Pergamon

Tetrahedron, Vol. 52, No. 26, pp. 8853-8862, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00432-2

Pyridazinium Ylides. Regiochemistry.

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Abstract: For the first time in the series of pyridazine we have been accomplished a theoretical and experimenal study looking to the regiochemistry of the 3+2 dipolar cycloadditions of 3-(4-halogenophenyl) pyridazinium ylides to acrylate and propiolate of ethyl. Eight new pyrrolopyridazine heterocycles have been obtained. A possible mechanism of reaction is presented.

Introduction

In previous research works we have already presented the cycloaddition of 3-(4-halogenophenyl) pyridazinium ylides to symmetrical substituted olefins[1] and alkynes.[2,3]

The addition of pyridazinium ylides to non-symmetrical substituted olefins and alkynes presents interest because of the reaction pathway and because of the possibility of preparing new pyrrolopyridazine heterocycles which are difficult to obtained otherwise.

That is why we decided to conduct, for the first time in the series of pyridazinium ylides, a theoretical and experimental study, regarding the regiochemistry of the reactions of 3-(4-halogenophenyl) pyridazinium ylides with acrylate and propiolate of ethyl.

The problem of orientation in cycloaddition reactions of cycloimmonium ylides to activated non symmetrical olefins and alkynes has interested many researchers[4,5,6] because addition of the dipole to the dipolarophile in a double sense has often been found, according to orbital, steric and electronic factors.

The theoretical studies which have been realized over a period of time,[7,8,9] regarding the regiochemistry of cycloaddition reactions of ylides (like dipole 1,3) to non symmetrical activated olefins or alkynes (like dipolarophil), have made use of the General Theory of Perturbation Limited of the Molecular Frontier Orbitals.[9, 10, 11, 12, 13]

Results and Discussion

The first part of the paper a theoretical study concerning the regiochemistry of cycloaddition reactions

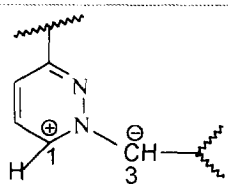
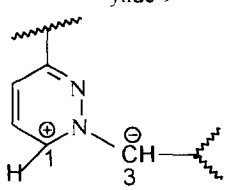
of 3-(4-halogenophenyl) piridazinium ylides to acrylate and propiolate of ethyl. We have used the General Theory of Perturbation Limited to the Molecular Frontier Orbitals.

The atomic charges, the coefficient of atomic orbitals and the values of the energy from the frontier molecular orbitals, have been calculated using the MNDO method (Table 1).[14, 15]

The geometry of pyridazinium ylides **7**-**10**, acrylate and propiolate of ethyl has been approximated using the data from chemistry literature.[4, 5]

Analysis of these data leads to the conclusion that 3-(4-halogenophenyl) pyridazinium ylides could have 1,3-dipolar structure of type **7**- **10a**, and, therefore, they can be used in cycloaddition reactions as 1,3-dipoles. In table 1, we present the energies (in eV) of frontier molecular orbitals (HOMO and LUMO), the coefficients of atomic orbitals p_Z, and the total atomic charges (in coulombs) of all the atoms involved in the cycloaddition reaction between ylides **9** and **10** and acrylate and propiolate of ethyl.

Table 1.

Molecule	Orbitale	Energy, eV	C_1	C_2	C_3
 ylide 9	HOMO	-7.8802	+0.3344	-	- 07341
	LUMO	-1.1810	+0.4995	-	+0.2628
	Q		-0.1517	-	-0.3120
 ylide 10	HOMO	-8.2520	+0.3316	-	-0.7399
	LUMO	-1.8160	+0.1267	-	-0.0444
	Q		-0.1598	-	-0.3233
$CH_2{=}CH\text{-}CO_2C_2H_5$	HOMO	-10.7625	+0.6196	+0.5789	-
	LUMO	-0.2246	+0.4927	-0.7131	-
	Q		-0.2245	+0.0798	-
$CH{\equiv}C{-}CO_2C_2H_5$	HOMO	-11.3143	-0.1791	-0.1794	-
	LUMO	+0.4186	+0.5655	-0.5621	-
	Q		-0.1856	-0.0311	-

Making use of the data in table 1, we have elaborated the correlation diagrams between HOMO and LUMO orbitals from ylides and dipolarophiles (Figure 1).

