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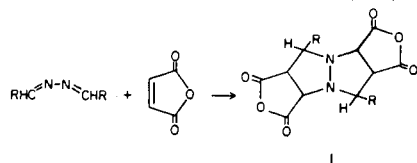
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The addition of maleic anhydride to phthalazine is confirmed to form a five-membered pyrrolidino ring fusion to phthalazine VI, rather than a pyridophthalazine II, by means of synthetic and degradative experiments, and proton and carbon-13 nmr. Two of probable three isomers obtained have been isolated and the stereochemistry partially established. Comparison of the data obtained for this adduct with the data obtained for the adduct of maleic anhydride with pyridazine demonstrates that it too possesses the pyrrolidino ring fusion. Electron impact fragmentations of the two adducts are compared and are related to the breakdown of 1*H*,2*H*-pyridazinone.

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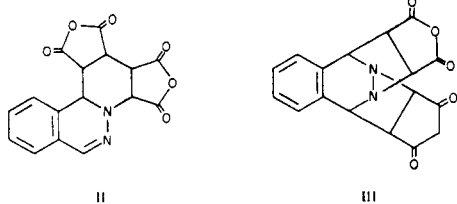
Introduction

Initial synthetic experiments were carried out with linear aldehydes and maleic anhydride, which, despite the prediction of a cisoid conformation for azines based on M.O. consideration of nitrogen lone pair overlap (2) and required for 2 + 4 electrocyclic additions, under a wide variety of conditions yielded 1,3- plus 2,4-bis-cycloaddition products I. Therefore, transoid azine must have predominated at the time of reaction. This type of "1,3-di-



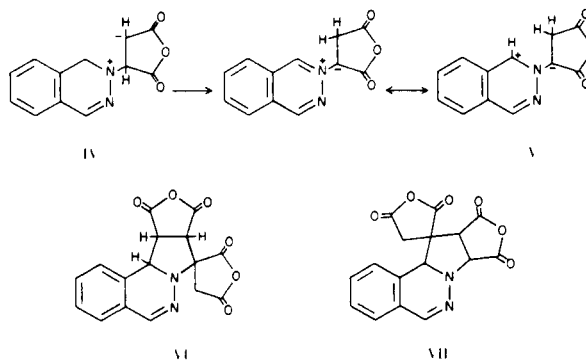
criss-cross cycloaddition" reaction, originally observed between cyanic acid and benzal azine (3), has been extensively investigated (4-7).

While the adducts of linear azines were cursorily studied under conditions suitable for cyclization of cisoid azine it was felt that the objective of (2 + 4) electrocyclic addition was more likely to be met by diaza dienes already constrained *cis*, and accordingly phthalazine, the simplest stable example, was reacted with maleic anhydride in boiling toluene. Again 1:2 adducts were obtained, in accordance with that found previously (5), and not 1:1 as anticipated. Since the 60 MHz proton nmr spectra of the adduct failed to show sufficient multiplicity to be consistent with either the pyridophthalazine structure II (5), or the pyrazolinopyrazoline III shown to be feasible by Stuart-Briegleb models, the adducts obtained were examined further. This paper confirms and substantiates preliminary structural evidence presented earlier (6).



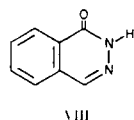
Results and Discussion

The initial gross structures considered for the phthalazine-maleic anhydride adduct obtained included II, incorporating a hexahydro pyridine ring, and III, involving the product of a "1,3-di-criss cross cycloaddition" as anticipated prior to experiment, and also the spiro structure. Precedence for the latter suggestion was taken by analogy from the isolated zwitterion obtained earlier from phthalazine and bis(benzoyl)methyl bromide (7) which, in this instance, would give an initial 1:1 adduct IV. 1,3-dipolar cycloaddition (8) with the resonance structure V formed from this initial adduct *via* a prototropic shift, with a further molecule of maleic anhydride would then yield the alternative adduct structure VI. For the sake of completeness, structure VII was also considered.



Structures analogous to the intermediate zwitterion V have been proposed earlier with experimental support (9), but apart from evidence from the precipitation of an initial salt-like intermediate from benzene solutions it was not possible to confirm this fully in our laboratory.

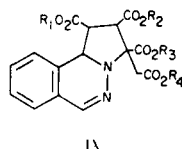
Catalytic hydrogenation of both the bis-anhydride adduct from phthalazine and its tetramethyl ester established that each possessed one non-aromatic double bond, and that this lay between carbon and nitrogen by the appearance in the infrared and nmr spectra of the products of an N-H absorption, eliminating structure III. The only fragment isolatable on oxidation with alkaline permanganate,



1*H*,2*H*-phthalazinone (VIII) suggested both that there was only a single point of attachment to carbon in the phthalazine ring, and that this was adjacent to nitrogen. This result, too, made structure III less likely but supported all the other possibilities. Attempted Hofmann degradation of the adduct was thwarted when the adduct was found to be completely resistant to methiodide formation, probably because of both reduced nitrogen basicity and steric factors, but confirmed that nitrogen was probably the other point of attachment for the adduct.

Sixty MHz proton nmr spectra of the bis-anhydride adduct were not amenable to direct first order analysis because of multiplet overlap confused by multiple diastereomeric centres. Nor were decoupling experiments, lanthanide shift reagents, or solvent changes fruitful, for the first because of the closeness of shift differences to coupling constants, and for the second probably because of the lack of any hydrogen bonded to electronegative atoms in the adducts.

