Pyrazine Chemistry. Part V.[1] Diels-Alder Reactions of Some 2,5-Dihydroxypyrazines [2]

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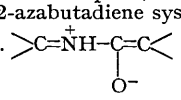
Certain 2,5-dihydroxypyrazines and related systems undergo 1,4-cycloaddition reactions. Dimethyl acetylenedicarboxylate reacts to give bicyclic adducts which readily undergo a retro-Diels-Alder reaction with elimination of cyanic acid and formation of substituted pyridones. 5-Ethoxy-1,3-dimethylpyrazin-2-one (16) has been synthesised and shown to undergo ready cycloaddition reactions even with non-activated double bonds. The implications of these reactions relative to the biosynthesis of the mould metabolite brevianamide A and related compounds are discussed.

In 1969 the mould metabolites brevianamide A (1) and brevianamide E (2) were isolated from cultures of *Penicillium brevicompactum* by Birch and Wright.[3] Subsequent feeding experiments showed that these metabolites are derived from tryptophan, proline, and mevalonate. The structures of several related natural products have also been determined.[4]

Consideration of possible pathways for the biosynthesis of these brevianamides suggested the intervention of the common progenitor (3) [3a] (see Scheme) and this compound has recently been isolated from another mould, *Aspergillus ustus*.[4b] Autoxidation of indoles is known to proceed by way of the indolin-3-yl hydroperoxides.[5] Reduction and intramolecular cyclisation would lead to the optically active brevianamide E (2) (Scheme, path a). The optical activity of brevianamide A (1) implies the existence of a chiral precursor. One route, of several possibilities, is depicted (Scheme, path b). The intramolecular Diels-Alder reaction between the isopentenyl unit and the hydroxy-pyrazinone (4) has no precedent. In this paper we describe some experiments which rectify this situation.

† No distinction is implied, in the present instance, between the 3-hydroxy-2-azabutadiene system and any of its tautomeric equivalents, *e.g.* 

A number of heterocyclic systems which contain the amide group have been shown to undergo Diels-Alder reactions.[6] Compounds which contain the 3-hydroxy-2-aza-butadiene system † [*e.g.* (5)] also participate in cycloaddition reactions [7] and it has been postulated that the equilibrium of the reaction may be favoured towards the adducts, in part, by removal of the ' diene ' system with the concomitant formation of an amide bond. 2,5-Dihydroxypyrazines (6), which contain such a structural feature, whether they exist in the aromatic form (6) or as the tautomeric pyrazinone (7), should also be expected to behave as ' dienes ' in Diels-Alder reactions.

Treatment of the dihydroxypyrazine (6; $R^1 = PhCH_2$, $R^2 = Me$) [8] with dimethyl acetylenedicarboxylate in dimethylformamide at 100° for several hours gave multicomponent mixtures, but one of the fractions showed a characteristic, brilliant blue fluorescence in u.v. light. Isolation of this fraction by preparative t.l.c. revealed the presence of two compounds, the isomeric pyridones (9; $R^1 = PhCH_2$, $R^2 = Me$) and (9; $R^1 = Me$, $R^2 = PhCH_2$). When the cycloaddition reaction was conducted at room temperature over a period of several days a new compound was formed. This product, isolated by

[1] Part IV, K. W. Blake, A. E. A. Porter, and P. G. Sammes, *J.C.S. Perkin I*, 1972, 2494.

[2] Preliminary communication, A. E. A. Porter, and P. G. Sammes, *Chem. Comm.*, 1970, 1103.

[3] (*a*) J. Birch and J. J. Wright, *Chem. Comm.*, 1969, 644; (*b*) A. J. Birch and J. J. Wright, *Tetrahedron*, 1970, **26**, 2329.

[4] (*a*) A. J. Birch and R. A. Russell, *Tetrahedron*, 1972, **28**, 2999; (*b*) P. S. Steyn, *Tetrahedron Letters*, 1971, 3331.

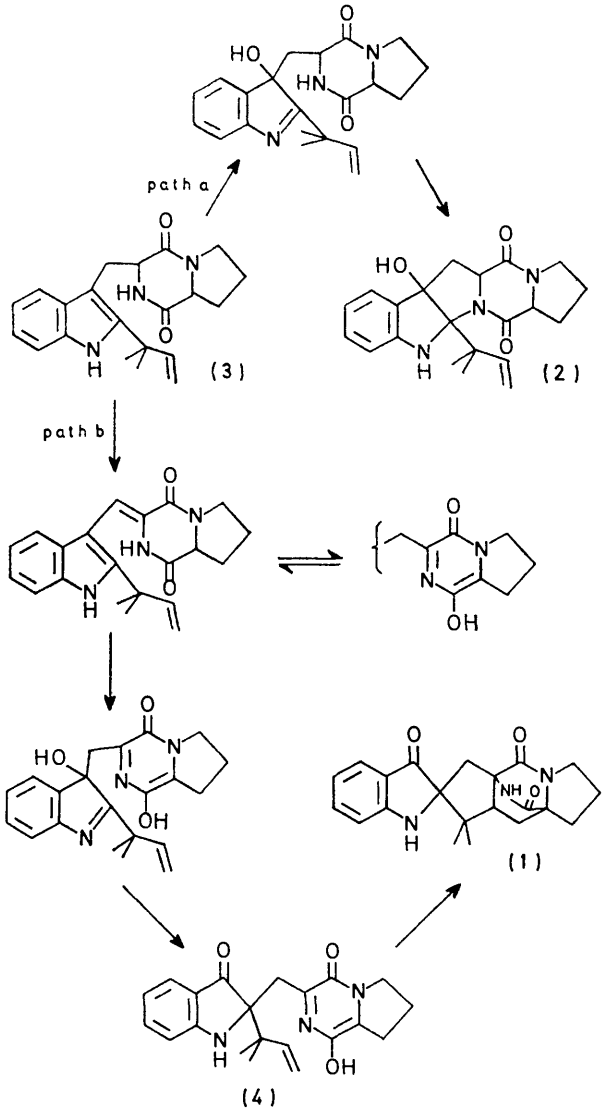
[5] B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.*, 1951, **73**, 2188; *cf.* M. Ohno, T. F. Spande, and B. Witkop, *ibid.*, 1970, **92**, 343.