The analysis of the correlation diagrams shows that the interactions HOMO ylide - LUMO dipolarophile are characterized by the lowest interaction energies (ΔE_1 = 8.1048 eV, $\Delta E_1'$ = 7.4616 eV for ylide **9** and ΔE_2 = 8.4774 eV, $\Delta E_2'$ = 7.8342 eV for ylide **10**). This means that, in a reaction ylide (donor) - dipolarophile

(acceptor), under orbital or charge control, the most likely interaction will take place between the C_3 atom from ylide and C_2 from acrylate or propiolate of ethyl (figure 2).

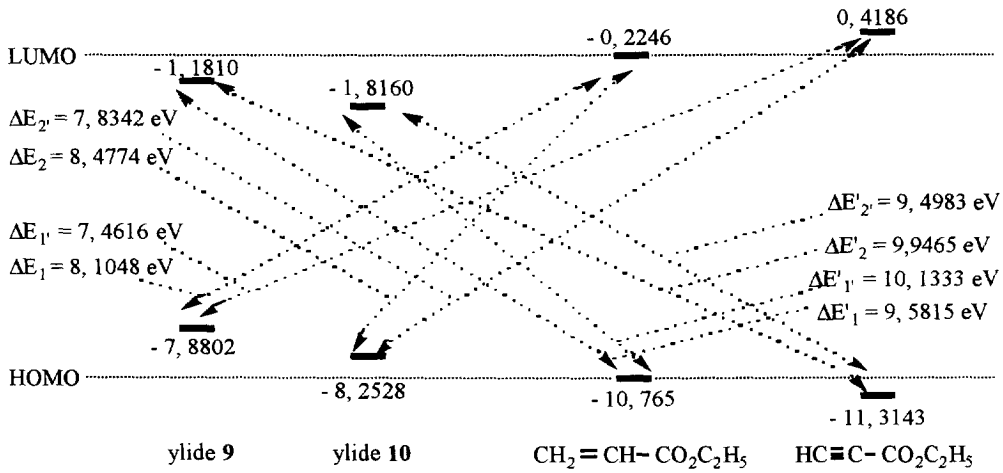


Figure 1. Correlation diagram between ylides **9** and **10** with acrylate and propiolate of ethyl.

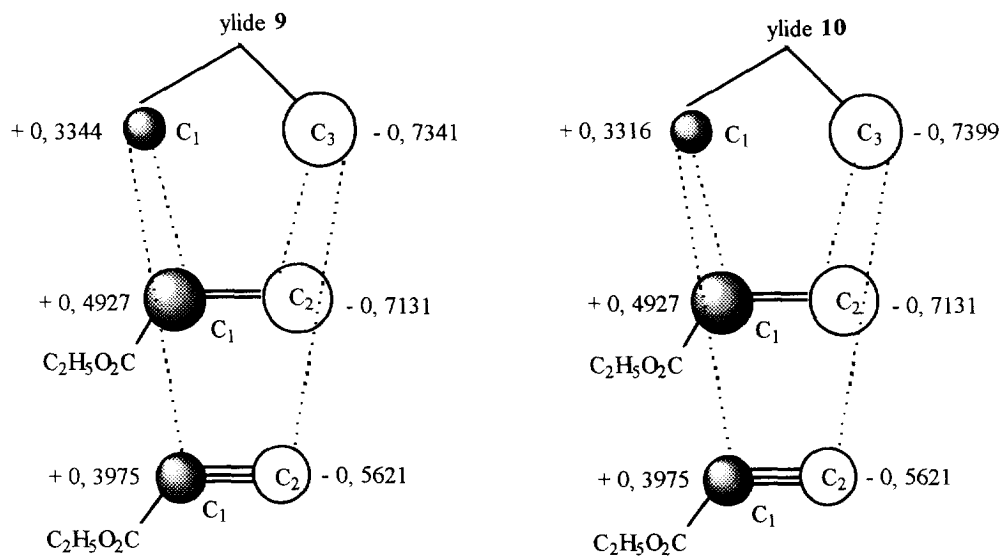


Figure 2. Graphical representation of the interaction between the frontier molecular orbitals.

