



Pyrrolodiazines. 4. Structure and Chemistry of 3,4-Dihydropyrrolo[1,2-*a*]pyrazine

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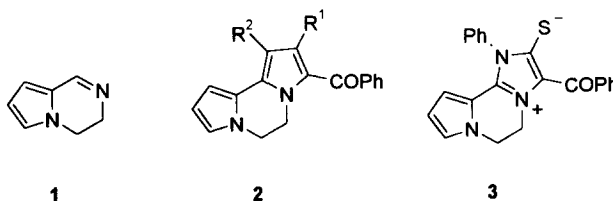
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Abstract. The structure of 3,4-dihydropyrrolo[1,2-*a*]pyrazine and its N-protonated form is studied by *ab initio* calculations. Examples of the reactivity of this poorly studied system are presented in which it is shown that the imino moiety does not react with dienes but does undergo inter- and intramolecular 1,3-dipolar cycloadditions by reaction of azomethine ylides of this bicyclic system with suitable dipolarophiles.

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INTRODUCTION

The 3,4-dihydropyrrolo[1,2-*a*]pyrazine **1** is the only known dihydroderivative of the pyrrolodiazine system¹ and its synthesis is reported in poor overall yield.² In the first report in this series we demonstrated that **1** could be prepared in an acceptable yield and transformed into some 2,2-biazole derivatives **2** and heterobetaines **3**³ despite its considerable instability.



Scheme 1

An interesting feature of this bicyclic heterocycle is the presumably high electronic density around the imine resulting from the π -excessive nature of the pyrrole moiety and the planarity imposed by the ethylene bridge. This characteristic spurred us to study its structure by *ab initio* calculations and we now report the results of this study along with further examples of the reactivity of this system, especially of some of its azomethine ylides in inter- and intramolecular 1,3-dipolar cycloadditions which in one case presents an interesting change in the regioselectivity of the reaction.

COMPUTATIONAL METHODS

The electronic structure of the 3,4-dihydropyrrolo[1,2-*a*]pyrazine **1** and its protonated form **1a** was studied using *ab initio* MO techniques. All the geometries were fully optimized at the closed shell Restricted Hartree-Fock (RHF) level of theory and using Möller-Plesset perturbation theory of second order (MP2). In both cases, the 6-31G* basis set⁴ was used to optimize the geometries. Charges were obtained from a Mulliken population analysis of the wave function. For the thermodynamic analysis the Hartree-Fock energy was corrected using the MP2 perturbation theory with frozen core MP2(FC)/6-31(d). Harmonic vibrational frequencies were computed at the RHF/6-31g(d) level (without exception all values were positive) and were used to determine the zero-point energy (ZPE) values, thermal corrections, and entropies for **1** and **1a**. ZPE were corrected with the factor 0.893. All the calculations were performed using the Gaussian 94 sets of programs.⁵

RESULTS AND DISCUSSION

Geometries and charges on heavy atoms of **1** and the N-protonated form **1a** (a model for either protonated or N-alkylated derivatives) are given in Figure 1 and the calculated geometrical parameters obtained are listed in Tables 1 and 2. The nitrogen atoms show negative charges, with N5 showing the highest electron density. Regarding the carbon atoms, C7 and C8 show comparatively high electronic densities, both in **1** and in **1a**, with C6 being affected by the conjugation with the imine group. Conversely, the imino C1 carbon shows comparatively lower electronic density in the salt structure **1a**. A similar effect would be expected in the quaternary salts. The fully optimized geometries show C₁ symmetries which are slightly non-planar, with the N2, C3 and C4 atoms being out of the plane of the pyrrole ring (-5.3°, -14.0° and +8.1° respectively). In **1a** these values for the parent atoms are -3.7°, -12.2° and +10.7° respectively. A value of 234.68 Kcal.mol⁻¹ for the gas-phase basicity (GB) and 227.03 Kcal.mol⁻¹ for the proton affinity (PA) of the 3,4-dihydropyrrolo[1,2-*a*]pyrazine (**1**) were obtained.⁶ In Fig 2 the HOMO and LUMO orbitals and their corresponding energies are presented. Only atomic orbitals with coefficients larger than 0.1 are depicted.

Although the feasibility of forming reactive azomethine ylides from quaternized salts of **1** has already been verified, the low stability of **1** at room temperature coupled with to the hygroscopic character of its salts was a serious limitation in our initial report, which focussed mainly on the reactivity of the 2-phenacyl-3,4-dihydropyrrolo[1,2-*a*]pyrazinium bromide, the most stable salt obtained.³ We recently found that distillation of **1** under reduced pressure, followed by immediate quaternization allowed us to isolate for the first time the 2-ethoxycarbonylmethyl salt **4a** and the trimethylsilylmethyl salt **4b** with a higher degree of purity. (Scheme 1). However all our attempts to isolate the 2-amino salt **4c** by amination of **1** with O-(mesitylenesulfonyl)-hydroxylamine (MSH)⁷ were fruitless, with extensive decomposition of the amination reagent being observed.

Although our previous attempts to trap the non-stabilized ylide generated from **4b** by fluoride-induced desilylation resulted in complex reaction mixtures with no evidence for the formation of the cycloadducts,³ our

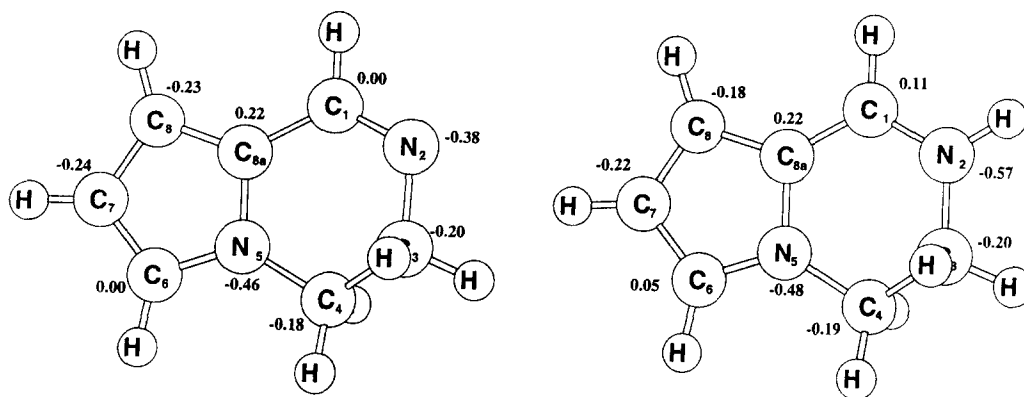


Figure 1. Optimized geometries and atomic charges for 3,4-dihydropyrrolo[1,2-*a*]pyrazine (**1**) (left) and the N-protonated form **1a** (right) obtained at the HF/6-31G** level.

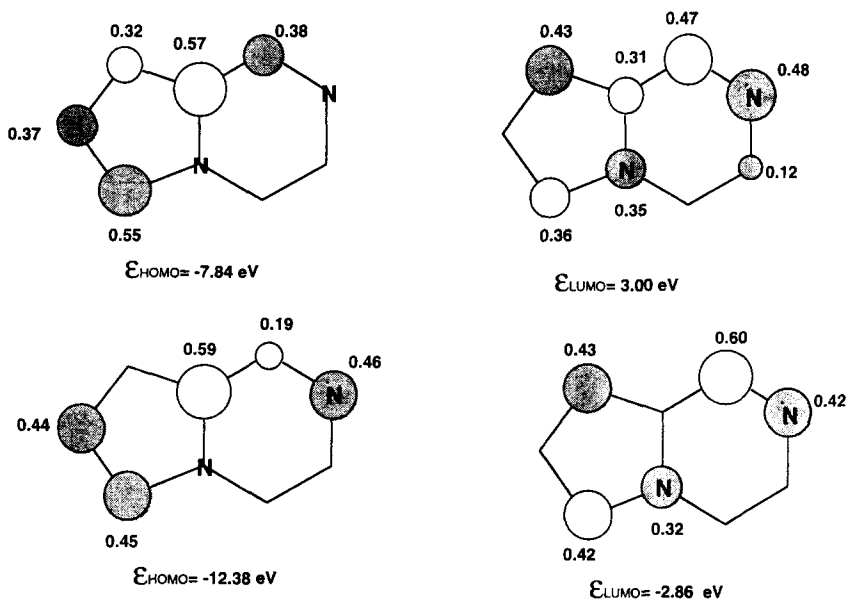


Figure 2. HOMO and LUMO of the 3,4-dihydropyrrolo[1,2-*a*]pyrazine (**1**) (above) and the N-protonated form **1a** (below) with the orbital energies and the renormalized HF/6-31G* MO coefficients

