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THE REACTION BETWEEN PYRIDAZINE AND MALEIC ANHYDRIDE

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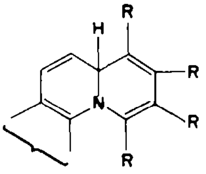
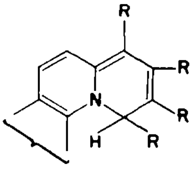
Abstract—Addition of pyridazine to two moles of maleic anhydride yields a product (III) analogous to the adducts of methyl acetylenedicarboxylate with pyridine and its derivatives.

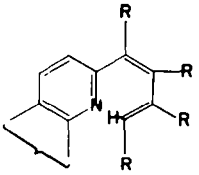
THE reactions of dimethyl acetylenedicarboxylate with various six-membered nitrogen heterocyclics have recently been re-examined[1] and shown to yield 9a-H-quinazolines (I), easily isomerized to the 4-H-quinazolines (IIa) or their chain tautomers (IIb).



I



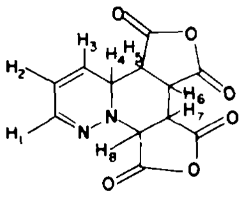
IIa



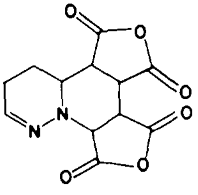
IIb

R = COOMe

To test whether this cyclization is applicable to other compounds with activated double bonds, (dienophiles in the Diels-Alder reaction), we have carried out reactions between maleic anhydride and nitrogen heterocyclics, and from pyridazine (1,2-diazine) have isolated in good yield a 1:2-adduct to which we have assigned the analogous structure, 1,2,3,4-tetrahydro-(1,2-b)-pyridopyridazine-1,2,3,4-tetracarboxylic bis-anhydride (III). This appears to be the first recorded example of the ring system.



III



IV

Maleic anhydride reacts exothermally with pyridine, quinoline and isoquinoline, although not with pyrazine. The products in these cases, however, were yellow to brown, amorphous solids, which appeared to be largely polymeric.

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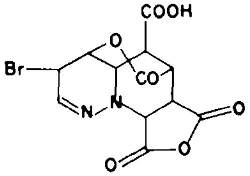
[1] A. Crabtree, A. W. Johnson and J. C. Tebby, *J. Chem. Soc.* 3497 (1961);
L. M. Jackman, A. W. Johnson and J. C. Tebby, *Ibid.* 1579 (1960);
R. M. Acheson and J. M. Vernon, *Ibid.* 1148 (1962);
R. M. Acheson and A. O. Plunkett, *Ibid.* 3758 (1962);
E. E. Van Tamelen, P. E. Aldrich, P. Bench and G. Miller, *Proc. Chem. Soc.* 309 (1959).

The adduct III was obtained in 85 per cent yield on allowing the reactants, in correct molar ratio, to stand for a few days in chloroform at room temperature. After recrystallization from ethyl acetate it formed a dense matte of fibrous white crystals melting at 180° with decomposition. The molecular weight (ebullioscopic in acetone) was 280 ± 10 (theoretical 276). The I.R. spectrum contained bands at 1850, 1790, 1775, 1550, 1395 cm^{-1}; the U.V. spectrum (Figure Ia) had, as its most prominent feature, a band of $\lambda_{\max}$ 325 mμ, ($\log \epsilon = 3{\cdot}34$), and further absorption at 241 ($\log \epsilon = 3{\cdot}25$) and 212 ($\log \epsilon = 3{\cdot}32$). Exact analogues are not available, but the absorption of the chromophore C=C—C=N—N seems to be very sensitive to its conformation. Crotonaldehyde semicarbazone has $\lambda_{\max}$ 265 mμ, $\log \epsilon$ 4·3; 5-phenyl-1,2,3,4-tetrahydropyridazines[2] have $\lambda_{\max}$ 292 mμ, $\log \epsilon$ ca. 4·2; 1,2-dihydropyridines are stated in a review[3] to have $\lambda_{\max}$ 340 mμ (ϵ?); 1,6-dihydronicotinamides,[4] where the amide group is conjugated through the diene system with the nitrogen atom, have $\lambda_{\max}$ ca. 350 mμ, $\log \epsilon$ 3·9. Thus 325 mμ seems acceptable for a 1,2-dihydropyridazine.

