Pyrrole Studies. Part 32.[1] A Novel Ring-cleavage Reaction of the Pyridazine Ring during the Reaction of 6*H*-Pyrrolo[3,4-*d*]pyridazines with Dimethyl Acetylenedicarboxylate

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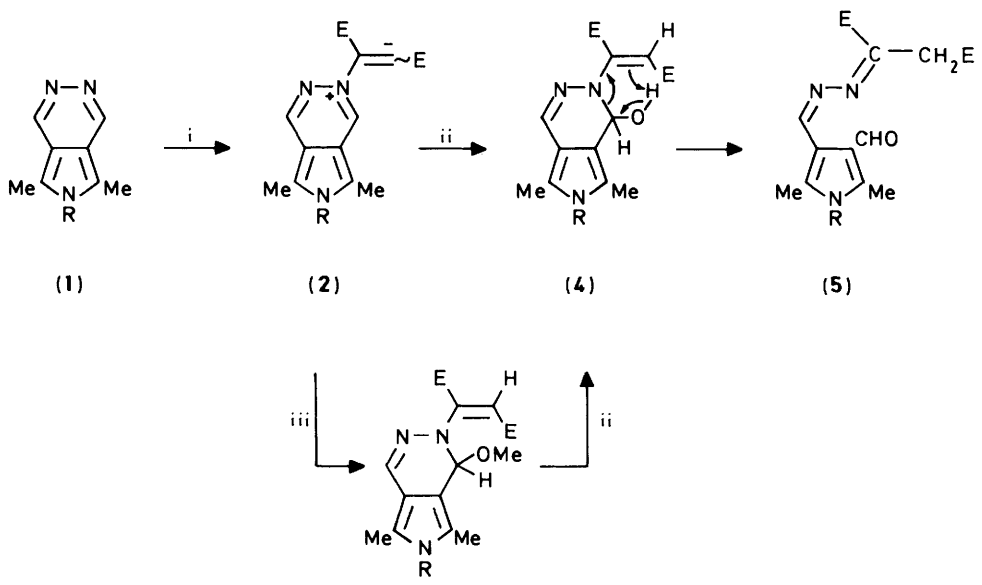
The reaction of 6*H*-pyrrolo[3,4-*d*]pyridazines with dimethyl acetylenedicarboxylate in methanol leads initially to (1,2-dihydro-1-methoxy-6*H*-pyrrolo[3,4-*d*]pyridazin-2-yl)fumaric esters, which are unstable in the presence of water and undergo a ring-cleavage reaction to yield 4,5-diaza-6-pyrrol-3-ylhexa-3,5-dienoates. The structure of the 4-formyl-2,5-dimethylpyrrol-3-yl derivative has been confirmed by *X*-ray crystallography.

The reaction of π-electron excessive and π-electron deficient *N*-heteroaromatic systems with dimethyl acetylenedicarboxylate (DMAD) have been extensively investigated.[2] Generally, π-electron excessive heterocycles undergo [$_{\pi}4 + {}_{\pi}2$] cycloaddition reactions, as exemplified by the reaction of some 1-substituted pyrroles, or they react to give Michael adducts, as illustrated by the reactions of indoles and of pyrroles.[3] In both types of reaction, further addition to and/or rearrangement of the initial adducts, may occur. In contrast, π-electron deficient systems generally react by initial nucleophilic attack by the heterocycle upon the acetylene to yield a zwitterionic species. The isolated products usually arise either from the reaction of the zwitterion with an electrophile to yield the heteroaromatic cation or by the further reaction of the zwitterion with a second molecule of DMAD.[2,4]

The reactions of phthalazine and of isoindole with DMAD follow these respective patterns and are well documented.[2] It was of interest, therefore, to examine the reactivity of 6*H*-pyrrolo[3,4-*d*]pyridazines with DMAD, as it was expected that the interaction of the fused π-electron excessive and π-electron deficient rings would modify the reactivity of each of the two systems and possibly lead to new reaction pathways.