Table 1. Optimized Geometrical Parameters for 3,4-dihydropyrrolo[1,2-*a*]pyrazine (1)^a

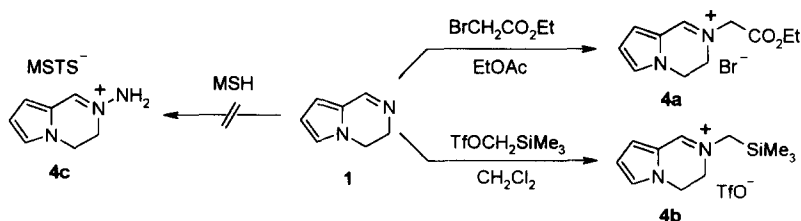
| Bond lengths | HF/6-31G* | MP2/6-31G* | Bond angles | RHF/6-31G* | MP2/6-31G* |
|--------------|-----------|------------|-------------|------------|------------|
| C8a-C1 | 1.458 | 1.445 | C8a-C1-N2 | 124.3 | 124.9 |
| C1-N2 | 1.258 | 1.298 | C1-N2-C3 | 117.4 | 114.7 |
| N2-C3 | 1.455 | 1.469 | N2-C3-C4 | 114.8 | 114.2 |
| C3-C4 | 1.528 | 1.525 | C3-C4-N5 | 108.5 | 107.5 |
| C4-N5 | 1.488 | 1.455 | C4-N5-C8a | 120.2 | 119.4 |
| N5-C8a | 1.364 | 1.378 | N5-C8a-C1 | 117.8 | 117.8 |
| N5-C6 | 1.353 | 1.366 | C8a-C8-C7 | 106.8 | 107.3 |
| C6-C7 | 1.366 | 1.392 | C8-C7-C6 | 107.1 | 107.7 |
| C7-C8 | 1.418 | 1.409 | C7-C6-N5 | 108.6 | 107.7 |
| C8-C8a | 1.365 | 1.397 | C6-N5-C8a | 109.1 | 109.9 |
| | | | N5-C8a-C8 | 108.4 | 107.4 |
| | | | C6-N5-C4 | 129.8 | 129.7 |

^a Bond lengths are in angstroms and bond angles in degrees

Table 2. Optimized Geometrical Parameters for N-Protonated 3,4-dihydropyrrolo[1,2-*a*]pyrazine (1a)^a

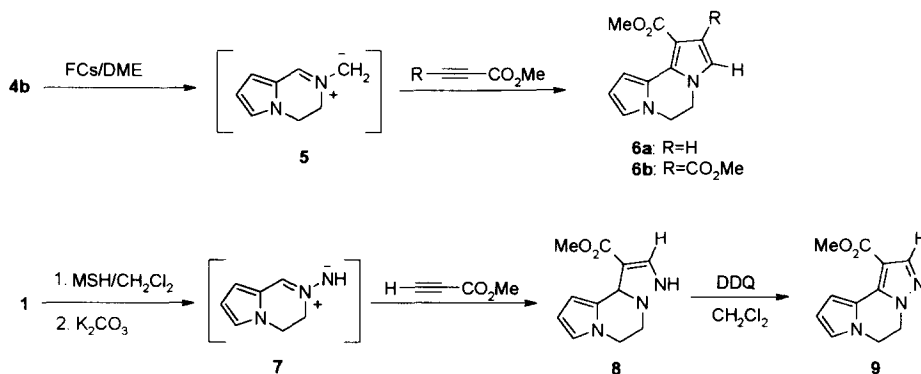
| Bond lengths | HF/6-31G* | MP2/6-31G* | Bond angles | RHF/6-31G* | MP2/6-31G* |
|--------------|-----------|------------|-------------|------------|------------|
| C8a-C1 | 1.384 | 1.396 | C8a-C1-N2 | 121.0 | 120.6 |
| C1-N2 | 1.307 | 1.321 | C1-N2-C3 | 121.5 | 120.9 |
| N2-C3 | 1.466 | 1.470 | N2-C3-C4 | 110.6 | 109.7 |
| C3-C4 | 1.528 | 1.522 | C3-C4-N5 | 108.5 | 107.7 |
| C4-N5 | 1.457 | 1.462 | C4-N5-C8a | 120.7 | 120.5 |
| N5-C8a | 1.386 | 1.386 | N5-C8a-C1 | 119.3 | 118.9 |
| N5-C6 | 1.324 | 1.354 | C8a-C8-C7 | 107.1 | 106.7 |
| C6-C7 | 1.386 | 1.404 | C8-C7-C6 | 107.0 | 108.0 |
| C7-C8 | 1.382 | 1.391 | C7-C6-N5 | 109.8 | 108.5 |
| C8-C8a | 1.398 | 1.414 | C6-N5-C8a | 108.5 | 108.9 |
| | | | N5-C8a-C8 | 107.6 | 107.9 |
| | | | C6-N5-C4 | 129.6 | 129.1 |

^a Bond lengths are in angstroms and bond angles in degrees



Scheme 2

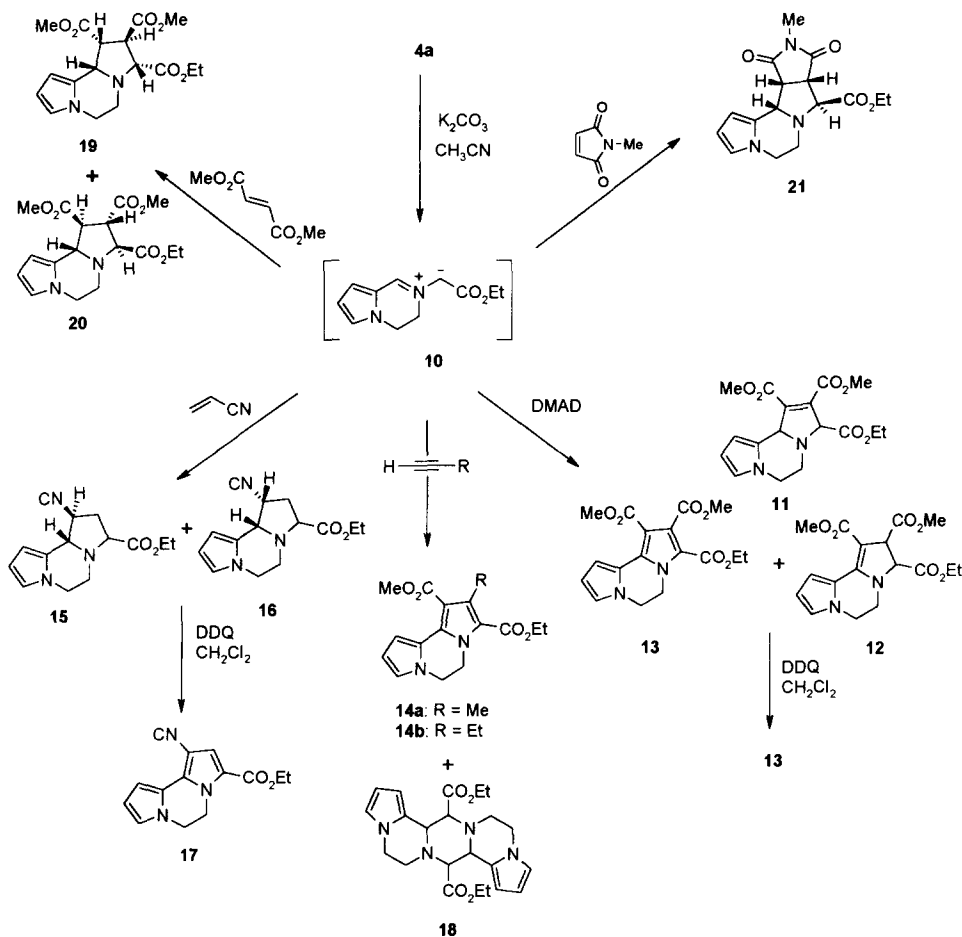
latest experiments have shown it possible to trap the ylide **5** from **4b** allowed us to trap **5** with dimethylacetylenedicarboxylate (DMAD) and methyl propiolate, although the best yields obtained for the 5,6-dihydrodipyrrolo[1,2-*a*,2',1'-*c*]pyrazine derivatives **6** were less than 20%. Moreover, although as stated earlier all our attempts to isolate and characterize the N-amino salt **4c** were unsuccessful, we were able to obtain ¹H NMR evidence that this salt had been formed. For this reason we tried to generate the aminide **7** *in situ* and react it with dipolarophiles. Only in the case of reaction with methyl propiolate were we able to isolate the cycloadduct **8**, albeit in low yield (8%). This dihydroderivative was quantitatively oxidized to the corresponding 1-methoxycarbonyl-5,6-dihydropyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine (**9**) with 2,3-dichloro-1,4-benzoquinone (DDQ) in CH₂Cl₂. The reaction with other dipolarophiles (DMAD, acrylonitrile, methylmaleimide) afforded complex mixtures from which any possible cycloaddition products could not be detected.



