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

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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. © 1997 Elsevier Science Ltd.

INTRODUCTION

The 3,4-dihydropyrrolo[1,2-a]pyrazine 1 is the only known dihydroderivative of the pyrrolodiazine system and its synthesis is reported in poor overall yield. 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 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.

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COMPUTATIONAL METHODS

The electronic structure of the 3,4-dihydropyrrolo[1,2-α]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 set 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-α]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 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-α]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-ethoxy-carbonylmethyl 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-α]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-α]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-α]pyrazine (1)*

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</tbody>
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* Bond lengths are in angstroms and bond angles in degrees

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

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* Bond lengths are in angstroms and bond angles in degrees
latest experiments have shown it possible to trap the ylide 5 from 4b allowed us to trap 5 with dimethyl-acetylenedicarboxylate (DMAD) and methyl propiolate, although the best yields obtained for the 5,6-dihydropyrrolo[1,2-α,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,l-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.

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. $^1$H NMR shows that this compound corresponds to the C-1 (CN) regioisomer (doublet for H10b and triplet for H3) arising from an exo approach of 4a and the dipolarophile (J1-10b=5.8 Hz). The $^1$H NMR of the isomer 16, which could not be completely separated and purified by chromatography shows a coupling constant between H1 and H10b 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-α;2',1'-c]pyrazine (17) in which H2 appeared at δ = 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, H10b 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 H11b and H11c (J = 8.0 Hz) and H11c and H3a (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 H3a 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-α]pyrazinium ylides10 and phenacyl salts of 4a.7 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-α]-pyrazinium salt could be associated with the electronic differences in both systems is not obvious, and the unusual behaviour should be further investigated.
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\textsuperscript{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 Cl position towards intramolecular attack of the sulfur atom, to give rise to 28.

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**Scheme 5**

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**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 (32b) and 3-iodoacetoxypropyrene (32c) while 33 was obtained from the reaction of 1 and 3-[2-(iodoacetoxy)phenyl]acrylate. 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.

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.

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. $^1$H 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 meshs). 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; $^1$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 (q, 2H, J=7.1 Hz) ppm; IR (KBr) ν$_{max}$ 1741, 1630, 1347, 1129 cm$^{-1}$. Anal. Calcd for C$_{14}$H$_{17}$BrN$_2$O$_2$: 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 CH$_2$Cl$_2$ 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 Et$_2$O. Recrystallization from EtOH gave 1.11 g (77%) of 4b as a yellow powder. Mp 97-98°C; $^1$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 C$_{12}$H$_{19}$F$_3$N$_2$O$_3$Si: C, 40.44; H, 5.37; N, 7.86. Found: C, 40.26; H, 5.39; N, 7.68.

1-Methoxycarbonyl-5,6-dihydropyrrolo[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. CH$_2$Cl$_2$ was then added and the organic phase was washed with H$_2$O and brine (2x10 mL). The organic extracts were dried over Na$_2$SO$_4$, filtered and evaporated to dryness. The oily residue was chromatographed using CH$_2$Cl$_2$ as eluent to give 16 mg (18%) of 6a as a pale yellow oil. $^1$H-NMR (CDCl$_3$) 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 C$_{12}$H$_{14}$N$_2$O$_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.49; H, 5.64; N, 12.67.
1,2-Dimethoxycarbonyl-5,6-dihydrodipyrrrolo[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. CHCl₃ 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, I-I₃); 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) νₘₐₓ 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 C₁₄H₁₂N₂O₄: 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. ¹H-NMR (CDCl₃) δ 6.82 (d, 1H, J=1.1 Hz); 6.51 (t, 1H, J=2Hz); 6.16 (dd, 1H, J=2-2.5 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) νₘₐₓ 1732, 1588, 1432, 1038 cm⁻¹; MS m/z (rel int) 219 (M⁺, 59); 160 (100); 159 (95); 119 (91).

l-Methoxycarbonyl-1,2,5,6-tetrahydropyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (8). ³H-NMR (CDCl₃) δ 6.82 (d, 1H, J=1.1 Hz); 6.51 (t, 1H, J=2Hz); 6.16 (dd, 1H, J=2-2.5 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) νₘₐₓ 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, H₃); 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) νₘₐₓ 1705, 1490, 1092 cm⁻¹. Anal. Calcd for C₁₄H₁₁N₃O₂: 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 0.25 g (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 dihydro-derivatives 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-dihydropyrrrolo[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) νₘₐₓ 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 C₁₄H₂₁N₃O₆: 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 K₂CO₃ 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 CH₂Cl₂ (3x5 mL). The combined organic extracts were dried over Na₂SO₄ 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 (CDCl₃) δ 7.46 (dd, 1H, J=1.5 Hz, J=3.6 Hz); 7.44 (s, 1H, H₂); 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; ¹³C-NMR (CDCl₃) δ 164.03 (CO₂); 161.08 (CO₂); 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; Ig (KBr) νₘₐₓ 1707, 1685, 1257, 1203, 1092 cm⁻¹, MS m/z (rel int) 288 (M⁺, 100), 260 (78), 229 (81), 155 (44). Anal. Calcd for C₁₅H₁₄N₂O₄: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.36; H, 5.35; N, 9.48.

