

## Regioselective Synthesis of Heterocycles and Theoretical Studies

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We report a 1,3-dipolar cycloaddition reaction between a oxazolium 5-oxide derivative with chloroacrylonitrile or ethyl propiolate as dipolarophiles, in order to obtain substituted pyrrolizidines. Experimentally we found that the reaction is regiospecific with chloroacrylonitrile and regioselective with ethyl propiolate. The secondary attractive orbital interactions from the Frontier Molecular Orbital Theory, the differences in stability of the possible biradical intermediaries postulated for the reaction and some hindrance effects, explain the regioselectivity observed experimentally.

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## Introduction.

We have been interested for some time in the synthesis of *N*-bridge substances as potential pharmacological active drugs [1-4].

Previous synthesis of these substances were reported as multiple-step procedures [5,6]. We have described a two step stereospecific route of synthesis of these substances with high overall yields, the key step being the cycloaddition of a dipolarophile to an easily available *N*-acyl-2-aminoacid [1-3]. We have been also interested in the theoretical aspects of the 1,3-dipolar cycloaddition reactions, used in our previous work, in order to obtain a better understanding of our experimental results [7].

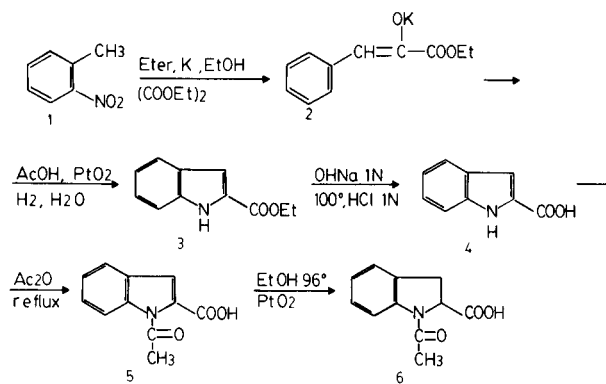
A considerable amount of studies have been reported in the last decade about the nature of the cycloaddition reactions. The main subject of controversy has been the synchronicity of the reaction and the experimental facts involved in it. The stereospecificity, the activation entropy, the activation energy, the solvent effect, the periselectivity, the regioselectivity and the reactivity of the dipolarophiles [8a-d], [9a-d] have been used as arguments in favor of one or other mechanism.

Our theoretical study for the 1,3-dipolar cycloaddition between substituted cyclic azomethine ylides and the ethylenic dipolarophile chloroacrylonitrile, which experimentally have shown to be regiospecific [4], showed it to occur in a concerted asynchronous way through a two step reaction with the successive formation of both new sigma bond *via* an intermediate with biradical character [7]. The reaction has a low potential barrier between the intermediate and the second transition state. Experimentally this reaction was shown to be regiospecific, the minimum energy potential surface calculated for it explains the regioselectivity observed [7].

In this paper we report a 1,3-dipolar cycloaddition reaction between an oxazolone 5-oxide derivative obtained

from a substituted indoline with chloroacrylonitrile or ethyl propiolate as dipolarophiles, in order to obtain substituted pyrrolizidines. Experimentally we found that the reaction is regiospecific with chloroacrylonitrile and regioselective with ethyl propiolate. Here we propose a theoretical explanation for the regioselectivity of the system.