Scheme 3

The azomethine ylide **10**, generated from **4a** in a two-phase system, reacted with DMAD to yield a mixture of three compounds **11-13**. Although the three components of the mixture could not be separated by chromatography, ¹H NMR revealed the presence of the expected cycloaddition product **11**, along with the more stable isomer **12**, resulting from a 1,3-hydrogen shift. Both compounds oxidize easily to the major product, **13**, and consequently this was the only compound to be chromatographically isolated. This was also the only compound obtained when the mixture was oxidized with DDQ in CH₂Cl₂.

The regioselectivity of the cycloaddition was also investigated using unsymmetrical acetylenic dipolarophiles (ethyl and methyl propiolate) and electron-poor olefins (acrylonitrile). In both cases, the cycloadducts **14-16** had identical regiochemistry, corresponding to that predicted by FMO theory. While from the reaction of **4a** with propiolates only the fully aromatized derivatives **14a,b** were isolated, the reaction with acrylonitrile afforded a mixture of two compounds one of which, **15**, could be separated by chromatography. ^1H NMR shows that this



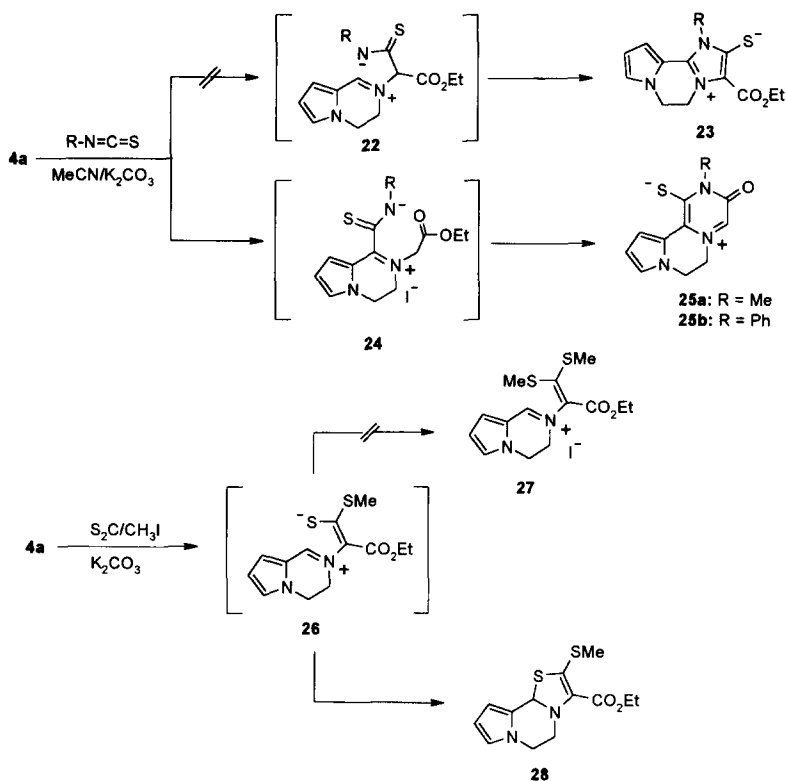
Scheme 4

compound corresponds to the C-1 (CN) regioisomer (doublet for $\text{H}_{10\text{b}}$ and triplet for H_3) arising from an *exo* approach of **4a** and the dipolarophile ($J_{1-10\text{b}} = 5.8$ Hz). The ^1H NMR of the isomer **16**, which could not be completely separated and purified by chromatography shows a coupling constant between H_1 and $\text{H}_{10\text{b}}$ of $J = 8.2$ Hz, which allowed the *cis* disposition to be assigned to these hydrogens in the cycloadduct, thus suggesting an *endo* approach during its formation. Oxidation of the mixture of **15** and **16** with DDQ gave the 1-cyano-3-ethoxy-

carbonyl-5,6-dihydropyrrolo[1,2-*a*;2',1'-*c*]pyrazine (**17**) in which H₂ appeared at $\delta=7.16$ ppm. It should be noted that the formation of the cycloadducts **14** is accompanied by variable amounts of the pentacyclic compound **18**. This compound which is ubiquitous, albeit in low yield, in all reactions involving the ylide **10** is formed by head-to-tail dimerization of this ylide, a favoured process when the iminium moiety, not integrated in the aromatic ring, shows high electrophilic character. Similar self-condensation reactions have been previously observed in the chemistry of related ylides.^{8,9}

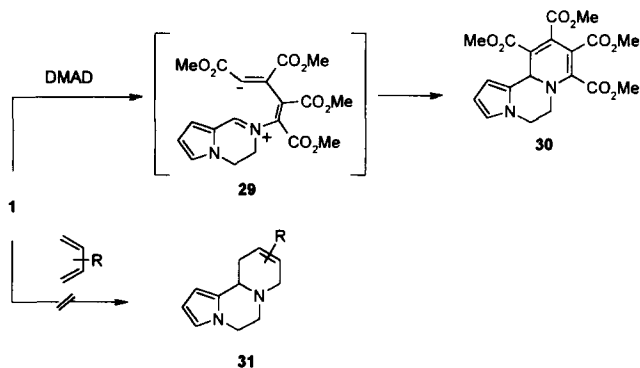
The stereoselectivity of the cycloaddition reaction of the ylide **10** was also studied using electron-poor alkenes. In the case of the reaction of **4a** with dimethyl fumarate, a mixture of the *trans* 1,2-dicarboxylic esters **19** and **20** was obtained in 31% and 21% yields respectively. The structure of these compounds was elucidated with the aid of ¹H NMR decoupling experiments. In the *endo* cycloadduct **19**, H_{10b} appears as a doublet with a coupling constant of $J=8.1$ Hz while the corresponding value for the *exo* product **20** is $J=6.0$ Hz. The coupling constant between H₁ and H₂ is $J=6.7$ Hz for both compounds and in **19** and **20** H₂ is coupled to H₃ with a coupling constant of $J=5.7$ Hz and $J=5.9$ Hz respectively, indicating a *trans* disposition in both compounds of the ethoxycarbonyl group at C₃ with respect to the methoxycarbonyl substituent at C₂. In contrast to this result, the reaction of methylmaleimide with **4a** afforded the *endo* cycloadduct **21** as the only reaction product. The stereochemical assignment of **21** was based on the coupling constants observed between H_{11b} and H_{11c} ($J=8.0$ Hz) and H_{11c} and H_{3a} ($J=8.0$ Hz) which suggest a *cis* disposition for these hydrogens while a *trans* coupling constant of $J=2.0$ Hz was observed for H_{3a} and H₄.

More unusual products were formed from the reaction of **4a** with heterocumulenes such as isothiocyanates and carbon sulphide. In the first case, the reaction of the ylide of **4a** with methyl- and phenyl isothiocyanate would normally be expected to produce the corresponding heterobetaines **23**, presumably via **22**, as we previously found with pyrrolo[1,2-*a*]pyrazinium ylides¹⁰ and phenacyl salts of **4a**.³ In this case, however, the structure of the products is consistent with the heterobetaines **25** which must be formed by initial attack of C-1 on the heterocumulene followed by cyclization of the intermediate **24** thus generated.¹¹ This change in the regioselectivity between the phenacyl and ethoxycarbonylmethyl ylides is associated with the acidities of the hydrogens of the methylene groups in both compounds. Although the acidities are not known, those corresponding to the analogous pyridinium derivatives were reported by Bordwell and *col.*¹² to have pK values of 14.10 for the ethoxycarbonylmethyl pyridinium salt and 10.7 for the phenacylpyridinium salt. In the light of this, differences in the ease of deprotonation between both salts are to be expected, which might affect the regioselectivity of the attack, especially if the intermediate is involved in a favourable intramolecular cyclization process. Whether the change in the regioselectivity observed between **4a** and the corresponding N-ethoxycarbonyl-pyrrolo[1,2-*a*]pyrazinium salt could be associated with the electronic differences in both systems is not obvious, and the unusual behaviour should be further investigated.



