Pyrazine Chemistry. Part VIII.[1] Oxidations involving 3-Arylmethylenepiperazine-2,5-diones

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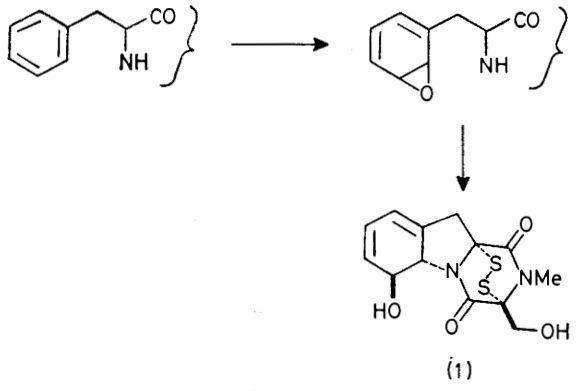
Oxidations of 3-benzylidenepiperazine-2,5-diones with singlet oxygen, lead(IV) acetate, and t-butyl hypochlorite have been studied. Cleavage of the benzylidene group occurs with singlet oxygen, *via* formation of a dioxetan. Diacetoxylation is effected by lead(IV) acetate; the 3-acetoxy-group is particularly labile under acidic conditions, and can be substituted by hydroxy-, alkoxy-, mercapto-, and hydroperoxy-groups. Evidence for acylimine formation during oxidation is presented. For example, with t-butyl hypochlorite chlorination of the α-position occurred with formation of the reactive acylimine (29); reactions of such species and its precursors included an acid- or base-catalysed rearrangement into 6-substituted pyrazines.

BIOSYNTHETIC studies on gliotoxin (1) have suggested that the unusual dienol function arises by oxidation of the phenyl group of the phenylalanine unit; a benzene oxide intermediate is invoked (Scheme 1).[2] The object

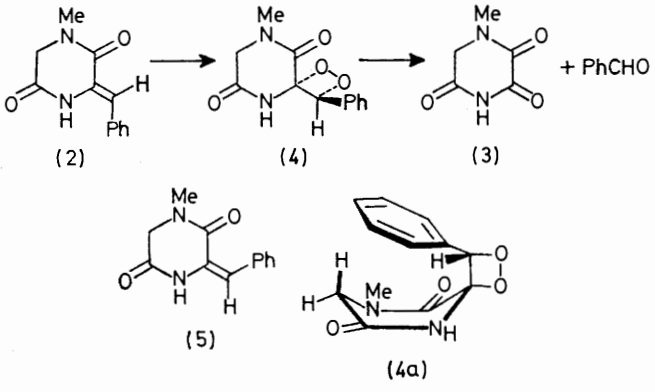


(1)

SCHEME 1

of the present work was to explore the possibility of effecting ring closure between the nitrogen atom (position 4) of the piperazinedione and the benzene group, *via* oxidative procedures. This objective demands specific oxidation of the aryl group in the *ortho*-position. Although this result was not achieved, interesting oxidation reactions were observed.

The initial approach capitalised on the observation[3] that oxidation of certain styrene derivatives with singlet oxygen proceeds in a 1,4-cycloaddition manner involving the aromatic ring. This reaction may mimic dioxygenases (*cf.* biosynthetic conversion of cyclopenol from phenylalanine).[4] Oxidation of the (*Z*)-benzylidenepiperazinedione (2) in dichloromethane with singlet oxygen, and Methylene Blue as sensitiser, at 25 °C, yielded benzaldehyde, and the crystalline piperazinetrione (3) was deposited. From the mother liquors, which gave a positive starch–iodide test, were detected, by ^{1}H n.m.r., traces of the trione and benzaldehyde, and new resonances were observed corresponding to the peroxide (4). A folded conformation (4a) for the peroxide is indicated since the methylene protons resonate as a widely separated AB quartet (*J* 19 Hz), the high-field proton being *cis* to and shielded by the phenyl ring.[5] The high-field position of the *N*-methyl signal (τ 7.30) is also associated with the nearby aromatic ring, indicating the configuration shown rather than the diastereoisomer (H and Ph reversed). No evidence for formation of the (*E*)-benzylidene isomer (5) was apparent in the reaction with singlet oxygen, and only n.m.r. signals for one peroxide could be detected amongst the products, indicating a stereospecific addition of oxygen. In order to check this point, oxidation of the (*E*)-isomer was carried out. Again the piperazinetrione (3) was the major product, but n.m.r. and t.l.c. analysis of the peroxide also produced indicated that it was identical with the peroxide (4). This suggests that oxidation of at least one of the arylmethylene isomers proceeds with inversion



(2) (4) (3) (5) (4a)

of configuration and hence that non-concerted dioxetan formation may be involved.[6] One possibility (Scheme 2) involves an acyliminium derivative (6). In order to inhibit nitrogen participation, the imidate ether (7) was prepared from compound (2) by treatment with methyl iodide and silver carbonate; a small quantity of the *N*-methylated isomer (8) was also formed. In contrast to the amide (2), the ether (7) proved completely inert to the

† *Present address:* Department of Chemistry, The City University, London EC1V 4PB

[1] Part VII, P. J. Machin and P. G. Sammes, preceding paper.

[2] N. Neuss, R. Nagarajan, B. B. Molloy, and L. L. Huckstep, *Tetrahedron Letters*, 1968, 4467.

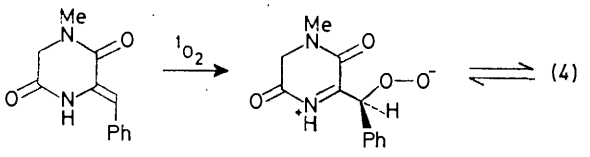
[3] C. S. Foote, S. Mazur, P. A. Burns, and D. Lerdal, *J. Amer. Chem. Soc.*, 1973, **95**, 586.

