THE REACTION OF 8-METHYLPYRROLO[1,2-a]PYRAZINES WITH DIMETHYL ACETYLENE-DICARBOXYLATE

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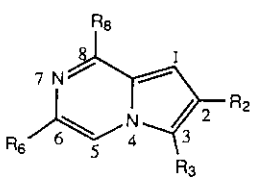
Abstract - 2,8-Dimethylpyrrolo[1,2-a]pyrazine reacts with two molecular proportions of dimethyl acetylenedicarboxylate (DMAD) in toluene to give a reaction mixture from which five crystalline products were isolated.Four of the products were shown to be the isomeric tetracarbomethoxy 1:2 adducts (**9**, **10**, **14** and **15**) and the fifth to be the tricarbomethoxydipyrrolopyrazine (**7**). A likely common reaction intermediate leading to the formation of all five products is suggested to be the 1:1 adduct (**21**). Reaction of 2,3,8-trimethylpyrrolo[1,2-a]pyrazine with DMAD in toluene gave the corresponding compounds (**17**, **18**, **19**, **20** and **16**).

Introduction

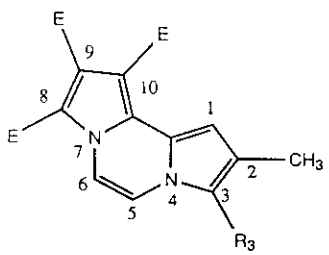
In a recent paper,[1] we reported that the parent pyrrolo[1,2-a]pyrazine (**1**) and its 2,3,6-trimethyl derivative (**2**) each react with two molecular proportions of dimethyl acetylenedicarboxylate (DMAD) in toluene at the N-7 and adjacent electron deficient C-8 sites to give the corresponding angular condensed pyrrolopyridine 1:2 adducts (**3** and **4**). Thus in its reaction with DMAD, pyrrolo[1,2-a]pyrazine resembles pyridine and quinoline.[1-4] This contrasts with the behaviour of indolizine(s) and other azaindolizines which react at the peri 3,5 sites, most generally with one molecular proportion of DMAD to give a 1:1 adduct which can be dehydrogenated to the corresponding cycl[3.2.2]azine or azacycl[3.2.2]azines.[5] In the 8-methylpyrrolo[1,2-a]pyrazines such as (**5** and **6**), reaction with DMAD may be forced to occur at the peri 3,5 sites to give the corresponding hitherto uncharacterised 6-azacycl[3.2.2]azines. Alternatively, reaction with DMAD may persist in occurring at the basic[1,6] N-7 non bridgehead nitrogen and the adjacent C-8 site or substituent in a manner analogous to the reaction of 2-methylpyridine[7,8] and 2-methylquinoline[9] with DMAD. In this paper we report the reaction of 2,8-dimethyl- and of 2,3,8-trimethylpyrrolo[1,2-a]pyrazines (**5** and **6**) with DMAD.



1 $R_2 = R_3 = R_6 = R_8 = H$
2 $R_2 = R_3 = R_6 = CH_3, R_8 = H$
5 $R_2 = R_8 = CH_3, R_3 = R_6 = H$
6 $R_2 = R_3 = R_8 = CH_3, R_6 = H$

Results and Discussion

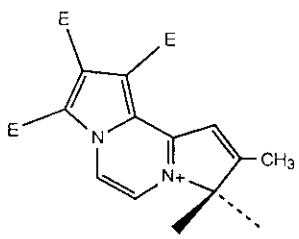
Reaction of 2,8-dimethylpyrrolo[1,2-a]pyrazine (5) with excess DMAD in toluene at room temperature for 24 hours gave, after removal of the solvent, an oil from which five compounds were separated by preparative tlc and subsequent recrystallization. Only the fastest moving band on the tlc plate was colorless and it showed strong fluorescence under uv light, three of the remaining four bands were yellow and the fifth band which was the second slowest moving band was red. The colorless compound from the fastest running band showed a strong molecular ion at m/z 344 which was also the base peak, the only significant fragmentation ion occurred at m/z 313 and is interpreted to be due to loss of a methoxy unit. Analysis of this compound showed it to have a molecular formula $C_{17}H_{16}N_2O_2$. Its ^1H nmr spectrum showed the presence of three ester methyl groups, a 3H singlet δ2.30, and two weakly split 1H doublets at δ7.06 and 7.69 and an AB doublet at δ7.34 and 8.50. This indicated the compound to be 2-methyl-8,9,10-tricarbomethoxydipyrrolo[1,2-a:2,1-c]pyrazine (7); the AB doublet is assigned to the protons on C-5 and C-6 and the weekly split 1H doublets at δ7.06 and 7.69 to the protons on C-3 and C-1, respectively.[10] Further confirmation of the dipyrrolopyrazine structure (7) was obtained from protonation and deuterium exchange studies. A comparison of the $CDCl_3$ and CF_3COOH spectra indicated in the later, the emergence of a 2H methylene signal at δ5.60, the disappearance of the 1H singlet due to H-3 and a general downfield shift of all the other resonances; this points to C-3 protonation and the formation of the conjugate acid cation (8). When a drop of CF_3COOD was added to the $CDCl_3$ solution, the resulting ^1H nmr spectrum showed firstly the disappearance of the 1H signal at δ7.06, due to H-3, followed by the signal at δ7.69 assigned to H-1. This protonation and deuterium exchange behaviour is consistent with that observed for previously reported dipyrrolopyrazines.[11]