The tetra-acid IX, $R_{1-4} = H$, which was prepared from the bis-anhydride to determine if resultant proton shift changes could yield useful correlations, was insoluble in organic solvents and only yielded poorly resolved spectra from solutions in dilute aqueous base or neat liquid hydrogen fluoride. On attempted regeneration of the original



bis-anhydride from this, a different anhydride was obtained from its higher melting point and significant melting point depression on carrying out a mixed melting point, but the same tetra-acid was obtained on re-hydrolysis.

While it was not possible to prepare the more soluble tetramethyl ester, IX, $R_{1-4} = CH_3$, directly from the tetra-acid, impure material was eventually obtained with difficulty by treatment of the mixed diesters with dimethyl sulfate, and more straightforwardly with diazomethane. Two stereoisomers of differing melting point were obtained, confirming suspicions of this from triturative fractionation of the initial bis-anhydride adduct. Again 50 MHz proton nmr spectra of the tetramethyl esters were not readily interpreted but 220 MHz spectra allowed unequivocal assignment of the resonances (Table I), which were confirmed by introducing the shift and coupling constant data from the 220 MHz spectrum of the bis-anhydride (Table II) into a 60 MHz computer simulation which generated a spectrum completely superimposable

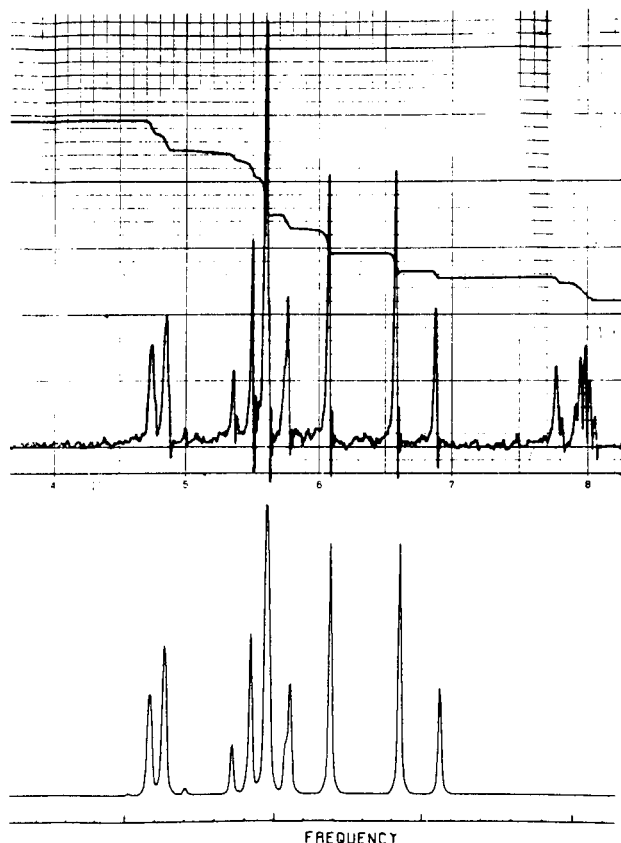


Figure 1: Upper, 60 MHz proton nmr spectrum of phthalazine adduct in deuterioacetone, and lower, 60 MHz computer simulation from 220 MHz spectral assignments.

on that obtained instrumentally (Figure 1). The key features supporting structure IX were the large coupling constants assigned to the methylenes of the two isomers isolated, 18.1-18.5 cps, which were more readily explicable by the normal range for geminal chemically dissimilar protons, 13.2-18.5 cps (10), than the usual range for cyclic vicinal ones, 7.1-14.1 cps (10). Also favouring IX over the analogous tetraester of VII is the fact that only three mutually coupled protons are observed, not two plus one isolated from one another, as would be required by the latter. The pathway to skeleton IX is also more readily rationalized mechanistically.

Substantiating the proton nmr evidence favouring the presence of a methylene were the non-decoupled and decoupled carbon-13 spectra of the bis-anhydride adduct. These clearly showed, by the presence of a triplet (at 35 ppm), that only one secondary carbon was present (Table III). All the other carbons were tertiary or quaternary. These also gave confirmation of the points of attachment, from the shift and coupling constant change for carbon A-2 from the normal 152.1 ppm, 181 Hz for phthalazine itself (11), to 58.6 ppm, 145.2 Hz for the adduct, reasonably near the published shift value of 47.9 ppm for piperidine (12). Support is given to this assignment from an

Table I
Proton Nmr Data for the Tetramethyl Esters of the Adducts of Phthalazine with Maleic Anhydride

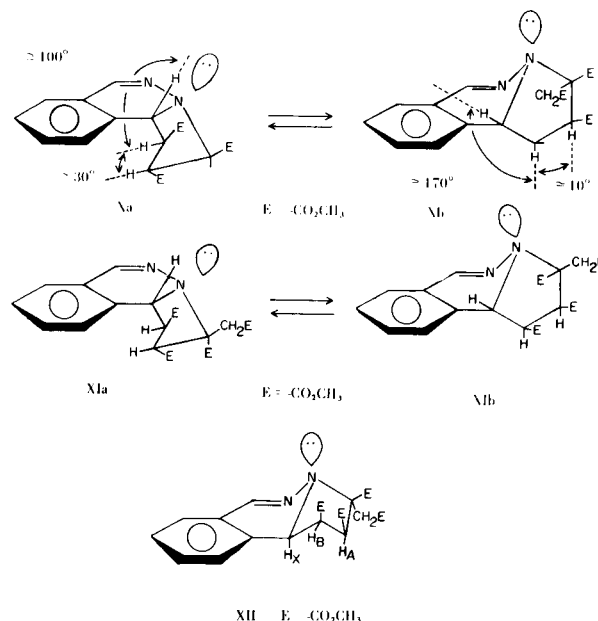
Assignment	Multiplicity	Tetramethyl Esters IX, R ₁₋₄ = CH ₃ (a)			
		M.p. 118-124°		M.p. 161.5-164°	
		δ (ppm)	J (Hz)	δ (ppm)	J (Hz)
-CH ₂ - (b)	doublet	3.58	-18.5	3.69	-18.1
	doublet	3.10	-18.5	3.60	-18.1
H _A	doublet	4.04	7.2	4.57	7.25
H _B	doublet pair	4.17	9.9, 7.2	3.84	6.5, 7.25
>CH _X -N<	doublet	5.53	9.9	4.78	6.5
-CH=N-	singlet	6.11	--	6.00	--
-COOCH ₃	singlets	3.82	--	3.89	--
		3.72	--	3.74	--
		3.50	--	3.48	--
		3.15	--	3.24	--