[6] H. Tomisawa and H. Hongo, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 925; H. Tomisawa, R. Fujita, K. Noguchi, and H. Hongo, *ibid.*, p. 941.

[7] D. W. Jones, *J. Chem. Soc. (C)*, 1969, 1729; N. J. Mruk and H. Tieckelman, *Tetrahedron Letters*, 1970, 1209.

[8] M. Bergman and A. Miekeley, *Annalen*, 1927, **458**, 40.

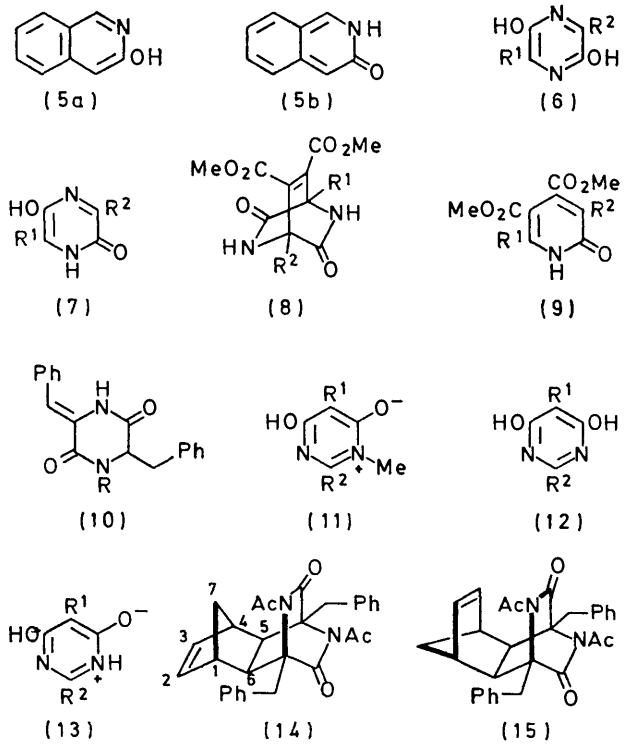
preparative t.l.c., absorbed at 3345, 1730, and 1690 cm^{-1} in its i.r. spectrum. Its ^1H n.m.r. spectrum showed that it was the bicyclic adduct (8; $R^1 = PhCH_2$, $R^2 = Me$).



SCHEME

Attempted purification by crystallisation from chloroform resulted in partial decomposition, and heating in dimethylformamide at 100° for 30 min resulted in the complete elimination of cyanic acid and clean formation of the two pyridones (9; $R^1 = PhCH_2$, $R^2 = Me$) and (9; $R^1 = Me$, $R^2 = PhCH_2$). Cyanuric acid, formed by the trimerisation of the eliminated cyanic acid, was also formed and isolated. Structural assignments for the two pyridones were mainly deduced from the ^1H n.m.r. spectra (see Experimental section).

In order to test the generality of the cycloaddition reaction the symmetric pyrazine (6; $R^1 = R^2 = PhCH_2$) was prepared. This model was chosen since subsequent elimination of either bridge from the bicyclic adduct of the type (8) would lead to the same product. Condensation of benzaldehyde with 3-benzylpiperazine-2,5-dione afforded (3*Z*)-1-acetyl-6-benzyl-3-benzylidenepiperazine-2,5-dione (10; R = Ac), the structure of which was confirmed by correlation of chemical shift values with those of known compounds of related stereochemistry.[9] Deacetylation of the piperazine (10; R = Ac) with methanolic potassium hydroxide gave the benzyl-benzylidenepiperazinedione (10; R = H). Isomerisation[9a] of compound (13; R = H) with aqueous sodium hydroxide at 100°, followed by acidification, resulted in the precipitation of the pyrazine (6; $R^1 = R^2 = PhCH_2$). The pyrazine was purified by several recrystallisations from dimethylformamide followed by sublimation. When purification was attempted by sublimation without prior crystallisation the material underwent complete reisomerisation into the benzyl-benzylidene-piperazinedione (10; R = H). That the reisomerisation was due to traces of acid was confirmed by treating the dihydroxypyrazine (6; $R^1 = R^2 = PhCH_2$) with toluene-*p*-sulphonic acid in dimethylformamide at 100°; the same result was observed. Acid quenching of the base mixture in the isomerisation of the benzylidene derivative into the corresponding pyrazine therefore represents a kinetic process, the equilibrium lying in favour of the benzylidene derivative under acidic conditions.[9a]



Reaction of the pyrazine (6; $R^1 = R^2 = PhCH_2$) with dimethyl acetylenedicarboxylate in dimethylformamide at 60° afforded a single compound, shown to be the bicyclic adduct (8; $R^1 = R^2 = PhCH_2$). Heating this

[9] A. E. A. Porter and P. G. Sammes, *J. Chem. Soc.* (*C*), 1970, 2530; K. W. Blake and P. G. Sammes, *ibid.*, p. 980.

adduct at 150° gave the pyridone (9; $R^1 = R^2 = PhCH_2$) in high yield.