1,3-Diethoxycarbonyl-5,6-dihydropyrrolo[1,2-a; 2',1'-c]pyrazine (14b). Yield: 48 %. Mp 76-78 °C (white needles, EtOH); ¹H-NMR (CDCl₃) δ: 7.45 (dd, 1H, J=1.5 Hz, J=3.9 Hz); 7.43 (s, 1H, H₂); 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, 6 H); 1.37 (t, 3H, J=7.1 Hz); 1.35 (t, 3H, J=7.1 Hz) ppm; Ig (KBr) νₘₐₓ 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 C₁₆H₁₄N₂O₄: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.11; H, 6.43; N, 8.98.

8,16-Diethoxycarbonyl-5,6,9,16a-octahydropyrrolo[1,2-a]pyrazinio[2,1-a: 2',1'-d]pyrazine (18). Yield: 11%. Mp 241-243 °C (white powder, EtOH); ¹H-NMR (CDCl₃) 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, 10 H); 3.70 (d, 1H, J=-16.4 Hz); 3.44-3.33 (m, 1H); 3.21-3.16 (m, 2H); 2.99 (td, 1H, J=11.4, 4.4 Hz) ppm; Ig (KBr) νₘₐₓ 1722, 1640, 1404, 1283 cm⁻¹; MS m/z (rel int) 412 (M⁺, 62), 339 (53), 325 (32), 220 (100). Anal. Calcd for C₂₂H₂₃N₄O₄: 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 K₂CO₃ 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 Na₂SO₄ 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 CH₂Cl₂ for 1 h afforded the aromatized derivative 17 (88 mg, 62%) as a white solid.

1-Cyano(1R,10bR)- and (1S,10bS)-3-ethoxycarbonyl-1,2,3,5,6,10h-hexahydropyrrolo[1,2-a; 2',1'-c]pyrazine (±)15. ¹H-NMR (CDCl₃) δ: 6.61 (t, 1H, J=2Hz); 6.19-6.17 (m, 2H); 4.60 (d, 1H, J₉₀₀ , 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, 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) νₘₐₓ 2243, 1731, 1450, 1189 cm⁻¹.

1-Cyano-3-ethoxycarbonyl-5,6-dihydropyrrolo[1,2-a; 2',1'-c]pyrazine (17). Mp 154-155°C (EtOH); ¹H-NMR (CDCl₃) δ 7.16 (s, 1H, H₂); 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).
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$_2$CO$_3$ 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$_2$Cl$_2$. The combined organic phases were dried over Na$_2$SO$_4$ 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-a;2',1'-c]pyrazine [(±)-19]. Mp 106-108°C (EtOH); $^1$H-NMR (CDCl$_3$) $\delta$: 6.55-6.51 (m, 1H); 6.08 (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); 3.78-3.70 (m, 1H, H$_5$); 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) $\tilde{\nu}$: 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$_{21}$H$_{22}$N$_2$O$_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.29; H, 6.31; N, 7.88.

Reaction of 4a with N-methylmaleimide

4-Ethoxycarbonyl-2-methyl-1,3-dioxo-3a,4,6,7,11b,11c-hexahydropyrrolo[3',4':3,4]pyrrolo[1,2-a]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$_2$CO$_3$ (193 mg, 1.74 mmol) and stirring was continued at room temperature for 15 h; then the precipitate was filtered and washed with CH$_2$Cl$_2$ (3x5 mL). The combined organic phases were dried over Na$_2$SO$_4$ 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); $^1$H-NMR (CDCl$_3$) $\delta$: 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); 4.21 (q, 2H, $J=7.2$ Hz); 3.96-3.85 (m, 2H); 3.66 (t, 1H, H$_1$, $J=8.0$ Hz); 3.60 (dd, 1H, H$_5$, $J_{2,10b}$=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$_3$) $\delta$: 177.42 (CO); 174.64 (CO); 169.50 (CO$_2$); 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) $\tilde{\nu}$: 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$_{21}$H$_{22}$N$_2$O$_6$: C, 60.56; H, 6.03; N, 13.24. Found: C, 61.89; H, 6.02; N, 13.24.

