Pyrazines. Part 5.[1] Preparation of 3,8-Diazabicyclo[3.2.1]octane-2,4-dione Derivatives

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The title compounds were formed by cycloaddition of 2,6-dihydroxy-3,5-diphenylpyrazine to acetylenes and electron-deficient olefins.

NUMEROUS 3,8-diazabicyclo[3.2.1]octane-2,4-diones (2) have been prepared from pyrrolidine-2,5-dicarboxylic acids (1). The diacids are converted into compounds of this type by cyclisation of the monoamides formed by reaction of their cyclic anhydrides with ammonia or a primary amine.[2-4] Interest in 3,8-diazabicyclo[3.2.1]-octane-2,4-diones partly derives from their subsequent conversion into bridged analogues of the antifilarial drug, diethylcarbamazine (3).[5]

Alternatively 3,8-diazabicyclo[3.2.1]octane-2,4-diones have been prepared from piperazine-2,6-diones via cyclo-addition reactions. Thus treatment of 1,4-diphenyl-piperazine-2,6-dione (4) with benzenesulphonyl chloride or benzenesulphenyl chloride in pyridine gives the mesoionic compound (5) which undergoes cycloaddition at positions 3 and 5 with either maleic anhydride or formaldehyde.[6,7] The dehydrogenation of 1,4-diphenyl-piperazine-2,6-dione has been effected with either chloranil or boiling nitrobenzene and evidence for the formation of the 3,5-didehydro-derivative (6) has been obtained by isolation of cyclic dimers and a cyclo-addition product with N-phenylmaleimide.[8,9] An analogous 3,5-didehydropiperazinedione (8) has been generated by photolysis of the bicyclic aziridine (7) and trapped by cycloaddition with either dimethyl acetyl-enedicarboxylate or norbornene.[10]

Our own interest in this topic stems from our earlier work[1] on 2,6-dihydroxy-3,5-diphenylpyrazine (9a) for which a dipolar tautomeric form (9b) can be written. Tautomer (9b) has structural similarity to the pyrylium betaine (10)[11] and pyridinium betaines of type (11)[12] and we now report that it too has the capacity to form 1 : 1 cycloadducts with a number of acetylenic and olefinic dipolarophiles. Addition occurs across positions 3 and 5; the pyrazine thus functions as a 4π-component in the [$\pi4 + \pi2$] cycloaddition process.

2,6-Dihydroxy-3,5-diphenylpyrazine formed an adduct (12) with phenylacetylene in boiling ethyl acetate and an adduct (13) with diphenylacetylene in boiling nitro-methane. A much longer period of reflux, 9 compared to 1 h, was required for the latter reaction. Orange solutions of the dihydroxypyrazine slowly decolourised on exposure to air and improved yields of cycloadducts were obtained when the reactions were carried out under nitrogen.

Reaction of the pyrazine (9) with a solution of dimethyl acetylenedicarboxylate in ethyl acetate at room tem-perature gave the adduct (14). This was also obtained by adding diethylamine to a solution of 2,6-diacetoxy-3,5-diphenylpyrazine in dimethylformamide at 40—50 °C, and, without isolation of the intermediate di-hydroxy-compound, adding the acetylenic ester. An isomeric by-product was also isolated from this reaction which had spectroscopic properties consistent with its formulation as compound (15).

2,6-Dihydroxy-3,5-diphenylpyrazine also formed 1 : 1-adducts with N-phenylmaleimide, diethyl maleate, and

(1)   (2)

(3)   (4)

(5)   (6)