The ease of the foregoing cycloaddition reactions suggested that they should be quite general for systems containing similar 3-hydroxy-2-azabutadiene groups. 4,6-Dihydroxypyrimidines, which are extremely easily prepared, fall into this category of 'diene-like' systems. For this reason, 4,6-dihydroxy-2-methylpyrimidine [10] was treated with dimethyl acetylenedicarboxylate in dimethylformamide. In this case no intermediate bicyclic adduct was isolated; instead, the pyridone (9; $R^1 = Me$, $R^2 = H$) was isolated directly. Recently, other workers have shown [11,12] that mesoionic pyrimidine systems, such as compound (11), can also undergo 1,4-addition reactions, but they gave no reference to the addition reactions of the *N*-unsubstituted 4,6-dihydroxypyrimidines (12), which can exist in tautomeric equilibrium with species such as (13).*

In order to design a closer analogy to the reaction predicted in the biosynthesis of brevianamide A (Scheme) the dihydroxypyrazine (6; $R^1 = R^2 = PhCH_2$) was treated with the unactivated olefin, norbornadiene, in dimethylformamide at 100°. The product consisted of a very polar mixture, which could not be further purified. It was therefore acetylated before separation by preparative t.l.c. In this manner a crystalline 1 : 1 adduct was isolated as its diacetyl derivative. The mass spectrum of this adduct was consistent with either of the structures (14) or (15). Norbornadiene has been shown to participate in the Diels-Alder reaction to give mainly *exo,exo*-adducts [13,14] and hence structure (14) would be most likely in the present instance. The 100 MHz n.m.r. spectrum of the adduct in deuteriochloroform showed a broad singlet at τ 2·82 (Ph), a broad two-proton singlet at 3·74 (H-2 and H-3), an AB quartet at 5·9 and 6·55 (J 15 Hz) and another at 6·19 and 6·39 (J 16 Hz), assigned to the benzylic groups, signals at 6·79 and 7·1. (H-1 and H-4), a broadened doublet at 7·42 (J 8·5 Hz, H-5 or H-6), two three-proton singlets at 7·95 and 8·07 (acetyl groups), and the presence of one proton (broadened d, J 8·5 Hz, H-6 or H-5) buried under the two acetyl peaks which was established by INDOR experiments. A broadened unsymmetrical two-proton AB quartet occurred at 8·48 and 8·56 (J_{AB} 10 Hz) of which the low-field portion was assigned to H-7-*syn* and the high-field part to H-7-*anti*. The appropriate double-irradiation experiments confirmed these assignments. In a number of such *exo,exo*-norbornadiene adducts [13,14] the coupling between H-7-*anti* and H-7-*syn* is *ca.* 10 Hz. The 7-*anti*-proton resonates in the region τ 8·7—9·2, the signal being broader than that of the 7-*syn*-proton by virtue of coupling both with H-1 and H-4 and with H-5 and H-6 (J *ca.* 2 Hz) (long-range 'zig-zag' coupling [15]). Few coupling constants have been recorded for protons at positions 5 and 6 since they often have identical chemical shifts. The chemical shift of the 7-*syn*-proton is not easy to predict on the basis of previous work since no closely related examples are known. If (as molecular models suggest) H-7-*syn* falls in the shielding zone of the imide group the relatively high shift observed could be explained. That the signal at τ 8·56 is broader than that at τ 8·48 in this AB system suggests that the former is due to the 7-*anti*-proton and the latter to the 7-*syn*-proton.

Changing the solvent to deuteriobenzene gives rise to a broad two-proton singlet at τ 4·12, an AB quartet at 5·9 and 6·73 (J 16 Hz), with another at 6·25 and 6·5 (J 15 Hz), a broadened singlet at 6·97 (H-1 or H-4), a one-proton broad doublet at 7·38 (J 8·5 Hz, H-5 or H-6), a one-proton proton signal at 7·47 (H-1 or H-4), two sharp singlets at 8·08 and 8·03 (acetyl groups), a doublet at 8·33 (J 8·5 Hz, H-5 or H-6), and an AB quartet at 8·42 and 8·80 (J_{AB} 10 Hz), again with the higher field signal being broader, suggesting that this is due to the 7-*anti*-proton.

The foregoing reactions clearly show that 2,5-dihydroxypyrazines undergo cycloaddition reactions with either electron-deficient or strained, unsaturated bonds. An attempted reaction of the pyrazine (6; $R^1 = R^2 = PhCH_2$) with the unstrained olefin cyclopentene, however, failed. A re-examination of the proposed intermediate (4), which has been put forward for the biosynthesis of brevianamide (Scheme), suggested that reactions of a pyrazine derivative in which one of the nitrogen atoms bears an alkyl substituent would bear a closer resemblance to the biosynthetic scheme. Such systems would also be expected to react with an unstrained, unactivated olefin.