7 $R_3 = H$

16 $R_3 = CH_3$

$E = COOCH_3$



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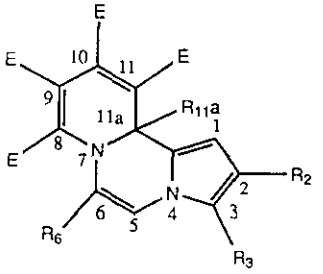
Elemental and spectroscopic analysis of the four colored compounds showed each to give a molecular ion at m/z 430 and a molecular formula $C_{21}H_{22}N_2O_8$ and each showed the presence of four carbomethoxy groups. This suggests all of these colored compounds to arise as 2:1 adducts of DMAD and 2,8-dimethylpyrrolo[1,2-a]pyrazine. The second fastest moving compound showed uv and ir spectra similar to that of the previously prepared pyrrolopyridine compounds (**3** and **4**)[1,12] with a λ_{max} at 285 nm and 290 nm respectively. Its ^1H nmr spectrum showed in addition to the four 3H methyl ester signals, higher field 3H singlets at δ1.82 and 2.02, and four other protons as an AB doublet centered at δ5.85 and 6.38 and two weakly coupled 1H singlets at δ5.86 and 6.38. These observations tend to indicate the pyrido[2,1-a]pyrrolo[1,2-a]pyrazine structure (**9**). The 3H singlets at δ1.82 and 2.02 are assigned to the methyl groups at C-11a and C-2, the weakly coupled signals to the protons at C-1 and C-3, and the AB doublet to the protons at C-5 and C-6, respectively. Confirmation of the pyrrolopyridine structure (**9**) was inferred from the interpretation of its ^{13}C nmr spectrum (see experimental).



3 $R_2 = R_3 = R_6 = R_{11a} = H$

4 $R_2 = R_3 = R_6 = CH_3 = R_{11a} = H$

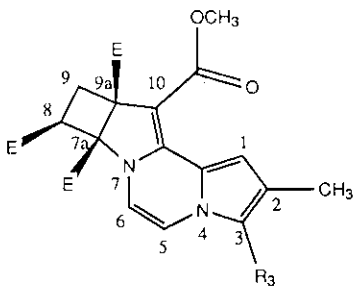
9 $R_2 = R_{11a} = CH_3$, $R_3 = R_6 = H$

17 $R_2 = R_3 = R_{11a} = CH_3$, $R_6 = H$

$E = COOCH_3$

The third fastest moving band showed in its ^1H nmr spectrum, in addition to the four carbomethoxy signals δ3.63 - 3.76, a single high field 3H singlet at δ2.20, two weakly coupled 1H signals at δ6.87 and 8.02, a 2H AB doublet at δ6.49 and 6.73 and most significantly in comparison to the ^1H nmr of **9** a complex 3H multiplet in the region between δ2.64 and 3.87 pointing to the presence of a -CH-CH_2- system in the molecule. These spectral characteristics suggested a cyclobutane structure such as **10** or **11** analogous to that of the cyclobutapyrroloquinoline compounds isolated from the reaction of 2-methylquinoline with DMAD.[9,13] The stereochemical assignment of the 8-carbomethoxy group follows from the ^1H nmr spectrum which showed a normal 8-ester methyl signal at δ~3.70 and not a high field ester methyl signal at δ~3.37. The methyl of the 8-carbomethoxy group of **11** is envisaged to be in the shielding region

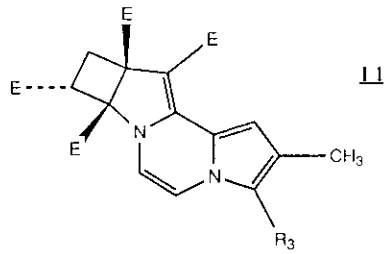
of the aromatic system thus structure (10) is preferred to 11 .[9,14,15] The weakly coupled 1H signal δ 8.02 is assigned to H-1 and occurs at low field due to the deshielding by the carbonyl group of the carbomethoxy at C-10.[14] The other weakly coupled 1H signal δ 6.87 is attributed to H-3 and the AB doublet at δ 6.49 and 6.73 ascribed to H-5 and H-6, respectively. The mass spectrum of this compound supported the cyclobutane structure by showing a molecular ion at m/z 430 (45%) and a fragmentation ion at m/z 344 (100%). The base peak (m/z 344) is inferred to arise through loss of methyl acrylate from the molecular ion to give the stable radical ion (12), a similar fragmentation pattern was observed for the cyclobutapyrroloquinoline system.[16]