[4] L. Nover and M. Luckner, *European J. Biochem.*, 1969, **10**, 268.

[5] G. Gawne, G. W. Kenner, N. H. Rogers, R. C. Shephard, and K. Titlestad, in 'Peptides,' ed. E. Bricas, North Holland Publishing Co., Amsterdam, 1968, p. 28; Ziauddin and K. D. Kopple, *J. Org. Chem.*, 1970, **35**, 253.

[6] For recent reviews on singlet oxygen reactions see D. R. Kearns, *Chem. Rev.*, 1971, **71**, 395; C. S. Foote, *Accounts Chem. Res.*, 1968, **1**, 104.

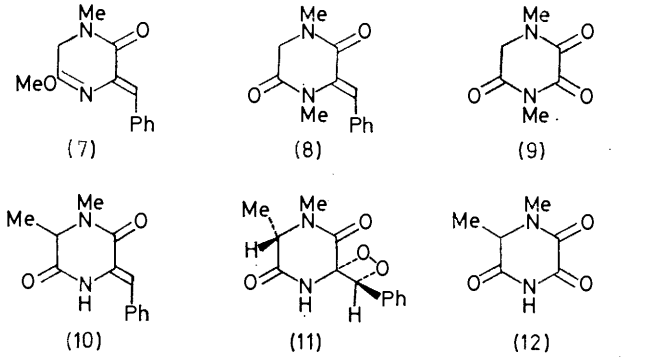
oxidation with singlet oxygen; as expected the isomer (8) afforded the unstable oxamide (9).



(6)

SCHEME 2

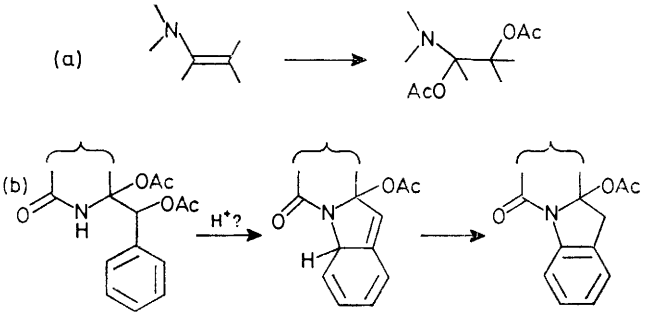
The generality of the oxidation reaction was tested with the (*Z*)-benzylidene-1,6-dimethyl derivative (10). Again ^{1}H n.m.r. analysis and t.l.c. behaviour indicated formation of a dioxetan intermediate (11). The chemical shift of the methyl group (τ 8.52) indicated a *trans*-relationship with the phenyl ring, as indicated, whereas high-field resonances (τ 9.0—10.0) consistent with the corresponding *cis*-isomer were absent. Attempts to isolate the dioxetan again yielded only the piperazinetrione (12).



(13) R = OAc
(14) R = OMe
(15) R = OH
(16) R = SH
(17) R = O·OH

Although attempted oxidation of piperazine-2,5-diones bearing free NH groups with lead(IV) acetate failed,[1] similar treatment of the arylmethylene systems has not been described. Oxidations of compounds capable of imine–enamine tautomerism with this reagent, however, are known to produce diacetates as primary products [Scheme 3(a)].[7] For the present systems such a process could yield a product of intramolecular cyclisation [Scheme 3(b)].

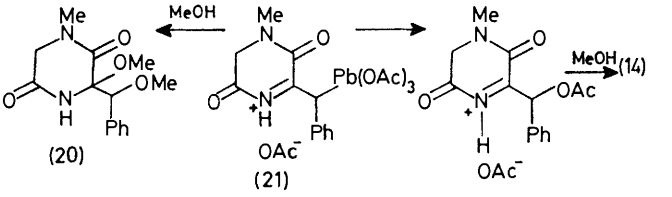
Treatment of the benzylidene derivative (2) with an excess of lead(IV) acetate in benzene at room temperature rapidly produced a new compound in high yield. This showed two acetate resonances in its ^{1}H n.m.r. spectrum (τ 7.83 and 7.88), but again the phenyl residue remained untouched (5 H signal at τ 2.7). The compound was assigned the constitution (13). It proved very reactive and attempted purification by t.l.c. (1 : 19 methanol–chloroform) gave instead the methoxy-derivative (14), and attempted isolation from t.l.c. with aprotic solvents afforded the hydroxy-acetate (15).



SCHEME 3

The solvolysis products could also be prepared from the diacetate by reaction with the corresponding nucleophile in dichloromethane containing an acid catalyst, *e.g.* trifluoroacetic acid or boron trifluoride–ether. Thus, addition of hydrogen sulphide gave the thiol (16), and hydrogen peroxide produced the peroxide (17).[8] In no case, however, was acid-catalysed elimination, to give the acetoxy-substituted benzylidene system (18), observed. With a stoicheiometric amount of oxidant, a small quantity of a new compound accompanied the diacetate (13). Although unstable, this side-product showed resonances compatible with the acylimine formulation (19).

Protic solvents enhanced the rate of oxidation. In the presence of methanol (5% v/v) the benzylidene derivative (2) reacted within 5 min to give, as the sole product, the methoxy-acetate (14). However, in neat methanol compound (14) was accompanied by considerable quantities of the dimethoxylated product (20). Formation of an intermediate organolead compound [*e.g.* (21)] best explains this result, excess of the nucleophilic solvent competing with the intramolecular substitution [9] involving acetate (Scheme 4).