In order to test this postulate the blocked pyrazinone (16) was prepared *via* reaction of the piperazinedione (17) with triethyloxonium fluoroborate, followed by oxidation with dichlorodicyanobenzoquinone. The pyrazinone proved to be extremely reactive and difficulty was experienced in obtaining a pure specimen. However, the material obtained in the described manner ran as a single compound in a variety of t.l.c. systems and gave a parent ion at *m/e* 168 in its mass spectrum, identified as the required species, $C_8H_{12}N_2O_2$. Reaction of the pyrazinone (16) with dimethyl acetylenedicarboxylate in refluxing dichloromethane gave one product, analysis of which agreed with the expected adduct structure (18). Unlike the dihydroxypyrazine adducts (8), this product showed no tendency to eliminate the bridging amide group (as methyl isocyanate) even up to 200°. The mass spectrum indicated that loss of the ethoxyimine bridge occurred more readily than loss of the amide bridge [$M^+ - 72$ (100%); $M^+ - 57$ (18%)].

Hydrolysis of the adduct (18) with dilute hydrochloric acid in tetrahydrofuran occurred rapidly at room temperature to give the triester (19) in high yield.

* For recent studies on the tautomerism of 4,6-dihydroxypyrimidines see Y. Inoue, N. Furutachi, and K. Nakanishi, *J. Org. Chem.*, 1966, **31**, 175; A. R. Katritzky, F. D. Popp, and A. J. Waring, *J. Chem. Soc.* (*B*), 1966, 565.

[10] A. W. Dox and L. Yoder, *J. Amer. Chem. Soc.*, 1922 **44**, 361.

[11] K. T. Potts and M. Sorm, *J. Org. Chem.*, 1972, **37**, 1422.

[12] T. Kappe and W. Lube, *Angew. Chem. Internat. Edn.*, 1972, **10**, 925.

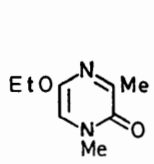
[13] R. McCulloch, A. R. Rye, and D. Wege, *Tetrahedron Letters*, 1969, 5163.

[14] M. P. Cava and F. M. Scheel, *J. Org. Chem.*, 1967, **32**, 1304.

[15] V. J. Kowalewski, *Progr. N.M.R. Spectroscopy*, 1959, **5**, 1.

Presumably protonation is followed by collapse of the bridge to give an intermediate (20), which is immediately hydrolysed to the corresponding ester.

The pyrazinone (16) rapidly reacted with oxygen on exposure to air. Evaporation of a solution in chloroform in an open vessel afforded a crystalline solid, $C_8H_{12}N_2O_4$,



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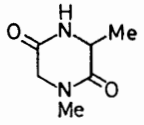

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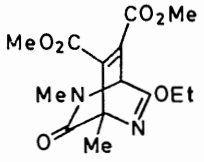

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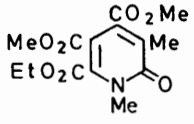

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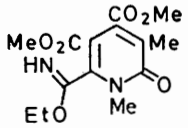

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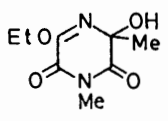

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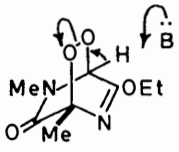

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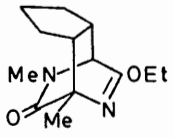

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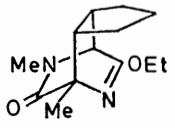

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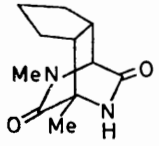

(25)

which gave a negative peroxide test. Its i.r. spectrum displayed strong hydroxyl and carbonyl stretching absorptions. This compound was characterised as the hydroxy-imide (21) and presumably arises *via* initial formation of the peroxide (22) followed by rearrangement (see arrows). Although the intermediate peroxide (22) was not isolated, evidence for its formation was obtained. Bubbling air through a solution of the pyrazinone (16), in either dichloromethane or deuteriochloroform, initially gave a new compound (t.l.c. evidence) which showed a methine proton signal at τ 6·65 and which gave a positive peroxide test (starch–iodide). Evaporation of the solution, however, only afforded the hydroxy-imide (21) as an isolable compound. Since a direct addition of triplet oxygen to the diene substrate is unlikely, the autoxidation is probably preceded by an electron-transfer process.[16]

As anticipated, the pyrazinone (16) reacted with an isolated olefinic bond. Treatment of the diene with cyclopentene at 100° in the dark gave a mixture of two 1 : 1 adducts. Monitoring the isolation procedure by ^{1}H n.m.r. indicated that one of the initial adducts underwent partial hydrolysis during the preparative t.l.c. purification. Although one of the adducts was stable to the isolation procedure, the other isomer could not be obtained pure and was therefore separated as its hydrolysis product. The stable adduct showed the presence of ethoxyl, methyl, *N*-methyl, methine, and cyclopentane protons in its n.m.r. spectrum, as well as the expected parent ion at *m/e* 236 in its mass spectrum. The hydrolysed compound had lost the ethoxy-group and the n.m.r. spectrum showed an amide N–H proton. The initial adducts must have the *syn-* (23) or *anti-* (24) configurations.* The stable isomer is assigned as the *anti*-adduct (24), since, in this species, hydrolysis of the imino-ether involving an sp^3-hybridised intermediate would be inhibited. The unstable adduct is therefore compound (23). Acid-catalysed hydrolysis of the initial reaction mixture caused selective hydrolysis of only the *syn*-adduct (23).

On the basis of the foregoing cycloaddition reactions, the biosynthetic scheme proposed for brevianamide A (Scheme, path b) appears reasonable.