E = $COOCH_3$

10 R_3 = H

18 R_3 = CH_3



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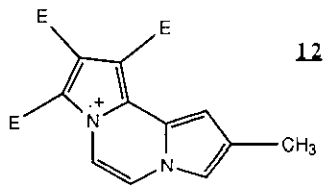

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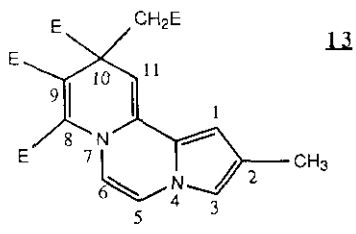
The red compound from the fourth fastest band showed a uv spectrum bathochromically displaced but with a similar pattern to that of compounds (3, 4 and 9). Its ^1H nmr spectrum showed in common with the ^1H nmr spectra of 9 and 10 four carbomethoxy 3H signals, two weakly coupled 1H signals, and an AB doublet; the significant feature of the ^1H nmr of the red compound was the presence of an aliphatic 2H singlet at δ 3.12 and an alkene 1H singlet at δ 5.05. Its mass spectrum showed a weak molecular ion (m/z 430, 10%) and a base peak at m/z 357 corresponding to the loss of a '$CH_2CO_2CH_3$' fragment. These spectral characteristics suggest the red compound to be either 13 or 14 . Structure (14) is tentatively preferred on the basis of the chemical shift of the C-6 proton δ 6.80; in structure (13), H-6 would be expected at lower field due to

the deshielding effect of the peri orientated carbomethoxy carbonyl at C-8. Further evidence for structure (**14**) is provided from the ^{13}C nmr spectrum (see experimental).



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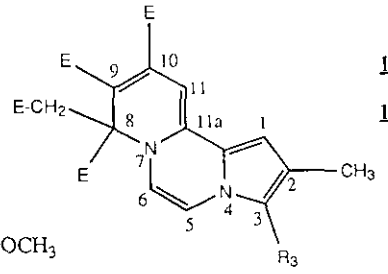
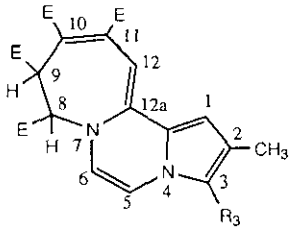


14 $R_3 = H$

19 $R_3 = CH_3$

$E = COOCH_3$

The ^1H nmr spectrum from the intense *yellow compound isolated from* the slowest moving band showed in addition to four carbomethoxy 3H singlets a higher field 3H singlet and at lower field two AB doublet systems, one at δ5.25 and 5.35 and the other at δ6.18 and 6.68, and three other 1H singlets at δ5.32, 6.56 and 6.75. These observations are consistent with the pyrrolo[2',1':3,4]pyrazino[1,2-a]azepine (**15**) where the higher field AB doublet is assigned to H-8 and H-9 and the lower field AB doublet to H-5 and H-6; the 1H singlets are assigned to H-12, H-1 and H-3. The ^{13}C nmr spectrum of this compound was also consistent with structure (**15**) (see experimental). Similar azepine structures have been obtained from the reaction of DMAD with dimethylthiazole.[17]