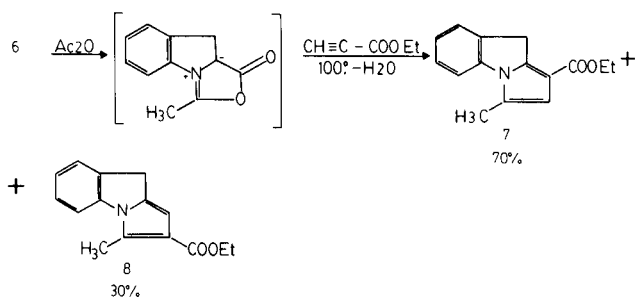
Scheme I



## Chemistry.

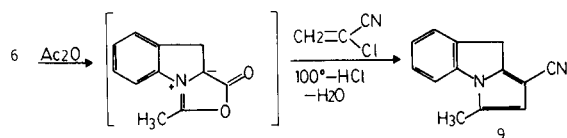
In order to obtain the 1,3-dipole, we synthesized 2-*N*-acetylindolinecarboxylic acid (**6**) (Scheme I). We found that the reduction of 2-*N*-acetylindolinecarboxylic acid may be done with normal quantities of catalyst, though a previous publication [10] indicates an equal amount to the weight of the substrate. The 1,3-dipole was generated "*in situ*" with acetic anhydride and the cycloaddition of the dipolarophiles was accomplished in the same pot without isolation of the 1,3-dipole. The reaction with ethyl propiolate (Scheme II) as dipolarophile afforded compounds **7** and **8** in a 70/30 ratio. The two products were isolated by preparative tlc and identified by  $^1\text{H}$  nmr.

Scheme II



The reaction with 2-chloroacrylonitrile (Scheme III) was regioselective and compound 9 was the only product in the crude reaction product. After work up it was isolated in 70% yield.

Scheme III



### Theoretical Considerations.

One alternative in order to explain the regioselectivity and regioselectivity found in the reactions studied is to consider the perturbational molecular orbital theory (PMO) [11] applied to the frontier molecular orbitals (FMO) [12]. According to Sustmann's [13] classification within Fukui's frontier orbital approximation the reactions are HOMO (HO) controlled (the interaction of the HO 1,3-dipole with the LUMO (LU) dipolarophile is the greatest). In dealing with asymmetric 1,3-dipoles and dipolarophiles four possible approximations are possible, Figure 1 and Figure 2. The geometries calculated for

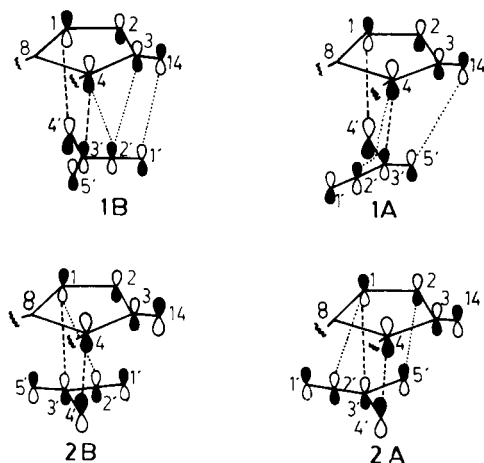


Figure 1. Chloroacrylonitrile as the dipolarophile. FMO interactions, --primary orbital interactions, ... secondary orbital interactions.

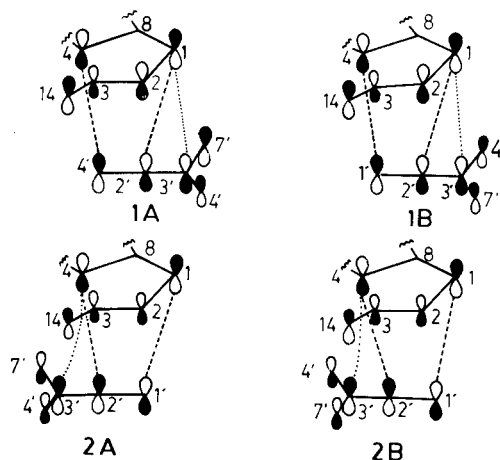


Figure 2. Ethyl propiolate as the dipolarophile. FMO interactions, -- primary orbital interactions, ... secondary orbital interactions.

compounds 7 to 9, 1,3-dipole and dipolarophiles, as well as the atom numbering used are shown in Figure 3, these calculations were carried out by means of the semiempirical MNDO [14] method with full geometry optimization.

The coefficients of the atomic orbital (AO) 2p<sub>z</sub> and the energy of HO and LU of the reactives are shown in Table 1.