As figure 3 shows, in the case of reactions between cycloimmonium ylides with acrylate or propiolate of ethyl, theoretically, there could be two reaction pathways (I and II) with the formation of two pairs of regioisomers (**A**, **A'** and **B**, **B'**). But analysing the data presented before, we notice that in the case of pyridazinium ylides the bound will be realized between the ylidic carbon and the non substituted carbon atom from the acrylate and propiolate of ethyl. This is in accordance with the electronic effects from the molecule of

acrylate and propiolate of ethyl, which means that the reaction is under charge control (path **I**, isomer **A**, figure 3).

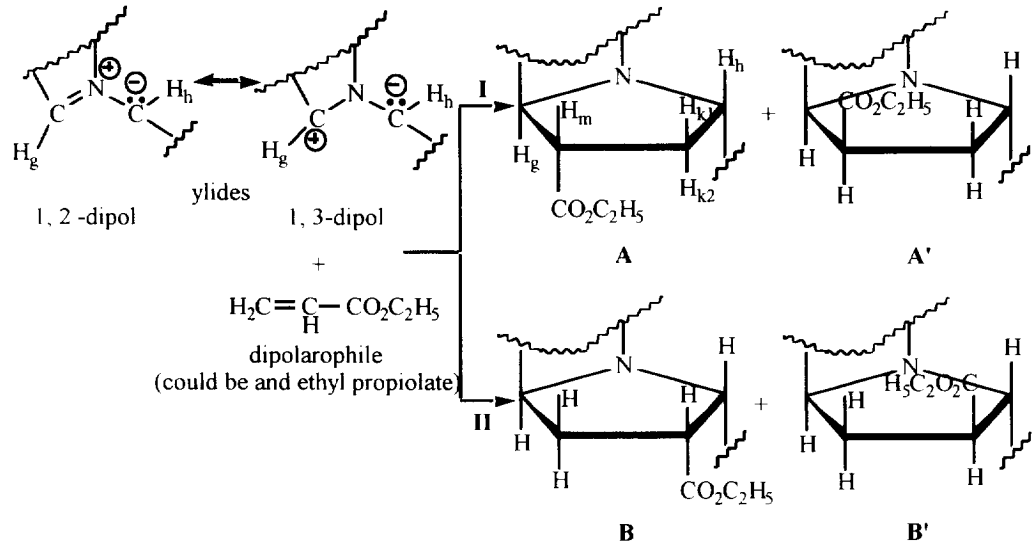


Figure 3. Reaction between cycloimmonium ylides and acrylate or propiolate of ethyl.

In order to verify the theoretical data presented, we have realized the 3+2 cycloaddition reactions between 3-(4-halogenophenyl) piridazinium ylides **7** - **10** (which were obtained *in situ* from the corresponding cycloimmonium salts[16]) and acrylate and propiolate of ethyl (figure 4). As can be seen in figure 4, a single regioisomer is obtained (type **A**, according to the **I** type way reaction from figure 3).

It is interesting that in the case of ylides **7** and **9**, under the same reaction conditions as ylides **8** and **10** (benzene refluxing, stirring, air), one does not obtain the expected tetrahydropyrrolopyridazinic heterocycles (type **A**, figure 4), but the dehydrogenated pyrrolopyridazinic compounds **15** and **16** are obtained (type **C**, figure 4).