$E = COOCH_3$

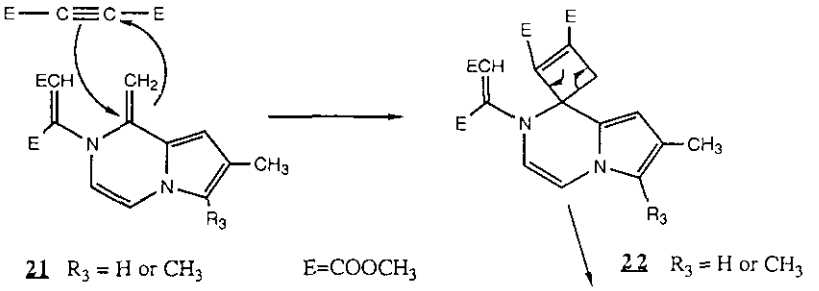
15 $R_3 = H$

20 $R_3 = CH_3$

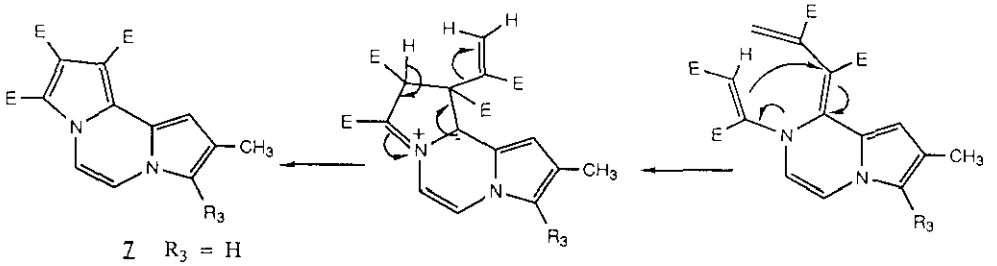
2,3,8-Trimethylpyrrolo[1,2-a]pyrazine (**6**) when similarly reacted with DMAD also gave five analogous bands on a tlc chromatogram. The compounds isolated from these bands showed spectral characteristics closely resembling the *compounds isolated from* the corresponding band in the reaction of DMAD with 2,8-dimethylpyrrolo[1,2-a]pyrazine (**5**) and are assigned the five homologue structure (**16**, **17**, **18**, **19** and **20**).

The formation of the five compounds from reaction of excess DMAD with 2,8-dimethyl- and with 2,3,8-trimethylpyrrolo[1,2-a]pyrazines is suggested to occur via the corresponding 1:1 adduct reaction intermediate (**21**). The 1:1 adduct (**21**) is envisaged to arise from

the bonding of one DMAD unit at the basic N-7 site, followed by proton transfer. Reaction schemes showing the involvement of a second DMAD unit have been previously suggested to account for structures analogous to **9**, **10**, **14** and **15**.[17-20] The suggested pathway leading to the dipyrrolopyrazine (**7**) is shown below. The cyclobutene intermediate (**22**) is analogous to the cyclobutene intermediate proposed and supported from carbon labelling in work performed by Acheson *et al*.[10,18] in accounting for the formation of a cyclobutapyrroloquinoline from the reaction of 2-methylquinoline with DMAD.

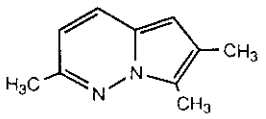


21 R_3 = H or CH_3 E=$COOCH_3$ **22** R_3 = H or CH_3



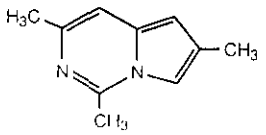
7 R_3 = H
16 R_3 = CH_3

Other similarly structured azaindolizines which possess a methyl group adjacent to the non-bridgehead nitrogen do not show analogous behaviour to that of the 8-methylpyrrolo[1,2-*a*]pyrazines (**5** and **6**). For example 6-methylpyrrolo[1,2-*b*]pyridazines unsubstituted at the 3-position have been shown to 3-substitute a unit of DMAD and to give 4*H*,5*H*-3,4-dicarbomethoxy-5-azacycl[3.2.2]azines.[21,22] When 2,3,6-trimethylpyrrolo[1,2-*b*]pyridazine (**23**) and 2,5,7-trimethylpyrrolo[1,2-*c*]pyrimidine (**24**) were each reacted with excess DMAD in toluene, **23** gave a mixture of the (E) and (Z) geometrical stereoisomers (**25** and **26**)[23] whereas **24** gave predominantly the (E) isomer (**27**).



23

E = $COOCH_3$



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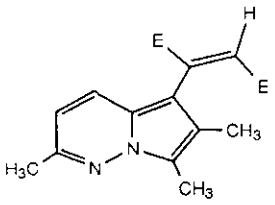

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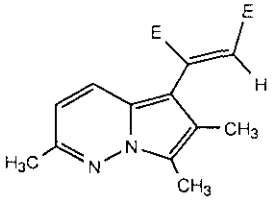

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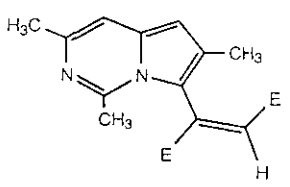

27

Thus pyrrolo[1,2-a]pyrazine(s) show a reactivity with DMAD uncharacteristic of other azaindolizines and in particular with the 8-methypyrrolo[1,2-a]pyrazines (5 and 6), show reaction more closely resembling that of 2-methylquinoline with DMAD.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ultraviolet absorption data refers to solutions in ethanol unless otherwise stated and were measured on a Perkin-Elmer 552 spectrophotometer; principal maxima are italicized and inflections are given in parentheses. Infrared spectra were recorded with a Perkin-Elmer 781 spectrophotometer and are for Nujol mulls unless otherwise stated. ^{1}H and ^{13}C nmr spectra refer to solutions in deuteriochloroform unless otherwise stated and were recorded on Perkin-Elmer R12B, Varian FT-80A, or JOEL FX90 Q spectrometers with tetramethylsilane as an internal standard. The ^{13}C nmr spectra were interpreted with the aid of the spin echo spectra, copies of these spectra are available from the authors. *Unless otherwise stated, values given on the* δ scale refer to singlet absorbtion, approximate coupling constants are in hertz, and integration and signal assignment are in parentheses. For multiplets d = doublet, dd = double doublet, t = triplet, q = quartet, and m = complex multiplet. Signals marked with an asterisk are broadened and or weakly split. Mass spectroscopy data was obtained from a VG-250 SE spectrometer. Elemental analysis and much of the spectroscopic analysis was by courtesy of the analytical laboratories of ICI Pharmaceuticals Division.