The perturbational molecular second order energy was calculated for each possible approximation in parallel planes at 1.75 Å of distance [15] following eq 1, where

$$\Delta E = - \sum_{\text{occup.}} \sum_{\text{unoccup.}} \frac{2}{E_{LU} - E_{HO}} (\sum C_a C_b \gamma_{ab}) \quad 1$$

$C_a$  and  $C_b$  are the coefficients of the AO 2p<sub>z</sub> of each reaction center,  $E_{LU}$   $E_{HO}$  are the energy of the FMO of dipolarophile and 1,3-dipole respectively and  $\gamma_{ab}$  is the two center resonance integral obtained with eq 2, where  $S_{ab}$  is the two

$$\gamma_{ab} = S_{ab}(\beta_a + \beta_b)/2 \quad 2$$

center overlap integral Slater type and  $\beta$ 's are the characteristic parameters of the atoms. The calculated perturbational energy differences for each approximation of both reactions are shown in Table 2. Therefore, the most favorable approximation conducts to a product that had not been obtained in the reaction with chloroacrylonitrile and that was minority in the reaction with ethyl propiolate. At this point we studied the possible secondary attractive orbital interactions. In order to estimate in a quantitative way these secondary orbital interactions in all the possible approximations we calculated the values of  $C_a C_b \gamma_{ab}$ , for a sigma overlap. The results are shown in Table 3. The approximation 1B is the most favorable on the basis of the second order interactions between the nitrile group of the dipolarophile and the carbonilic group of the 1,3-dipole for the reaction with chloroacrylonitrile.

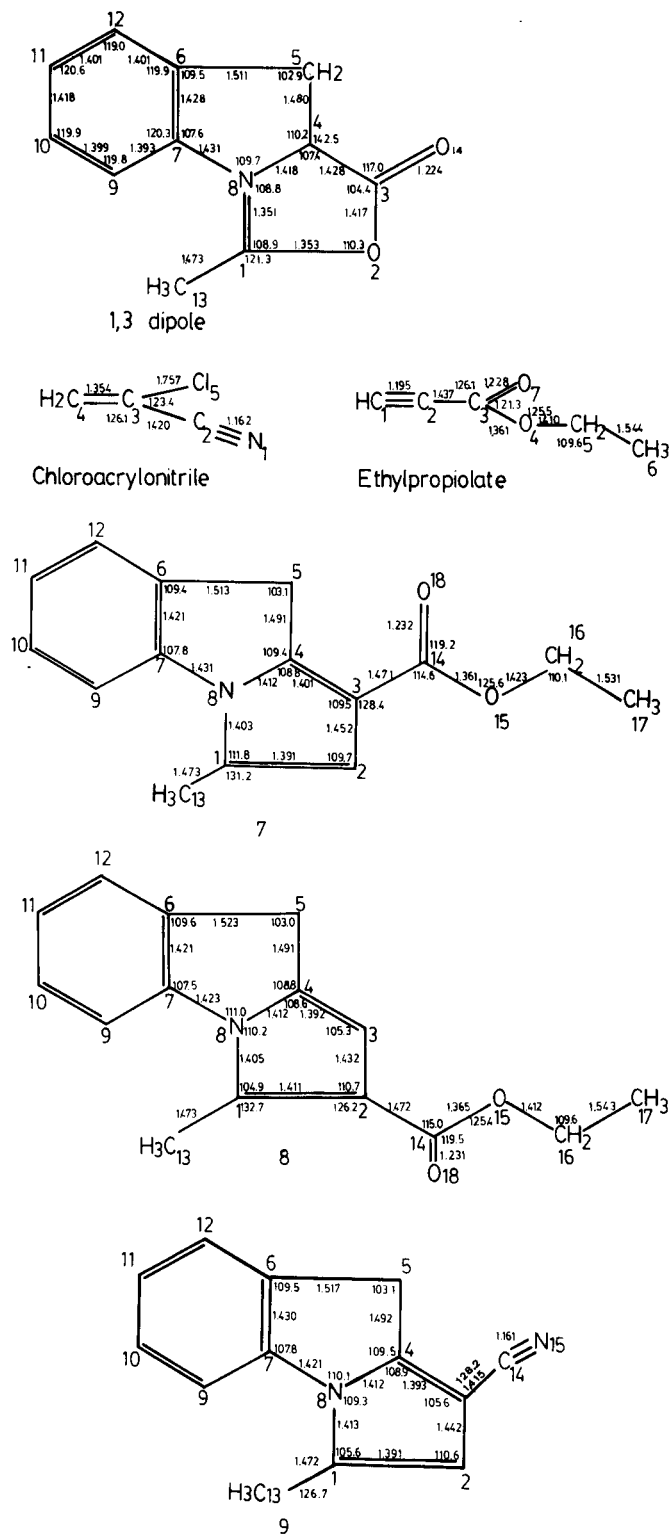


Figure 3. Bond distances (angstrom), bond angles (degrees).