EXPERIMENTAL

M.p.s were recorded on a Kofler hot-stage apparatus. I.r. spectra were recorded on a Unicam SP 200 spectrometer, and u.v. spectra on a Unicam SP 800 instrument for solutions in ethanol. ^{1}H n.m.r. spectra were obtained on Varian T60, A60, or HA100 instruments, generally with deuteriochloroform as solvent containing tetramethylsilane as internal reference. For AB systems the chemical shift of each proton was taken as the midpoint of the appropriate doublet without correction. Mass spectra were obtained on an A.E.I. MS9 spectrometer.

Dimethylformamide was purified by distillation from calcium hydride under reduced pressure before use. Light petroleum refers to the fraction of boiling range 60—80° unless otherwise stated.

Reaction of 3-Benzyl-2,5-dihydroxy-6-methylpyrazine with Dimethyl Acetylenedicarboxylate.—The pyrazine (6; R^1 = $PhCH_2$, R^2 = Me) (0·20 g) and dimethyl acetylenedicarboxylate (0·66 g) were stirred in dry dimethylformamide at room temperature for 2 days. The solvent was removed *in vacuo* below 30°, the residue was slurried with chloroform and the mixture filtered. The filtrate was purified by preparative t.l.c. (SiO_2; 9 : 1 $CHCl_3$–MeOH) and the major component was eluted to give the bicyclic adduct (8) as a homogeneous solid (0·22 g, 66%), $\nu_{max.}$($CHCl_3$) 3450, 1730, 1690, and 1250 cm^{-1}, τ 2·67 (1H, exchangeable), 2·80 (5H, s, Ph), 3·82 (1H, exchangeable), 6·38 (3H, s, MeO), 6·45 (3H, s, MeO), 6·25 and 6·69 (2H, ABq, *J* 15 Hz), and 8·37 (3H, s, Me). Attempts to obtain an analytical sample always gave material contaminated with traces of pyridones. Heating the adduct at 100° for 15—30 min in dimethylformamide caused its complete decomposition. Evaporation of the

[16] *Cf.* F. A. Bell, A. Ledwith, and D. C. Sherrington, *J. Chem. Soc.* (*C*), 1969, 2719; D. H. R. Barton, G. Leclerc, P. D. Magnus,

solvent followed by preparative t.l.c. (SiO_2; 1 : 1 benzene–ethyl acetate) afforded the two isomeric pyridones. The less polar material was *dimethyl 5-benzyl-1,6-dihydro-2-methyl-6-oxopyridine-3,4-dicarboxylate* (9; R^1 = Me, R^2 = $PhCH_2$), m.p. 178—179° (from ethyl acetate), $\nu_{max.}$($CHCl_3$) 3310, 1720, 1660, 1600, and 1300—1200 cm^{-1}, $\lambda_{max.}$ 267 and 307 nm (ε 7750 and 4800), τ 2·73 (5H, s, Ph), 5·71 (2H, s, CH_2), 6·11 (3H, s, MeO), 6·22 (3H, s, MeO), and 8·76 (3H, s, Me) (Found: C, 64·5; H, 5·3; N, 4·3. $C_{17}H_{17}NO_5$ requires C, 64·75; H, 5·4; N, 4·4%).

The more polar isomer was *dimethyl 2-benzyl-1,6-dihydro-5-methyl-6-oxopyridine-3,4-dicarboxylate* (9; R^1 = $PhCH_2$, R^2 = Me), m.p. 191—193° (from benzene–light petroleum), $\nu_{max.}$ ($CHCl_3$) 3310, 1730, 1650, 1260—1300, and 1220—1200 cm^{-1}, $\lambda_{max.}$ 266 and 308 nm (ε 6150 and 3800), τ 2·82 (5H, s, Ph), 6·24br (8H, s), and 7·56 (3H, s, Me) (Found: C, 64·5; H, 5·3; N, 4·3%). The ratio of the two pyridones was approximately 1 : 1 on the basis of n.m.r. assay. From the neck of the reaction vessel was obtained cyanuric acid.[17]

Reaction between the dihydroxypyrazine (6; R^1 = $PhCH_2$, R^2 = Me) and dimethyl acetylenedicarboxylate in dimethylformamide at 100° gave the two pyridones directly.

3,6-Dibenzyl-2,5-dihydroxypyrazine (6; R^1 = R^2 = $PhCH_2$).—3-Benzylpiperazine-2,5-dione (4·0 g), fused sodium acetate (4·2 g), benzaldehyde (2·08 g) and acetic anhydride (8·0 g) were thoroughly mixed and heated under nitrogen at 130° for 12 h. The resulting homogeneous solution was evaporated to dryness under reduced pressure. The residue was triturated with water and ether (1 : 2; 75 ml); the ether phase was separated and washed with saturated aqueous sodium hydrogen carbonate solution (2 × 50 ml), saturated sodium hydrogen sulphite solution (2 × 50 ml), and water (2 × 50 ml), and then dried (Na_2SO_4). The aqueous washings were washed with more ether. Evaporation afforded *(3Z)-1-acetyl-6-benzyl-3-benzylidenepiperazine-2,5-dione* (10; R = Ac) (7 g) as a partially crystalline oil. A sample recrystallised from cyclohexane had m.p. 114—115°, $\nu_{max.}$($CHCl_3$) 3390, 3100, 3000—2850, 1700, and 1635 cm^{-1}, $\lambda_{max.}$ 320 and 230 nm (ε 15,900 and 14,800), τ 2·4—3·0 (10H), 3·30 (1H, s), 4·63 (1H, t, *J* 5 Hz), 6·74 (2H, d, *J* 5 Hz), and 7·37 (3H, s) (Found: C, 71·7; H, 5·45; N, 8·45. $C_{20}H_{18}N_2O_3$ requires C, 71·85; N, 5·4; N, 8·4%). The remaining material was immediately dissolved in N-potassium hydroxide in methanol (2 equiv.) and kept at room temperature for 2 h. The mixture was acidified with 2N-sulphuric acid and the precipitate was collected. A sample of the racemic product (3·3 g) crystallised from dimethylformamide had m.p. 260—265°; its analytical figures were as expected for (3*Z*)-6-benzyl-3-benzylidenepiperazine-2,5-dione [18] (Found: C, 73·8; H, 5·5; N, 9·5. Calc. for $C_{18}H_{16}N_2O_2$: C, 74·0; H, 5·5; N, 9·6%).