5,6,7-Trimethyl-6*H*-pyrrolo[3,4-*d*]pyridazine (**1a**) reacted with DMAD in methanol at −70 °C by a route analogous to that reported[5] for phthalazine to give the adduct (**3a**), resulting from the addition of methanol to the initially formed zwitterion



(1) (2) (4) (5)

(3)

a; R = Me
b; R = H
c; R = Ph

E = CO_2Me

Reagents: i, DMAD; ii, H_2O; iii, MeOH

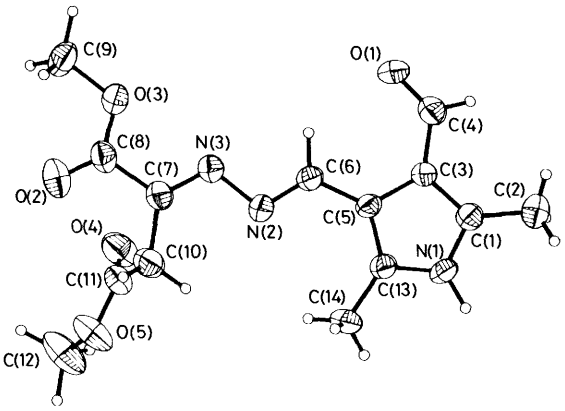


Figure. Molecular structure for compound (**5b**)[7] showing the crystallographic numbering scheme

(**2a**). The 1,2-dihydro-1-methoxypyridazine system is well characterised by ^{1}H n.m.r. signals at 5.54 and 7.48 p.p.m., which we assigned, respectively, to the 1- and 4-protons of the dihydropyridazine ring (*cf.* ref. 5). The vinylic proton of the fumaric ester group resonates at 6.38 p.p.m. and the configuration of the ester is confirmed by the value of *ca.* 6 Hz for the $^3J_{CO,H}$ coupling constant.[6] The adduct (**3a**) precipitated from the reaction solution in an analytically pure form, but an n.m.r. spectroscopic examination of the residue, obtained upon evaporation of the reaction solution, showed the presence of a second product which gave three sharp singlets at 3.90, 8.94, and 10.40 p.p.m. All attempts to isolate the second product in an analytically pure form failed.

In contrast with the reaction of the 6-methyl compound, no solid material separated from the corresponding reactions of DMAD with either 5,7-dimethyl-6*H*-pyrrolo[3,4-*d*]pyridazine (**1b**) or 5,7-dimethyl-6-phenyl-6*H*-pyrrolo[3,4-*d*] pyridazine (**1c**) in methanol at −70 °C; however, evaporation of the reaction solutions yielded solids, the n.m.r. spectra of which showed signals characteristic of the methoxy derivatives (**3b**) and (**3c**), together with singlets at *ca.* 3.9, 8.9, and 10.4 p.p.m. analogous to those produced by the second product detected in the reaction of compound (**1a**).

Chromatographic purification on silica of the impure adducts (**3b**) and (**3c**) resulted in their complete conversion into the secondary compounds detected in the crude reaction product. Elemental analyses and spectroscopic data indicated that the most probable structure for these products was that of the ring-opened system (**5**). This structure was confirmed for compound (**5b**), as shown in the Figure, by *X*-ray crystallography.

The formation of the ring-opened products (**5**) can be rationalised in terms of a 1,5-sigmatropic rearrangement of the hydroxy intermediate (**4**), which is produced by nucleophilic displacement of the 1-methoxy group by water on the silica.[8] The formation of the hydroxy compounds (**4**) and their subsequent conversion into the products (**5**) also occurred directly from the zwitterion (**2**) when the reaction of the pyrrolo[3,4-*d*]pyridazines with DMAD was conducted in 'wet' methanol or 'wet' chloroform.

It is of interest to note that a major fragmentation pathway of the ring-opened compounds (**5**) under electron impact involved the initial loss of the elements of water. This implies that compounds (**5**) undergo a 1,5-sigmatropic reversion to the hydroxy compound (**4**) in a McLafferty-type rearrangement.