Scheme 5

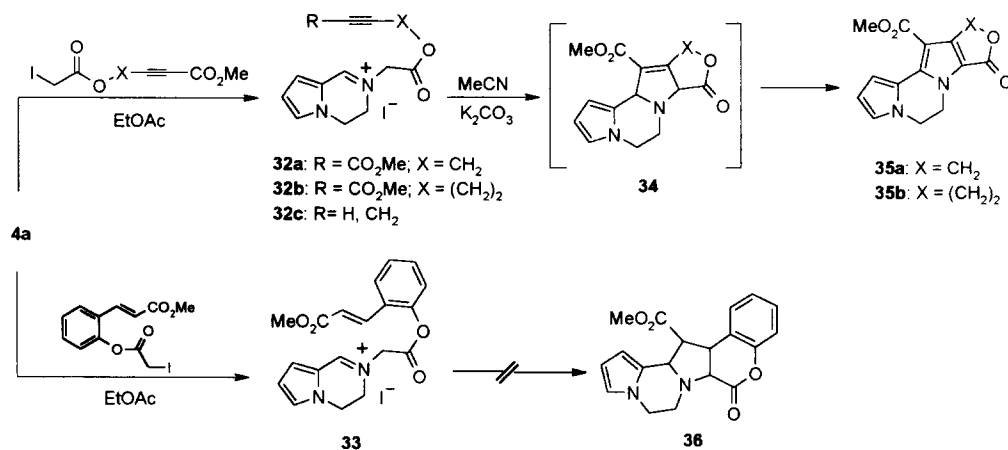
On the other hand, the ketene diacetal **27** or the precursor ylide **26**, which were the compounds expected from the reaction of **4a** with carbon sulphide/methyl iodide^{11,13} were not detected, with the tricyclic derivative **28** being isolated in moderate yield. Here, the non-aromatic character of the dihydropyrazinium ring would explain the electrophilic behaviour of the C1 position towards intramolecular attack of the sulfur atom, to give rise to **28**.



Scheme 6

Both the nucleophilic character of the imine nitrogen and the lack of aromaticity of the pyrazine moiety in **1** explain the high yield of **30** (61%) obtained in the reaction with DMAD. However, when **1** was tested as a dienophile in Diels-Alder processes with electron-rich dienes no traces of cycloadducts were detected. Under prolonging heating or Lewis acid catalysis, **1** extensively decomposed or gave polymeric materials. Electron-poor dienes were also tested and gave the same results.

Finally, intramolecular cycloaddition was also examined with different acetylenic and olefinic salts **32** and **33** which are suitable for intramolecular reactions. Salts **32** were prepared by N-alkylation of **1** with methyl 4-(iodoacetoxy)-2-butynoate (**32a**), 2-pentynoate^{3,14} (**32b**) and 3-iodoacetoxypropyne (**32c**) while **33** was obtained from the reaction of **1** and 3-[2-(iodoacetoxy)phenyl]acrylate.³ The treatment of salts **32a,b** with K₂CO₃ in dry MeCN, afforded the expected tetracyclic compounds **35a,b**, albeit in low yields (24% and 30% respectively). All our attempts to improve the yields were unsuccessful since these salts seem to be rather unstable either under the two-phase liquid-liquid conditions or by refluxing in toluene or xylene under basic or neutral conditions. However, salt **32c**, in which the acetylene was not activated by the presence of a carboxylate group, produced under the same conditions dimeric products related to **18**, with none of the expected cycloadduct being detected. Refluxing this salt in xylene gave similar results. As with **32c**, the attempted intramolecular process with the ylide generated from **33** afforded dimeric products as the main components of a complex reaction mixture.



Scheme 7

In conclusion, the structure of the 3,4-dihydropyrrolo[1,2-*a*]pyrazine **1** and its protonated form has been studied by *ab initio* calculations. The existence of a cyclic imine conjugated with a pyrrole moiety seems to generate a system which possesses a high electronic density nitrogen, which on quaternization should produce salts with a highly reactive carbon in the α -position. The isolation and purification of **1**, as reported here, allowed the preparation of suitable salts which could be employed in either inter- or intramolecular cycloadditions

to give novel tri- and tetracyclic systems containing two bridgehead nitrogens. In addition, based on the HOMO and LUMO energies calculated for this system, it was tested as a dienophile in [4+2] cycloadditions with appropriate dienes, with results which were however, unsuccessful in all cases.

Experimental

General Procedures. Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. ^1H NMR were recorded on a Varian Unity 300 spectrometer and were referenced to TMS. IR spectra were obtained on a Perkin-Elmer 1310 spectrophotometer. Microanalyses were performed on a Heraeus CHN Rapid analyzer and MS were obtained on a Hewlett-Packard 5988 A spectrometer. Chromatography was performed on silica gel 60 (230-400 meshes). All reagents were obtained from commercial sources and were used as acquired. Solvents were dried before use. The 3,4-dihydropyrrolo[1,2-*a*]pyrazine (**1**) was prepared following the reported procedure and was purified by distillation under reduced pressure (0.5 mm Hg, 50°C). The colourless oil obtained was immediately used.

2-[(Ethoxycarbonyl)methyl]-3,4-dihydropyrrolo[1,2-*a*]pyrazinium Bromide (4a). To 0.5 g (4.17 mmol) of freshly distilled 3,4-dihydropyrrolo[1,2-*a*]pyrazine (**1**) in 14 mL of EtOAc 0.56 mL (4.5 mmol) of ethyl bromoacetate was added. The mixture was refluxed for 2 h. The solvent was then evaporated under reduced pressure and the oily residue was triturated with MeCN and Et₂O to give 0.7 g (61%) of a dark green solid which was recrystallized from EtOH. Mp 194-196°C; $^1\text{H-NMR}$ (DMSO-*d*₆) δ 8.87 (s, 1H); 7.83-7.79 (m, 1H); 7.44 (d, 1H, J=4.2 Hz); 6.62 (dd, 1H; J=2.2 Hz, J=4.2 Hz); 4.88 (s, 2H); 4.44 (t, 2H, J=6.4 Hz); 4.21 (q, 2H; J=7.1 Hz); 4.10 (t, 2H, J=6.4 Hz); 1.24 (t, 3H, J=7.1 Hz) ppm; IR (KBr) ν_{max} 1741, 1630, 1347, 1129 cm⁻¹. Anal. Calcd for C₁₁H₁₃BrN₂O₂: C, 46.01; H, 5.27; N, 9.76. Found: C, 46.23; H, 5.08; N, 9.80.

2-[(Trimethylsilyl)methyl]-3,4-dihydropyrrolo[1,2-*a*]pyrazinium Trifluoromethanesulfonate (4b). A mixture of **1** (0.50 g, 4.1 mmol) and trimethylsilylmethyl trifluoromethane sulfonate (0.98 g, 4.1 mmol) in 20 mL of dry CH₂Cl₂ was stirred at room temperature under argon for 4 h. The solvent was removed under reduced pressure to leave a yellow solid which was filtered off and washed with Et₂O. Recrystallization from EtOH gave 1.11 g (77 %) of **4b** as a yellow powder. Mp 97-98°C; $^1\text{H-NMR}$ (DMSO-*d*₆) δ : 8.73 (s, 1H); 7.64-7.61 (m, 1H); 7.20 (dd, 1H, J=2.2 Hz, J=1.3 Hz); 6.51 (dd, 1H, J=2.2 Hz, J=4.0 Hz); 4.39 (t, 2H, J=6.6 Hz); 4.04 (t, 2H, J=6.6 Hz); 3.63 (s, 2H); 0.16 (s, 9H) ppm; IR (KBr) ν_{max} 3115, 1631, 1354, 1262, 1154, 1030 cm⁻¹. Anal. Calcd for C₁₂H₁₉F₃N₂O₃SSi: C, 40.44; H, 5.37; N, 7.86. Found: C, 40.26; H, 5.39; N, 7.68.

1-Methoxycarbonyl-5,6-dihydrodipyrrolo[1,2-*a*;2',1'-*c*]pyrazine (6a). To a mixture of 0.15 g (0.42 mmol) of **4b** in 10 mL of dry DME was added 64 mg (0.42 mmol) of CsF and 35 mg (0.42 mmol) of methyl propiolate. The mixture was refluxed under argon overnight. CH₂Cl₂ was then added and the organic phase was washed with H₂O and brine (2x10 mL). The organic extracts were dried over Na₂SO₄, filtered and evaporated to dryness. The oily residue was chromatographed using CH₂Cl₂ as eluent to give 16 mg (18%) of **6a** as a pale yellow oil. $^1\text{H-NMR}$ (CDCl₃) δ 7.31 (dd, 1H, J=1.5 Hz, J=4.0 Hz); 6.69 (dd, 1H, J=2.6 Hz, J=1.5 Hz); 6.62 (d, 1H, J=3.3 Hz); 6.53 (d, 1H, J=3.3 Hz); 6.25 (dd, 1H, J=2.6 Hz, J=4.0 Hz); 4.24-4.19 (m, 4H); 3.84 (s, 3H) ppm; IR (KBr) ν_{max} 1692, 1438, 1208, 1140, 1075 cm⁻¹; MS *m/z* (rel int) 216 (M⁺, 100); 185 (85); 158 (19); 130 (14). Anal. Calcd for C₁₂H₁₂N₂O₂: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.49; H, 5.64; N, 12.67.