(7)   (8)
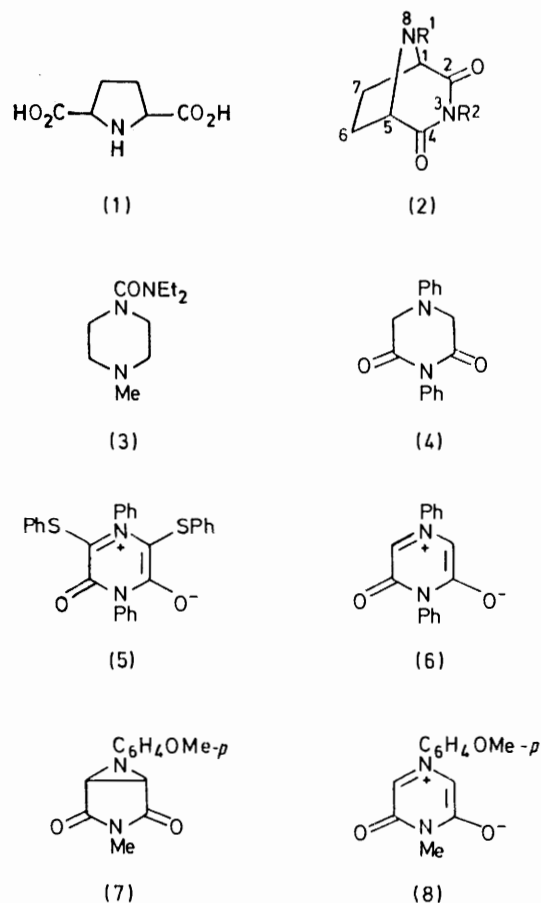
diethyl fumarate. It failed to react with the electron-rich alkene, ethyl vinyl ether. The isolation of isomeric adducts (17) and (18) from the cis- and trans-esters, respectively, indicates that concerted cycloaddition is occurring.
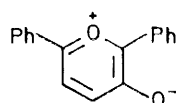
The structure of the adducts was confirmed by spectroscopic measurements. ¹H N.m.r. spectra revealed the presence of two N–H groups, the signal from the imide proton attached to N-3 appeared at a much lower field than that bonded to the bridging nitrogen, N-8. Both
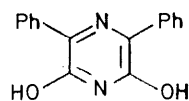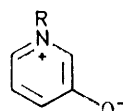

(9a)
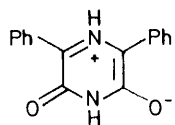
(9b)

(10)

(11)

signals disappeared on deuterium exchange. The ¹H n.m.r. spectrum of the dimethyl acetylenedicarboxylate adduct (14) showed that both methyl groups were identical and thus confirmed the bicyclic nature of the adduct. The ¹H n.m.r. spectrum of the diethyl maleate adduct (17) also demonstrated the symmetrical structure of the adduct; this and the adduct (16) from N-phenyl-maleimide are suggested to have endo-stereochemistry in analogy with the adducts derived from the pyrylium
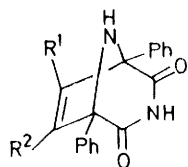
(12) R¹ = Ph , R² = H
(13) R¹ = R² = Ph
(14) R¹ = R² = CO₂Me
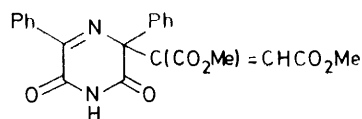
(15)
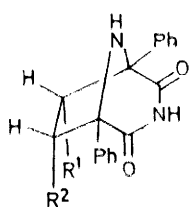
(16) R¹ + R² = CONPhCO   (18)
(17) R¹ = R² = CO₂Et
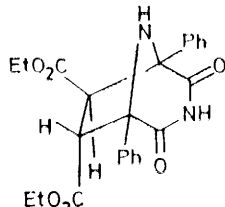
betaine (10).[11] These deductions from the ¹H n.m.r. data are supported by ¹³C n.m.r. measurements (see Experimental section).

The structure of the cycloadducts was also confirmed by mass spectral measurements. The adducts derived

from the acetylenic dipolarophiles fragmented mainly by loss of HCNO and CO to give pyrrolic ions, whereas those derived from alkenes underwent retrocycloaddition giving the ion of 2,6-dihydroxy-3,5-diphenylpyrazine (m/e 264). The phenylacetylene and diphenylacetylene adducts also fragmented with loss of HCNO and H to give a pyridone-type ion. We briefly examined the thermal stability of these compounds and found that whereas the diphenylacetylene adduct was stable in diphenyl ether at 280—300 °C, the phenylacetylene adduct fragmented to 3,4,6-triphenylpyridin-2-one.