The structure of **A** type products **11-14**, was proven through elemental and spectral analysis. Obviously, the data furnished by the elemental analysis are compatible with both types of regioisomers. But the data furnished by the IR and ^{1}HNMR spectra, confirm that **A**-type products are obtained, according to the **I** type route (figure 3).

In the IR specra of products **11** - **14** the C=O ester groups appear at wave numbers between 1705 cm^{-1} (**11** and **13**) and 1715 cm^{-1}(**12**). The ketone bands are present at wave numbers between 1660 cm^{-1}(**13**) and 1675 cm^{-1} (**12**). Both types of bands are very intense.

The ^{1}HNMR spectra supply essential data concerning the structure of **11** - **14** products. Analysis of the spectra, such as that of product **12** a representative of the series, reveals the following data:

The H_h proton appears at 5.67 ppm, like a triplet, which excludes the **B** and **B'** structures (where these protons would appear under the form of a doublet). The H_m and H_g protons are in *trans* position one against the other because: the H_m proton posses high vicinal coupling constants (J_{mk} = 7 Hz, J_{mg} = 6.5 Hz) and the H_g proton has a high vicinal coupling constant (J_{gm} = 6.5 Hz) and a low one (J_{gd} = 3.5 Hz). At the same time, the H_{k1} and H_{k2} protons appear like a multiplet, centred at 2.48 ppm, which shows that they are two non-equivalent protons.

On the basis of these data and of the data found in the chemistry literature,[4, 9] we have proposed a tetrahydropyrrolo structure for the **11 - 14** type compounds, as shown in fig. 3 and 4. All the remaining protons appear at chemical shifts and with coupling constants in accordance with the proposal structure.

As we have already mentioned, in the case of 3-(4-halogenophenyl) pyridazinium phenacylides **7** and **9**, when the reaction takes place under air, we have unexpectedly obtained the dehydrogenated products **15** and **16**, with pyrrolopyridazine structure (type **C**, figure 4).

The structure of the products **15** and **16** was proven by chemical neans as well as through elemental and spectral analysis. Thus we performed the reaction between ylides **7 - 10** and ethyl propiolate, and we obtained the pyrrolopyridazine products **17 - 20**. The structure of the products **15** and **16** was identical with the of products **17** and **19** [the elemental and spectral data (IR and ^{1}HNMR) were identical].

In the IR spectra of the products **15 - 20**, the C=O ester groups appear at wave numbers between 1695 cm^{-1} (**15** and **16**) and 1680 cm^{-1} (**18**). The ketone groups appear at wave numbers between 1637 cm^{-1} (**16**) and 1645 cm^{-1} (**15** and **20**). Both type of bands are very intense.

The ^{1}HNMR spectra confirm **C** type structure of products **15 - 20**. In compararison with the products **11 - 14**, the signals furnished by the proton H_g, H_m, H_h and H_{k1} are missing in the compounds **15 - 20**. H_k proton appears in products **15 - 20** at much higher chemical shifts (between 7.10 and 7.67 ppm, compared to the compounds **11 - 14**, where they appear at chemical shifts between 2.47 and 2.75 ppm), because now they are heteroaromatic protons. The remaining protons appear at chemical shifts in accordance with the proposed structure.

The production of compounds **15** and **16** has made us suppose that, when the reaction between ylides **7** and **9** and ethyl acrylate has been carried out under air, compounds **11** and **13** are formed as unisolated intermediates. Most likely, under the catalytical action of the oxygen from air, those intermediates are dehydrogenated and compounds **15** and **16** are obtained according to the supposed reaction mechanism presented in figure 5.

In order to verify this hypothesis we have carried out the reaction between **7** and **9** ylides and ethyl acrylate in inert atmosphere, using nitrogen. As expected, we obtained the tetrahydropyrrolopyridazine compounds **11** and **13**. The structure of compound **11** and **13** was demonstrated through elemental and spectral (IR and ^{1}HNMR) analysis and we have already presented these data (see page 8856).