1,2-Dimethoxycarbonyl-5,6-dihydrodipyrrolo[1,2-a;2',1'-c]pyrazine (6b). To a mixture of 0.15 g (0.42 mmol) of **4b** in 10 mL of dry DME was added 64 mg (0.42 mmol) of CsF and 60 mg (0.42 mmol) of DMAD. The mixture was refluxed under argon overnight. CH₂Cl₂ was then added and the organic phase was washed with H₂O and brine (2x10 mL). The organic extracts were dried over Na₂SO₄ then filtered and evaporated. The oily residue was chromatographed (hexane-EtOAc, 1:1) and the eluates rechromatographed (CH₂Cl₂) to give 21 mg (18%) of **6b** as a colourless oil. ¹H-NMR (CDCl₃) δ 7.14 (s, 1H, H₃); 6.86 (dd, 1H, J=1.5 Hz, J=3.8 Hz); 6.68 (dd, 1H, J=1.5 Hz, J=2.5 Hz); 6.21 (dd, 1H, J=3.8 Hz, J=2.5 Hz); 4.19 (s, 4H); 3.87 (s, 3H); 3.80 (s, 3H) ppm; IR (KBr) ν_{max} 1704, 1486, 1439, 1203, 1069 cm⁻¹; MS *m/z* (rel int) 274 (M⁺, 95); 243 (100); 213 (34); 184 (35); 157 (33). Anal. Calcd for C₁₄H₁₄N₂O₄: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.18; H, 5.00; N, 10.52.

Generation of salt **4c** and reaction with methyl propiolate

To a solution of 0.23 g (1.1 mmol) of MSH in 5 mL of dry CH₂Cl₂ at 0°C, was added 0.1 g (0.85 mmol) of **1**. After stirring for 5 min, 0.46 g (3.39 mmol) of K₂CO₃ and 0.22 g (2.5 mmol) of methyl propiolate were added. After stirring for 15 h at room temperature, the precipitate formed was filtered and washed with CH₂Cl₂. The filtrate was dried over Na₂SO₄ and evaporated to dryness. The residue was chromatographed (hexane-EtOAc 7:3) and the eluate subjected to a second chromatographic process (CH₂Cl₂) affording **8** (14 mg, 8%) as a yellow oil.

1-Methoxycarbonyl-1,2,5,6-tetrahydropyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (8). ¹H-NMR (CDCl₃) δ 6.82 (d, 1H, J=1.1 Hz); 6.51 (t, 1H, J=2Hz); 6.16 (dd, 1H, J=2.5 Hz, J=4.0Hz); 5.96-5.94 (m, 1H); 5.31 (s, 1H); 4.10-3.84 (m, 4H); 3.77 (s, 3H); 3.52-3.46 (m, 1H) ppm; IR (KBr) ν_{max} 1732, 1588, 1432, 1038 cm⁻¹; MS *m/z* (rel int) 219 (M⁺, 59); 160 (100); 159 (95); 119 (91).

1-Methoxycarbonyl-5,6-dihydropyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (9). Treatment of the dihydro-derivative **8** with DDQ (16 mg, 0.07 mol) in CH₂Cl₂ (2 mL) yielded the aromatized compound **9** as a colourless oil. ¹H-NMR (CDCl₃) δ 7.90 (s, 1H, H₂); 7.37 (dd, 1H, J=4.0 Hz, J=1.5 Hz); 6.80 (dd, 1H, J=2.5 Hz, J=1.5 Hz); 6.31 (dd, 1H, J=4.0 Hz, J=2.5 Hz); 4.50-4.46 (m, 2H); 4.35-4.31 (m, 2H); 3.87 (s, 3H) ppm; IR (KBr) ν_{max} 1705, 1490, 1208, 1092 cm⁻¹. Anal. Calcd for C₁₁H₁₁N₃O₂: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.49; H, 5.38; N, 19.41.

Reaction of **4a** with DMAD

To 0.25g (0.87 mmol) of **4a** in 15 mL of dry CH₃CN were added 308 mg (2.17 mmol) of DMAD and 480 mg (3.48 mmol) of anhydrous K₂CO₃. After stirring for 20 h at room temperature, the precipitate was filtered off and washed with CH₂Cl₂. The organic liquids were dried over Na₂SO₄ and evaporated and the oily residue was chromatographed. Elution with hexane-EtOAc (9:1) gave a mixture of the dihydroderivatives **11**, **12** and the aromatized compound **13**, 183 mg (61%). Treatment of the mixture with DDQ (120 mg, 0.52 mmol) in 10 mL of CH₂Cl₂ for 2 h gave **13** exclusively (146 mg, 81%) as a pale yellow solid.

3-Ethoxycarbonyl-1,2-dimethoxycarbonyl-5,6-dihydrodipyrrolo[1,2-a;2',1'-c]pyrazine (13). Mp 96-97°C (EtOH); ¹H-NMR (CDCl₃) δ 7.38 (dd, 1H, J=1.5 Hz, J=4.0 Hz); 6.77 (dd, 1H, J=1.5 Hz, J=2.5 Hz); 6.28 (dd, 1H, J=2.5 Hz, J=4.0 Hz); 4.78 (t, 2H, J=6.1 Hz); 4.28 (q, 2H, J=7.2 Hz); 4.22 (t, 2H, J=6.1 Hz); 1.33 (t, 2H, J=7.2 Hz) ppm; IR (KBr) ν_{max} 1705, 1439, 1257, 1208 cm⁻¹; MS *m/z* (rel int) 346 (M⁺, 100), 301 (16), 243 (57), 211 (36), 184(38). Anal. Calcd for C₁₇H₁₈N₂O₆: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.76; H, 5.12; N, 7.89.

Reaction of 4a with alkyl propiolates

To 0.2 g (0.69 mmol) of **4a** in 12 mL of dry MeCN were added 0.38 g (2.78 mmol) of K_2CO_3 and 1.04 mmol of methyl or ethyl propiolate. The reaction mixture was stirred at room temperature for 24 h. Then the precipitate formed was filtered and washed with CH_2Cl_2 (3x5 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated. Chromatography of the residue using a mixture of hexane-EtOAc (9:1) as eluent gave the corresponding cycloadducts **14a,b** and the dimeric derivative **18**.

3-Ethoxycarbonyl-1-methoxycarbonyl-5,6-dihydropyrrolo[1,2-a;2',1'-c]pyrazine (14a). Yield: 54 %. Mp 131-132 °C (white needles, EtOH); 1H -NMR ($CDCl_3$) δ 7.46 (dd, 1H, $J=1.5$ Hz; $J=3.6$ Hz); 7.44 (s, 1H, H_2); 6.76 (dd, 1H, $J=2.5$ Hz, $J=1.5$ Hz); 6.28 (dd, 1H, $J=2.5$ Hz, $J=3.6$ Hz); 4.81 (t, 2H, $J=6.1$ Hz); 4.29 (q, 2H, $J=7.1$ Hz); 4.23 (t, 2H, $J=6.1$ Hz); 3.86 (s, 3H); 1.36 (t, 2H, $J=7.1$ Hz) ppm; ^{13}C -NMR ($CDCl_3$) δ 164.03 (CO_2); 161.08 (CO_2); 133.81; 123.14; 121.97; 120.82; 120.22; 113.11; 109.53; 60.27; 51.14; 43.78; 43.05; 14.36 ppm; IR (KBr) ν_{max} 1707, 1685, 1257, 1203, 1092 cm^{-1} ; MS m/z (rel int) 288 (M^+ , 100), 260 (78), 229 (81), 155 (44). Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.36; H, 5.35; N, 9.48.

1,3-Diethoxycarbonyl-5,6-dihydrodipyrrolo[1,2-a;2',1'-c]pyrazine (14b). Yield: 48 %. Mp 76-78 °C (white needles, EtOH); 1H -NMR ($CDCl_3$) δ : 7.45 (dd, 1H, $J=1.5$ Hz, $J=3.9$ Hz); 7.43 (s, 1H, H_2); 6.73 (dd, 1H, $J=1.5$ Hz, $J=2.5$ Hz); 6.26 (dd, 1H, $J=2.5$ Hz, $J=3.9$ Hz); 4.78 (t, 2H, $J=6.2$ Hz); 4.33-4.21 (m, 6H); 1.37 (t, 3H, $J=7.1$ Hz); 1.35 (t, 3H, $J=7.1$ Hz) ppm; IR (KBr) ν_{max} 1693, 1479, 1255, 1202, 1159 cm^{-1} ; MS m/z (rel int) 302 (M^+ , 100), 274 (31), 246 (59), 229 (31), 202 (15). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.11; H, 6.43; N, 8.98.