SCHEME 4

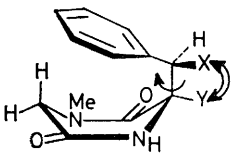
The stereospecificity of this oxidation is again pronounced, all products appearing to be single isomers

[7] F. Corbani, B. Rindone, and C. Scolastico, *Tetrahedron*, 1973, **29**, 3253 *et seq.*

[8] *Cf.* K. Öhler, F. Tataruch, and U. Schmidt, *Chem. Ber.*, 1973, **106**, 165.

[9] A. Lethbridge, R. O. C. Norman, and C. B. Thomas, *J.C.S. Perkin I*, 1974, 1929.

[*i.e.* not *erythro*- (22) and *threo*- (23) mixtures]. During addition, therefore, rotation about the benzyl–dipeptide bond occurs, as required, to reduce steric interactions between the two large groups at the benzylic positions and the piperazinedione ring, particularly for the introduced substituents [(22) and (23); group X] and the oxo-group at position 2. Addition of the nucleophile



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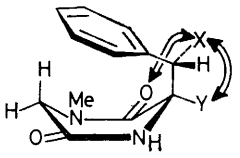
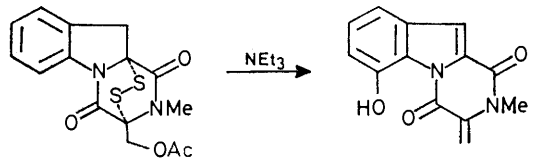


(23)

(Y) will occur so as to maximise the stabilising interaction between the piperazinedione ring and the phenyl group. This is accomplished best in the *erythro*-configuration (22).[10] Furthermore, with this stereochemistry, release of the interaction between the substituents X and Y forces the phenyl residue further over the *N*-methylamide group, an effect reflected in the n.m.r. spectra of these compounds in which the *N*-methyl signal is shifted even further upfield (0.2—0.4 p.p.m.) compared to the simpler derivatives (22; X = H).

The chemistry of some of these products was briefly explored. Treatment of the crystalline thiol (16) with 1 equiv. of sodium hydride in dimethylformamide initially produced a bright yellow solution, but this gradually assumed a deep red colour associated with solutions of elemental sulphur in basic media; t.l.c. confirmed the liberation of sulphur. The product isolated was the original benzylidene derivative (2). The reaction therefore involves an intramolecular reduction reminiscent of the transformation of didehydrogliotoxin acetate (24) into the desulphurised compound (25) with triethylamine and which commences by nucleophilic attack of base on the disulphide bridge.[11] The thiol (16) could be methylated (methyl iodide–potassium carbonate in acetone) and

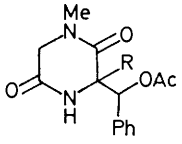


(24) (25)

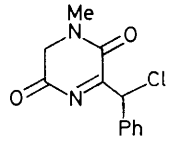
the sulphide (26) produced was oxidised. The derived sulphoxide (27) proved labile; attempted isolation gave instead the hydroxy-acetate (15).

The fate of the hydroperoxide (17) under acidic or basic conditions was also of interest because substitution into the aromatic ring was again conceivable. With trifluoroacetic acid it gave benzaldehyde and the piperazinetrione (12) in high yield. The same products were formed under basic conditions but were accompanied by benzoic acid and the hydroxy-acetate (15). Presumably, under these conditions, the hydroperoxide can act as an oxidant of the benzaldehyde initially liberated. In all the above transformations no phenyl oxidation products were detected and no cleavage (opening) of the piperazinedione ring occurred.

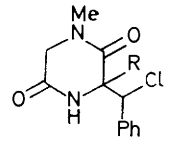
Attempts were made to isolate the acylimine intermediate (19) postulated in the above transformations about position 3. Such species are capable of existence.[12] For the isolation a better leaving group at position 3 was necessary. Treatment of the hydroxy-acetate (15) with thionyl chloride gave a mixture of two products (ratio 8 : 5), the major one being the unstable α-chloroamide (28). The minor component was the desired acylimine (19), although this was too labile to be isolated in a pure state. The n.m.r. signals of the latter were



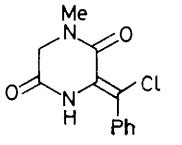
(26) R = SMe
(27) R = SOMe
(28) R = Cl



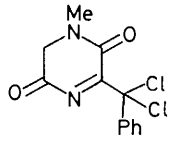
(29)



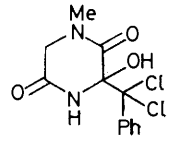
(30) R = OH
(31) R = OMe



(32)



(33)



(34)

identical with those observed in the reaction mixture from formation of the diacetate (13). A similar mixture of compounds (28) and (19) was prepared by oxidation of the methylthio-derivative (26) with t-butyl hypochlorite. Addition of nucleophiles to this mixture occurred with great ease. For example, methanol added to give a quantitative yield of the methoxy-adduct (14).

Acylimine formation also occurred on treatment of the piperazinedione (2) with t-butyl hypochlorite. Although the saturated analogue proved stable to this reagent, the benzylidene derivative (2) reacted rapidly to give the chloro-compound (29). This rapidly absorbed water, to form the hydroxy-derivative (30). Reaction of the benzylidene compound with t-butyl hypochlorite in methanol gave the expected methoxy-chloride (31).