(a) Data obtained at 220 MHz from solutions in deuteriochloroform at room temperature. Shifts reported from internal tetramethylsilane. (b) Geminal coupling as consequence of adjacent diastereomeric center. Negative sign of coupling constant based on that normally observed.

analogous spiro adduct from *N*-phenylmaleimide and phthalazine suggested earlier, but without stereochemistry (13).

From mechanistic considerations, primarily that the second maleic anhydride would be likely to undergo *cis*-1,3-dipolar cycloaddition to the intermediate ylide V, and from the high frequency proton nmr evidence, it is suggested that the stereochemistry of the adduct tetraesters isolated is as indicated in structures X and XI. Both of these diastereomers possess *cis*-fused dihydropyridazine to pyrrolidine rings and represent structures with nitrogen in a flexible conformation. Xa and Xb represent the extremes, from Dreiding models, of the isomer with the spiro-linked succinate ester moiety with methylene down. This is probably the stereochemistry of the low melting point isomer since it can be used to explain simultaneously the significant deshielding of one of the methylene hydrogens with respect to the other, 3.10 versus 3.58 ppm, and the marked deshielding of one of the methyl ester groups to 3.15 ppm, significantly upfield of the normal range of 3.5-3.9 ppm normally observed for methyl esters (10), both occasioned by the close proximity of these protons to the heteroaromatic residue in this isomer (Table I).

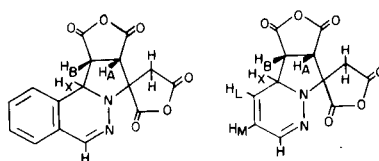
Compounds XIa and XIb represent the extremes of the isomer, still with *cis*-fused dihydropyridazine to pyrrolidine rings, but with the spiro-linked succinate ester moiety with methylene up. This we tentatively assign to the high melting isomer in keeping with the observed lack of any significant magnetic anisotropy of either of the methylene hydrogens, together with continued evidence of nearly as strong shielding of one ester methyl as shown by the low melting isomer. A minor point supporting this assignment is the marked upfield shift of H_X in the high melting when compared with the low melting ester. This possibly



occurs *via* the vicinal *gauche* interaction with the adjacent nitrogen lone pair (14), a suggestion which is strengthened by the concomitant decrease in the H_X coupling constant from 9.9 to 6.5 Hz as would be expected to be simultaneously observed from the approach towards 90° of the H_B, H_X dihedral angle.

Structure XII possesses *trans*-fused dihydropyridazine to pyrrolidine rings which simultaneously places the nitrogen lone pair *trans* to H_X and freezes the nitrogen conformation. Two 1,2-diaxial interactions severely detract from the ease of formation of this particular structure. Also, none of the ester groups nor the methylene hydrogens are in close proximity to the aromatic residue in this structure of any other *trans*-fused variation, and hence the specific nmr shieldings observed cannot be explained by

Table II
Proton Nmr Data for Phthalazine and Pyridazine Adducts (a)



Assignments	Multiplicity	Phthalazine Adducts				Pyridazine Adduct	
		M.p. 187-189°		M.p. 205-207° dec.		δ (ppm)	J (Hz)
		δ (ppm)	J (Hz)	δ (ppm)	J (Hz)		
-CH ₂ -	doublet	3.44	-18.4	3.35	-18.6	3.10	-18.5
	doublet	4.09	-18.4	4.12	-18.6	4.15	-18.5
H _A	doublet	4.40	8.4	4.43	8.5	4.30	8.5
H _B	doublet pair	4.60	8.4, 7.5	4.60	8.5, 7.7	4.19	8.5, 8.0
H _X	doublet	5.30	7.5	5.26	7.7	--	--
	double triplet	--	--	--	--	4.45	8.0, 2.4, 2.6
-CH=N-	singlet	7.72	--	7.72	--	--	--
	double quartet	--	--	--	--	6.52	9.2, 2.3, 1.7
H _L	double triplet	--	--	--	--	6.09	9.2, 2.9, 2.6
H _M	double doublet	--	--	--	--	7.24	2.9, 1.7

(a) Data obtained on sweep width expansions to 250 Hz using a 220 MHz instrument on solutions in deuterio-acetone at 18°. Shifts reported from internal tetramethylsilane.

this alternative.