8,16-Diethoxycarbonyl-5,6,8a,13,14,16,16a-octahydrodipyrrolo[1,2-a]pyrazinio[2,1-a:2',1'-d]pyrazine (18). Yield: 11%. Mp 241-243 °C (white powder, EtOH); 1H -NMR ($CDCl_3$) δ 6.58 (d, 1H, $J=3.0$ Hz); 6.54-6.52 (m, 1H); 6.31 (d, 1H, $J=2.5$ Hz); 6.15-6.12 (m, 2H); 5.23 (s, 1H); 4.23-3.89 (m, 10H); 3.70 (d, 1H, $J=16.4$ Hz); 3.44 (d, 1H, $J=16.4$ Hz); 3.41-3.33 (m, 1H); 3.21-3.16 (m, 2H); 2.99 (td, 1H, $J=11.4$, 4.4 Hz) ppm; IR (KBr) ν_{max} 1722, 1640, 1404, 1283 cm^{-1} ; MS m/z (rel int) 412 (M^+ , 62), 339 (53), 325 (32), 220 (100). Anal. Calcd for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.87; H, 6.90; N, 13.47.

Reaction of 4a with acrylonitrile

To 0.4 g (1.39 mmol) of **4a** in 15 mL of dry MeCN was added 0.77 g (5.57 mmol) of K_2CO_3 and 110 mg (2 mmol) of acrylonitrile. The reaction was stirred for 30 h at room temperature, the precipitate formed was filtered off and the organic phase dried over Na_2SO_4 and evaporated under reduced pressure. Chromatography of the residue using hexane-EtOAc (8:2) as eluent gave a mixture of the tetrahydroderivatives **15** and **16** (144 mg, 81%). Chromatography of the mixture allowed the separation of 33 mg of **15** as a colourless oil. Treatment of the mixture of **15** and **16** with DDQ (252 mg, 1.11 mmol) in 5 mL of CH_2Cl_2 for 1 h afforded the aromatized derivative **17** (88 mg, 62%) as a white solid.

1-Cyano(1R,10bR)- and (1S,10bS)-3-ethoxycarbonyl-1,2,3,5,6,10b-hexahydrodipyrrolo[1,2-a;2',1'-c]pyrazine [(±)15]. 1H -NMR ($CDCl_3$) δ : 6.61 (t, 1H, $J=2$ Hz); 6.19-6.17 (m, 2H); 4.60 (d, 1H, H_{10b} , $J=5.9$ Hz); 4.19 (q, 2H, $J=7.0$ Hz); 4.12-4.05 (m, 1H); 3.93-3.87 (m, 2H); 3.43 (q, 1H, H_1 , $J=6.0$ Hz); 3.34-3.26 (m, 2H); 2.52-2.45 (m, 2H); 1.28 (t, 3H, $J=7.0$ Hz); IR (KBr) ν_{max} 2243, 1731, 1450, 1189 cm^{-1} .

1-Cyano-3-ethoxycarbonyl-5,6-dihydrodipyrrolo[1,2-a;2',1'-c]pyrazine (17). Mp 154-155 °C (EtOH); 1H -NMR ($CDCl_3$) δ 7.16 (s, 1H, H_2); 6.94 (dd, 1H, $J=1.5$ Hz, $J=4.0$ Hz); 6.77 (dd, 1H, $J=1.5$ Hz, $J=2.5$ Hz); 6.30 (dd, 1H, $J=2.5$ Hz, $J=4.0$ Hz); 4.79 (t, 2H, $J=6.2$ Hz); 4.29 (q, 2H, $J=7.0$ Hz); 4.24 (t, 2H, $J=6.2$ Hz); 1.35 (t, 3H, $J=7.0$

Hz) ppm; IR (KBr) ν_{\max} 2219, 1699, 1479, 1255, 1098 cm^{-1} ppm; MS m/z (rel int) 255 (M^+ , 93); 227 (100); 182 (70); 180 (45); 129 (54); Anal Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46; Found: C, 65.54; H, 5.18; N, 16.29.

Reaction of 4a with dimethyl fumarate

To a mixture of 0.4 g (1.4 mmol) of 4a in 15 mL of dry MeCN was added 0.77 g (5.57 mmol) of anhydrous K_2CO_3 and 0.24 g (1.67 mmol) of dimethyl fumarate. The reaction was stirred at room temperature for 30 h. Then, the precipitate was filtered and washed with CH_2Cl_2 . The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The oily residue was chromatographed using hexane-EtOAc (1:1) as eluent to give a 60:40 mixture of 19 and 20. Recrystallization of the mixture from ethanol gave 19 as a white solid (150 mg (31%). From the mother liquids compound 20 was isolated as a colourless oil (100 mg, 21%).

1,2-Dimethoxycarbonyl (1R,2S,10bS)- and (1S,2R,10bR)-3-ethoxycarbonyl-1,2,3,5,6,10b-hexahydro-dipyrrolo[1,2- α ;2',1'-c]pyrazine [(±)-19]. Mp 106-108°C (EtOH); 1H -NMR ($CDCl_3$) δ 6.55-6.51 (m, 1H); 6.08 (dd, 1H, $J=2.5$ Hz, $J=3.6$ Hz); 5.75 (dd, 1H, $J=2.5$ Hz, $J=1.3$ Hz); 4.93 (d, 1H, H_{10b} , $J=8.1$ Hz); 4.21-4.13 (m, 3H); 4.08-4.01 (m, 1H); 3.95-3.84 (m, 2H); 3.78-3.70 (m, 1H, H_1); 3.67 (s, 3H); 3.62 (s, 3H); 3.40-3.32 (m, 1H); 3.19-3.10 (m, 1H); 1.17 (t, 3H, $J=7.1$ Hz) ppm; IR (KBr) ν_{\max} 1724, 1375, 1236, 1183 cm^{-1} ; MS m/z (rel int) 350 (M^+ , 6); 245 (13); 206 (41); 192 (39); 158 (44); Anal Calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.29; H, 6.31; N, 7.88.

1,2-Dimethoxycarbonyl (1R,2S,3R,10bR)- and (1S,2R,3S,10bS)-3-ethoxycarbonyl-1,2-3,5,6-hexahydro-dipyrrolo[1,2- α ;2',1'-c]pyrazine [(±)-20]. 1H -NMR ($CDCl_3$) δ : 6.57-6.54 (m, 1H); 6.11 (dd, 1H, $J=2.5$ Hz, $J=3.6$ Hz); 5.92 (dd, 1H, $J=1.5$ Hz, $J=2.5$ Hz); 4.74 (d, 1H, H_{10b} , $J=5.9$ Hz); 4.28-4.18 (m, 2H); 4.08 (d, 1H, H_3 , $J=5.9$ Hz); 4.07-4.01 (m, 1H); 3.89-3.82 (m, 2H); 3.79 (s, 3H); 3.63 (s, 3H); 3.47 (dd, 1H, H_1 , $J_{1-10b}=5.9$ Hz, $J_{1-2}=6.5$ Hz); 3.30-3.25 (m, 2H); 1.29 (t, 3H, $J=7.2$ Hz) ppm; IR (KBr) ν_{\max} 1720, 1438, 1340, 1166 cm^{-1} .

Reaction of 4a with N-methylmaleimide

4-Ethoxycarbonyl-2-methyl-1,3-dioxo-3a,4,6,7,11b,11c-hexahydro-pyrrolo[3',4':3,4]pyrrolo[1,2- α]pyrrolo[2,1- c]pyrazine (21). To a stirred two phase mixture of 4a (0.25 g, 0.87 mmol) in dry MeCN (10 mL) and K_2CO_3 (480 mg, 3.48 mmol), was added N-methylmaleimide (193 mg, 1.74 mmol) and stirring was continued at room temperature for 15 h; then the precipitate was filtered and washed with CH_2Cl_2 (3x5 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to give a residue which was chromatographed using a mixture of hexane-EtOAc (7:3) yielding 158 mg (57%) of a white solid. Mp 147-148°C (EtOH); 1H -NMR ($CDCl_3$) δ 6.55-6.52 (m, 1H); 6.21 (dd, 1H, $J=1.5$ Hz, $J=2.5$ Hz); 6.16 (dd, 1H, $J=2.5$ Hz, $J=4.0$ Hz); 4.43 (d, 1H, H_{10b} , $J=8.0$ Hz); 4.23 (q, 2H, $J=7.2$ Hz); 4.21 (d, 1H, H_3 , $J=2.0$ Hz); 3.96-3.85 (m, 2H); 3.66 (t, 1H, H_1 , $J=8.0$ Hz); 3.60 (dd, 1H, H_2 , $J_{2-10b}=8.0$ Hz, $J_{2-3}=2.0$ Hz); 3.29-3.23 (m, 1H); 3.09-3.04 (m, 1H); 2.90 (s, 3H); 1.32 (t, 3H, $J=7.2$ Hz) ppm; ^{13}C -NMR ($CDCl_3$) δ : 177.42 (CO); 174.64 (CO); 169.50 (CO₂); 123.90; 119.13; 107.99; 106.36; 65.40; 61.41; 59.10; 48.13; 46.87; 45.16; 44.30; 25.23; 14.38 ppm; IR (KBr) ν_{\max} 1721, 1692, 1430, 1244, 1122 cm^{-1} ; MS m/z (rel int) 317 (M^+ , 12), 288 (38), 244 (24), 206 (35), 159 (38). Anal Calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 61.89; H, 6.02; N, 12.84.