* Overlap of ester CH_3 and CH_2 signals.

Experimental

I.r. spectra were measured for solutions in $CHBr_3$ using a Perkin-Elmer 577 spectrometer. ^{1}H and ^{13}C N.m.r. spectra were recorded using either a JEOL FX-100 or a Varian FX-2 spectrometer for *ca.* 40% solutions in $CDCl_3$. All chemical shifts are reported downfield from the internal standard (Me_4Si) and the solvent was used as the deuterium lock for the ^{13}C n.m.r. measurements. Low resolution mass spectra were obtained using a Kratos MS25 spectrometer and accurate mass measurements were recorded by the Food Research Institute Mass Spectrometry Unit, Norwich, using an AEI MS902 spectrometer.

Reaction of 5,6,7-*Trimethyl*-6H-*pyrrolo*[3,4-d]*pyridazine* (**1a**) *with DMAD.*—DMAD (0.28 g, 0.0019 mol) in dry methanol (0.5 ml) was added slowly during 2 h with stirring to 5,6,7-trimethyl-6*H*-pyrrolo[3,4-*d*]pyridazine[9] (**1a**) (0.34 g, 0.002 mol) in dry methanol (3 ml) at −70 °C. The precipitate, which formed during the period of the reaction, was collected and recrystallised from dimethylsulphoxide to give *dimethyl* 2-(1,2-*dihydro*-1-*methoxy*-5,6,7-*trimethyl*-6H-*pyrrolo*[3,4-d]*pyridazin*-1-*yl*)*but*-2-*enedioate* (**3a**) (0.33 g, 49.7%), as a thermally labile white solid, m.p. 160 °C (decomp.) (Found: C, 56.9; H, 6.1; N, 12.4. $C_{16}H_{21}N_3O_5$ requires C, 57.3; H, 6.3; N, 12.5%); δ_H 2.22 (3 H, s), 2.28 (3 H, s), 2.85 (3 H, s), 3.47 (3 H, s), 3.69 (3 H, s), 5.54 (1 H, s), 6.38 (1 H, s), and 7.48 (1 H, s); δ_C 10.0 (q, two coincident signals), 30.3 (q), 49.2 (q), 51.1 (q), 52.7 (q), 78.8 (d), 89.7 (d), 107.3 (s), 108.8 (s), 125.1 (s), 134.3 (d), 153.0 (s), 158.1 (s), 162.0 (s), and 167.4 (s); $\nu_{C=O}$ and $\nu_{C=N}$ 1 740, 1 705, and 1 620 cm^{-1}.

Evaporation of the reaction solution gave a solid (0.27 g), the ^{1}H n.m.r. spectrum of which, in addition to the signals characteristic of the 1,2-dihydro-1-methoxypyridazine system, showed signals at δ 2.44 (3 H, s), 2.54 (3 H, s), 3.46 (3 H, s), 3.90 (5 H, s), 8.94 (1 H, s), and 10.40 (1 H, s) expected for the ring-opened structure (**5a**). Attempted purification of compound (**5a**) by recrystallisation or chromatography failed.

Reaction of 5,7-*Dimethyl*-6H-*pyrrolo*[3,4-d]*pyridazine* (**1b**) *with DMAD.*—DMAD (0.88 g, 0.0062 mol) in dry methanol (1 ml) was added slowly with stirring during 30 min to 5,7-dimethyl-6*H*-pyrrolo[3,4-*d*]pyridazine[9] (**1b**) (0.92 g, 0.0062 mol) in dry methanol (7 ml) at −70 °C. The reaction mixture was allowed to reach room temperature and the solvent was removed under reduced pressure. Chromatographic purification of the residue on Merck silica gel 60, using ethyl acetate–toluene (3:1) as the eluant, gave, as the major product, *methyl* 6-(4-*formyl*-2,5-*dimethylpyrrol*-3-*yl*)-3-*methoxycarbonyl*-4,5-*diaza*-3,5-*dienoate* (**5b**) (0.67 g, 34.9%), R_F 0.32, m.p. 152—153 °C (Found: C, 54.3; H, 5.45; N, 13.5%; M^+ 307.1179. $C_{14}H_{17}N_3O_5$ requires C, 54.7; H, 5.6; N, 13.7%; M^+ 307.1167); δ_H 2.40 (3 H, s), 2.50 (3 H, s), 3.60 (3 H, s), 3.90 (5 H, s),* 8.90 (1 H, s), 10.40 (1 H, s), and 10.60 (1 H, s); δ_C 11.4 (q), 12.4 (q), 33.1 (t), 51.8 (q), 52.4 (q), 113.5 (s), 119.4 (s), 135.7 (s), 139.1 (s), 152.1 (s), 160.5 (d), 164.5 (s), 168.5 (s), and 186.6 (d); $\nu_{C=O}$ and $\nu_{C=N}$ 1 780, 1 700, and 1 670 cm^{-1}.