Meanwhile the approximation 2A or 2B are the most favorable for the reaction with ethyl propiolate. Then the

frontier orbital theory explains the experimental results only if we include the secondary orbital interactions at the transition state level. Besides, the steric hindrances were analyzed according to the possible approximation geometries for both reactions, using a PC model software [16] with a "space filling mode" proportional to the van der Waals radius and internuclear distances, and we found that the bulky carboxylic group of the ethyl propiolate produces a bigger steric hindrance than the nitrile group and the chloro atom of the chloroacrylonitrile.

We have not considered the rehybridization effect and the possible stabilization by charge transfer in the study of the ethyl propiolate reaction to calculate the MNDO potential surface energy of the different approximations, in order to estimate the electronic repulsion effects in each one of them. Several rotamers were analyzed for two of the four approximations (1A and 1B) due to the free possible rotation of the methyl groups of the 1,3-dipole. Therefore, the hydrogens of the methyl group of the 1,3-dipole may interact with both oxygen atoms of the ethyl propiolate in the approximations 1A and 1B and the hydrogens of the methylene group ( $C_6$ ) of the 1,3-dipole may interact with both of the oxygen atoms of the dipolarophile in the approximations 2A and 2B.

The rotamers with the longest and shortest distances between the oxygen-hydrogen atoms of the all approximation complexes were studied using the optimized geometries of the 1,3-dipole and the dipolarophiles, fixing the reaction centers in parallel planes 1.75 Å apart and defining the new sigma bonds. Then the energy of each rotamer was calculated by MNDO method without optimization (Table 4). The less hindered approximation is 1B, but a difference of only 9 Kcal/mole is observed for approximation 2B. The model used in the study of the steric effect in the reaction with ethyl propiolate is not valid to study the reaction with chloroacrylonitrile. Whereas the change of hybridization in the reaction centers,  $sp$  to  $sp^2$ , of the acetylenic dipolarophile lets the substituents in the same approximation plane, the process  $sp^2$  to  $sp^3$  of the ethylene dipolarophiles pulls the substituents out of that plane making negligible the steric hindrance.

On the other hand, theoretical calculations for the complete potential surface of these reactions as well as for Diels-Alder cycloadditions carried out with semiempirical or ab-initio methods proposed these reactions to be placed in a concerted nonsynchronous process or in a two step mechanism involving a biradical intermediate.

Previous MNDO calculations for 1,3-dipolar cycloaddition reactions between substituted cyclic azomethine ylides and the dipolarophile chloroacrylonitrile [7] explained the regioselectivity observed experimentally on the basis of an asynchronous mechanism.

Based on these previous results and instead of applying

Table 1  
FMO Energy and Coefficients 2pz of the 1,3-Dipole and Dipolarophiles

		1,3-Dipole				
		Coefficients				
	Energy (eV)	C <sub>1</sub>	C <sub>2</sub>	C <sub>3</sub>	C <sub>4</sub>	N <sub>8</sub>
HOMO	-7.969338	0.46992	-0.16836	-0.14695	-0.70431	0.10885
LUMO	-1.118275	-0.47243	0.20651	-0.02987	-0.25982	0.24451
		C <sub>9</sub>	C <sub>10</sub>	C <sub>11</sub>	C <sub>12</sub>	O <sub>14</sub>
		-0.02241	0.03253	0.03413	-0.01521	0.39533
		0.28061	-0.17434	0.41183	-0.12340	0.03514
		Ethyl Propiolate				
		Coefficients				
	Energy (eV)	C <sub>1</sub>	C <sub>2</sub>	C <sub>3</sub>	O <sub>4</sub>	O <sub>7</sub>
HOMO	-11.475147	-0.43112	-0.37811	-0.56567	0.18993	0.43927
LUMO	0.267039	0.54912	-0.43242	0.12369	-0.43902	0.54481
		Chloroacrylonitrile				
		Coefficients				
	Energy (eV)	N <sub>1</sub>	C <sub>2</sub>	C <sub>3</sub>	C <sub>4</sub>	Cl <sub>7</sub>
HOMO	-10.792657	-0.29694	-0.13809	0.59114	0.62256	-0.38867
LUMO	-10.792657	0.32176	-0.21997	-0.57226	0.71114	0.10112