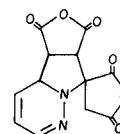
From models, the other set of stereoisomers to be considered involving *trans* addition of maleic anhydride to the intermediate ylide V effectively freezes the conformation of the *cis*-fused dihydropyridazine to pyrrolidine structure, holds both methylene hydrogens away from any possible ring shielding effects, and introduces significant strain throughout the fused ring system. *Trans*-addition of maleic anhydride to the *trans*-fused dihydropyridazine to pyrrolidine system introduces a 1,2-diaxial interaction and additionally places even more severe strain into the fused ring system than displayed by the model of the *trans/cis* stereoisomer above. Because the observed magnetic resonance data could not be explained by either of these sets of possibilities, and because introduction of strain would hinder their formation, these possibilities were not considered further.

Unfortunately no such clear distinctions emerged from the high frequency nmr results of the initial bis-anhydride adducts themselves. Resonance data was obtained for all the different decomposition temperature fractions isolated and yet even a comparison of the data for lowest and highest decomposition temperatures show only minor differences (Table II). Nor did tetramethyl ester preparations from bis-anhydrides of differing decomposition temperatures yield any useful correlations of ester melting point to bis-anhydride decomposition temperature, all preparations giving roughly the same proportions of the low and high melting point tetraesters. The only magnetic reso-

nance stereochemical cues, which could only be ascribed to gross features of both isomers, are the much larger shift differences for the methylene hydrogens of the bis-anhydrides 1.35, and 1.23 ppm as compared with the tetraesters 0.48, and 0.09 ppm, and the intermediate range H_B,H_X coupling constants found for the bis-anhydrides 8.4, and 8.5 Hz versus the more extreme values of 9.9 and 6.5 Hz for the tetraesters. The greater fused ring structural rigidity in the bis-anhydride may explain both distinguishing features, but at the same time the possibility that the tetraesters isolated were not necessarily derived from the stereochemically analogous bis-anhydrides cannot be discarded, since the yields of tetraester were invariably low. Clearly, at least one of the initial stereoisomers was quite labile from the epimerization experiment aimed at obtaining a significant proportion of the most stable isomer.

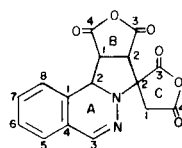
Thermal decompositions at a variety of pressures served only to establish that the cycloaddition process was a reversible one, at least at low pressures, and did not provide fragments of value in structural elucidation.

While the author reporting the first preparation of a pyridazine adduct with maleic anhydride strongly favoured the pyridopyridazine structure analogous to II for this,



XIII

Table III

¹³C Nmr Data for the Phthalazine and Pyridazine Adducts of Maleic Anhydride (a)

Carbon Assignment	Phthalazine Adduct			Pyridazine Adduct		
	δ (ppm)	Multiplicity (b)	J _{C-H} (Hz) (e)	δ (ppm)	Multiplicity	J _{C-H} (Hz)
A-1	130.6	1	--	120.4	2 + 4 (e)	169.3, 11.5
A-2	58.6	2	145.2	55.1	2	145.2
A-3	145.5	2	185.3	144.5	2 + 4 (e)	188.2, 12.3
A-4	125.1	1	--	129.3	2 + 4 (e)	173.5, 8.6
A-5	127.4 (d)	2+	162.3	--	--	--
A-6	131.5	2+	162.5	--	--	--
A-7	129.0	2 + 2	162.8, 6.8	--	--	--
A-8	126.7 (d)	2	166.7	--	--	--
B-1	45.6 (d)	2 + 2	149.7, 3.4	45.1 (d)	2	148.9
B-2	47.3 (d)	2	150.0	46.9 (d)	2	150.7
B-3	170.1 (d)	1	--	170.8 (d)	1	--
B-4	169.9 (d)	1	--	170.6 (d)	1	--
C-1	35.0	3	142.2	35.5	3	141.6
C-2	71.7	1	--	70.6	1	--
C-3	169.0 (d)	1	--	170.3 (d)	1	--
C-4	168.1	1	--	168.7	1	--

(a) Spectra run at 15.09 MHz on deuterio-acetone solutions at ambient temperature. Shifts reported from internal tetramethylsilane in proton decoupled spectra. (b) Where specified 2+, additional complex fine structure with indeterminate coupling constants present, attributed to long range coupling. (c) Probable error $< \pm 0.2$ Hz. (d) Assignments between A-5 and A-8; B-1 and B-2; and B-3, B-4 and C-3 uncertain. (e) Each of main resonances split by long range coupling into 4 unevenly spaced peaks, of separations 2.4-5.2 Hz. Total width of multiplets given as second figure under J.

the spiro alternative XII was not ruled out (15). This preparation was repeated because, with the similarity of substrates, it was thought to be highly likely that the pyridazine adduct also had a spiro structure. Proton and carbon-13 nmr as well as mass spectrometric data obtained for this adduct were therefore, compared in detail to the equivalent data for the phthalazine adduct for which a spiro structure had just been established.

Proton nmr established the presence of a similar type of methylene bearing chemically distinct hydrogens with shifts of 3.10 and 4.15 ppm and coupling constant of -18.5 Hz, both very close to the values found for the phthalazine adduct (Table II), and which was the key distinguishing feature in the latter favouring structure XIII. The remaining proton nmr spectral parameters for the pyrrolidine ring in particular were also completely in accord with this assignment.

Non-decoupled and decoupled carbon-13 nmr provided unequivocal support to confirm the proton nmr evidence for the presence of a methylene (carbon C-1) in the pyridazine adduct, and that the environment was very similar, by a triplet at 35.5 ppm split by 141.6 Hz, very close to

the 35 ppm 142.2 Hz found for the phthalazine adduct (Table III). As with the phthalazine adducts, confirmation of the points of cyclization was obtained too, by the change in shift and coupling constant for carbon A-2 only from the normal 152.8 ppm, 185 Hz reported for carbons A-2 and A-3 of the starting pyridazine (16) to 55.1 ppm, 145.2 Hz in the adduct, and again quite close to the values found for the phthalazine adduct. At the same time the nmr parameters for carbons A-1 and A-4 did not change significantly from the 127.6 ppm, 167 Hz reported for these positions of pyridazine itself (16).