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$_2$CO$_3$
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 CH₂Cl₂ (3 × 5 mL). The organic phase was dried over Na₂SO₄ and evaporated under reduced pressure. Chromatography (hexane-CH₂Cl₂ 9:1 as eluent for 25a and CH₂Cl₂ for 25b) gave pure heterobetaines.

2-Methyl-3-oxo-6,7-dihydropyrazino[1,2-a]pyrrolo[2,1-c]pyrazin-5-ium-1-thiolate (25a). Yield: 21%. Mp 187-189°C (EtOH, orange powder). ¹H-NMR (CDCl₃) 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; ¹³C-NMR (CDCl₃) 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~ 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 C₁₁H₁₁N₃O₃S: 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-dihydropyrazino[1,2-a]pyrrolo[2,1-c]pyrazin-5-ium-1-thiolate (25b). Yield: 49%. Mp 237-238°C (hexane-CH₂Cl₂ yellow plates). ¹H-NMR (CDCl₃) 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~ 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 C₁₆H₁₃N₃O₃S: 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) at the biphasic system of K₂CO₃ 50% (8 mL) and CS₂ (8 mL), was added Mel (0.49 g, 3.48 mmol). After stirring for 20 h at room temperature, the mixture was extracted with CH₂Cl₂, dried over Na₂SO₄ and evaporated. Silica gel chromatography in Hex-EtOAc (9:1) afforded the title compound as a yellow solid (144 mg, 56%). ¹H-NMR (CDCl₃) 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~ 1682, 1483, 1259, 1232, 1057 cm⁻¹. Anal. Calcd for C₁₃H₁₄N₂O₂S₂: 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 3 h, the solvent was evaporated under reduced pressure and the residue was triturated with Et₂O to give 30 as a brown powder. Recrystallization from EtOH gave 405 mg (61%). Mp 162-163°C (EtOH); ¹H-NMR (CDCl₃) 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~ 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 C₁₉H₂₀N₂O₄: 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-propionylxycarbonylmethyl)dihydropyrazino[1,2-al]pyrazinium Iodide (32a).
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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), 5.15 (s, 1H), 4.44 (t, 2H, J=6.4 Hz); 4.12 (t, 2H, J=6.4 Hz), 3.69 (s, 3H) ppm; IR (KBr) νmax 2944, 2240, 1755, 1725, 1626, 1342, 1180, 1126 cm⁻¹. Anal Calcd for C14H13N2O4: 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 ºC (brown powder, EtOH-Et2O); 1H-NMR (DMSO-d6) δ 8.82 (s, 1H); 7.80 (s, 1H); 7.44 (dd, 1H, J=4.4, 2.2 Hz); 4.89 (s, 2H); 4.44 (t, 2H, J=6.4 Hz); 4.11 (t, 2H, J=6.4 Hz), 3.68 (s, 3H); 2.85 (t, 2H, J=6.0 Hz) ppm; IR (KBr) νmax 2906, 2245, 1756, 1712, 1633, 1343, 1271, 1201, 1179, 774 cm⁻¹. Anal Calcd for C15H17N2O4: 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 (d, 2H, J=2.2 Hz); 4.44 (t, 2H, J=6.4 Hz), 4.10 (t, 2H, J=6.4 Hz), 3.69 (d, 1H, J=2.2 Hz) ppm; IR (KBr) νmax 3210, 2123, 1755, 1628, 1373, 1352, 1197, 1137 cm⁻¹. Anal. Calcd for C12H13N2O4: C, 41.88; H, 3.81; N, 8.14. Found: C, 42.11; H, 3.75; N, 8.01.

2-(2-Methoxycarbonylvinyldihydropyrrolo[2-a]pyrazinium Iodide (33). Yield: 49%. Mp 127-128 ºC (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=16.1 Hz); 6.59 (dd, 1H, J=3.6, 2.6 Hz); 4.36 (t, 2H, J=6.0 Hz), 3.85 (s, 3H); 3.70 (s, 2H) ppm; IR (KBr) νmax 2948, 1743, 1707, 1456, 1433, 1324, 1279, 1172, 1127, 760 cm⁻¹; Anal Calcd for C19H19N2O4: C, 49.48; H, 3.74; N, 8.01.

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) νmax 2925, 2857, 1748, 1439, 1360, 1276, 1096, 1029, 740 cm⁻¹; MS m/z (rel int) 272 (M⁺, 15); 271 (100); 255 (15); 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 yield the title compound (165 mg, 30%). 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) νmax 2925, 2857, 1748, 1439, 1360, 1276, 1096, 1029, 740 cm⁻¹; MS m/z (rel int) 272 (M⁺, 15); 271 (100); 255 (15); 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.
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REFERENCES


6. These magnitudes are defined respectively as the standard Gibbs energy and enthalpy charges for the following reaction in the gas phase: BH+(g) ~ B(g) + H*(g)


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