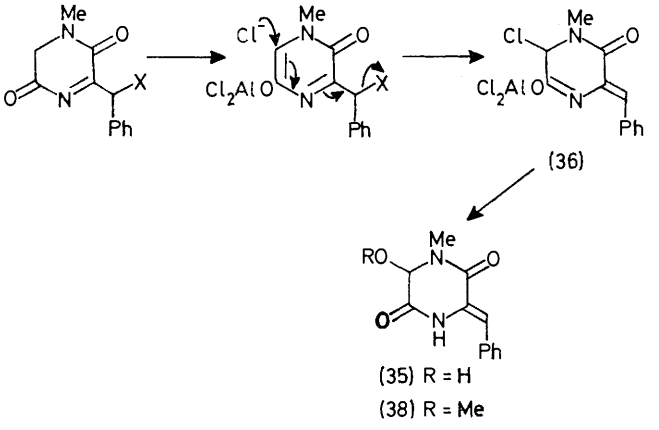
In contrast to the acetoxyacylimine (19), which remained inert to enamide formation, the chloro-acylimine (29) slowly rearranged to the chlorobenzylidene derivative (32) with Lewis acids. Thus, treatment with boron trifluoride–ether for 3 days at 25 °C gave compound (32) in >90% yield. The *E*-configuration was assigned to the double bond by comparison of the n.m.r. spectra with those of similar compounds.

Further reaction of the chlorinated derivative (32) with

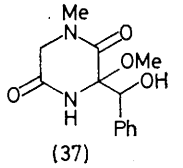
[10] *Cf.* C. Gallina and A. Liberatori, *Tetrahedron*, 1974, **30**, 667.
[11] G. Lowe, A. Taylor, and L. C. Vining, *J. Chem. Soc.* (*C*), 1966, 1799.
[12] *Cf.* S. W. Breuer, T. Bernath, and D. Ben-Ishai, *Tetrahedron*, 1967, **23**, 2869; Y. H. Suen, A. Horeau, and H. B. Kagan, *Bull. Soc. chim. France*, 1965, 1454, 1457.

more t-butyl hypochlorite afforded the dichlorinated isomer (33), which was characterised as its hydroxy-derivative (34).

A novel rearrangement was observed with the acylimines (19) and (29). Treatment of either with aluminium chloride in nitromethane did not effect the expected intramolecular cyclisation to an indolic derivative but gave, in low yields, the alcohol (35). A possible path (Scheme 5) for these is indicated, hydrolysis of intermediates such as (36) occurring during isolation. A similar rearrangement was also observed when the methoxy-acetate (14) was treated with methanolic N-hydrogen chloride. The major product was the hydrolysed material (37) but, from the mother liquors, a small quantity of the 6-methoxy-derivative (38) was isolated. Again a pyrazine-type intermediate must be involved (*cf.* Scheme 5).



SCHEME 5



(37)

Since pyrazine-type intermediates should also be formed under basic conditions, treatment of the chlorinated acylimine (29) with an equivalent of sodium methoxide in anhydrous tetrahydrofuran was attempted. After work-up, preparative t.l.c. afforded the expected 6-methoxy-compound (38) as the major product (38%). These rearrangements are reminiscent of some intramolecular redox reactions encountered with certain azlactones.[13]

EXPERIMENTAL

General experimental details were as reported in the previous paper.[1] TFA refers to trifluoroacetic acid.

(A) *Oxidations with Singlet Oxygen.*—1-*Methylpiperazine*-2,3,5-*trione* (3).—(*Z*)-3-Benzylidene-1-methylpiperazine-2,5-dione (2) (0.43 g) in dichloromethane (15 ml) containing Methylene Blue (2 mg) was irradiated with a 350 W tungsten lamp at room temperature while dry oxygen was passed through the solution. After 60 h the precipitate was collected to afford *compound* (3) (0.21 g, 76%), m.p. (from acetone) 201—202°, $\nu_{max.}$ 2 170, 3 090, 1 725, 1 690, 1 505, 1 450, 1 410, 1 380, 1 340, 1 295, 1 228, 995, 840, 815, 790, and 675 cm^{-1}, τ (TFA) 2.97br (1 H, s), 5.80 (2 H, s), and 7.18 (3 H, s) (Found: C, 42.1; H, 4.4; N, 19.9. $C_5H_6N_2O_3$ requires C, 42.3; H, 4.3; N, 19.7%).

The filtrates were evaporated and the resulting oil triturated with light petroleum to give benzaldehyde (spectral comparison); the residue, which gave a positive starch–iodide test, was shown to consist of the intermediate dioxetan (4), τ 2.60 (5 H, s), 3.00br (1 H, s), 4.80 (1 H, s), 6.44 and 7.48 (2 H, ABq, J 19 Hz), and 7.30 (3 H, s). The compound slowly decomposed into the trione (3) and benzaldehyde.

Reaction with the (E)-*isomer* (5a). The (*E*)-isomer [96 mg; prepared from the (*Z*)-isomer by photoisomerisation] in dichloromethane (10 ml) containing Methylene Blue (1 mg) was photo-oxygenated at room temperature for 24 h. Work-up as above gave the crystalline trione (3) (46 mg; 76%) and a residue containing benzaldehyde and the dioxetan (4).

Methylation of the benzylidenepiperazinedione (7). The piperazinedione (432 mg) in benzene (40 ml) was stirred with freshly prepared silver carbonate (700 mg) and methyl iodide (5 ml), for 7 days in the dark. The mixture was filtered, the filtrate evaporated, and the residue chromatographed through silica (70 g) (elution with 1 : 4 acetone–hexane). The first band afforded was (Z)-*benzylidene*-3,6-*dihydro*-1-*methyl*-5-*methoxypyrazine*-2(1H)-*one* (7) (193 mg, 42%) isolated as plates, m.p. 149° (from hexane), $\nu_{max.}$ 1 665, 1 610, 1 595, 1 500, 1 440, 1 400, 1 378, 1 275, 1 250, 1 210, 1 015, and 930 cm^{-1}, τ 1.95 (2 H, m), 2.63 (3 H, m), 268 (1 H, s), 5.90 (2 H, s), 6.08 (3 H, s), and 6.97 (3 H, s), $\lambda_{max.}$ (EtOH) 220, 224, 231, 295, 307, and 320 nm (ε 11 500, 13 500, 12 000, 27 000, 32 500, and 23 000) (Found: C, 67.65; H, 6.3; N, 12.1. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%).