Heating the benzylidene derivative (0·5 g) in N-sodium hydroxide at 100° for 1 h, followed by acidification, gave a pale yellow precipitate of the *title compound* (0·12 g); recrystallisation from dimethylformamide (4×) followed by sublimation at 200° and 10^{-4} Torr gave material of m.p. 259—261°, $\nu_{max.}$(KBr) 3200—2400, 1680—1620w, 1460, 1430, 1370, 1170, 730, and 705 cm^{-1}, τ [$(CD_3)_2SO$] −1·52 (2H, s), 2·85 (10H, s), and 6·19 (4H, s) (Found: C, 73·9; H, 5·5; N, 9·6. $C_{18}H_{16}N_2O_2$ requires C, 74·0; H, 5·5; N, 9·6%). When the dihydroxypyrazine was sublimed without prior crystallisation the off-white sublimate had m.p. and an i.r. spectrum identical with those of the tautomeric benzylidene derivative (10; R = H). Similarly, heating the dihydroxypyrazine (0·15 g) in dimethylformamide (5 ml) in the presence of toluene-*p*-sulphonic acid (0·15 g) at 100° for 12 h afforded, on cooling, crystals of the benzylidene derivative (0·06 g), identical with an authentic specimen.

Reaction of 3,6-Dibenzyl-2,5-dihydroxypyrazine with Dimethyl Acetylenedicarboxylate.—The pyrazine (0·04 g) and the diester (0·1 g) in dimethylformamide (1 ml) were stirred at room temperature for 2 days and then at 60—70° for 24 h. The solvent was removed *in vacuo* and the major product was isolated by preparative t.l.c. (SiO_2; $CHCl_3$) to give *dimethyl 1,4-dibenzyl-3,6-dioxo-2,5-diazabicyclo*[2.2.2]*oct-7-ene-7,8-dicarboxylate* (8; R^1 = R^2 = $PhCH_2$) (0·037 g, 62%), m.p. 160—170° (decomp.) (from benzene), $\nu_{max.}$($CHCl_3$) 3400, 3100, and 1700—1720 cm^{-1}, τ 2·9 (10H, s), 4·03br (2H, s), 6·74 and 6·23 (ABq, 4H, J_{AB} 15 Hz), and 6·32 (6H, s) (Found: C, 70·4; H, 5·5; N, 5·0. $C_{26}H_{22}N_2O_6,C_6H_6$ requires C, 70·3; H, 5·5; N, 5·5%).

The adduct (0·025 g) was heated in dimethylformamide (1 ml) at 150° for 30 min. The solvent was evaporated off and the residue gave, by preparative t.l.c. (SiO_2; 9 : 1 $CHCl_3$–MeOH) *dimethyl 2,5-dibenzyl-1,6-dihydro-6-oxopyridine-3,4-dicarboxylate* (9; R^1 = R^2 = $PhCH_2$) (0·018 g, 95%), m.p. 189—191° (from ethyl acetate), $\nu_{max.}$($CHCl_3$) 3350, 1720, 1650, 1595, 1500, and 1300—1180 cm^{-1}, $\lambda_{max.}$ 266 and 312 nm (ε 5100 and 3800), τ 2·82 (10H, s), 5·82 (2H, s), 6·22 (2H, s), 6·28 (3H, s), and 6·25 (3H, s) (Found: C, 70·3; H, 5·4; N, 3·6. $C_{23}H_{21}NO_5$ requires C, 70·5; H, 5·5; N, 3·6%).

Reaction of 3,6-Dibenzyl-2,5-dihydroxypyrazine with Norbornadiene.—The pyrazine (1·0 g) and norbornadiene (1·5 g) in dimethylformamide (20 ml) were heated at 100° with stirring, under nitrogen, for 5 days. Portions (1·5 g) of norbornadiene were added at daily intervals. The mixture became homogeneous before depositing a pale yellow precipitate. The solvent was removed *in vacuo* and the residue heated with acetic anhydride at 100° for 24 h. After removal of the acetic anhydride and preparative t.l.c. (SiO_2; $CHCl_3$), crystallisation from light petroleum (b.p. 100—120°) gave *9,11-diacetyl-1,8-dibenzyl-9,11-diazatetracyclo*[6,2,2,$1^{3,6}$,$0^{2,7}$]*tridec-4-ene-10,12-dione* (14) (0·33 g, 18%), m.p. 174—175°, $\nu_{max.}$(CCl_4) 3100—2900, 1735, 1710, 1605, 1505, 1460, 1430, 1365, 1310, 1275, 1200, and 1040 cm^{-1} (for n.m.r. see Discussion section) (Found: C, 74·3; H, 6·1; N, 5·8%; M^+, 468·2033. $C_{29}H_{28}N_2O_4$ requires: C, 74·3; H, 6·0; N, 6·0%; *M*, 468·2049).