Table 2  
Perturbational Second Order Energy

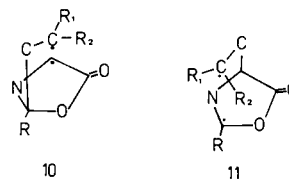
Dipolarophile	Approximations	ΔE (eV)
Chloroacrylonitrile	1A or 1B	-11.627
	2A or 2B	-12.650
Ethyl Propiolate	1A or 1B	-4.956
	2A or 2B	-4.277

Table 3  
Secondary Attractive Orbital Interactions

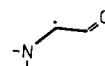
		Chloroacrylonitrile		
Approximations	Atoms	γ <sub>ab</sub> (eV)	γ <sub>ab</sub> C <sub>a</sub> C <sub>b</sub> (eV)	Σ(γ <sub>ab</sub> C <sub>a</sub> C <sub>b</sub> )
1A	O <sub>14</sub> C <sub>15'</sub>	-1.745	0.070	0.105
	C <sub>4</sub> C <sub>2'</sub>	-0.952	0.035	
1B	C <sub>3</sub> C <sub>2'</sub>	-1.414	0.046	0.199
	O <sub>14</sub> N <sub>1'</sub>	-0.931	0.118	
	C <sub>4</sub> C <sub>2'</sub>	-0.952	0.035	
2A	C <sub>1</sub> C <sub>2'</sub>	-0.817	0.085	0.119
2B	C <sub>1</sub> C <sub>2'</sub>	-0.817	0.084	
	O <sub>2</sub> C <sub>15'</sub>	-2.066	0.035	

		Ethyl Propiolate		
Approximations	Atoms	γ <sub>ab</sub> (eV)	γ <sub>ab</sub> C <sub>a</sub> C <sub>b</sub> (eV)	
1A	C <sub>1</sub> C <sub>3'</sub>	-1.328	0.353	
1B	C <sub>1</sub> C <sub>3'</sub>	-1.328	0.353	
2A	C <sub>4</sub> C <sub>3'</sub>	-1.178	0.469	
2B	C <sub>4</sub> C <sub>3'</sub>	-1.178	0.469	

FMO theory we can assume that all these reactions occur through a nonsynchronous biradicaloid mechanism, the energy of the transition state should differ little from those of the corresponding biradicals. As Dewar [17] has pointed out it would be possible to predict their regioselectivities in a qualitative sense by assuming that the transition state corresponds in each case to the biradical. Since any conjugative substituent stabilizes radicals and since the stabilization is greater if the substituent is in the radical position we can propose two possible biradicals for the compounds under study. Now we have to consider which



radical derived from the 1,3-dipole is the most stable, if that corresponding to structure **10** or that of structure **11**. Previous calculations for this type of biradical for which R = H clearly indicates structure **10** as the most stable, the allylic analog radical, is more stable than that of structure



**11**. The methyl substituent at the radical center of **11** not being a conjugative substituent does not exert a stabiliza-