2,8-Dimethyl- and 2,3,8-trimethylpyrrolo[1,2-a]pyrazine (5 and 6) were prepared by the procedures given in ref. 24; 2,3,6-trimethylpyrrlo[1,2-b]pyridazine (23) and 2,5,7-

trimethylpyrrolo[1,2-c]pyrimidine (**24**) were prepared by the procedures given in references 25 and 26 respectively.

Reaction between 2,8-dimethylpyrrolo[1,2-a]pyrazine and DMAD

2,8-Dimethylpyrrolo[1,2-a]pyrazine (**5**) (0.9 g, 6.16 mmol) was dissolved in toluene (15 ml). DMAD (1.7 g, 12.0 mmol) was then added dropwise to give an exothermic reaction which resulted in a deep orange solution. The reaction mixture was left to stand for 1 day at room temperature. Evaporation of the solvent gave a red oil. The examination of this oil by tlc showed separate bands when viewed under uv light. The compounds were isolated by preparative tlc on silica gel by using toluene/ethyl acetate (3:1) as the mobile phase.

The fastest moving band gave 8,9,10-tricarbomethoxy-2-methyldipyrrolo[1,2-a:2,1-c]pyrazine (**7**) (0.07 g, 3.3%) as straw coloured crystals, (from 95% ethanol) mp 124°C; ir 795, 1120, 1215, 1690, 1710, 1745, 3160cm^{-1}; ^{1}H nmr 2.30 (3H,CH_3-2), 3.18 (6H, $COOCH_3$-9, $COOCH_3$-10), 3.95 (3H, $COOCH_3$-8), 7.06* (1H, H-3), 7.34 (1H, d, J = 6.0 Hz, H-5), 7.69* (1H, H-1), 8.50 (1H, d, J = 6.0 Hz, H-6); Mass calcd for $C_{17}H_{16}N_2O_6$: 344.1008. Found: 344.3237 (M^+,100), 313 (M-OCH_3, 48).

The second band gave an orange solid which recrystallized from methanol to give tetramethyl 2,11a-dimethyl-11aH-pyrido[2,1-c]pyrrolo[1,2-a]pyrazine-8,9,10,11-tetracarboxylate (**9**) (0.4 g, 15%) as orange crystals; mp 86.2°C; λ_{max} (226.6), (260), 284, (340) nm (log ε 4.10, 4.00, 4.18, 3.08); ir 1140, 1230, 1550, 1620, 1705, 1740, 3120 cm^{-1}; ^{1}H nmr 1.82 (3H, CH_3-11a), 2.02 (3H, CH_3-2), 3.69 (3H, $COOCH_3$-11), 3.74(3H, $COOCH_3$-10), 3.76 (3H, $COOCH_3$-9), 3.93 (3H, $COOCH_3$-8), 5.85 (1H, d, J = 6.0 Hz, H-5), 5.86* (1H, H-1) 6.38 (1H, d, J = 6.0 Hz, H-6), 6.38* (1H, H-3); ^{13}C nmr 11.44 (CH_3-11a), 25.14 (CH_3-2), 51.63, 52.12, 52.12, 53.10 (ester methyl at C-8, C-9, C-10, C-11), 61.33 (C-11a), 100.98 (C-2), 109.43, 110.03, 110.63, 115.56 (C-1, C-3, C-5, C-6), 120.16, 124.71, 125.69, 128.83 (four quaternary carbons C-8, C-9, C-10, C-11), 143.40 (C-11b), 163.55, 163.72, 165.45, 166.48 (four carbonyl carbons at C-8, C-9, C-10, C-11); Anal. Calcd for $C_{21}H_{22}N_2O_8$: C, 58.6; H, 5.2; N; 6.5. Found: C, 58.2, H, 5.1; N, 6.2. Mass calcd for $C_{21}H_{22}N_2O_8$: 430. Found: 430(M^+, 5), 415 (M-CH_3, 100).