Finally it may be noted that our work on the cyclo-addition reactions of 2,6-dihydroxy-3,5-diphenylpyrazine complements the work of Sammes and his co-workers who demonstrated the ability of 2,5-dihydroxypyrazines to participate in Diels–Alder addition reactions.[13]

EXPERIMENTAL

M.p.s were determined with a Gallenkamp apparatus. I.r. spectra were recorded on a Unicam SP200 spectrometer for potassium bromide discs. ¹H N.m.r. spectra were recorded, unless otherwise specified, at 60 MHz on a Perkin-Elmer R12B spectrometer, and ¹³C n.m.r. spectra on a Bruker WP 60 spectrometer operating at 15.08 MHz, for solutions in [²H₆]dimethyl sulphoxide with tetramethylsilane or sodium 3-trimethylsilylpropanesulphonate as internal standard. Mass spectra were recorded at 70 eV on an AEI MS 30 mass spectrometer. T.l.c. was performed using commercially supplied plates (plastic backing; Merck silica gel 60F₂₅₄; 20 × 20 cm; layer thickness 0.2 mm), visualisation being effected with iodine vapour. Column chromatography was carried out with Merck silica gel 60, particle size 0.063—0.200 mm, 70—230 mesh ASTM, catalogue no. 7734.

1,5,6-Triphenyl-3,8-diazabicyclo[3.2.1]oct-6-ene-2,4-dione (12).—To a suspension of 2,6-dihydroxy-3,5-diphenyl-pyrazine [1] (1.08 g, 4.08 mmol) in dry ethyl acetate (10 ml) was added phenylacetylene (2.16 g, 21.20 mmol), and the mixture was refluxed under nitrogen for 1 h. A slight precipitate was filtered off and removal of solvent from the filtrate gave the crude solid which was recrystallised from benzene–light petroleum (b.p. 60—80 °C). The purified imide (12) (0.97 g, 65%) had m.p. 216—219 °C, R_F 0.62 (benzene–ethyl acetate, 4 : 1); $\nu_{max.}$ 3 250s (NH) and 1 710s (C=O) cm⁻¹; m/e 366 (M^+) 322 (M − HCNO − H); and 295 (M − CONHCO); ¹H n.m.r.: δ 10.59 [1 H, s, N(3)-H, exchangeable with D₂O], 7.63—7.14 (15 H, m, ArH), and 5.34 [1 H, s, N(8), exchangeable with D₂O]; ¹³C n.m.r.: 175.34, 175.01 (C=O); 150.25 (C-6/C-7); 138.75, 138.35, 136.21, 134.47 (C-6/C-7 and phenyl C-1); 130.92, 129.92, 129.31, 128.85, 128.45 (phenyl C-2, C-3, and C-4); 77.74 and 76.39 p.p.m. (C-1 and C-5) (Found: C, 78.6; H, 5.2; N, 7.5. $C_{24}H_{18}N_2O_2$ requires C, 78.7; H, 4.95; N, 7.65%).

1,5,6,7-Tetraphenyl-3,8-diazabicyclo[3.2.1]oct-6-ene-2,4-dione (13).—A suspension of 2,6-dihydroxy-3,5-diphenyl-pyrazine (0.96 g, 3.65 mmol) and diphenylacetylene (1.372 g, 7.71 mmol) in dry nitromethane (15 ml) was refluxed under nitrogen for 9 h, filtered, and the filtrate evaporated to dryness. The crude product was adsorbed on silica gel (4 g) and chromatographed over silica gel (60 g) with benzene–ethyl acetate, gradually increasing the proportion of ethyl acetate from 7 : 1 to 4 : 1. Fractions containing the adduct were combined and dried. Crystallisation from benzene gave the imide (13) (0.71 g, 44%), m.p. 216—218 °C, R_F