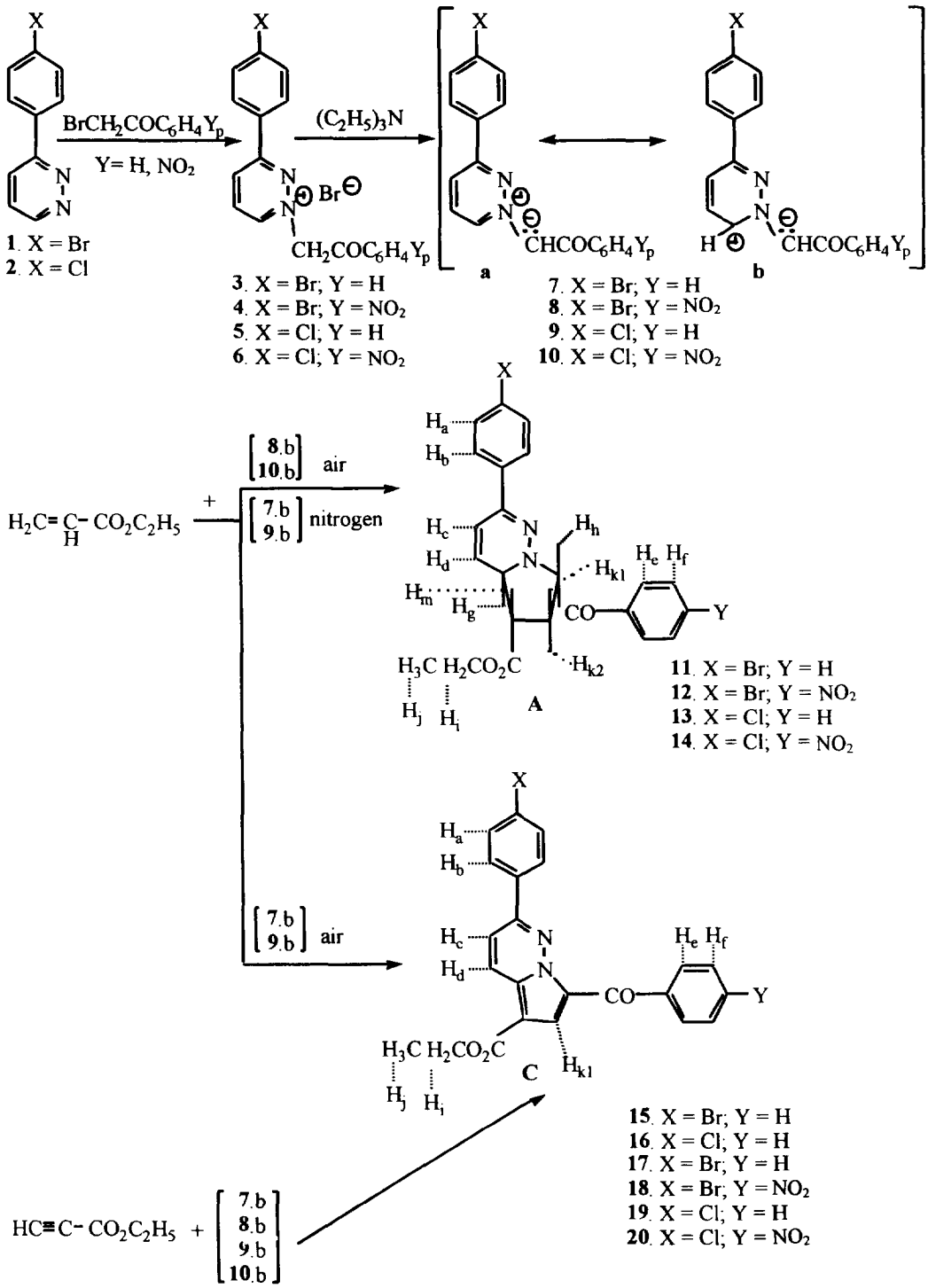


Figure 4. Reaction between 3-(4-halogenophenyl)-piridazinium ylides and acrylate and propiolate of ethyl.