The ^{1}H n.m.r. spectrum of the crude reaction product also showed signals which were characteristic of the 1,2-dihydro-1-methoxypyridazine system (**3b**) at δ 2.18 (6 H, s), 2.82 (3 H, s), 3.66 (3 H, s), 3.75 (3 H, s), 5.46 (1 H, s), 6.25 (1 H, s), and 7.36 (1 H, s).

Reaction of 5,7-*Dimethyl*-6-*phenyl*-6H-*pyrrolo*[3,4-d]*pyridazine* (**1c**) *with DMAD.*—(*a*) Using a procedure similar to that described above, DMAD (0.126 g, 0.0009 mol) and 5,7-dimethyl-6-phenyl-6*H*-pyrrolo[3,4-*d*]pyridazine[10] (0.20 g, 0.0009 mol) gave, as the major product, *methyl* 6-(4-*formyl*-2,5-*dimethyl*-1-*phenylpyrrol*-3-*yl*)-3-*methoxycarbonyl*-4,5-*diazahexa*-3,5-*dienoate* (**5c**) (0.11 g, 32%), R_F 0.64, m.p. 120 °C (Found: C, 62.0; H, 5.5; N, 10.4%; M^+ 383.1469. $C_{20}H_{21}N_3O_5$ requires C, 62.65; H,

Table 1. Fractional atomic co-ordinates ($\times 10^4$) for compound (**5b**) with e.s.d.s. in parentheses

	x	*y*	*z*
N(1)	5 349(3)	2 448(3)	2 144(5)
C(1)	4 708(3)	1 859(3)	2 708(5)
C(2)	3 838(5)	2 213(4)	3 389(9)
C(3)	5 038(3)	975(3)	2 478(5)
C(4)	4 577(4)	142(4)	2 940(6)
O(1)	4 867(3)	−643(2)	2 822(5)
C(5)	5 908(3)	1 048(3)	1 730(5)
C(6)	6 478(4)	283(3)	1 253(6)
N(2)	7 219(3)	383(3)	503(5)
N(3)	7 616(3)	−492(2)	202(5)
C(7)	8 302(3)	−459(3)	−699(6)
C(8)	8 764(4)	−1 362(4)	−1 061(6)
O(2)	9 488(3)	−1 376(3)	−1 677(6)
O(3)	8 292(3)	−2 099(2)	−669(4)
C(9)	8 686(6)	−2 995(4)	−1 066(9)
C(10)	8 694(4)	397(4)	−1 460(7)
C(11)	8 447(4)	393(4)	−3 357(7)
O(4)	7 813(3)	−43(3)	−4 082(4)
O(5)	8 991(3)	952(3)	−4 087(5)
C(12)	8 777(6)	1 007(8)	−5 906(8)
C(13)	6 074(3)	1 983(3)	1 538(5)
C(14)	6 879(4)	2 501(4)	897(7)