0.46 (benzene–ethyl acetate, 7 : 1); $\nu_{max.}$ 3 200s (N–H), 1 730, and 1 690s cm^{-1} (C=O); m/e 442 (M^+), 398 (M − HCNO − H), and 371 (M − CONHCO); ^{1}H n.m.r.: δ 10.59 [1 H, s, N(3)-H, exchangeable with D$_2$O], 7.54—6.44 (20 H, m, ArH), and 5.47 [1 H, s, N(8)-H, exchangeable with D$_2$O]; ^{13}C n.m.r.: 175.08 (C=O); 146.44 (C-6 and C-7); 138.21, 134.80 (phenyl C-1); 130.45, 129.92, 129.52, 129.18, 128.78 (phenyl C-2, C-3, and C-4); and 76.80 p.p.m. (C-1 and C-5) (Found: C, 82.5; H, 5.0; N, 6.25. C$_{30}$H$_{22}$-N$_2$O$_2$ requires C, 81.45; H, 5.0; N, 6.3%).

Dimethyl 1,5-*Diphenyl*-2,4-*dioxo*-3,8-*diazabicyclo*[3.2.1]-*oct*-6-*ene*-6,7-*dicarboxylate* (14).—(a) 2,6-Dihydroxy-3,5-di-phenylpyrazine (1.01 g, 3.83 mmol) was suspended in dry ethyl acetate (8 ml). Dimethyl acetylenedicarboxylate (2.12 g, 14.93 mmol) was added and the orange suspension stirred at room temperature under nitrogen for 1 h. The cycloadduct was filtered off and an additional amount of product was obtained by evaporating the filtrate to dryness. Recrystallisation from benzene afforded the *diester* (14) (0.93 g, 60%), m.p. 190—193 °C, R_F 0.46 (benzene–ethyl-acetate 4 : 1); $\nu_{max.}$ 3 200s (N–H), 1 740s (ester C=O), and 1 720s cm^{-1} (amide C=O); m/e 406 (M^+) and 335 (M − CONHCO); ^{1}H n.m.r.: δ 11.08 [1 H, s, N(3)-H, exchange-able with D$_2$O], 7.76—7.11 (10 H, m, ArH), 5.79 [1 H, s, N(8)-H, exchangeable with D$_2$O], and 3.59 (6 H, s, CO$_2$Me); ^{13}C n.m.r.: 171.79 (amide C=O); 164.24 (ester C=O); 145.97 (C-6 and C-7); 136.14 (phenyl C-1); 129.98, 129.7, 129.38 (phenyl C-2, C-3, and C-4); 75.53 (C-1 and C-5); and 54.32 p.p.m. (ester Me) (Found: C, 64.9; H, 4.5; N, 6.8. C$_{22}$-H$_{18}$N$_2$O$_6$ requires C, 65.0; H, 4.5; N, 6.9%).

(b) 2,6-Diacetoxy-3,5-diphenylpyrazine (1.79 g, 5.14 mmol) was dissolved in dry dimethylformamide (15 ml) and diethylamine (0.825 g, 11.0 mmol) was added. The solution was stirred under nitrogen at 40 °C for 15 min. Dimethyl acetylenedicarboxylate (1.46 g, 10 mmol) was added and stirring continued at 40 °C for a further 1 h. Solvent was removed under reduced pressure and the residue was chromatographed on silica gel (70 g) using benzene–ethyl acetate, gradually increasing the proportion of ethyl acetate from 7 : 1 to 3 : 1. The expected cycloadduct (14) was eluted first and obtained in 29% yield (0.605 g) and a second isomeric product was isolated (0.227 g, 11%), which was tentatively identified as the Michael adduct (15). Recrystallisation from ethanol gave white needles, m.p. 246—247 °C, R_F 0.22 (benzene–ethyl acetate, 4 : 1); $\nu_{max.}$ 3 300s (N–H), 1 790s (ester C=O), 1 740s (ester C=O), 1 720s (amide C=O), and 1 640s cm^{-1} (C=N); m/e 406 (M^+) and 347 (M − CO$_2$CH$_3$); ^{1}H n.m.r.: δ 11.75 (1 H, s, N–H, exchange-able with D$_2$O), 7.85—7.22 (10 H, m, ArH), 5.12 (1 H, s, CH=C–), 3.42, and 3.17 (6 H, s, 2 × CO$_2$Me); ^{13}C n.m.r.: 174.94, 170.39, 165.84, 157.48 or 151.73 (carbonyl C); 151.73 or 157.48 (C=N); 136.54, 132.06, 131.39, 131.06, 130.59, 130.12, 129.32 (Ar); 127.04, 114.30 (vinylic); 74.33 (C-3); 58.94 and 53.32 p.p.m. (ester Me) (Found: C, 64.65; H, 4.4; N, 6.6%).