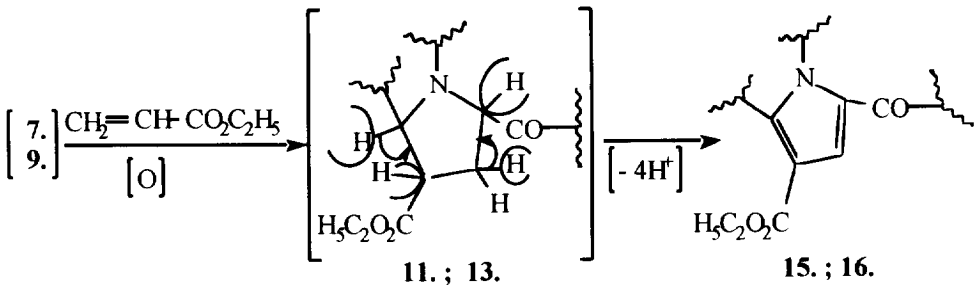


Figure 5. Reaction mechanism.

Conclusions

1. The cycloaddition reactions between 3-(4-halogenophenyl) pyridazinium ylides, ethyl acrylate and propiolate are regioselective. The reaction is HOMO controlled from ylides and only one regioisomer is formed, the one in which the ylide carbanion makes a new bound with the most electrophilic carbon from acrylate or propiolate of ethyl. The theoretical and experimenal data are in accordance with each other.

2. In the reactions between 3-(4-halogenophenyl) pyridazinium ylides **7** and **9** and ethyl acrylate, the reaction took place in a different way, and the unexpected pyrrolopyridazine heterocycles **15** and **16** have been obtained. A possible explanation could be the fact that ylides 7 and **9** are less reactive and more soluble possible than **8** and **10** ylides, and this makes the oxidative dehydrogenation of the intermediates **11** and **13** in accordance with the proposed mechanism in figure 5.

3. Eight new pyrrolopyridazine heterocycles have been obtained.

Experimental

The ^{1}HNMR spectra were obtained on a JEOL-60 spectrometer and were recorded in ppm downfield from an internal standard, TMS in $CDCl_3$. The coupling constants are given in Hertz.

The IR spectra were recorded with a SPECORD-71 spectrometer in KBr.

General procedure. 1 Mmol cycloimmonium salt was suspended in 20 ml anhydrous benzene. Then, 1 mmol acrylate or propiolate of ethyl and 1 mmol triethylamine (dissolved in 3 ml benzene) was added. The solution was heated ot reflux for two hours and the solvent evaporated on a steam bath. The crude product was recrystallized from an appropriate solvent. In the case of the reaction between ylides 7 and **9** and ethyl acrylate the reaction was also run under nitrogen.

2-(4-Bromophenyl)-6-carbethoxy-8-benzoyl-5,6,7,8-tetrahydropyrrolo [1,2-b] pyridazine (11). The reaction was run under nitrogen. The product was recrystallized from acetonitrile and red crystals were obtained. Yield 68%, mp 159-160 ^oC. Anal. $C_{23}H_{21}BrN_2O_3$. Calcd. C 60, 92; H 4, 63; N 6, 18. Found C 60,

80; H 4, 55; N 6, 05. IR (KBr, cm^{-1}): 1705 ($C=O_{ester}$), 1665 ($C=O_{ketone}$). ^{1}HNMR($CDCl_3$): δ : 7, 85 (m, $2H_e$, $2H_b$); 7, 60-6, 85(m, $2H_a$, $2H_f$, H_y); 5, 85 (m, H_c); 5, 60 (m, H_d); 5, 40 (m, H_h); 4, 25 (m, H_g); 4, 10 (q, $2H_i$, J_{ij}=6, 80); 3,20 (m, H_m); 2, 75 (m, H_{k1}, H_{h2}); 1,25 (t, $3H_j$, J_{ji}=6, 80).