The third band afforded a pale yellow solid which upon crystallization from methanol/petroleum ether gave tetramethyl 7a,8,9,9a-tetrahydro-2-

methylcyclobuta[4,5]dipyrrolo[1,2-a:2,1-c]pyrazine-7a,8,9a,10-tetracarboxylate (**10**) (0.15 g, 6%) as colourless crystals; mp 191.9°C, λ_{max} (239.5) 244.4, (285), 293.5, (308), 331.8, (376), 383.4 nm (log ε 4.07, 4.09, 4.18, 4.27, 3.19, 4.06, 4.22, 4.03); ^{1}H nmr 2.20 (3H , CH_3-2), 3.36 (3H, $COOCH_3$-8), 3.66 (3H, $COOCH_3$-9a), 3.70 (3H, $COOCH_3$-7a), 3.76 (3H, $COOCH_3$-10), 2.64 - 3.87 (3H, m, CH_2CHO), 6.87* (1H, H-3), 6.49 (1H, d, J = 6.0 Hz, H-5), 6.73 (1H, d, J = 6.0 Hz, H-6), 8.02* (1H, H-1). Anal. Calcd for $C_{21}H_{22}N_2O_8$: C, 48.6; H, 5.1; N, 6.5. Found: C, 58.2; H, 5.2; N, 6.3. Mass calcd for $C_{21}H_{22}N_2O_8$: 430. Found 430 (M^+, 45): 344 (M- CH_2=$CHCOOCH_3$, 100).

The fourth band gave a solid which after recrystallization from methanol yielded trimethyl 8-(methoxycarbonyl)methyl-2-methyl-8H-pyrido[2,1-c]pyrrolo[1,2-a]pyrazine-8,9,10-tricarboxylate (**14**) (0.07 g, 3.3%) as red crystals; mp 191°C; λ_{max} (215), 240, 272.5, (282), 300, 325 nm (log ε 4.04, 4.26, 4.25, 3.59, 3.58); ir 1160, 1250, 1670, 1730, 1740, 3120 cm^{-1}; ^{1}H nmr 2.20 (3H, CH_3-2), 3.12 (2H, CH_2-8), 3.60 (3H, $COOCH_3$), 3.70 (3H, $COOCH_3$), 3.82 (3H, $COOCH_3$), 3.85 (3H, $COOCH_3$), 5.05 (1H, H-11), 6.02 (1H, d, J = 6.0 Hz, H-5), 6.55 (1H, H-1), 6.80 (1H, d, J = 6.0 Hz, H-6), 6.84 (1H, H-3); ^{13}C nmr 11.81 (CH_3-2), 40.96, (CH_2-8), 51.41, 51.99, 52.17, 53.41 (four ester methyls), 69.54 (C-8), 84.79 (C-11), 100.00 (C-2), 109.49, 110.41, 113.01, 117.04 (C-1, C-3, C-5, C-6), 121.89, 124.98 (C-9, C-10), 138.15, 142.81 (C-11a, C-11b), 164.21, 164.35, 170.00, 170.38 (four carbonyl carbons); Anal. Calcd for $C_{21}H_{22}N_2O_8$: C, 58.6; H , 5.1; N, 6.5. Found: C, 58.2; H, 5.0; N, 6.3. Mass calcd for $C_{21}H_{22}N_2O_8$: 430. Found: 430 (M^+, 10), 371 (M-$COOCH_3$, 15), 357 (M-CH_2COOCH_3, 100).

The fifth band gave a yellow solid which was recrystallized from methanol to give tetramethyl 8,9-dihydro-2-methylpyrrolo[2',1':3,4]pyrazino[1,2-a]azepine-8,9,10,11-tetracarboxylate (**15**) (0.15 g, 6%) as intense yellow crystals; mp 197-198°C; λ_{max} (212), 240, (268), 314 nm (log ε 3.99, 4.28, 3.72, 3.67); ir 1125, 1250, 1530, 1680, 1735, 1750, 3120 cm^{-1}; ^{1}H nmr 2.15 (3H, CH_3-2), 3.59 (3H, $COOCH_3$-9), 3.65 (3H, $COOCH_3$-8), 3.74 (3H, $COOCH_3$-10), 3.83 (3H, $COOCH_3$-11), 5.25 (1H, d, J = 6.0 Hz, H-9), 5.32 (1H, H-12), 5.35 (1H, d, J = 6.0Hz, H-8), 6.56* (1H, H-1), 6.18 (1H, d, J = 6.0 Hz, H-5), 6.68 (1H, d, J = 6.0 Hz, H-6), 6.75* (1H, H-3); ^{13}C nmr 11.87 (CH_3-2), 48.99 (C-9), 52.00, 52.41, 52.63, 52.96 (four ester methyls), 67.49 (C-8), 88.38 (C-12), 108.45, 108.59 (C-5, C-6), 109.58 (C-2), 119.05 (C-1), 123.65 (C-3), 124.56 and 125.38 (quaternary carbons at C-10 and C-11), 139.04 (C-12a), 143.25 (C-12b), 166.12, 167.20,

170.45, 171.10 (four carbonyl carbons); Anal. Calcd for $C_{21}H_{22}N_2O_8$: C, 58.6; H, 5.2; N, 6.5. Found: C, 58.1; H, 5.2; N, 6.2. Mass calcd for $C_{21}H_{22}N_2O_8$: 430. Found: 430 (M^+, 45) 399 ($M-OCH_3$, 12) 371 ($M-COOCH_3$, 100).