1,4,7-*Triphenyl*-4,9,11-*triazatricyclo*[5.3.1.0^{2,6}]*undecane*-3,5,8,10-*tetraone* (16).—2,6-Dihydroxy-3,5-diphenylpyrazine (2.10 g, 7.95 mmol) and *N*-phenylmaleimide (2.80 g, 16.2 mmol) were stirred in ethyl acetate (10 ml) at room tem-perature under nitrogen for 30 min. The colour of the mixture changed from yellow to green. The mixture was filtered, solvent removed, and the residue crystallised from nitromethane to give the *imide* (16) (0.80 g, 23%), m.p. 285 °C, R_F 0.46 (benzene–ethyl acetate, 4 : 1); $\nu_{max.}$ 3 300s (N–H), 1 770m, 1 740s, and 1 720s cm^{-1} (C=O); m/e 437 (M^+),

366 (M − CONHCO), and 264 (M − C$_{19}$H$_7$NO$_2$); ^{1}H n.m.r.: δ 11.70 [1 H, s, N(9)-H, exchangeable with D$_2$O], 8.10—7.10 (15 H, m, ArH), 5.60 [1 H, s, N(11)-H, exchangeable with D$_2$O], and 4.20 (2 H, s, 2- and 6-H) (Found: C, 71.5; H, 4.3; N, 9.3. C$_{26}$H$_{19}$N$_3$O$_4$ requires C, 71.4; H, 4.4; N, 9.6%).

Diethyl 2,4-*Dioxo*-1,5-*diphenyl*-3,8-*diazabicyclo*[3.2.1]-*octane* endo-6,endo-7-*dicarboxylate* (17).—A suspension of 2,6-dihydroxy-3,5-diphenylpyrazine (0.959 g, 3.64 mmol) and diethyl maleate (1.25 g, 7.27 mmol) in dry ethyl acetate (15 ml) was refluxed under nitrogen for 4 h. The solvent was removed, and residue adsorbed on silica gel (5 g) and chromatographed on silica gel (70 g), elution being per-formed with benzene–ethyl acetate mixtures, gradually increasing the proportion of ethyl acetate from 7 : 1 to 4 : 1. Fractions containing the adduct were combined and dried, and recrystallisation from ethanol afforded needles of the *diester* (17) (0.69 g, 44%), m.p. 160—161 °C, R_F 0.35 (benzene–ethyl acetate 4 : 1); $\nu_{max.}$ 3 250s (N–H), 1 740s (ester C=O), and 1 710s cm^{-1} (amide C=O); m/e 436 (M^+), 363 (M − CO$_2$CH$_2$CH$_3$), and 264 [M − (CHCO$_2$CH$_2$CH$_3$)$_2$]; ^{1}H n.m.r.: δ 11.35 [1 H, s, N(3)-H, exchangeable with D$_2$O], 7.80—7.20 (10 H, m, ArH), 4.73 [1 H, s, N(8)-H, exchangeable with D$_2$O], 4.23 (2 H, s, 6- and 7-H), 3.69 (4 H, q, J 7 Hz, CO$_2$CH_2Me), and 0.84 (6 H, t, J 7 Hz, CO$_2$CH$_2$$Me$); ^{13}C n.m.r.: δ 173.74 (amide C=O); 169.99 (ester C=O), 137.75 (phenyl C-1), 129.18, 128.85 (phenyl C-2, C-3, and C-4); 73.72 (C-1 and C-5); 61.95 (C-6 and C-7); 56.66 (CO$_2$CH$_2$-Me); and 14.85 p.p.m. (CO$_2$CH$_2$$Me$) (Found: C, 65.8; H, 5.3; N, 6.5. C$_{24}$H$_{24}$N$_2$O$_6$ requires C, 66.1; H, 5.5; N, 6.4%).