Table 4

MNDO Energies (Heat of Formation); Ethyl Propiolate as the Dipolarophile

Approximations	Rotamers	Atoms	Distances (Å)	$\Delta E_1$ (Kcal/mole)	$\Delta E_2$ (Kcal/mole)
1A	1	H-O <sub>7'</sub>	1.97	$E_1-E_2 = 63.0$	$E_2-E_3 = 39.9$
		H-O <sub>4'</sub>	0.94		
	2	H-O <sub>7'</sub>	1.28		
		H-O <sub>4'</sub>	1.70		
1B	3	H-O <sub>7'</sub>	1.58	$E_4-E_5 = 63.9$	$E_6-E_3 = 9.0$
		H-O <sub>4'</sub>	1.52		
	4	H-O <sub>7'</sub>	0.78		
		H-O <sub>4'</sub>	2.12		
2A	5	H-O <sub>4'</sub>	1.10	$E_5-E_6 = 48.0$	
2B	6	H-O <sub>7'</sub>	0.96		

tion effect strong enough to make structure **11** more stable than **10**.

### Conclusion.

On the basis of the biradical stabilization postulated above we can conclude that the favored transition states of these reactions would have a similar geometry to that of structure **10** in which both new sigma bonds are being created to a different extent. If this is so the regioselectivity predicted for the reaction is that observed experimentally. The regioselectivity observed for the reaction with the dipolarophile ethyl propiolate can be ascribed to a lower difference in energy between the two possible transition states leading to compounds **7** and **8** than that observed for the reaction with chloroacrylonitrile. The different stability between the possible biradicals could be estimated, from a FO point of view, considering the secondary attractive orbital interactions, as an important effect that stabilizes the transition states of these cycloaddition reactions, so as to overcome the primary orbital interactions. Besides the steric hindrance is important in these reaction pathways.

The regiospecificity found in the chloroacrylonitrile reaction is in account with the values calculated for the  $\Sigma(C_a C_b \gamma_{ab})$ . The most favorable approximation 1B has an overlap value two fold over the other possible approximation that would conduct to the other regioisomer (Table 3). Meanwhile, the difference between the overlap values calculated for the possible approximations with ethyl propiolate reaction is not so important and both isomers are obtained in a 70:30 ratio according to those values. Besides, the steric hindrance found in the approximation that conducts to the majority product favors the loss of regiospecificity in this reaction. So, the quantitative evaluation of the secondary attractive orbital interaction proposed here is a good way to weight the contribution of each one of them to the stabilization of the approximations. This approach could also have a useful synthetic ap-

plication predicting the regioselectivity of those cycloaddition reactions with possible secondary orbital interaction.

### EXPERIMENTAL

Elemental analysis obtained for all new compounds reported, were performed by UMYMFOR, CONICET. All melting points were obtained in open capillary tubes and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 735-B spectrophotometer. The <sup>1</sup>H nmr spectra were determined with a Varian FT-80 instrument, all data being related to internal TMS. All solvents were technical grade and were purified in our laboratory, the reagents used were reagent grade.

#### Ethyl Indole-2-carboxylate (**3**).

A solution of 25 ml of anhydrous ethyl alcohol in 20 ml of anhydrous ethyl ether was added dropwise to 3.91 g (0.1 mole) of potassium in 30 ml of anhydrous ethyl ether under nitrogen atmosphere. This mixture was stirred until all the potassium was dissolved and a solution of 14.6 g (0.1 mole) of ethyl oxalate in 250 ml of anhydrous ethyl ether was added dropwise. The mixture was stirred 10 minutes and 13.7 g (0.1 mole) of *o*-nitrotoluene were added. After 24 hours the solid was filtered, washed with ethyl ether and dried (sodium sulphate) to give 20.72 g (74%) of the potassium salt. Then 3 g (0.1 mole) of this material were dissolved in 20 ml of acetic acid and 20 mg of platinum oxide were added. The mixture was hydrogenated in a Parr apparatus under a hydrogen atmosphere at 32 psi. After shaking for 24 hours the mixture was filtered and 300 ml of water were added dropwise and the solid was filtered and dried to give 1.1 g (58%) of **3**, mp 125-128° (lit 121-123°).

#### Indole-2-carboxylic Acid (**4**).

A suspension of 7.2 g (38.0 mmoles) of ethyl indole-2-carboxylate in 95 ml of sodium hydroxide was refluxed in a steam bath 1 hour until all the solid was dissolved. The solution was acidified with hydrochloric acid 1*N* and the solid was filtered, washed with water and dried under reduced pressure to afford 5.4 g (90%) of **4**, mp 200-204° (lit 204-206°).