Reaction of 4a with isothiocyanates

To a stirred two phase mixture of 4a (0.2 g, 0.7 mmol) in 10 mL of dry MeCN and anhydrous K_2CO_3 (0.38,

2.8 mmol) methyl- or phenylisothiocyanate was added (2 mmol) and stirring was continued at room temperature for 70 h. The precipitate was filtered off and washed with CH_2Cl_2 (3×5 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. Chromatography (hexane-EtOAc 9:1 as eluent for **25a** and CH_2Cl_2 for **25b**) gave pure heterobetaines.

2-Methyl-3-oxo-6,7-dihydropyrazinio[1,2-a]pyrrolo[2,1-c]pyrazin-5-ium-1-thiolate (25a). Yield: 21%. Mp 187-189°C (EtOH, orange powder); $^1\text{H-NMR}$ (CDCl_3) δ : 6.89 (dd, 1H, $J=1.5$ Hz, $J=2.5$ Hz); 6.79 (s, 1H); 6.60 (dd, 1H, $J=1.5$ Hz, $J=4.0$ Hz); 6.25 (dd, 1H, $J=2.5$ Hz, $J=4.0$ Hz); 4.80-4.42 (bs, 2H); 4.38-4.29 (m, 2H); 3.37 (s, 3H) ppm; $^{13}\text{C-NMR}$ (CDCl_3) δ 175.60; 163.27; 129.70; 128.57; 122.24; 119.59; 110.91; 105.82; 48.92; 45.79; 29.69 ppm; IR (KBr) ν_{max} 1723, 1643, 1356, 1297, 1087 cm^{-1} ; MS m/z (rel int) 233 (M^+ , 89); 145 (16); 132 (100); 131 (77); 105 (40). Anal Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{OS}$: C, 56.63; H, 4.75; N, 18.01. Found: C, 56.21; H, 4.72; N, 17.89.

3-Oxo-2-phenyl-6,7-dihydropyrazinio[1,2-a]pyrrolo[2,1-c]pyrazin-5-ium-1-thiolate (25b). Yield: 49%. Mp 237-238°C (hexane- CH_2Cl_2 , yellow plates); $^1\text{H-NMR}$ (CDCl_3) δ : 7.52-7.45 (m, 3H); 7.39-7.36 (m, 2H); 6.94 (dd, 1H, $J=1.5$ Hz, $J=2.5$ Hz); 6.87 (s, 1H); 6.64 (dd, 1H, $J=1.5$ Hz, $J=4.0$ Hz); 6.27 (dd, 1H, $J=2.5$ Hz, $J=4.0$ Hz); 4.80-4.37 (bs, 4H) ppm; IR (KBr) ν_{max} 1718, 1642, 1280, 1056 cm^{-1} ; MS m/z (rel int) 295 (M^+ , 79); 147 (6); 132 (100); 131 (72); 105 (33). Anal Calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{OS}$: C, 65.06; H, 4.44; N, 14.23. Found: C, 64.60; H, 4.12; N, 13.60.

Reaction of **4a** with carbon disulphide/methyl iodide

3-Ethoxycarbonyl-2-methylthio-5,6,10b-trihydrothiazolo[3,2-a]pyrrolo[2,1-c]pyrazine (28). To a suspension of the salt **4a** (0.25 g, 0.87 mmol) a the biphasic system of K_2CO_3 50% (8 mL) and CS_2 (8 mL), was added MeI (0.49 g, 3.48 mmol). After stirring for 20 h at room temperature, the mixture was extracted with CH_2Cl_2 , dried over Na_2SO_4 and evaporated. Silica gel chromatography in Hex-EtOAc (9:1) afforded the title compound as a yellow solid (144 mg, 56%). $^1\text{H-NMR}$ (CDCl_3) δ 6.82 (s, 1H); 6.61 (d, 1H, $J=1.6$ Hz); 6.16 (d, 1H, $J=2.5$ Hz); 6.13-6.11 (m, 1H); 4.38-4.05 (m, 4H); 3.52-3.20 (m, 2H); 2.51 (s, 3H); 1.34 (t, 3H, $J=7.1$ Hz) ppm; IR (KBr) ν_{max} 1682, 1483, 1259, 1232, 1057 cm^{-1} . Anal Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2\text{S}_2$: C, 52.68; H, 5.44; N, 9.45. Found: C, 52.43; H, 5.39; N, 9.61.

Reaction of **1** with DMAD

To a solution of 0.2 g (1.66 mmol) of **1** in 10 mL of toluene was added dropwise 0.47 g (3.33 mmol) of DMAD. After stirring for 3h, the solvent was evaporated under reduced pressure and the residue was triturated with Et_2O to give **30** as a brown powder. Recrystallization from EtOH gave 405 mg (61%). Mp 162-163°C (EtOH); $^1\text{H-NMR}$ (DMSO-d_6) δ 6.73-6.70 (m, 1H); 6.00-5.97 (m, 2H); 5.58 (dd, 1H, $J=1.4$ Hz, $J=3.5$ Hz); 4.11-3.94 (m, 4H); 3.86 (s, 3H); 3.70 (s, 3H); 3.67 (s, 3H); 3.50 (s, 3H) ppm; IR (KBr) ν_{max} 2953, 1723, 1613, 1435, 1204, 1125 cm^{-1} ; MS m/z (rel int) 404 (M^+ , 59); 373 (100); 345 (58); 315 (16). Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_8$: C, 56.44; H, 4.99; N, 6.93; Found: C, 56.31; H, 4.90; N, 6.67.

Synthesis of Salts **32**. General Procedure

A solution of **1** (200 mg, 1.66 mmol) and the corresponding iodo derivative (1.66 mmol) in EtOAc (10 mL) was stirred at room temperature for 24 h. The reaction mixture was cooled and the resulting precipitate was filtered off to give salts **32a-c**.

2-(3-Methoxycarbonyl-2-propionyloxycarbonylmethyl)dihydropyrrolo[1,2-a]pyrazinium Iodide (32a).

Yield: 64%. Mp 119-120°C (brown powder, EtOH-Et₂O); ¹H-NMR (DMSO-d₆) δ 8.85 (s, 1H); 7.82 (s, 1H); 7.47 (d, 1H, *J*=4.1 Hz); 6.89 (s, 1H); 6.63 (s, 2H); 5.11 (s, 2H); 4.44 (t, 2H, *J*=6.4 Hz); 4.12 (t, 2H, *J*=6.4 Hz); 3.69 (s, 3H) ppm; IR (KBr) ν_{\max} 2944, 2240, 1755, 1725, 1626, 1342, 1180, 1126 cm⁻¹. Anal Calcd for C₁₄H₁₅I N₂O₄: C, 41.81; H, 3.76; N, 6.97. Found: C, 42.01; H, 3.46; N, 7.13.

2-(4-Methoxycarbonyl-3-butynyloxycarbonylmethyl)dihydropyrrolo[1,2-a]pyrazinium Iodide (32b). Yield: 69%. Mp 142-143°C (brown powder, EtOH-Et₂O); ¹H-NMR (DMSO-d₆) δ 8.82 (s, 1H); 7.80 (s, 1H); 7.44 (dd, 1H, *J*= 4.4, 1.1 Hz); 6.62 (dd, 1H, *J*=4.4, 2.2 Hz); 4.89 (s, 2H); 4.44 (t, 2H, *J*= 6.4 Hz); 4.11 (t, 2 H, *J*= 6.4 Hz); 3.68 (s, 3H); 2.85 (t, 2 H, *J*= 6.0 Hz) ppm; IR (KBr) ν_{\max} 2906, 2245, 1756, 1712, 1633, 1343, 1271, 1201, 1179, 774 cm⁻¹. Anal Calcd for C₁₅H₁₇IN₂O₄: C, 43.29; H, 4.12; N, 6.73. Found: C, 43.15; H, 4.00; N, 6.48.