The second band gave (Z)-3-*benzylidene*-1,4-*dimethylpiperazine*-2,5-*dione* (8) (113 mg, 25%), prisms from hexane, m.p. 122°, $\nu_{max.}$ 1 685, 1 665, 1 625, 1 450, 1 425, 1 370, 1 315, 1 295, 1 240, 1 225, 1 210, and 988 cm^{-1}, τ 2.60 (5 H, s), 2.67 (1 H, s), 5.87 (2 H, s), 6.99 (3 H, s), and 7.10 (3 H, s), $\lambda_{max.}$ 224 and 289 nm (ε 21 000 and 29 000) (Found: C, 68.0; H, 5.95; N, 12.4. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%).

No oxidation of the imino-ether occurred with singlet oxygen under the conditions described above.

The *N*-methylamide (8) underwent oxidation to benzaldehyde and a compound possessing spectra compatible with the expected trione structure (9), but the latter decomposed on attempted purification by t.l.c.

Preparation and reaction of (Z)-3-*benzylidene*-1,6-*dimethylpiperazine*-2,5-*dione* (10). 1,6-Dimethylpiperazine-2,5-dione (5.2 g) and anhydrous sodium acetate (3.8 g) in acetic anhydride (15 ml) were heated at 100 °C for 90 min. The cooled mixture was poured into water (100 ml) and stirred until homogeneous. The solute was extracted with dichloromethane (2 × 100 ml), the extracts were washed with water (50 ml), and solid sodium carbonate was added until all the acetic acid was neutralised. Drying and evaporation afforded a crystalline solid (6.3 g, 90%) which (from ether) gave prisms of 4-*acetyl*-1,6-*dimethylpiperazine*-2,5-*dione*, m.p. 78—79°, $\nu_{max.}$ 1 720, 1 700, 1 665, 1 505, and 1 465 cm^{-1}, τ 5.17 and 5.98 (2 H, ABq, J 18 Hz), 5.93 (1 H, q,

[13] M. Bergmann, V. Schmidt, and A. Mickeley, *Z. physiol. Chem.*, 1930, **187**, 264.

J 7 Hz), 6.98 (3 H, s), 7.41 (3 H, s), and 8.44 (3 H, d, *J* 7 Hz) (Found: C, 52.0; H, 6.45; N, 15.1. $C_8H_{12}N_2O_3$ requires C, 52.2; H, 6.6; N, 5.2%).

This compound (0.92 g) was dissolved in dry dimethylformamide (10 ml) under nitrogen and benzaldehyde (1.1 ml) and potassium t-butoxide (0.56 g) in t-butyl alcohol (10 ml) were added dropwise over 45 min. The pale yellow solution was stirred at room temperature for a further 6 h then neutralised with acetic acid (0.5 ml) and poured into water (100 ml). The solution was washed with light petroleum (50 ml) and then extracted with ethyl acetate (2 × 100 ml). The extract was washed with dilute sodium hydrogen sulphite solution (2 × 50 ml), saturated sodium hydrogen carbonate solution (50 ml), then water (50 ml). Isolation of the organic product by chromatography through silica gel gave, with benzene as eluant, (Z)-3-*benzylidene*-1,6-*dimethylpiperazine* (10) (0.45 g, 40%) as needles (from ethanol–petroleum), m.p. 106°, $\nu_{max.}$ 3 170, 3 080, 1 690, 1 668, 1 630, 1 500, 1 460, 1 450, and 1 400 cm^{-1}, τ 1.95br (1 H, s), 2.60br (5 H, s), 2.95 (1 H, s), 5.94 (1 H, q, *J* 7 Hz), 6.92 (3 H, s), and 8.42 (3 H, d, *J* 7 Hz), $\lambda_{max.}$ 224 and 296 nm (ε 16 000 and 24 000) (Found: C, 68.05; H, 6.1; N, 12.4. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%).

Reaction of the benzylidene product (100 mg) in dichloromethane (100 ml) with singlet oxygen (Methylene Blue as sensitiser) at room temperature for 24 h gave, after removal of benzaldehyde by light petroleum, a mixture of the trione (12) and the dioxetan (11), τ 2.73 (5 H, s), 3.00br (1 H, s), 4.82 (1 H, s), 6.83 (1 H, q, *J* 7 Hz), 7.20 (3 H, s,) and 8.52 (3 H, d, *J* 7 Hz). Preparative t.l.c. (1 : 19 MeOH–$CHCl_3$) gave 1,6-dimethylpiperazine-2,3,5-trione (12) (43 mg, 65%) as an oil, $\nu_{max.}$ (film) 3 195, 3 090, 3 000—2 820, 1 720, 1 680, 1 450, and 1 410 cm^{-1}, τ 2.68 (1 H, s), 5.71 (1 H, q, *J* 7 Hz), 6.90 (3 H, s), and 8.31 (3 H, d, *J* 7 Hz), *m/e* 156 (M^+).

(B) *Oxidations with Lead*(IV) *Acetate*.—3-*Acetoxy*-3-(α-*acetoxybenzyl*)-1-*methylpiperazine*-2,5-*dione* (13). The piperazinedione (2) (1.08 g) and lead(IV) acetate (2.12 g) in anhydrous benzene (50 ml) were stirred at room temperature for 1 h. The lead(II) acetate was filtered off and the filtrate evaporated. A solution of the residue in dichloromethane (100 ml) was washed with water (30 ml), dried, and evaporated to give *compound* (13), m.p. (from ether) 140—144° (decomp.), $\nu_{max.}$ 3 190, 3 080, 1 755, 1 690, 1 460, 1 425, 1 380, 1 335, 1 230, 1 198, 1 090, and 1 045 cm^{-1}, τ 2.38br (1 H, s), 2.67 (5 H, s), 3.65 (1 H, s), 6.10 and 6.77 (2 H, ABq, *J* 19 Hz), 7.38 (3 H, s), 7.83 (3 H, s), and 7.88 (3 H, s) (Found: C, 57.4; H, 5.5; N, 8.2. $C_{16}H_{18}N_2O_6$ requires C, 57.5; H, 5.4; N, 8.4%).