#### *N*-Acetylindole-2-carboxylic Acid (**5**).

A solution of 2.4 g (14.9 mmoles) of indole-2-carboxylic acid in

45 ml of acetic anhydride was refluxed 10 hours with stirring and then evaporated. The residue was triturated with 5 ml of methyl chloride and the solid obtained was collected and air dried to give 1.6 g (65%) of **(5)**, mp 162-165° (lit 164-166°) [10].

*N*-Acetylindoline-2-carboxylic Acid (**6**).

To a solution of 1.61 g (10 mmoles) of **5** in 50 ml of ethanol was added 500 mg of platinum oxide. The mixture was hydrogenated in a Parr apparatus under a hydrogen atmosphere at 32 psi. After shaking for 6 hours the mixture was filtered and evaporated to give a quantitative yield of **6**, mp 186-189° (literature 187-189°) [10], after recrystallization with ethyl alcohol.

1-Methyl-2-ethoxycarbonyl-9*H*-pyrrole[1,2-*a*]indole (**8**) and 1-Methyl-3-ethoxycarbonyl-9*H*-pyrrole[1,2-*a*]indole (**7**).

A mixture of 102 mg (0.5 mmole) of **6** and 0.4 ml of ethyl propionate dissolved in 0.8 ml of acetic anhydride was heated at 100° under nitrogen atmosphere for 10 hours. The solution was evaporated and recrystallized from ethanol to give 63 mg of a mixture of **7** and **8**. This mixture was separated on a silicagel GF254 preparative layer with benzene as eluent to give 44 mg (70%) of **7** and 19 mg (30%) of **8**; <sup>1</sup>H nmr (deuteriochloroform): for **7** δ 7.3 (m, 4H, aromatics), 6.4 (s, 1H, CH=), 4.25 (c, 2H, CH<sub>2</sub>-CH<sub>3</sub>), 3.95 (s, 2H, CH<sub>2</sub>), 2.55 (s, 3H, CH<sub>3</sub>), 1.35 (t, 3H, CH<sub>2</sub>-CH<sub>3</sub>) ppm; for **8** δ 7.3 (m, 4H, aromatics), 6.4 (s, 1H, CH=), 4.25 (c, 2H, CH<sub>2</sub>-CH<sub>3</sub>), 3.75 (s, 2H, CH<sub>2</sub>), 2.85 (s, 3H, CH<sub>3</sub>), 1.25 (t, 3H, CH<sub>2</sub>-CH<sub>3</sub>) ppm.

*Anal.* Calcd. for C<sub>15</sub>H<sub>15</sub>NO<sub>2</sub> (**7**): C, 74.68; H, 6.22; N, 5.80. Found: C, 74.35; H, 6.01; N, 6.16.

*Anal.* Calcd. for C<sub>15</sub>H<sub>15</sub>NO<sub>2</sub> (**8**): C, 74.68; H, 6.22; N, 5.80. Found: C, 74.44; H, 6.39; N, 5.75.

1-Methyl-3-cyano-9*H*-pyrrolo[1,2-*a*]indole (**9**).

A solution of 1.7 g (8.3 mmoles) of **6** and 8 ml of chloroacrylonitrile in 18 ml of acetic anhydride was heated at reflux under a nitrogen atmosphere for 5 hours. The clear solution obtained was

evaporated and the residue was purified by column chromatography (silicagel, chloroform:benzene 9:1) to give 1.2 g (70%) of **9** which was crystallized from ethyl alcohol, mp 124-126°; ir (potassium bromide): CN 2,200 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 7.45 (m, 4H, aromatic), 6.3 (s, 1H, CH=), 3.95 (s, 2H, CH<sub>2</sub>), 2.6 (s, 3H, CH<sub>3</sub>) ppm.

*Anal.* Calcd. for C<sub>15</sub>H<sub>10</sub>N<sub>2</sub>: C, 80.42; H, 5.15; N, 14.43. Found: C, 80.10; H, 5.36; N, 14.50.

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