Reaction of 4,6-Dihydroxy-2-methylpyrimidine with Dimethyl Acetylenedicarboxylate.—The pyrimidine [10] (0·13 g) and the ester (0·28 g) in dimethylformamide (2 ml) were heated at 60° for 72 h until a clear dark solution had formed. Evaporation of the solvent under reduced pressure, allowing the temperature to rise to 100° for 30 min, followed by preparative t.l.c. (SiO_2; 9 : 1 $CHCl_3$–MeOH) afforded, as the major component, *dimethyl 1,6-dihydro-2-methyl-6-oxopyridine-3,4-dicarboxylate* (9; R^1 = Me, R^2 = H) (0·144 g, 62%), m.p. 169—171° (from ethyl acetate), $\nu_{max.}$ ($CHCl_3$) 3430, 3100, 1730, 1665, 1560, 1450, 1420, 1280, and 1310 cm^{-1}, τ 3·27 (1H, s), 6·0—6·15 (6H, two s), and 7·40 (3H, s) (Found: C, 53·5; H, 5·0; N, 6·1. $C_{10}H_{11}NO_5$ requires C, 53·5; H, 4·9; N, 6·2%).

5-Ethoxy-1,3-dimethylpyrazin-2(1H)-one (16).—1,3-Dimethylpiperazine-2,5-dione (17) [19] (2·0 g) and triethyl-

[17] *Cf.* W. E. McEwen, I. C. Mineo, Y. H. Shan, and G. Y. Han, *Tetrahedron Letters*, 1968, 5157.

[18] R. Brown, C. Kelley, and S. E. Wibberley, *J. Org. Chem.*, 1965, **30**, 277.

[19] G. Gaudiano and A. Ricca, *Gazzetta*, 1957, **87**, 789.

oxonium fluoroborate (10·8 g) in dichloromethane (60 ml) were stirred at room temperature under nitrogen for 3 h. The mixture was poured into cold, saturated sodium hydrogen carbonate solution (40 ml) before separation and extraction of the aqueous phase with more dichloromethane. The combined organic extracts were dried (Na_2SO_4), and evaporated to give an oil. Sublimation afforded crystals of *5-ethoxy-1,3-dimethyl-3,6-dihydropyrazin-2(1H)-one* (1·5 g, 64%), m.p. 58—59°, $\nu_{max.}$(Nujol) 1710, 1650, 1520, 1465, 1415, 1380, 1275, 1237, 1160, 1053, 900, and 790 cm^{-1}, τ 5·6—6·1 (5H, m), 7·02 (3H, s), 8·56 (3H, d, *J* 7 Hz), and 8·70 (3H, t, *J* 7 Hz) (Found: C, 56·7; H, 8·4; N, 16·45. $C_8H_{14}N_2O_2$ requires C, 56·45; H, 8·3; N, 16·5%).

Oxidation of this imino-ether (0·40 g) with dichlorodicyanobenzoquinone (0·53 g) in dry benzene (20 ml) at room temperature under nitrogen for 1 h, followed by removal of the quinol by filtraton, and evaporation of solvent under nitrogen, afforded the crude oxidation product. This was chromatographed through alumina (grade III; 15 g), with dichloromethane as eluant. Evaporation of the eluate afforded 5-ethoxy-1,3-dimethylpyrazin-2(1H)-one (0·152 g, 38%) as pale yellow needles, m.p. 61—75°, $\nu_{max.}$(Nujol) 3100, 1660, 1600, 1420, 1370, 1340, 1328, 1257, 1190, 1100, 1050, 895, 860, 810, and 758 cm^{-1}, τ 2·40 (1H, q, *J* 1 Hz), 5·89 (2H, q, *J* 7 Hz), 6·48 (3H, 2), 7·53 (3H, d, *J* 1 Hz), and 8·63 (3H, t, *J* 7 Hz). Attempts to obtain a satisfactory microanalysis failed; oxygen was rapidly absorbed in air. Passing air through a solution of the pyrazinone (0·114 g) in dichloromethane (20 ml) for 4 days, replenishing solvent as required, followed by evaporation, afforded a gummy solid which gave a positive peroxide test (starch–iodide). Its ^1H n.m.r. spectrum showed a methine proton signal at τ 6·65. The gummy solid crystallised from acetone–light petroleum to give *5-ethoxy-3-hydroxy-1,3-dimethylpyrazine-2(3H),6(1H)-dione* (21) (0·114 g, 84%), m.p. 83—84°, $\nu_{max.}$(Nujol) 3340, 1740, 1695, 1670, 1590, 1462, 1410, 1370, 1360, 1335, 1300, 1280, 1200, 1155, 1100, 1080, 1032, 1000, 988, 930, 867, 818, 795, and 760 cm^{-1}, τ 5·61 (2H, q, *J* 7 Hz), 6·55br (1H, s, exchangeable), 6·72 (3H, s), 8·35 (3H, s), and 8·58 (3H, t, *J* 7 Hz), $\lambda_{max.}$ 218 nm (ε 12,000) (Found: C, 48·0; H, 6·1; N, 13·7. $C_8H_{12}N_2O_4$ requires C, 48·0; H, 6·0; N, 14·0%).