Reaction between 2,3,8-trimethylpyrrolo[1,2-a]pyrazine (6) and DMAD.

To 2,3,8-trimethylpyrrolo[1,2-a]pyrazine (6) (1.7 g, 10 mmol) in toluene (25 ml) was added dropwise DMAD (3.1 g, 20 mmol). This resulted in an exothermic reaction and a deep orange solution. The reaction mixture was left at room temperature for one day. Evaporation of the solvent afforded an oil. Preparative tlc of this oil gave five compounds. The first fastest moving band gave 2,3-dimethyl-8,9,10-tricarbomethoxydipyrrolo[1,2-a:2,1-c]pyrazine (16) (0.2 g, 6%) as cream crystals, (from 95% ethanol) mp 182°C; ir 782, 1095, 1210, 1530, 1690, 1700, 1745, 2160 cm^{-1}; ^1H nmr 2.20 (3H, CH_3-2), 2.30 (3H, CH_3-3), 3.88 (6H, $COOCH_3$-9, $COOCH_3$-10), 3.98 (3H, $COOCH_3$-8), 7.28 (1H, d, J = 6.0 Hz, H-5), 7.75 (1H, H-1), 8.58 (1H, d, J = 6.0 Hz, H-6); Mass calcd for $C_{18}H_{18}N_2O_6$: 358.3539. Found: 358.3518 (M^+, 100), 357 (M-H, 11), 327 ($M-OCH_3$, 21).

The second fastest running band afforded a yellow solid which was recrystallized from methanol to give tetramethyl 2,3,11a-trimethyl-11aH-pyrido[2,1-c]pyrrolo[1,2-a]pyrazine-8,9,10,11-tetracarboxylate (17) (0.58 g, 13%) as yellow crystals (from 95% ethanol) mp 152-153°C; λ_{max} (220), (224), 281, (340) nm (log ε 4.13, 4.01, 4.22, 3.07); ir 1000, 1210, 1245, 1540, 1605, 1700, 1740 cm^{-1}; ^1H nmr 1.83 (3H, CH_3-11a), 1.94 (3H, CH_3-2), 2.09 (3H, CH_3-3), 3.68 - 3.92 (four carbomethoxy methyl signals), 5.76 (1H, H-1), 5.77 (1H, d, J = 6.0 Hz, H-5), 6.31 (1H, d, J = 6.0 Hz, H-6). Mass calcd for $C_{22}H_{24}N_2O_8$: 444. Found: 444 (M^+, 5) 429 ($M-CH_3$, 100).

The third band yielded tetramethyl 7a,8,9,9a-tetrahydro-2,3-dimethylcyclobuta[4,5]dipyrrolo[1,2-a:2,1-c]pyrazine-7a,8,9a,10-tetracarboxylate (18), (0.08g, 2%) as colourless crystals, (methanol/petroleum ether) mp 249-250°C; ir 1045, 1060, 1095, 1210, 1530, 1680, 1745, 3040cm^{-1}; ^1H nmr 2.15 (3H, CH_3-2), 2.27 (3H, CH_3-3), 2.55-3.95 (3H, m, $CHCH_2$), 3.65 - 3.77 (four carbomethoxy methyl signals), 6.55 (1H, d, J = 6.0 Hz, H-5), 6.70 (1H, d, J = 6.0 Hz, H-6), 8.10 (1H, H-1); Mass calcd for $C_{22}H_{24}N_2O_8$: 444. Found: 444 (M^+, 8), 385 ($M-CH_2$=$CHCOOCH_3$, 100).

The fourth band yielded trimethyl 8-(methoxycarbonyl)methyl-2,3-dimethyl-8H-pyrido[2,1-c]pyrrolo[1,2-a]pyrazine-8,9,10-tricarboxylate (**19**) (0.08 g, 2%) as red crystals, (from methanol) mp 176-177°C; ir 1120, 1170, 1250, 1500 1660, 1730, 1740, 3120 cm^{-1}; ^1H nmr 2.10 (3H, CH_3-2), 2.23 (3H, CH_3-3), 3.09 (2H, CH_2-8), 3.57 - 3.83 (four carbomethoxy methyl signals), 5.09 (1H, H-11), 6.24 (1H, d, J = 6.2 Hz, H-5), 6.53 (1H, H-1), 6.74 (1H, d, J = 6.2 Hz, H-6); Mass calcd for $C_{22}H_{24}N_2O_8$: 444. Found: 444 (M^+, 65), 412 (M-CH_3, 45), 385 (M- $COOCH_3$, 100), 371 (M-CH_2COOCH_3, 25).