Table 2. Bond lengths (Å) for compound (**5b**) with e.s.d.s. in parentheses

C(1)–N(1)	1.354(6)	C(13–N(1)	1.359(6)
C(2)–C(1)	1.490(8)	C(3)–C(1)	1.373(6)
C(4)–C(3)	1.431(7)	C(5)–C(3)	1.432(6)
O(1)–C(4)	1.207(6)	C(6)–C(5)	1.441(7)
C(13)–C(5)	1.375(6)	N(2)–C(6)	1.274(6)
N(3)–N(2)	1.409(5)	C(7)–N(3)	1.275(6)
C(8)–C(7)	1.496(7)	C(10)–C(7)	1.508(9)
O(2)–C(8)	1.186(6)	O(3)–C(8)	1.308(7)
C(9)–O(3)	1.453(6)	C(11)–C(10)	1.517(9)
O(4)–C(11)	1.181(6)	O(5)–C(11)	1.298(6)
C(12)–O(5)	1.454(7)	C(14)–C(13)	1.498(8)

5.5; N, 11.0%; M^+ 383.1480); δ_H 2.20 (3 H, s), 2.30 (3 H, s), 3.60 (3 H, s), 3.90 (5 H, s),* 7.00—7.60 (5 H, m), 8.90 (1 H, s), and 10.20 (1 H, s); δ_C 11.0 (q), 12.1 (q), 32.6 (t), 51.3 (q), 52.1 (q), 114.1 (s), 118.7 (s), 126.8 (d), 128.0 (d), 136.6 (s), 138.8 (s), 140.8 (d), 152.1 (s), 159.2 (d), 163.9 (s), 164.2 (s), 167.8 (s), and 186.9 (d); $\nu_{C=O}$ and $\nu_{C=N}$ 1 780, 1 700, and 1 670 cm^{-1}.

The ^1H n.m.r. spectrum of the crude reaction product also showed signals which were characteristic of the 1,2-dihydro-1-methoxypyridazine system (**3c**), at δ 2.09 (3 H, s), 2.18 (3 H, s), 3.18 (3 H, s), 3.20 (3 H, s), 3.69 (3 H, s), 5.56 (1 H, s), 6.35 (1 H, s), and 7.00—7.60 (6 H, m).

(*b*) Using a procedure analogous to that described above, DMAD (0.31 g, 0.0022 mol) and 5,7-dimethyl-6-phenyl-6*H*-pyrrolo[3,4-*d*]pyridazine (**1c**) (0.50 g, 0.0022 mol) were allowed to react in $CHCl_3$ (5 ml) at −70 °C. Methyl 6-(4-formyl-2,5-dimethyl-1-phenylpyrrol-3-yl)-3-methoxycarbonyl-4,5-diaza-hexa-3,5-dienoate (**5c**) (0.23 g, 26.7%) was isolated by chromatographic elution from Merck silica gel 60 with ethyl acetate–toluene (3:1).

Crystal and Molecular Structure of Compound (**5b**).—*Crystal data.* $C_{14}H_{17}N_3O_5$ M = 307.31, monoclinic, a = 14.069(3), b = 14.370(4), c = 8.018(3) Å, β = 97.15(2)°, U = 1 608.49 Å^3, space group $P2_1/c$, Z = 4, D_c = 1.27 g cm^{-3}, μ(Mo-K_α) = 0.61 cm^{-1}, F(000) = 648. A total of 2 831 unique intensity data were measured, of which 1 544 were deemed observed [$I > 1.5\sigma(I)$].

