 3.94 (3 H, s, 6-$CH_3$), 4.58 (1 H, s, 5-H), 5.34 (1 H, s, 2-H), 7.27 (1 H, t, Σ*J* 14.6, 9-H), 7.34 (1 H, t, Σ*J* 15.3, 8-H), 7.65 (1 H, d, *J* 8.0, 7-H) and 7.95 (1 H, d, *J* 7.3, 10-H); $\delta_C$(DMSO) 30.4 (6-$CH_3$), 40.6 (br, 4-$CH_3$), 58.3 and 59.3 (C-5, C-11), 82.8 (C-2), 111.3 (C-7), 120.2 (C-9), 122.6 (C-10), 123.4 and 123.5 (C-8 and C-1a), 137.9 (C-10a), 148.2 (C-6a), 169.6 (C=O, acid) and 189.3 (C=O, ketone); a signal for C-5a was not detected; *m/z* 286 ($M^+$, 11), 285 (73), 240 (100), 226 (47), 213 (78), 199 (44), 182 (27), 168 (16), 153 (21), 143 (17) and 130 (8).

**(2*R**,5*S**)-4,6-Dimethyl-1-oxo-3,4-oxaza-1,2,3,4,5,6-hexahydro-2,5-methanocyclohepta[*b*]indole 11d.** This *compound* was obtained from the reaction of **6c** (116 mg, 48%) as well as from the reaction of **6f** (94 mg, 39%) in refluxing dichloromethane for 15 h as an oil (Found: C, 69.28; H, 5.72; N, 11.51. Calc. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56%); $\nu_{max}$(neat)/cm$^{-1}$ 1650 (C=O); $\delta_H$ 2.32 (3 H, s, 4-$CH_3$), 2.56 (1 H, d, *J* 11.3, *endo* 11-H), 2.89 (1 H, ddd, *J* 4.0, 5.6, 11.3, *exo* 11-H), 3.85 (3 H, s, 6-$CH_3$), 4.62 (1 H, d, *J* 5.6, 5-H), 4.79 (1 H, d, *J* 4.0, 2-H), 7.23–7.46 (3 H, m, 7-, 8-, 9-H) and 8.22 (1 H, d, *J* 6.6, 10-H); $\delta_C$ 30.3 (6-$CH_3$), 41.6 (4-$CH_3$), 43.8 (C-11), 60.0 (C-5), 82.9 (C-2), 109 (C-7), 121.9 (C-9), 123.1 (C-10), 124.0 (C-8), 124.3 (C-1a), 137.8 (C-10a), 147.7 (C-6a) and 190.7 (C=O, ketone); a signal for C-5a was not detected; *m/z* 242 ($M^+$, 79), 213 (28), 199 (100), 184 (37), 168 (53), 158 (30), 144 (25) and 131 (31).

**Dimethyl 4-methyl-3-methylimino-1,2,3,4-tetrahydrocyclopenta[*b*]indole-1,2-dicarboxylate 12a {⟸ dimethyl 4-methyl-3-methylamino-1,4-dihydrocyclohepta[*b*]indole-1,2-dicarboxylate 12b}.** This *compound* was isolated from the reactions of **6a** (15%), **7a** (29%) and **7b** (10%) in dichloromethane and from the reaction of **7a** (16%) in boiling toluene, mp 199–201 °C (from dichloromethane–diethyl ether) (Found: C, 65.00; H, 6.00; N, 8.80. Calc. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91%); $\nu_{max}$(Nujol)/cm$^{-1}$ 3250 and 3150 (NH), 1720 (C=O) and 1625 (C=N); $\delta_H$(enamine tautomer) 3.35 (3 H, d, *J* 5.5, N-$CH_3$, enamine, it changes to singlet upon addition of $D_2O$), 3.70, 3.75, 3.98 (9 H, three s, two $OCH_3$, 4-$CH_3$), 4.56 (1 H, s, 1-H), 7.17 (1 H, t, Σ*J* 14.6, 7-H), 7.23–7.40 (2 H, m, 5-, 6-H), 7.69 (1 H, d, *J* 7.7, 8-H), 8.05 (1 H, br, NH, exchangeable); $\delta_H$(imine tautomer; low intensity signals) 3.42 (3 H, s, =N-$CH_3$), 3.75, 3.78, 3.97 (9 H, three s, 4-$CH_3$, two $OCH_3$), 4.42 and 4.78 (2 H, two s, 1-, 2-H), 7.17 (1 H, t, Σ*J* 14.6, 7-H), 7.23–7.40 (2 H, m, 5-, 6-H) and 7.69 (1 H, d, *J* 7.7, 8-H); $\delta_C$(mixture of tautomers) 30.3, 34.0, 34.8, 41.2, 45.0, 45.7, 50.5, 52.2, 52.6, 52.7, 53.5, 99.5, 99.8, 110.4, 110.7, 119.7, 120.3, 120.7, 120.8, 122.5, 122.7, 123.7, 124.4, 125.4, 126.7, 127.2, 140.0, 143.5, 143.9, 158.1, 167.6, 170.8, 171.6 and 172.4; *m/z* 314 ($M^+$, 60), 282 (27), 255 (10), 223 (100), 209 (41), 195 (41), 181 (47), 168 (35), 154 (26), 140 (33), 127 (30), 77 (29) and 59 (39).