The slowest band gave an orange solid which was recrystallized from methanol to give tetramethyl 8,9-dihydro-2,3-dimethylazepino[2,1-c]pyrrolo[1,2-a]pyrazine-8,9,10,11-tetracarboxylate (**20**) (0.3 g, 7%) as orange crystals, mp 214-215°C; ^1H nmr 2.05 (3H, CH_3-2), 2.20 (3H, CH_3-3), 3.56-3.82 (four carbomethoxy methyl signals), 5.24 (1H, d, J = 6.0Hz, H-9), 5.28 (1H, d, J = 6.0Hz, H-8), 5.28 (1H, H-12), 6.02 (1H, d, J = 6.0Hz, H-5), 6.54 (1H, H-1), 6.65 (1H, d, J = 6.0 Hz, H-6). Mass calcd for $C_{22}H_{24}N_2O_8$: 444.4452. Found: 444.4415 (M^+, 37), 413 (M - OCH_3, 10), 385 (M-$COOCH_3$, 100).

Reaction of 2,3,6-trimethylpyrrolo[1,2-b]pyridazine (23) with DMAD

To a solution of **23** (1.10 g, 6.88 mmol) in toluene (50 ml) was added DMAD (1.95 g, 13.70 mmol) and the mixture left at room temperature for four days. Tlc gave two main bands, the faster moving being isolated as 1-(E)-dicarbomethoxyethenyl-2,3,6-trimethylpyrrolo[1,2-b]pyridazine (**25**) (0.79 g, 38.1%) as red crystals, (from 95% ethanol) mp 86-87°C; ir 1031, 1156, 1201, 1220, 1255, 1301, 1332, 1432, 1550, 1608, 1710, 1724 cm^{-1}; ^1H nmr 2.10 (3H, CH_3-2), 2.44 (6H, CH_3-3 and CH_3-6), 3.55 and 3.76 (3H, $COOCH_3$), 6.33 (1H, d, J = 10.0 Hz, H-7), 7.00 (1H, ethenyl H), 7.30 (1H, d, J = 10.0 Hz, H-8); Anal. Calcd for $C_{16}H_{18}H_2O_4$: C, 63.6; H, 6.0; N, 9.3. Found: C, 63.1; H, 5.9; N, 9.1. Mass calcd for $C_{16}H_{18}N_2O_4$: 302. Found: 302 (M^+, 100), 243 (M-$COOCH_3$, 69).

The slower moving band was isolated as 1-(Z)-dicarbomethoxyethenyl-2,3,6-trimethyl-5-pyrrolo[1,2-b]pyridazine (**26**) (0.32 g, 15.5%) as green crystals, (from 95% ethanol) mp 113°C; ir 1163, 1200, 1249, 1335, 1437, 1590, 1711, 1726 cm^{-1}; ^1H nmr 2.30 (3H, CH_3-2), 2.46 (6H, CH_3-3 and CH_3-6), 3.77 and 3.91 (3H, $COOCH_3$), 6.06 (1H, ethenyl H), 6.49 (1H, d, J = 11.0 Hz, H-7), 7.78 (1H, d, J = 11.0 Hz, H-8). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.6; H, 6.0; N, 9.3. Found: C, 63.2; H, 5.7; N, 8.8. Mass calcd for $C_{16}H_{18}N_2O_4$: 302. Found: 302 (M^+, 100), 243 (M-$COOCH_3$, 71).

Reaction of 2,5,7-trimethylpyrrolo[1,2-c]pyrimidine (24) with DMAD

To a solution of **24** (0.2 g, 1.25 mmol) in toluene (10 ml) was added DMAD (0.36 g, 2.50 mmol) and the mixture left at room temperature for four days. Tlc gave one main band which was isolated as 3-(E)-dicarbomethoxyethenyl-2,5,7-trimethylpyrrolo[1,2-c]pyrimidine (**27**) (0.06 g, 15.9%) as a red solid, (from 95% ethanol) mp 65-67°C; ^{1}H nmr 2.05 (3H, CH_3-2), 2.33 (3H, CH_3-7), 2.57 (3H, CH_3-5), 3.27 and 3.75 (3H, $COOCH_3$), 6.18 (1H, H-1), 6.88 (1H, H-8), 7.21 (1H, ethenyl H). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.6; H, 6.0; N, 9.3. Found: C, 63.2; H, 6.2; N, 9.1. Mass calcd for $C_{16}H_{18}N_2O_4$: 302. Found: 302 (M^+, 100), 243 (M-$COOCH_3$, 79).

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