Reaction of the Pyrazinone (16) *with Dimethyl Acetylenedicarboxylate.*—The pyrazinone (0·11 g) and the diester (0·09 g) in dichloromethane (15 ml) were heated at reflux under nitrogen for 20 h. The products were separated by preparative t.l.c. (20 : 1 $CHCl_3$–MeOH) to give, as the major omponent, *dimethyl 3-ethoxy-1,5-dimethyl-6-oxo-2,5-diazabicyclo[2.2.2]oct-2,7-diene-7,8-dicarboxylate* (18) (0·118 g, 59%), m.p. 92—94°, $\nu_{max.}$ (Nujol) 1740, 1728, 1705, 1637, 1460, 1390, 1370, 1325, 1270, 1200, 1145, 1050, 1010, 815, 780, and 737 cm^{-1}, τ 4·87 (1H, s), 5·78 (2H, q, *J* 7 Hz), 6·10 (3H, s), 6·15 (3H, s), 7·05 (3H, s), 8·22 (3H, s), and 8·67 (3H, t, *J* 7 Hz), $\lambda_{max.}$ 264·5 nm (ε 2400) (Found: C, 54·2; H, 5·8; N, 8·9. $C_{14}H_{18}N_2O_6$ requires C, 54·2; H, 5·9; N, 9·0%).

Hydrolysis of the adduct (0·034 g) in 60% aqueous tetrahydrofuran (4 ml) containing 2N-hydrochloric acid (0·5 ml) at room temperature for 10 min, followed by neutralisation with sodium hydroxide and extraction with dichloromethane, afforded *2-ethyl 3,4-dimethyl 1,6-dihydro-1-methyl-6-oxopyridine-2,3,4-tricarboxylate* (19) (0·029 g, 85%), m.p. 68—69° (from acetone–light petroleum), $\nu_{max.}$(Nujol) 1740, 1732, 1725, 1662, 1605, 1545, 1443, 1400, 1378, 1265, 1255, 1205, 1178, 1108, 880, 795, 718, and 690 cm^{-1}, τ 5·53 (2H, d, *J* 7 Hz), 6·07 (3H, s), 6·20 (3H, s), 6·45 (3H, s), 7·87 (3H, s), and 8·60 (3H, t, *J* 7 Hz), $\lambda_{max.}$ 270 and 306 nm (ε 12,000 and 6500) (Found: C, 54·2; H, 5·55; N, 4·35. $C_{14}H_{17}NO_7$ requires C, 54·0; H, 5·5; N, 4·5%).

Reaction of the Pyrazinone (16) *with Cyclopentene.*—The pyrazinone (0·088 g) in cyclopentene (4 ml) and a few drops of ethyl acetate (to aid dissolution) were heated in a Carius tube at 100° for 4 days. The products were separated by preparative t.l.c. to give the hydroxy-imide (21) (0·028 g), identical with the material obtained previously, and two, more polar products. The less polar of these products proved to be *11-ethoxy-1,8-dimethyl-8,10-diazatricyclo-[5.2.2.0^{2,6}]undec-10-en-9-one* (24) (0·021 g, 17%), m.p. 36—43° (*ex* sublimation), $\nu_{max.}$(film) 3000—2870, 1675, 1640, 1445, 1410, 1375, 1348, 1315, 1260, 1205, 1188, 1070, 1030, 887, 815, and 773 cm^{-1}, τ 5·72 (2H, q, *J* 7 Hz), 6·21 (1H, d, *J* 3 Hz), 7·07 (3H, s), 7·28—8·83 (8H, m), 8·45 (3H, s), and 8·63 (3H, s), *m/e* 236 (M^+, 22%), 179 (80), 168 (65), 164 (94), 150 (100), 122 (60), and 42 (70) (Found: C, 66·3; H, 8·45; N, 11·9. $C_{13}H_{20}N_2O_2$ requires C, 66·1; H, 8·5; N, 11·85%).

The most polar material, which streaked along the plate, was *1,8-dimethyl-8,10-diazatricyclo[5.2.2.0^{2,6}]undecane-9,11-dione* (25) (0·018 g, 17%), m.p. 211—212° (from acetone), $\nu_{max.}$(Nujol) 3170, 3080, 1700, 1680, 1455, 1395, 1385, 1233, 1068, 762, and 720 cm^{-1}, τ 3·30br (1H, s), 6·25 (1H, m), 6·92 (3H, s), 7·2—8·8 (8H, m), and 8·57 (3H, s), *m/e* 208 (M^+, 80%), 165 (30), 140 (100), 137 (60), 123 (35), 108 (80), 93 (55), 71 (40), and 42 (95) (Found: C, 63·3; H, 7·6; N, 13·45. $C_{11}H_{16}N_2O_2$ requires C, 63·4; H, 7·7; N, 13·45%).

An examination (n.m.r.) of the initial reaction mixture from a similar preparation showed no peaks due to the hydrolysed adduct (25). However, after treatment of the mixture with a little silica gel in wet chloroform, filtering, drying, and dissolution in deuteriochloroform, the hydrolysed adduct was shown to be formed. The ratio of the adducts (24) and (25) was *ca.* 1 : 1.

We thank Mr. P. N. Jenkins for the INDOR experiments. We thank the S.R.C. for a studentship (to A. E. A. P.) and, with the Lilly Research Centre, Windlesham, Surrey, for a CAPS studentship (to P. J. M.).

[2/1827 *Received, 2nd August,* 1972]