The oxidation of the benzylidene derivative (2) (0.22 g) and lead(IV) acetate (0.56 g) in 1 : 19 methanol–benzene (20 ml) was over in 15 min at room temperature. Isolation of the product in the normal manner gave 3-(α-*acetoxybenzyl*)-1-*methyl*-3-*methoxypiperazine*-2,5-*dione* (14) (0.28 g, 92%), m.p. (from acetone–light petroleum) 198—201° (decomp.), $\nu_{max.}$ 3 180, 3 060, 1 745, 1 680, 1 455, 1 430, 1 420, 1 405, 1 370, 1 320, 1 230, 1 190, 1 100, 1 045, and 1 000 cm^{-1}, τ 2.43br (1 H, s), 2.68br (5 H, s), 3.78 (1 H, s), 6.38 and 7.37 (2 H, ABq, *J* 18 Hz), 6.68 (3 H, s), 7.32 (3 H, s), and 7.83 (3 H, s) (Found: C, 58.7; H, 5.8; N, 9.05. $C_{15}H_{18}N_2O_5$ requires C, 58.8; H, 5.9; N, 9.15%).

When the piperazinedione (2) (108 mg) was oxidised with lead(IV) acetate (225 mg) in neat methanol (5 ml), the reaction took 5 min. ^1H N.m.r. analysis of the product showed the presence of a 1 : 1 mixture of the methoxy-acetate (14) and a new product. The latter was isolated by preparative t.l.c. (1 : 19 MeOH–$CHCl_3$) to give 3-*methoxy*-3-(α-*methoxybenzyl*)-1-*methylpiperazine*-2,5-*dione* (20) (42 mg, 30%), m.p. (from acetone–light petroleum) 200—202° (decomp.), $\nu_{max.}$ 3 230, 3 100, 1 670, 1 460, 1 440, 1 410, 1 320, 1 275, 1 183, and 1 100 cm^{-1}, τ 2.58br (5 H, s), 3.32br (1 H, s), 5.23 (1 H, s), 6.40 and 7.37 (2 H ABq, *J* 18 Hz), 6.57 (3 H, s), 6.65 (3 H, s), and 7.37 (3 H, s) (Found: C, 60.4; H, 6.4; N, 10.0. $C_{14}H_{18}N_2O_4$ requires C, 60.4; H, 6.5; N, 10.1%).

(C) *Reactions of the Oxidation Products*.—*Acid-catalysed reactions of the diacetate* (13). (i) The diacetate (0.33 g) in dichloromethane (20 ml) containing boron trifluoride–ether complex (0.5 ml) and methanol (3 ml) was stirred at room temperature for 30 min. The solution was washed with water (10 ml), dried, and evaporated to yield a crystalline solid (0.30 g, 100%) identical with the methoxy-acetate (14).

(ii) The diacetate (0.33 g) in dichloromethane (20 ml), boron trifluoride–ether (0.5 ml), and water (5 ml) were stirred at room temperature for 1 h. The organic phase was separated, dried, and evaporated to yield prisms of 3-(α-*acetoxybenzyl*)-3-*hydroxy*-1-*methylpiperazine*-2,5-*dione* (15), m.p. 158—161° (decomp.), $\nu_{max.}$ 3 190, 3 090, 1 745, 1 665, 1 460, 1 375, 1 325, 1 230, 1 125, 1 060, 1 045, 825, 795, 750, and 710 cm^{-1}, τ 2.57 (5 H, s), 3.25br (1 H, s), 3.80 (1 H, s), 5.58br (1 H, s), 6.44 and 7.31 (2 H, ABq, *J* 19 Hz), 7.22 (3 H, s), and 7.77 (3 H, s) (Found: C, 57.8; H, 5.75; N, 9.7. $C_{14}H_{16}N_2O_5$ requires C, 57.5; H, 5.5; N, 9.6%).

(iii) The diacetate (1.67 g) in dichloromethane (40 ml) containing boron trifluoride–ether complex (0.3 ml) was stirred while a slow stream of hydrogen sulphide was passed through the solution for 1 h. The solvent was evaporated off and the residue redissolved in dichloromethane (50 ml); the solution was washed with water (20 ml), dried, and evaporated to yield a foam (1.54 g, 100%). Crystallisation (from acetone–light petroleum) gave 3-(α-*acetoxybenzyl*)-3-*mercapto*-1-*methylpiperazine*-2,5-*dione* (16), m.p. 170—173°, $\nu_{max.}$ 3 195, 3 080, 2 510, 1 745, 1 680, 1 460, 1 415, 1 375, 1 320, 1 238, 1 050, 940, 810, 720, 710, and 625 cm^{-1}, τ 2.38br (1 H, s, exchanged by D_2O), 2.60br (5 H, s), 3.63 (1 H, s), 6.23 and 7.05 (2 H, ABq, *J* 18 Hz), 6.62 (1 H, s, exchangeable), 7.25 (3 H, s), and 7.77 (3 H, s) (Found: C, 54.7; H, 5.5; N, 8.9. $C_{14}H_{16}N_2O_4S$ requires C, 54.5; H, 5.2; N, 9.1%).