**4-Methyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole-1,3-dione 13.** This *compound* was obtained from the reactions of **7a**, **7b**, **8c** and **8f** in refluxing toluene (1–2 h) in 19, 55, 25 and 20% yield, respectively. Compound **13** was also detected in lower amounts (10%) in the product of the corresponding reaction of **8c** in refluxing dichloromethane; mp 228–231 °C (from dichloromethane–diethyl ether) (Found: C, 72.25; H, 4.59; N, 6.93. Calc. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1670 and 1715 (C=O); $\delta_H$ 3.47 (2 H, s, $CH_2$), 4.07 (3 H, s, $CH_3$), 7.34–7.60 (3 H, m, 5-, 6-, 7-H) and 8.08 (1 H, d, *J* 7.9, 8-H); $\delta_C$ 31.3 ($CH_3$), 50.2 ($CH_2$), 111.4 (C-5), 123.4 (C-7), 124.0 (C-8), 128.0 (C-6), 132.9 (C-8a), 144.9 and 149.5 (C-4a, C-3a), 188.6 and 188.9 (two C=O); a signal for C-1a was not detected; *m/z* 199 ($M^+$, 100), 171 (30), 156 (18), 143 (70), 128 (41), 114 (34) and 102 (25).

### Crystal data for compound 11a

$C_{16}H_{16}N_2O_4$, $M = 300.31$. Monoclinic, $a = 9.316(6)$, $b = 15.273(6)$, $c = 11.004(6)$ Å, $\beta = 105.96(1)°$, $V = 1505.3(14)$ Å$^3$, space group $P2_1/n$ (alt. $P2_1/c$, No. 14), $Z = 4$, $D_x = 1.325$ g cm$^{-3}$. Transparent prisms, crystal dimensions 0.40 × 0.30 × 0.25 mm, $\mu$(Mo-K$\alpha$) = 0.097 mm$^{-1}$.

### Data collection and processing

Mar Research Image Plate Scanner. Arndt-Wonacott oscillation method, graphite monochromated Mo-K$\alpha$ radiation $\lambda = 0.710\ 73$ Å. 95 Frames measured with oscillation range of two degrees with an exposure time of 120 s per frame. The crystal-detector distance was 75 mm. Data were processed using the XDS package.[19] The program MARSCALE (incorporated into XDS) gave 9862 reflections, 2707 of them considered unique with $R_{merge} = 0.04$, in a range of $2.41 \le \theta \le 24.86°$ ($0 < h < 11$, $0 < k < 18$, $-13 < l < 12$). Reflections observed 2593 [$I > 2\sigma(I)$].

### Structure analysis and refinement

Most atom positions were found by direct methods using the program SHELXS-86.[20] SHELXL-93[21] revealed the position of all remaining atoms, including hydrogens, by difference Fourier synthesis. Atomic scattering factors from SHELXL-93. Refinement by full-matrix least-squares calculations on $F^2$ using SHELXL-93 with anisotropic thermal factors for all non-hydrogen atoms and isotropic thermal factors for hydrogen atoms located from difference synthesis. Maximum shift/error ratio for the last cycle of refinement was less than 0.001 and the final difference Fourier map showed residual electron density peaks from −0.27 to 0.28 e Å$^{-3}$. No. of data/parameters 2507/200 goodness-of-fit on $F^2 = 1.078$. Final factors $R = 0.0559$ for $2507F_o > 4\sigma(F_o)$, $R_w = 0.1417$, weighting scheme $w = 1/[\sigma^2(F_o)^2 + (0.072P)^2 + 0.8018P]$ with $P = [\max(F_o^2,0) + F_c^2]/3$. All computations were performed on a VAX9000 computer. Fig. 1 was drawn using the PLATON-94[22] program. Supplementary tables with atomic coordinates, anisotropic displacement coefficients, hydrogen atom parameters, bond lengths and angles and structure factor tables have been deposited with the Cambridge Crystallographic Data Centre.§ All requests for this material should be accompanied by a full bibliographic reference together with the serial number CCDC 207/85.

§ For details of the Supplementary Publication Scheme, see *Instructions for Authors* (1997), *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1.

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