Table 3. Bond angles (°) for compound (**5b**) with e.s.d.s. in parentheses

C(13)–N(1)–C(1)	111.9(4)	C(2)–C(1)–N(1)	121.3(5)
C(3)–C(1)–N(1)	106.4(5)	C(3)–C(1)–C(2)	132.2(5)
C(4)–C(3)–C(1)	124.5(5)	C(5)–C(3)–C(1)	108.0(5)
C(5)–C(3)–C(4)	127.4(5)	O(1)–C(4)–C(3)	126.4(6)
C(6)–C(5)–C(3)	126.0(5)	C(13)–C(5)–C(3)	106.6(5)
C(13)–C(5)–C(6)	127.4(5)	N(2)–C(6)–C(5)	123.7(5)
N(3)–N(2)–C(6)	110.2(5)	C(7)–N(3)–N(2)	114.1(5)
C(8)–C(7)–N(3)	117.1(5)	C(10)–C(7)–N(3)	126.9(5)
C(10)–C(7)–C(8)	116.0(5)	O(2)–C(8)–C(7)	120.8(6)
O(3)–C(8)–C(7)	114.2(5)	O(3)–C(8)–O(2)	125.0(6)
C(9)–O(3)–C(8)	116.5(5)	C(11)–C(10)–C(7)	110.7(5)
O(4)–C(11)–C(10)	124.1(6)	O(5)–C(11)–C(10)	112.1(6)
O(5)–C(11)–O(4)	123.8(6)	C(12)–O(5)–C(11)	115.2(6)
C(5)–C(13)–N(1)	107.1(5)	C(14)–C(13)–N(1)	120.8(5)
C(14)–C(13)–C(5)	132.1(4)		

Solution and refinement of structure.—Intensities were measured on a Nonius CAD4 diffractometer to $\theta_{max.}$ = 25 (Mo-K_α radiation) using the ω–2θ mode as described previously.[11] The structure was solved by direct methods (SHELX84 programme for crystal structure solution), the best E map enabling the non-hydrogen atoms to be located. Refinement was by standard least-squares methods.[12] All hydrogen atoms were located on subsequent difference Fourier maps and included in the refinement, the methyl groups being treated as rigid bodies in the final stages. At the termination of the refinement, with anisotropic thermal parameters for all non-hydrogen atoms, R was 0.055 (unit weights employed). Final atomic positional parameters are given in Table 1, bond lengths and angles in Tables 2 and 3. Thermal parameters and positional parameter, bond angles, and bond lengths for the hydrogen atoms are available as a Supplementary Publication (SUP No. 56167, 5 pp).† Observed and calculated structure factors are available on request from the editorial office.

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References

1 Part 31, S. Inel, R. A. Jones, and C. Ogretir, *Tetrahedron*, 1984, **40**, 3979.
2 R. M. Acheson and N. F. Elmore, *Adv. Heterocycl. Chem.*, 1978, **23**, 263.
3 R. A. Jones in 'Comprehensive Heterocyclic Chemistry, vol. 4,' eds. C. W. Bird and G. H. W. Cheeseman, Pergamon Press, Oxford, 1984, p. 201.
4 P. J. Abbott, R. M. Acheson, and J. D. Aplin, *J. Chem. Res.*, 1979, (*S*), 394; (*M*), 4772.
5 R. M. Acheson and M. W. Foxton, *J. Chem. Soc. C*, 1966, 2218.
6 B. Gregory, W. Hinz, R. A. Jones, and J. Sepúlveda Arques, *J. Chem. Res.*, 1984, (*S*), 311; (*M*), 2801.
7 E. K. Davies, 'SNOOPI programme for drawing molecular structures,' University of Oxford, 1983.
8 *Cf.* N. Kawahara, T. Nakajima, T. Itoh, and H. Ogura, *Heterocycles*, 1982, **19**, 1623.

* Overlap of ester CH_3 and CH_2 signals.

† For details of the Supplementary Publication Scheme see Instructions for Authors (1985) in *J. Chem. Soc., Perkin Trans. 1*, 1985, Issue 1.

9 F. Acar, S. S. Badesha, W. Flitsch, R. Gözoğul, O. Inel, S. Inel, R. A. Jones, C. Öğretir, and D. C. Rustidge, *Chim. Acta Turc.*, 1981, **9**, 225.
10 R. Rips and N. P. Buu-Hoï, *J. Org. Chem.*, 1959, **24**, 372.
11 M. B. Hursthouse, R. A. Jones, K. M. A. Malik, and G. Wilkinson, *J. Am. Chem. Soc.*, 1979, **101**, 4128.
12 G. M. Sheldrick, 'SHELX76 programme for crystal structure determination,' University of Cambridge, 1976.

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