(iv) The diacetate (167 mg) in 1 : 1 ether–dichloromethane (15 ml) and boron trifluoride–ether complex (0.1 ml) was treated with anhydrous ethereal hydrogen peroxide (10% w/v; 5 ml) and the solution was stirred at room temperature for 1 h. The solvents were evaporated off and the residue dissolved in dichloromethane (20 ml); the solution was washed with water (cooled), dried, and evaporated to give fine needles of 3-(α-*acetoxybenzyl*)-3-*hydroperoxy*-1-*methylpiperazine*-2,5-*dione* (17) (146 mg, 95%), m.p. 135—137°, $\nu_{max.}$ 3 190, 3 110, 1 760, 1 675, 1 460, 1 378, 1 342, 1 220, 1 082, 1 040, 1 035, and 950 cm^{-1}, τ (TFA) 2.70 (5 H, s), 3.73 (1 H, s), 6.10 and 7.00 (2 H, ABq, *J* 20 Hz), 7.30 (3 H, s), and 7.80 (3 H, s) (Found: C, 54.55; H, 5.2; N, 9.0. $C_{14}H_{16}N_2O_6$ requires C, 54.5; H, 5.2; N, 9.1%). The compound gave the expected, strongly positive starch–iodide test.

Reactions of the thiol (16). The thiol (154 mg) in dry tetrahydrofuran (5 ml) was stirred with sodium hydride (20 mg) under nitrogen. After the initial release of gas a yellow solution was formed, turning, over 2 h, to a deep red. After a further 10 h the solution was poured into dichloro-

methane (20 ml) and washed with water (*not* acid), which removed most of the colour. Drying and evaporation of the organic phase gave the 3-benzylidene derivative (2) (110 mg, 100%), identical with an authentic sample.

A further sample of the thiol (1.5 g) was alkylated with methyl iodide (25 ml) in acetone (50 ml) containing suspended potassium carbonate (2.50 g). Normal work-up and crystallisation from acetone–light petroleum gave prisms of 3-(α-*acetoxybenzyl*)-1-*methyl*-3-*methylthiopiperazine*-2,5-*dione* (26) (1.45 g, 90%), m.p. 176—178°, $\nu_{max.}$ 3 190, 3 100, 1 755, 1 690, 1 666, 1 495, 1 455, 1 405, 1 372, 1 313, 1 225, 1 172, and 1 047 cm^{-1}, τ 1.98br (1 H, s), 2.57br (5 H, s), 3.55 (1 H, s), 6.13 and 6.92 (2 H, ABq, *J* 18 Hz), 7.23 (3 H, s), 7.70 (3 H, s), and 7.78 (3 H, s) (Found: C, 55.9; H, 5.8; N, 8.7; S, 10.0. $C_{15}H_{18}N_2O_4S$ requires C, 55.9; H, 5.6; N, 8.7; S, 9.95%).

Oxidation of the methyl sulphide (26) (161 mg) with *m*-chloroperbenzoic acid (123 mg, 70% pure) in dichloromethane (6 ml) gave, by usual work-up, the hydroxy-acetate (15) (61 mg, 40%).

Reactions of the hydroperoxide (17). The reaction of the piperazinedione (23 mg) in trifluoroacetic acid (0.7 ml) was followed by n.m.r. spectroscopy. After 4 h (30 °C) only resonances for the starting material (40%), the piperazinetrione (3) (60%), benzaldehyde, and acetic acid were detected. After 20 h the solvent was evaporated off, the residue triturated with ether, and the solid trione (10.6 mg; 100%) isolated. A suspension of the piperazinedione (77 mg) and sodium hydride (6 mg) in dry tetrahydrofuran (2 ml) was stirred at room temperature for 20 h, after which it gave a negative starch–iodide test. The mixture was poured into dichloromethane (20 ml) and neutralised with N-hydrochloric acid (0.25 ml) in water (5 ml), and the aqueous phase was back-extracted with dichloromethane (10 ml). The combined extracts were dried and evaporated, and the residue was triturated with ether, to remove the benzoyl compounds, affording the hydroxy-acetate (15) (17 mg, 23%). The aqueous fraction was evaporated to dryness and the residue triturated with hot acetone. Filtration removed the inorganic material and the acetone was evaporated off to leave the piperazinetrione (3) (27 mg, 75%).

Reaction of the hydroxy-acetate (15) *with thionyl chloride.* The piperazinedione (26 mg) was added to deuteriochloroform (1 ml) and thionyl chloride (0.2 ml). Dissolution was effected in 15 min and, after 90 min, all the alcohol had reacted (n.m.r. assay). Evaporation of the solvent and excess of thionyl chloride gave a mixture (8 : 5) of the 3-chloropiperazinedione (28), τ 1.70br (1 H, s), 2.63 (5 H, s), 3.38, (1 H, s), 5.89 and 6.48 (2 H, ABq, *J* 19 Hz), 7.12 (3 H, s), and 7.79 (3 H, s), and the 3-acetoxybenzylpyrazinedione (19), τ 2.45 (5 H, s), 3.47 (1 H, s), 5.78 and 5.98 (2 H, ABq, *J* 18 Hz), 6.87 (3 H, s), and 7.90 (3 H, s), as an oil. A similar mixture was also prepared by treatment of the methylthio-derivative (26) with t-butyl hypochlorite in dichloromethane at room temperature.

The freshly prepared mixture was treated as follows. (i) Reaction with methanol for 10 min at room temperature gave, after evaporation, a quantitative yield of the methoxy-acetate (14). (ii) Treatment with pyridine at room temperature gave a deeply coloured solution and an intractable foam. (iii) The mixture (from 146 mg of the hydroxy-acetate) in dichloromethane (10 ml) containing boron trifluoride–ether complex (0.1 ml) was stirred at room temperature for 1 week. Work-up in the normal manner afforded only the hydroxy-acetate (15) (90 mg, 63%).