The adduct (III) was hydrolysed by hot water to a tetracarboxylic acid ($\nu_{\max}$ 1720 cm^{-1}) which could be recrystallized with difficulty from methanol and decomposed at 140°. It appeared to decarboxylate readily and satisfactory combustion data were not obtained. On boiling with methanol, III was converted to a mixture of half-esters which, when treated with diazomethane, yielded an amorphous tetracarboxylic ester.

Reduction of III proceeded with difficulty; hydrogenation in ethyl acetate over 10 per cent palladium-charcoal at 70° and 80 p.s.i. for 12 hr yielded quantitatively the dihydro-derivative (IV). The I.R. spectrum of IV was substantially different from that of III, the band at 1550 cm^{-1} being notably absent but being replaced by weak absorption at 1640 cm^{-1}. There was no band attributable to an N-H group. The U.V. spectrum showed a single weak band, $\lambda_{\max}$ 245 mμ, ($\log \epsilon = 3{\cdot}41$), (Fig. 1b) (cf. cyclohexanone hydrazone $\lambda_{\max}$ 218 mμ, $\log \epsilon$ 3·26; acetone semicarbazone $\lambda_{\max}$ 220 mμ, $\log \epsilon$ 3·79).

Bromination of III in ethyl acetate produced a crystalline monobromo compound. Analytical data and I.R. bands at 1850, 1780 and 1725 cm^{-1} corresponding to both anhydride and ester (lactone) groups agree with the structure V, although alternatives were not excluded. The contrast in U.V. spectrum (Fig. 1c) with that of the dihydro-derivative (Fig. 1b), however, is remarkable.



V

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[2] C. H. Wang, S. -H. Hsiao, E. Saklad and S. G. Cohen, *J. Amer. Chem. Soc.* **79**, 2661 (1957).

[3] J. J. Panouse, *Bull Soc. Chim. Fr.* **11/12**, D60 (1953).

[4] K. Wallenfels and H. Schüly, *Angew. Chem.* **67**, 517 (1955); *Liebigs Ann.* **621**, 106, 188 (1959).

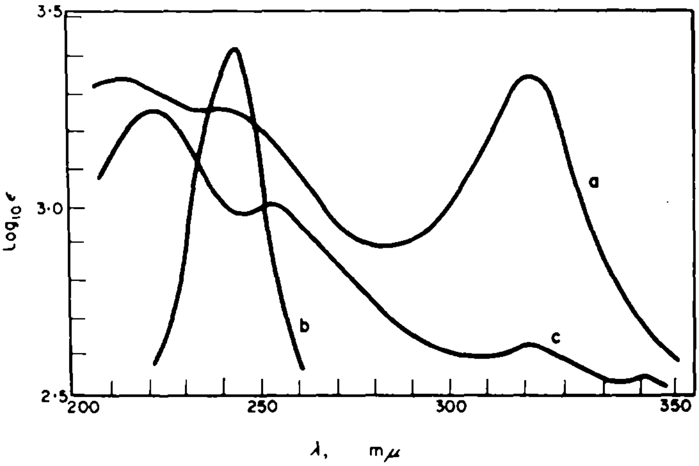


FIG. 1

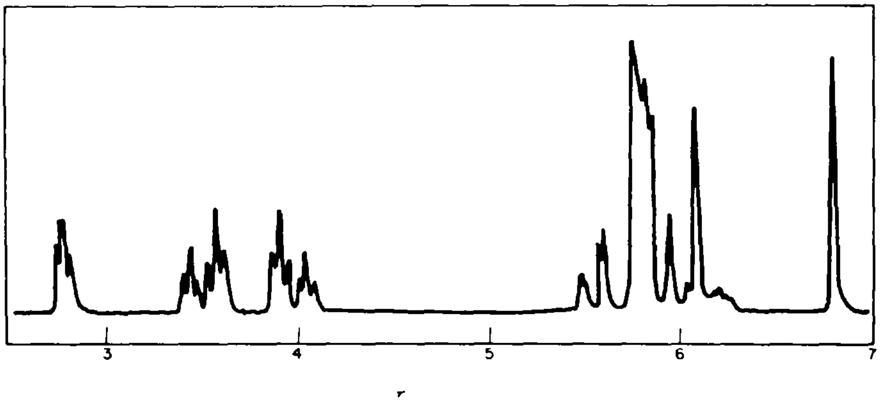


FIG. 2

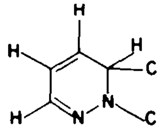
Prolonged oxidation of III with concentrated nitric acid at 90° yielded pyridazine-3-carboxylic acid. This demonstrates one point of attachment of a maleic anhydride residue to the pyridazine ring.