Mass spectra of the adducts favoured the same structure for the pyridazine adduct as already documented for the phthalazine adduct by the closely parallel electron impact fragmentation patterns (Figure 2). The only fragmentations for which metastables could be observed were losses of molecular and atomic hydrogen but the other suggested fragmentation pathways were at least supported by correct accurate mass determinations on the fragments involved, and by fragmentations confirmed with metastables already observed for 3-pyridazinones and 1*H*,2*H*-phthalazinone (17). While phthalazine and particularly pyridazine dis-

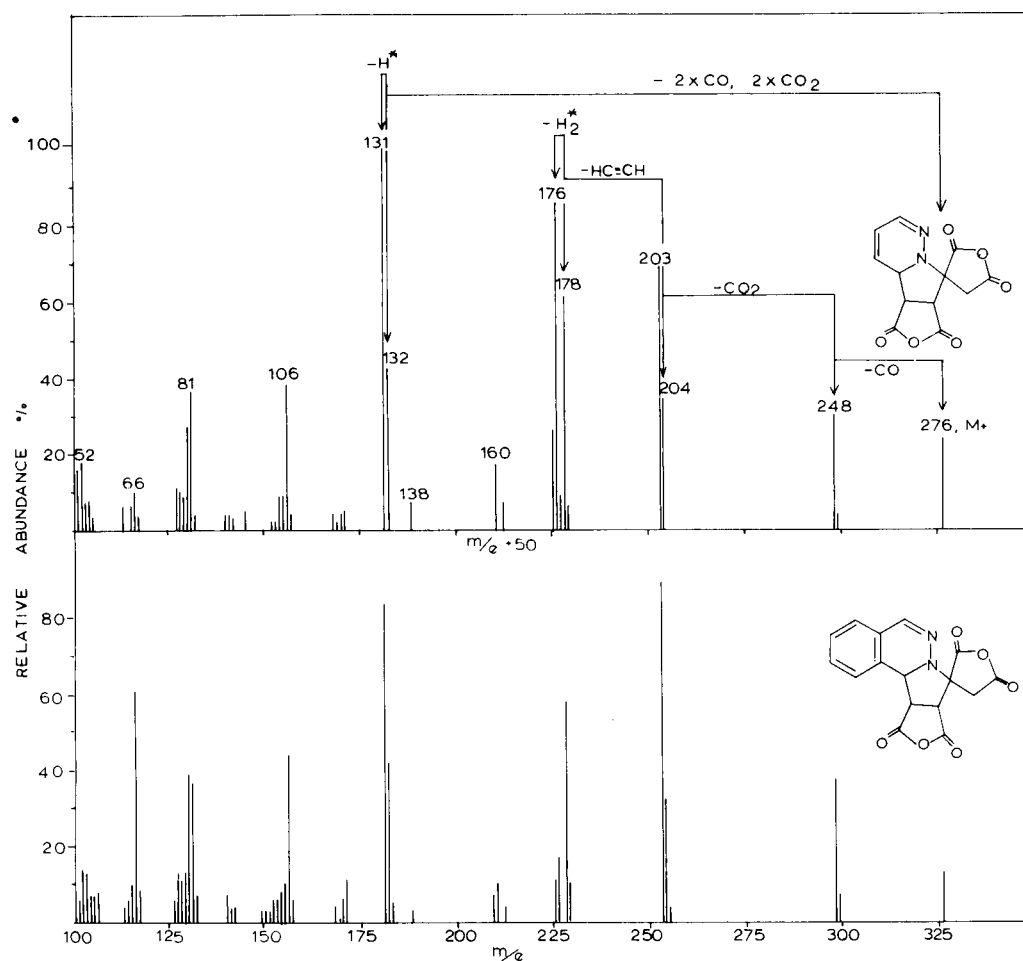


Figure 2: Comparison of fragmentation patterns of pyridazine and phthalazine adducts. Metastables observed for asterisked transformations. Ion compositions for other fragmentation paths confirmed by accurate mass determinations for suggested fragmentation path: Found: 276.049; $C_{12}H_9O_6N_2$ requires 276.038; Found: 248.044; $C_{11}H_8O_5N_2$ requires 248.043; Found: 204.055; $C_{10}H_8O_3N_2$ requires 204.050; Found: 203.044, $C_{10}H_7O_3N_2$ requires 203.050; Found: 178.039, $C_8H_6O_3N_2$ requires 178.038.

play nitrogen loss as significant initial decomposition processes (17), in the above ketones this was a far less dominant process, and in the adducts did not appear to occur to any significant extent. Chemical ionization with methane of each adduct gave recognizable $M + 1$ fragments which served to confirm molecular weights plus, as a dominant process in each, significant loss of carbon monoxide.

EXPERIMENTAL

Solvents were dried, methanol and toluene with molecular sieves activated at $200^\circ/0.1$ mm pressure for 12 hours (Union Carbide type 4A, 1.5 mm pellets) and ethyl acetate by distillation after acetic anhydride plus potassium carbonate treatment (18), and were removed from preparations by rotary evaporation under reduced pressure unless otherwise stated. Melting points were

obtained using thermometers calibrated at the same immersions against National Bureau of Standards thermometers and are uncorrected.