Diethyl 2,4-*Dioxo*-1,5-*diphenyl*-3,8-*diazabicyclo*[3.2.1]-*octane*-exo-6,endo-7-*dicarboxylate* (18).—2,6-Dihydroxy-3,5-diphenylpyrazine (1.11 g, 4.20 mmol) was suspended in dry ethyl acetate (14 ml) and diethyl fumarate (2.89 g, 16.8 mmol) was added. The solution was stirred under nitrogen at 60 °C for 1 h, filtered, and solvent removed yielding an oily residue which was adsorbed on silica gel (7 g) and chromatographed over silica gel (67 g) in benzene–ethyl acetate mixtures, gradually increasing the proportion of ethyl acetate from 7 : 1 to 3 : 1. The fractions containing the cycloadduct were combined and dried and yielded, on recrystallisation from benzene–light petroleum (b.p. 40—60 °C), the *diester* (18) (0.84 g, 46%), m.p. 133—135 °C, R_F 0.53 (benzene–ethyl acetate, 4 : 1); $\nu_{max.}$ 3 200s (NH), 1 740, 1 730s, (ester C=O), and 1 710s cm^{-1} (amide C=O); m/e 436 (M^+) and 264 [M − (CHCO$_2$CH$_2$CH$_3$)$_2$]; ^{1}H n.m.r.: δ (100 MHz) 11.16 [1 H, s, N(3)-H, exchangeable with D$_2$O], 7.90—7.20 (10 H, m, ArH), 5.02 [1 H, s, N(8)-H, exchangeable with D$_2$O], 4.12 (2 H, q, J 7 Hz, CO$_2$CH_2Me), 3.88—3.22 (4 H, m, CO$_2$CH_2Me and 6- and 7-H), 1.20 and 0.75 (6 H, 2 × t, J 7 Hz, CO$_2$CH$_2$$Me$); ^{13}C n.m.r.: δ 174.47, 173.67 (amide C=O); 171.86, 171.46 (ester C=O); 139.48, 136.07 (phenyl C-1); 130.11, 129.38, 128.51 (phenyl C-2 C-3, and C-4), 73.32, 72.79 (C-1 and C-5); 63.22, 62.48 (C-6 and C-7); 58.42, 57.27 (CO$_2$CH$_2$Me); 15.32 and 14.78 p.p.m. (CO$_2$CH$_2$$Me$) (Found: C, 65.9; H, 5.6; N, 6.45. C$_{24}$H$_{24}$-O$_6$N$_2$ requires C, 66.05; H, 5.5; N, 6.4%).

3,4,6-*Triphenylpyridin*-2-*one*.— 1,3,5-Triphenyl-3,8-diazabicyclo[3.2.1]oct-6-ene (1.0 g, 2.73 mmol) in diphenyl ether (20 ml) was heated in a sealed tube at 280—320 °C for 6 h. After 3 d at room temperature, the white solid which appeared was filtered off and crystallised from dimethyl-formamide. Recrystallisation from methanol gave 3,4,6-triphenylpyridin-2-one (0.2 g, 18%), m.p. 299—301 °C

(lit.,[14] 295 °C), identical in all respects with an authentic sample.

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