2-(4-Bromophenyl)-6-carbethoxy-8-(4-nitrobenzoyl)-5,6,7, 8-tetrahydropyrrolo [1, 2-b] pyridazine (12). Recrystallized from acetonitrile. Acicular red crystals. Yield 72%, mp 109-110 °C. Anal. $C_{23}H_{20}BrN_3O_5$. Calcd. C 55, 42; H 4, 01; N 8, 43. Found C 55, 24; H 3, 94; N 8, 20. IR(KBr, cm^{-1}): 1715 ($C=O_{ester}$), 1675 ($C=O_{ketone}$). ^{1}HNMR ($CDCl_3$): δ: 8, 40(m, $2H_f$, $2H_e$); 7, 62-7, 20 (m, $2H_a$, $2H_b$); 6, 49 (d, H_c, J_{cd}=10, 30); 6, 15 (dd, H_d, J_{dc}=10, 30, J_{dg}=3, 50); 5, 67(t, H_h, J_{hk}=6,00); 4, 35 (t, H_g, J_{gd}=3,50, J_{gm}=6, 50); 4, 13 (q, $2H_i$, J_{ij}=7, 10); 3,30(q, H_m, J_{mg}=6, 50, J_{mk}=7, 00); 2, 48 (m, H_{k1}, H_{k2}, J_{kh}=6,00); 1,25(t, $3H_j$, J_{ji}=7, 10).

2-(4-Chlorophenyl)-6-carbethoxy-8-benzoyl-5,6,7,8-tetrahydropyrrolo [1,2-b] pyridazine (13). The reaction was run under nitrogen. Recrystallized from acetonitrile. Acicular cream coloured crystals. Yield 75%, mp 156 °C. Anal. $C_{23}H_{21}ClN_2O_3$. Calcd. C 67, 56; H 5, 14; N 6, 85. Found C 67, 48; H 5, 10; N 6, 60. IR (KBr, cm^{-1}): 1705 ($C=O_{ester}$), 1660 ($C=O_{ketone}$). ^{1}HNMR ($CDCl_3$): δ: 7, 85 (m, $2H_e$, $2H_b$); 7, 50-6, 90 (m, $2H_a$, $2H_f$, H_y); 5, 85 (m, H_c); 5, 60 (m, H_d); 5, 35 (m, H_h); 4, 20 (m, H_g); 4, 08 (q, $2H_i$); 3, 15 (m, H_m); 2, 75 (m, H_{k1}, H_{h2}); 1,25 (m, $3H_j$).

2-(4-Chlorophenyl)-6-carbethoxy-8-(4-nitrobenzoyl)-5,6,7,8-tetrahydropyrrolo [1,2-b] pyridazine (14). Recrystallized from ethanol. Acicular red crystals. Yield 65%, mp 115 - 116 °C. Anal. $C_{23}H_{20}ClN_3O_5$. Calcd. C 60, 86; H 4, 41; N 9, 26. Found C 60, 70; H 4, 25; N 9, 05. IR (KBr, cm^{-1}): 1710 ($C=O_{ester}$), 1670 ($C=O_{ketone}$). ^{1}HNMR ($CDCl_3$) :δ: 8, 35 (m, $2H_f$, $2H_e$); 7, 70-7, 17 (m, $2H_a$, $2H_b$); 6, 42 (d, H_c, J_{cd}=9, 50); 6, 28 (dd, H_d, J_{dc}=9, 50, J_{dg}=3,5o); 5, 67 (t, H_h, J_{hk}=6,00); 4, 30 (t, H_g, J_{gd}=4, 00, J_{gm} =6, 00); 4, 21(q, $2H_i$, J_{ij}=7, 00); 3,30 (q, H_m, J_{mg}=6, 00, J_{mk}=7, 00); 2, 47 (m, H_{k1}, H_{k2}, J_{kh}=6,00); 1,25 (t, $3H_j$, J_{ji}=7, 00).