Infrared spectra are from nujol mulls measured on a Perkin-Elmer 337 Grating Spectrophotometer. Proton nmr spectra were obtained at 60 MHz on a Perkin-Elmer R-12 instrument, and at 220 MHz from the Canadian 220 MHz nmr Centre, Ontario Research Foundation, Sheridan Park, solvents as specified. Electron impact mass spectra were generated at 70 eV on an Hitachi RMU-7E instrument with inlet chamber at 250° and source at 90° , and methane ionization was used for the chemical ionization spectra obtained on a Finnigan Model 3300 quadrupole mass spectrometer.

Carbon-13 nmr spectra were obtained on a Nicolet model TT-14 spectrometer operating at 15.1 MHz in the pulsed Fourier transform mode and coupled to a NIC-80 computer and data system. Adducts dissolved in deuterio-acetone were run at ambient temperature in 10 mm diameter tubes and shifts were reported from internal tetramethylsilane. The phthalazine adduct required $\sim 10,000$ scans and $\approx 19,000$ on 4,000 Hz sweep width for the

proton-decoupled (decoupler power level 10 W) and non-decoupled (gated mode; retaining nuclear overhauser enhancement) spectra respectively for a solution of 270 mg./2 ml., and the pyridazine adduct similarly 15,000 and 16,000 scans for 170 mg./2 ml. Results reported in Table III.

1,2,3,10b-Tetrahydropyrrolo[1,2-*b*]phthalazine-1,2-dicarboxylic Anhydride-3-spiro-3'-tetrahydrofuran-2',5'-dione (VI, Phthalazine-Maleic Anhydride Adduct).

Solutions of phthalazine (9.84 g., 76 mmoles) in toluene (100 ml.) and maleic anhydride (16.01 g., 163 mmoles) in toluene (75 ml.) were combined with protection from moisture and boiled under reflux for 1 hour. The brown solid formed was filtered hot from the reaction solution, and then triturated with 100 ml. portions of boiling toluene. Filtering each extract hot and then cooling gave the following weights of white slender needles, melting points given (and not significantly raised by recrystallization): #1, 1.84 g., 183-186° dec.; #2, 0.50 g., 170-175° dec.; #3, 1.14 g., 193-195° dec.; #4, 7.11 g. (300 ml.), 196-201° dec.; #5, 2.51 g., 202-206° dec. A further 2.18 g. (total yield 62%) impure material, m.p. 147-174° dec., was recovered from the reaction mother liquor. Fraction 5 recrystallized from toluene gave m.p. 204-208° dec. Calcd. atomic mass: 326.0549. Found: 326.0443 ± 0.0120, details with Figure 2. Infrared max: 1860, 1790, 1775 cm⁻¹. Nmr, see Tables II and III.

Anal. Calcd. for C₁₆H₁₀N₂O₆: C, 58.90; H, 3.09; N, 8.66. Found: C, 59.20; H, 3.22; N, 8.66.

1,2,3,10b-Tetrahydropyrrolo[1,2-*b*]-5,6-dihydrophthalazine-1,2-dicarboxylic Anhydride-3-spiro-3'-tetrahydrofuran-2',5'-dione (Dihydro VI, Dihydrophthalazine-Maleic Anhydride Adduct).

A partially dissolved suspension of bis-anhydride VI, (1.00 g.) in dry ethyl acetate in the presence of 0.20 g. of previously activated 2% palladium/strontium carbonate took up 65.7 ml. hydrogen corrected to STP (Theory, one double bond requires 68.7 ml.). Melting point, 184° dec.; ir: broad band 3500-3000 cm⁻¹, N-H; proton nmr: several unassigned new bands upfield of original.

1,2,3,10b-Tetrahydropyrrolo[1,2-*b*]phthalazine-1,2,3-tricarboxylic Acid 3-Acetic Acid (IX, R₁₋₄ = H).

The bis-anhydride VI (4.04 g., m.p. 202-205° dec.) was boiled in 100 ml. of distilled water for ½ hour, filtered hot, and rinsed with 2 small portions of hot distilled water. The tetra-acid, IX, R₁₋₄ = H, (2.25 g.) an insoluble white solid, was obtained, which when recrystallized from ethanol in poor yield melted at 247-252° dec., without charring, ir: 3275 sharp (OH); 1730, 1675 cm⁻¹ (C=O). This was insoluble in chloroform or water, even with prolonged heating, and soluble in acetone, neat hydrogen fluoride, and dilute aqueous sodium hydroxide. The tetra-acid could not however be recovered from aqueous base on acidification. Nmr spectra obtained on neat hydrogen fluoride solutions in Kel-F lined 4 mm. diameter sample tubes were only poorly resolved, even at 100 MHz.

Chilling the reaction mother liquor from the hydrolysis above failed to precipitate any further material. Evaporation of the water under reduced pressure yielded 1.64 g. of an amorphous yellow solid, m.p. 190-192° dec. without charring; ir: 3450, 3200 (both broad), 1725 cm⁻¹ (with fine structure). This apparent mixture could not be further resolved.

Starting with bis-anhydride with decomposition temperatures of 192-195°, or 186-189°, gave tetra-acids m.p. 246-250° dec., and m.p. 245-248° dec., respectively.

Tetra-acid IX, R₁₋₄ = H, (500 mg.; m.p. 247-252° dec.) in 12 ml. of water was boiled under reflux for 1 hour and filtered hot

followed by a water rinse. When dried this recovered material (455 mg.) gave an identical ir spectrum to the starting tetra-acid and decomposition temperature was depressed to 246-248°.