2-(2-Propionyloxycarbonylmethyl)dihydropyrrolo[1,2-a]pyrazinium Iodide (32c). Yield: 81%. Mp 157-158°C (yellow powder from EtOH-Et₂O); ¹H-NMR (DMSO-d₆) δ 8.83 (s, 1H); 7.82 (s, 1H); 7.46 (d, 1H, *J*=4.1 Hz); 6.89 (s, 1H); 6.64-6.60 (m, 1H); 4.94 (s, 1H); 4.86 (d, 2H, *J*=2.2 Hz); 4.44 (t, 2H, *J*=6.4 Hz); 4.10 (t, 2 H, *J*= 6.4 Hz); 3.69 (d, 1H, *J*=2.2 Hz) ppm; IR(KBr) ν_{\max} 3210, 2123, 1755, 1628, 1373, 1352, 1197, 1137 cm⁻¹. Anal. Calcd for C₁₂H₁₃IN₂O₂: C, 41.88; H, 3.81; N, 8.14. Found: C, 42.11; H, 3.75; N, 8.01.

2-[2-(2-Methoxycarbonylvinyl)-phenoxy carbonylmethyl]dihydropyrrolo[1,2-a]pyrazinium Iodide (33). Yield: 49%. Mp 127-128°C (brown powder, EtOH-Et₂O); ¹H-NMR(DMSO-d₆) δ 8.82 (s, 1H); 7.85 (d, 1H, *J*= 16.1 Hz); 7.82-7.74 (m, 2H); 7.69 (s, 1H); 7.46-7.35 (m, 2H); 7.31 (dd, 1H, *J*=4.0, 1.1 Hz); 6.79 (dd, 1H, *J*=4.0, 2.1 Hz); 6.59 (d, 1H, *J*= 16.1 Hz); 5.54 (s, 2H); 4.36 (t, 2H, *J*=6.6 Hz); 3.95 (t, 2H, *J*= 6.6 Hz); 3.73 (s, 3H) ppm; IR (KBr) ν_{\max} 2948, 1743, 1707, 1628, 1456, 1433, 1324, 1279, 1172, 1127, 760 cm⁻¹; Anal Calcd for C₁₉H₁₉IN₂O₄: C, 48.94; H, 4.11; N, 6.01. Found: C, 49.04; H, 3.82; N, 6.22.

Intramolecular Cycloadditions

1-Methoxycarbonyl-4-oxo-2,6,7-trihydrofuran[4',3':4,5]pyrrolo[1,2-a]pyrrolo[2,1-c]pyrazine (35a).

A solution of the salt **32a** (0.5 g, 1.25 mmol) and K₂CO₃(0.18 g, 1.25 mmol) in dry MeCN (12 mL) was stirred at room temperature for 24 h. The reaction mixture was filtered and the solvent was removed under reduced pressure to give a residue which was chromatographed (hexane-EtOAc, 8:2) to yield **35a** (80 mg, 24%). Mp 174-175°C (white powder, EtOAc); ¹H-NMR (CDCl₃) δ 7.55 (dd, 1H, *J*=3.6, 1.5 Hz); 6.83 (dd, 1H, *J*=2.5, 1.5 Hz); 6.33 (dd, 1H, *J*=3.6, 2.5 Hz); 5.26 (s, 2H); 4.44 (t, 2H, *J*=6.0 Hz); 4.33 (t, 2H, *J*=6.0 Hz); 3.85 (s, 3H); 3.70 (s, 2H) ppm; IR (KBr) ν_{\max} 2925, 2857, 1748, 1439, 1360, 1276, 1096, 1029, 740 cm⁻¹; MS *m/z* (rel int) 272 (M⁺, 15); 271 (100); 270 (13); 255 (1); 239 (2). Anal. Calcd for C₁₄H₁₂N₂O₄: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.63; H, 4.21; N, 10.46.

1-Methoxycarbonyl-5-oxo-2,3,7,8-tetrahydropyran[4',3':4,5]pyrrolo[1,2-a]pyrrolo[2,1-c]pyrazine (35b).

A solution of **32b** (0.8 g, 1.93 mmol) and K₂CO₃(0.28 g, 1.93 mmol) in dry MeCN(18 mL) was stirred at room temperature for 24 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel (hexane-EtOAc, 9:1) to give the title compound (165 mg, 30%). Mp 163-164°C (white needles, EtOAc); ¹H-NMR (CDCl₃) δ 7.45 (dd, 1H, *J*=3.6, 1.6 Hz); 6.80 (dd, 1H, *J*=2.6, 1.6 Hz); 6.30 (dd, 1H, *J*=3.6, 2.6 Hz); 4.76 (t, 2H, *J*=6.0 Hz); 4.52 (t, 2H, *J*= 6.2 Hz); 4.25 (t, 2H, *J*=6.0 Hz); 3.87 (s, 3H); 3.19 (t, 2H, *J*= 6.2 Hz) ppm; IR (neat) ν_{\max} 1698, 1440, 1312, 1272, 1214, 1131, 1092, 1078, 716 cm⁻¹; MS, *m/z* (rel int) 286 (M⁺, 100); 255 (17); 253 (15); 227 (25); 211(15); 210 (16); 169 (12); 142 (12); 128 (12); 115 (13). Anal. Calcd for C₁₅H₁₄N₂O₄: C, 63.93; H, 4.93; N, 9.78. Found: C, 64.23; H, 4.79; N, 9.86.

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REFERENCES

1. For a review of azaindolizines see: (a) Amarnath, V.; Madhav, R. *Synthesis*, **1974**, 837-859. (b) Kuhla, D. E.; Lombardino, J. G. *Adv. Heterocyclic Chem.*, **1977**, *21*, 1-63. (c) Blewit, H. L. *Chem. Heterocyclic Comp.* **1977**, *30*, 117-178. (d) Maury, G. *Chem. Heterocyclic Comp.* **1977**, *30*, 179-244.
2. Skoldinov, A.; Peresada, B.; Likhosherstov, A. *Zh. Org. Khim.* **1983**, *19*, 450-456; *Chem. Abstr.* **1983**, *98*, 198162u.
3. Pablo, M. S.; Gandasegui, T.; Vaquero, J. J.; Garcia Navio, J. L.; Alvarez-Builla, J. *Tetrahedron*, **1992**, *48*, 8793-8800.
4. a) Hehre, W. J.; Ditchfield, R.; Pople, J. A.; *J. Chem. Phys.* **1972**, *56*, 2257-2261. b) Frisch, M. J.; Pople, J. A.; Binkley, J. S.; *J. Chem. Phys.* **1984**, *80*, 3265-3269. c) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. V. R. *J. Comp. Chem.* **1983**, *4*, 294-301.
5. *Gaussian 94, Revision B.3*, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, **1995**.
6. These magnitudes are defined respectively as the standard Gibbs energy and enthalpy charges for the following reaction in the gase phase: $\text{BH}^+(\text{g}) \rightarrow \text{B}(\text{g}) + \text{H}^+(\text{g})$
7. Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis*, **1977**, 1-17.
8. Bátori, S.; HaJós, G.; Sándor, P.; Messmer, A. *J. Org. Chem.* **1989**, *54*, 3062-3068.
9. Cuadro, A.; Alvarez-Builla, J.; Vaquero, J. J. *Heterocycles*, **1989**, *29*, 57-65.
10. Minguez, J. M.; Castellote, M. I.; Vaquero, J. J.; Garcia-Navio, J. L.; Alvarez-Builla, J.; Castaño, O.; Andrés, J. L. *J. Org. Chem.* **1996**, *61*, 4655-4665.
11. a) Cuadro, A. M.; Novella, J. L.; Molina, A.; Alvarez-Builla, J.; Vaquero, J. J. *Tetrahedron*, **1990**, *46*, 6033-6046. b) Molina, A.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J.; Garcia Navio, J. L. *Heterocycles*, **1990**, *31*, 1451-1458. c) Minguez, J. M.; Gandasegui, T.; Vaquero, J. J.; Alvarez-Builla, J. L.; Garcia Navio, J. L.; Gago, F.; Ortiz, A. R.; Gomez-Sal, P.; Torres, R.; Rodrigo, M. M. *J. Org. Chem.* **1993**, *58*, 6030-6037.
12. Zhang, X.-M.; Bordwel, F.; Van Der Puy, M.; Fried, H. E. *J. Org. Chem.* **1993**, *58*, 3060-3066.
13. Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Heterocycles*, **1988**, *27*, 1233-1240.
14. Munt, P. S.; Thomas, E. J. *J. Chem. Soc. Chem. Commun.* **1989**, 480-482.

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