2-(4-Bromophenyl)-5-carbethoxy-7-benzoyl-pyrrolo [1,2-b] pyridazine (15), (17). Recrystallized from acetonitrile. Prismatic cream dark coloured crystals. Yield 56%, mp 170-171 °C. Anal. $C_{23}H_{17}BrN_2O_3$. Calcd. C 61, 47; H 3, 78; N 6, 23. Found C 61, 28; H 3, 60; N 6, 00. IR(KBr, cm^{-1}): 1695 ($C=O_{ester}$), 1665 ($C=O_{ketone}$). ^{1}HNMR($CDCl_3$):δ: 8, 67 d, H_c, J_{cd}=10, 20); 8, 18-7, 80 (m, $2H_b$, H_d, $2H_e$); 7, 67-7, 34 (m, $2H_a$, $2H_f$, H_k, H_y); 4, 48 (q, $2H_i$, J_{ij}=7, 30); 1,48 (t, $3H_j$, J_{ji}=7, 30).

2-(4-Chlorophenyl)-5-carbethoxy-7-benzoyl-pyrrolo [1,2-b] pyridazine (16), (19). Recrystallized from acetonitrile. Prismatic cream coloured crystals. Yield 87%, mp 155-156 ^{o}C. Anal $C_{23}H_{17}ClN_2O_3$. Calcd. C 68, 23; H 4, 20; N 6, 92. Found C 68, 05; H 4, 10; N 6, 70. IR (KBr, cm^{-1}): 1695 ($C=O_{ester}$), 1637 ($C=O_{ketone}$). ^{1}HNMR ($CDCl_3$):δ: 8, 60 (d, H_c, J_{cd}=9, 50); 8, 05-7, 60 (m, $2H_b$, H_d, $2H_e$); 7, 55-7, 12 (m, $2H_a$, $2H_f$, H_k, H_y); 4, 40(q, $2H_i$, J_{ij}=7, 10); 1,47 (t, $3H_j$, J_{ji}=7, 10).

2-(4-Bromophenyl)-5-carbethoxy-7-(4-nitrobenzoyl)-pyrrolo [1,2-b] pyridazine (18). Recrystallized from *o*-xylene. Cream brownish crystals. Yield 54%, mp 214-215 ^{o}C. Anal. $C_{23}H_{16}BrN_3O_5$, Calcd. C 55, 87; H 3, 24; N 8, 50. Found C 55, 68; H 3, 10; N 8, 20. IR (KBr, cm^{-1}): 1680 ($C=O_{ester}$), 1640 ($C=O_{ketone}$). ^{1}HNMR ($CDCl_3$):δ: 8, 60 (d, H_c, J_{cd}=10, 30); 8, 40-8, 10 (m, Hd, 2Hf); 8, 05-7, 48 (m, $2H_b$, $2H_e$); 7, 45-7, 10 (m, $2H_a$, H_k); 4, 38 (q, $2H_i$, J_{ij}=7, 30); 1,51 (t, $3H_j$, J_{ji}=7, 30).

2-(4-Chlorophenyl)-5-carbethoxy-7-(4-nitrobenzoyl)-pyrrolo [1,2-b] pyridazine (20). Recrystallized from o-xylene. Dark brown crystals. Yield 58%, mp 223-224 ^{o}C. Anal. $C_{23}H_{16}ClN_3O_5$, Calcd. C 61, 40; H 3, 56; N 9, 34. Found C 61, 20; H 3, 38; N 9, 05. IR (KBr, cm^{-1}): 1690 ($C=O_{ester}$), 1645 ($C=O_{ketone}$). ^{1}HNMR ($CDCl_3$):δ: 8, 55 (d, H_c, J_{cd}=10, 00); 8, 38-8, 05 (m, H_d, 2Hf); 8, 00-7, 48 (m, $2H_b$, $2H_e$); 7, 42-7, 11 (m, 2Ha, H_k); 4, 40 (q, $2H_i$, J_{ij}=7, 30); 1,48 (t, $3H_j$, J_{ji}=7, 30).

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(*Received in UK* 16 *March* 1995; *revised* 16 *January* 1996; *accepted* 9 *May* 1996)