1,2,3,10b-Tetrahydropyrrolo[1,2-*b*]phthalazine-1,2-dicarboxylic Anhydride-3-spiro-3'-tetrahydrofuran-2',5'-dione (VI) from IX, R₁₋₄ = H.

A solution of tetra-acid (0.90 g.) and thionyl chloride (1.5 ml.) in 2.5 ml. of trifluoroacetic acid was boiled under reflux for 0.5 hour. On cooling, the product (0.80 g.) was precipitated by dilution with dry ether, and collected by filtration and rinsing with fresh ether. Infrared: 1850, 1790, 1724 cm⁻¹ (C=O). Melting and mixed melting points of 205° dec., 182° dec., respectively (with original bis-anhydride which decomposed at 196°) were observed. Milder procedures using neat acetyl chloride, acetyl chloride plus a catalytic amount of dimethylformamide, or neat acetic anhydride failed to yield a bis-anhydride even on prolonged boiling.

The bis-anhydride prepared here (0.50 g.) in water (12.5 ml.) was boiled for 1 hour and filtered hot. The water-washed and dried product (0.33 g.) melted at 240°, mixture m.p. (with original tetra-acid, m.p. 246° dec.) 244° dec.; ir: 3260, 1735, 1680 cm⁻¹.

Dimethyl Esters of 1,2,3,10b-Tetrahydropyrrolo[1,2-*b*]phthalazine-1,2,3-tricarboxylic Acid-3-acetic Acid (IX, R₁₋₄ = 2 x H + 2 x CH₃).

Bis-anhydride VI (0.50 g., m.p. 202-206° dec.), in 10 ml. of methanol was completely dissolved after 5 minutes boiling. After boiling for 10 minutes the methanol was removed under reduced pressure leaving yellow crystals (0.53 g.); ir: 3400 (broad, OH), 1750, 1730, 1680 cm⁻¹ (C=O); m.p. 121-133° dec. Recrystallization from methanol (10 ml.) gave 120 mg. of colourless crystals, m.p. 146-152° dec.; nmr 60 MHz (methanol-d₄): 2.1, 3.3 ppm singlets, ester methyls.

Anal. Calcd. for C₁₈H₁₈N₂O₈: C, 55.39; H, 4.65; N, 4.65. Found: C, 55.69; H, 4.74; N, 6.70.

Tetramethyl 1,2,3,10b-Tetrahydropyrrolo[1,2-*b*]phthalazine-1,2,3-tricarboxylate-3-acetate (IX, R₁₋₄ = CH₃).

To a stirred solution of mixed dimethyl esters IX, R₁₋₄ = 2 x H + 2 x CH₃, freshly prepared from 5 g. (15.3 mmoles) of bis-anhydride (m.p. 187-189° dec.), in 50 ml. of dry, ice cold methanol, was added portionwise over 2 hours, 250 ml. of ~0.25 M diazomethane (62.5 mmoles) in dry ether prepared from bis(*N*-methyl-*N*-nitroso)-terephthalamide (18) and codistilled with ether. After 14 hours, 2 or 3 drops of acetic acid were added and the ether removed, to leave 6.3 g. of a reddish brown glass. This was crystallized with difficulty from amyl acetate to yield three crops of colourless to pale yellow crystals, melting points 111-125°, 136-139°, and 151-160°; ir: no OH, plus 1725, 1695, 1275, 1225 cm⁻¹ (ester C=O and C-O-Me) for each crop. The first and last crops were twice recrystallized, raising melting points to 117-128° (nmr: 4 sharp methyl singlets, *cf.* Table I) and 161.5-165° (nmr: 4 strong and 4 minor methyl singlets).

Anal. Calcd. for C₂₀H₂₂N₂O₈: C, 57.42; H, 5.30; N, 6.69. Found, for low melting isomer: C, 56.88; H, 5.60; N, 6.44. For high melting isomer: C, 57.60; H, 5.37; N, 6.55.

Experiments starting with the bis-anhydride of decomposition temperatures 182-186°, 191-196.5°, or 200-205° using the same procedure gave roughly the same proportion of low and high melting point isomers of the tetra-ester.

High pressure analytical liquid chromatography (HPLC, Pye Model LCM2) of samples of tetra-ester from new preparations, on a 10 x 0.3 cm. silica gel column and elution with 2% methanol in methylene chloride gave three peaks, two much larger, elution times 42, 90, 120 seconds. The first was the highest melting

material, and the second the lowest melting by comparison with injected samples of the recrystallized material prepared earlier. Thin layer chromatography (TLC) in silica gel, using the same solvent, showed three spots on development, but despite careful (78 fractions) preparative solvent column chromatography no better isomeric resolution could be achieved than obtained by crystallization; 220 MHz proton nmr spectra, Table I; mass spectra, Figure 2.

An attempt to epimerize a sample of tetra-ester (0.80 g.) from a further preparation *via* diazomethane in 10 ml. of methanol, by the addition of 70 mg. of sodium and refluxing for 2 hours, gave only an intractable brown polymeric product insoluble in amyl acetate.

Attempts to prepare the tetra-ester from the tetra-acid *via* methanol/anhydrous hydrogen chloride, thionyl chloride followed by methanol, methyl fluorosulfonate (20), diazomethane diethyl ether, dimethyl sulfate in dimethylformamide, or methanol/ neat hydrogen fluoride, with or without sulfuric acid catalysis, were unsuccessful. Preparation using the dimethyl sulfate-dimethyl formamide-potassium carbonate procedure (21) gave recognizable tetra-ester (by nmr and HPLC) from initial mixed dimethyl esters but it was not possible to crystallize the crude product.