Figure 2 shows the proton magnetic resonance spectrum of the adduct at 60 Mc/s in acetone with tetramethylsilane as internal reference. The three olefinic protons appear clearly at low field as an ABC system with the chemical shifts and coupling constants given in Table 1. The two protons at higher field (H_2 and H_3) each form a pair of triplets, rather than the expected pair of doublets, because each is coupled also to a fourth X proton (H_4) with a coupling constant that happens in each case to be very nearly the same as that for H_1. That the X proton is indeed H_4 is confirmed by the spectrum of the tetradeutero-adduct (made from pyridazine and maleic anhydride-d_2) in which the spectrum at low field is quite unchanged, the resonance from H_4 being revealed by a peak at $5{\cdot}64\tau$. Although this multiplet is poorly resolved the shoulders on either side suggest that it is a "triplet" of the required spacing. The disappearance of the isolated peak at highest field ($6{\cdot}70\tau$) in the spectrum of the tetradeutero-adduct shows that it is due to a specially shielded proton on a maleic anhydride residue, perhaps H_8. In the spectrum of the dihydro-adduct (IV) the absorption ascribed to

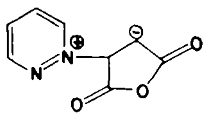
H_2 and H_3 in III is missing and there is a corresponding increase in the number and complexity of the peaks at higher field. The multiplet from H_1 falls to even lower field.

The presence of the group A in the adduct is clearly established.

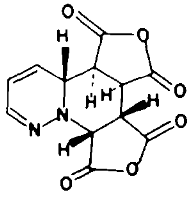
For comparison the proton magnetic resonance spectra of pyridazine, sodium pyridazine-3-carboxylate and 3-hydroxymethylpyridazine were also measured (see Table). As expected, the disruption of the aromatic ring current in the dihydropyridazine (III) shifts the resonance to substantially higher fields.



A



VI



VII

Since repeated crystallization of the adduct failed to change its physical properties we conclude that only one of the sixteen possible DL-isomers is formed. If the reaction proceeds by addition of a second molecule of maleic anhydride to the ylid (VI), both anhydride rings are probably fused *cis* to the piperidine ring. If, further, the second addition is more or less concerted, H_4 must be *cis* to the two hydrogen atoms of the first maleic anhydride group. Formation of an *endo* type of transition state by analogy with the Diels-Alder reaction would lead to the all-*cis* adduct. However, the electron-withdrawing character of both partners and the usual steric repulsion would more probably compel the *exo* type of addition to give the isomer (VII), which we therefore regard as the most likely structure.

Tautomerization of VI to the more stable ylid (VIII) before addition of maleic anhydride as a dipolarophile[5] would produce the alternative IX. However, the adduct is transparent in the usual methylene deformation region (1420–1440 cm^{-1}), though there is a band at 1400 cm^{-1}: succinic anhydride has a strong band at 1430 cm^{-1}.

TABLE 1. PROTON MAGNETIC RESONANCE SPECTRA
Chemical shifts in τ, coupling constants in c/s.

	τ	J
Adduct (III) in acetone	H_1 2·81	J_{12} 2
	H_2 3·53	J_{13} 2·5
	H_3 3·95	J_{23} 9·5
	H_4 5·64	
Dihydro-adduct (IV) in acetone	H_1 0·13	
Sodium pyridazine-3-carboxylate in water*	H_1 0·72	J_{12} 5
	H_2 2·07	J_{13} 2
	H_3 1·78	J_{23} 9
3-Hydroxymethylpyridazine in $CHCl_3$*	H_1 0·63	J_{12} 5
	H_2 2·17	J_{13} 2
	H_3 1·73	J_{23} 9
Pyridazine in CCl_4*	H_1 0·68	J_{12} 3·5
	H_2 2·28	J_{13} 3·5

* Protons are numbered to correspond with those in III.

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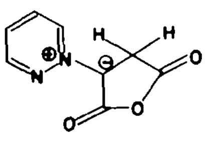
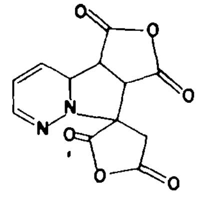
[5] R. Huisgen, *Proc. Chem. Soc.* 357 (1961).

Although inspection suggests that VII is also rather more consistent with the N.M.R. spectrum, IX has not been eliminated.



VIII



IX

EXPERIMENTAL

I.R. and U.V. spectra were measured on Unicam "S.P. 200" and "S.P. 700" spectrophotometers, respectively. Proton resonance spectra measurements were performed on a Varian A60 instrument with tetramethylsilane as internal reference.