Tetramethyl 1,2,3,10b-Tetrahydropyrrolo[1,2-*b*]-5,6-dihydrophthalazine-1,2,3-tricarboxylate-3-acetate (IX, $R_{1-4} = \text{CH}_3$, 5,6-dihydro).

Tetramethyl ester, IX, $R_{1-4} = \text{CH}_3$ (0.120 g.) in 5 ml. of ethyl acetate was reduced in the presence of 100 mg. of previously activated 2% palladium/strontium carbonate at atmospheric pressure and took up 10.5 ml. of hydrogen. Theory for one double bond = 8.9 ml.; nmr in hexadeuterioacetone: $\delta = 6.0$ ppm, singlet (new $-\text{CH}_2-$); 2.00 ppm, broad singlet (N-H).

Permanganate Oxidation of 1,2,3,10b-tetrahydropyrrolo[1,2-*b*]-phthalazine-1,2,3-tricarboxylic Acid-3-acetic Acid IX, $R_{1-4} = \text{H}$.

The bis-anhydride adduct (1.6 g., 4.9 mmoles) was dissolved in 20 ml. of ice-cold 5*M* aqueous sodium hydroxide. Aqueous 0.2*M* potassium permanganate was added slowly, with stirring, to the solution of the adduct maintained at 0 to 5°, until a drop of the mixture placed on filter paper gave a purple fringe (120 ml., 24 mmoles). The curdy green suspension was then contacted with sulfur dioxide gas (22) until a clear pale yellow solution was obtained, which was then saturated with sodium chloride. Extraction with ether, followed by washing of the combined extracts with saturated aqueous sodium bicarbonate and water, drying with sodium sulfate and solvent removal yielded 7 mg. of white crystals. Recrystallization from water gave white rosettes of needles, m.p. 179-181°; ir: 3170 (N-H) and 1670 cm^{-1} (C=O); of 1*H*,2*H*-phthalazine VIII, which gave no depression of m.p. and was identical in all other respects with an authentic (23) purchased sample. No other discrete compound could be isolated from the remaining aqueous phases.

In another degradation on the same scale but using a total of 37 ml. (7.4 mmoles) of 0.2*M* potassium permanganate only gave a larger quantity (21 mg.) of 1*H*,2*H*-phthalazine, 600 mg. of recovered tetra-acid IX, $R_{1-4} = \text{H}$, and no other discrete compounds.

Thermal Decompositions of 1,2,3,10b-Tetrahydropyrrolo[1,2-*b*]-phthalazine-1,2-dicarboxylic Anhydride-3-spiro-3'-tetrahydrofuran-2',5'-dione (bis-Anhydride, VI).

Bis-anhydride (0.1057 g., m.p. 190-195.5° dec.) in a round-bottomed flask was heated in an oil bath at 170° and raised to 205° during 15 minutes. The frothy black material formed was powdered in the flask, heating at 205° continued for 5 minutes, and then the flask removed from the bath. Weight loss when cool was 27.5 mg. (26.0%). Fragmentation of two moles of carbon

dioxide per mole of adduct requires 27.0%, and a mole of carbon dioxide plus a mole of carbon monoxide requires 22.1% weight loss, respectively.

The experiment above was repeated, but with 79.1 mg. of bis-anhydride, and at 0.1 mm pressure and showed a weight loss of 2.3 mg. (2.9%). However, two sublimates were obtained, the more volatile comprised 7-8 mg. of white needles, m.p. and mixed m.p. with phthalazine 89-92° and identical ir spectra, and the less volatile was recovered dianhydride. The small amount of residue was an amorphous brown solid, m.p. 250-260° dec., which gave a poorly defined ir spectrum.

Repeating the experiment at 0.2, 1, and 10 mm pressure gave weight losses without sublimation of 51.8, 45.6 and 36.4%, and no other significant information. Fragmentation of two moles of (carbon dioxide + carbon monoxide) requires 44.2% weight loss.

Other Degradative Reactions of 1,2,3,10b-Tetrahydropyrrolo[1,2-*b*]-phthalazine-1,2-dicarboxylic Anhydride-3-spiro-3'-tetrahydrofuran-2',5'-dione (bis-Anhydride, VI).

Oxidative decarboxylation/decarbonylation reactions using lead tetra-acetate/ethyl acetate, manganese dioxide/acetone or acetonitrile (24), and air/pyridine failed to yield any tractable products. Boiling the bis-anhydride with methyl iodide in benzene for one hour gave no salt formation and quantitative recovery of starting bis-anhydride VI.

4a,5,6,7-Tetrahydropyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylic Anhydride-7-spiro-3'-tetrahydrofuran-2',5'-dione (XIII, Pyridazine-Maleic Anhydride Adduct).

The adduct was prepared without difficulty by the method of Cookson and Isaacs (15). When twice recrystallized from dry ethyl acetate, colourless fibrous needles were obtained, m.p. 168-170° dec. (lit. (15), 170° dec.); ir: 1860, 1810, 1790 cm^{-1} ; nmr and mass spectral data, see Tables II and III, and Figure 2.

4a,5,6,7-Tetrahydropyrrolo[1,2-*b*]pyridazine-5,6,7-tricarboxylic Acid-7-acetic Acid (Tetracid of Pyridazine Adduct XIII).

This derivative was prepared by prolonged stirring of bis-anhydride (190 mg.) in 3 ml. of distilled water, and then removal of the water by evaporation at room temperature. A pale yellow amorphous solid, m.p. 96° dec. (*cf.* (15)) was obtained which could not be crystallized.

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