1,2,3,4-*Tetrahydro*(1,2-b)-*pyridopyridazine*-1,2,3,4-*tetracarboxylic bis-anhydride* (III). Pyridazine (prepared according to Mizzoni and Spoerri[6]; 4·0 g, 0·05 mole) was added to a solution of resublimed maleic anhydride (9·8 g, 0·1 mole) in 100 ml dry chloroform. The solution was allowed to stand at room temp for 2 days and at 40° for 2 days at the end of which the fibrous white precipitate was filtered. This was extracted with 3 × 100 ml of boiling ethyl acetate from which pure III was crystallized after reduction of the volume of solvent, yield, 11·8 g 85%. The ethyl acetate-insoluble residue, a brown, amorphous material, presumably analogous to the products of reaction of maleic anhydride and pyridine, etc., amounted to 1 g. (Found: C, 52·0; H, 3·15; N, 10·0; $C_{12}H_8O_6N_2$ requires: C, 52·2; H, 2·9; N, 10·1%)

Hydrogenation of III. The adduct (III, 1·0 g), in 50 ml ethyl acetate was hydrogenated in a shaking autoclave with 50 mgs 10% pallidium on charcoal at 80 p.s.i. and 70° for 12 hr. Filtration and removal of solvent yielded 1,2,3,4,5,6-*hexahydro*-(1,2-b)-*pyridopyridazine*-1,2,3,4-*tetracarboxylic bis-anhydride* (IV); yield, 1·0 g (95%), m.p. (from ethyl acetate), 203°. (Found: C, 51·9; H, 3·64; N, 10·0; $C_{12}H_{10}N_2O_6$ requires: 51·8; H, 3·59; N, 10·0%).

Hydration of III. The adduct III (0·1 g) was dissolved in warm water and the solution left at 50° for a few hr before the water was removed at 12 mm. The residue was taken up in methanol and precipitated with acetone. Recrystallization from methanol gave a small quantity of the tetracarboxylic acid as a fine white crystalline solid, decomposing sharply at 140° (rapid heating). The analytical figures indicate that the compound was never obtained uncontaminated by a decarboxylation product.

Oxidation of III. By dissolving III (0·5 g) in conc. nitric acid (60 ml) and maintaining the mixture at 90° for 24 hr, a clear solution was obtained. Water and nitric acid were removed at 12 mm press. and the residue washed with ethanol and recrystallized twice from water, when it had m.p. 200° and was identified as pyridazine-3-carboxylic acid (lit. m.p. 200–201°)[7] by mixed m.p. and I.R. spectum.

An authentic sample of pyridine-3-carboxylic acid was prepared as follows; 3-hydroxymethylpyridazine (0·5 g) prepared from furfuryl acetate according to the method of Clauson-Kaas,[8] in 20 ml water was added to 1·0 g potassium permanganate in 100 ml water at 70°. Manganese dioxide was filtered and the volume of liquid reduced to 5 ml. After acidification with conc. HCl, the acid (0·5 g, 88%) was filtered, and crystallized from water.

Bromination of III. To III (1·0 g) in cold ethyl acetate (10 ml) was added dropwise bromine (0·5 g) in an equal volume of ethyl acetate. The solution was cooled in ice and the white crystalline precipitate of the bromo-lactonic acid (V) filtered, washed with ethyl acetate and dried in a desiccator. After recrystalization from methyl cyanide it had m.p. 180° (dec). The compound is hygroscopic, and tends to redissolve in excess bromine. (Found: C, 38·50; H, 3·06; N, 7·67; Br, 21·52; $C_{12}H_9O_7N_2Br$ requires: C, 38·60; H, 2·42; N, 7·52; Br, 21·41%).

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[6] R. H. Mizzoni and P. E. Spoerri, *J. Amer. Chem. Soc.* **73**, 1873 (1951).

[7] W. J. Leanza, H. J. Becker and E. F. Rogers, *J. Amer. Chem. Soc.* **75**, 4086 (1953).

[8] N. Clauson-Kaas and F. Limborg, *Acta Chem. Scand.* **1**, 619 (1947).

Deuterated adduct. Maleic anhydride-d_2 was prepared in quantitative yield by the reduction of acetylenedicarboxylic acid (200 mg) in deuterium over palladium on barium sulphate, allowing the theoretical quantity of gas to be absorbed. Sublimation of the maleic acid-d_2 from a large excess of P_2O_5 gave maleic anhydride-d_2 (yield, 155 mg). This was allowed to react with pyridazine in the usual way to give III-d_4 (150 mg).

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