(D) *Reaction of the Piperazinedione* (2) *with t-Butyl Hypochlorite.*—The piperazine (0.54 g) in dichloromethane (25 ml) was treated with t-butyl hypochlorite (2 ml) at room temperature for 1 h. Evaporation afforded 3-(α chlorobenzyl)-5,6-dihydro-1-methylpyrazine-2,5-dione (29) (0.63 g, 100%) as a yellow glass, $\nu_{max.}$ ($CHCl_3$) 1 745, 1 680, 1 620, 1 455, 1 410, 1 320, 1 260, 1 155, and 695 cm^{-1}, τ 2.5 (5 H, m), 3.45 (1 H, s), 5.70 (3 H, s), and 7.00 (3 H, s), $\lambda_{max.}$ (tetrahydrofuran) 232, 250sh, 274, and 378 nm.

Reactions of the acylimine (29). (i) On treating the acylimine (125 mg) with methanol at room temperature for 15 min the pale yellow colour was quickly discharged and evaporation afforded a white solid (140 mg) (100%). Crystallisation from methanol gave 3-(α-*chlorobenzyl*)-3-*methoxy*-1-*methylpiperazine*-2,5-*dione* (31), m.p. 199—202° (decomp.), $\nu_{max.}$ 3 190, 3 080, 1 680, 1 445, 1 415, 1 380, 1 324, 1 275, 1 205, 1 180, 1 100, 1 065, 1 000, and 985 cm^{-1}, τ (TFA) 1.90br (1 H, s), 2.78 (5 H, s), 4.70 (1 H, s), 6.36 and 7.54 (2 H, ABq, *J* 19 Hz), 6.78 (3 H, s), and 7.45 (3 H, s) (Found: C, 55.3; H, 5.4; Cl, 12.7; N, 10.0. $C_{13}H_{15}ClN_2O_3$ requires C, 55.2; H, 5.35; Cl, 12.5; N, 9.9%). The same compound was formed quantitatively by oxidation of the benzylidene compound (2) with t-butyl hypochlorite in methanol at room temperature for 1 h.

(ii) Stirring the acylimine (29) (125 mg) with acetone (2 ml) containing water (0.1 ml) discharged the yellow colour immediately and gave a white precipitate, which was collected and dried (132 mg, 100%). Crystallisation from acetone gave 3-(α-*chlorobenzyl*)-3-*hydroxy*-1-*methylpiperazine*-2,5-*dione* (30), m.p. 207—208° (decomp.), $\nu_{max.}$ 3 330, 3 240, 3 080, 1 690, 1 670, 1 452, 1 415, 1 380, 1 330, 1 270, 1 238, 1 192, 1 125, 1 100, 1 040, 935, and 865 cm^{-1}, τ (TFA) 2.78 (5 H, s), 4.73 (1 H, s), 6.53 and 7.48 (2 H, ABq, *J* 19 Hz), and 7.38 (3 H, s) (Found: C, 53.5; H, 4.9; Cl, 13.2; N, 10.4. $C_{12}H_{13}ClN_2O_3$ requires C, 53.6; H, 4.9; Cl, 13.2; N, 10.4%).

(iii) The acylimine (29) (1.25 g) in dichloromethane (30 ml) containing boron trifluoride–ether complex (0.5 ml) was left at room temperature for 3 days. The solution was washed with water (15 ml), dried, and evaporated to give a pale yellow solid (1.25 g, 100%). Crystallisation from acetone–light petroleum gave (E)-3-(α-*chlorobenzylidene*)-1-*methylpiperazine*-2,5-*dione* (32), m.p. 179—180°, $\nu_{max.}$ 3 220, 1 705, 1 675, 1 610, 1 598, 1 465, 1 435, 1 385, 1 323, 1 307, 1 225, 962, 885, 830, 765, 740, and 695 cm^{-1}, τ 1.80br (1 H, s), 2.60 (5 H, s), 5.83 (2 H, s), and 7.05 (3 H, s), $\lambda_{max.}$ 223.5 and 259 nm (ε 29 000 and 28 000) (Found: C, 57.5; H, 4.6; Cl, 14.1; N, 11.4. $C_{12}H_{11}ClN_2O_2$ requires C, 57.5; H, 4.4; Cl, 14.1; N, 11.2%).

The piperazine (32) (125 mg) in dry dichloromethane (5 ml) was treated with t-butyl hypochlorite (0.5 ml) at room temperature for 20 h. The solution was evaporated to dryness to give, as a yellow foam, crude 3-(αα-dichlorobenzyl)-1-methyl-5,6-dihydropyrazine-2,5-dione (33) τ 2.1—2.7 (5 H, m), 5.58 (2 H, s), and 7.00 (3 H, s). This material was characterised as its adduct with water as follows. The acylimine was stirred with acetone (3 ml) containing water (1 ml) for 20 min during which time the yellow colour was discharged. Work-up in the usual manner afforded 3-(αα-*dichlorobenzyl*)-3-*hydroxy*-1-*methylpiperazine*-2,5-*dione* (34) (98 mg, 66%), m.p. 210—213° (decomp.), $\nu_{max.}$ 3 270, 1 670, 1 455, 1 382, 1 330, 1 260, 1 190, 1 143, 1 124, 829, 804, 750, 705, and 670 cm^{-1}, τ 2.17 (2 H, m), 2.50 (3 H, m), 3.30br (1 H, s), 4.95br (1 H, s), 6.38 and 7.03 (2 H, ABq, *J* 18 Hz), and 7.08 (3 H, s) (Found: C, 47.5;

H, 4.1; Cl, 23.5; N, 9.1. $C_{12}H_{12}Cl_2N_2O_3$ requires C, 47.55; H, 4.0; Cl, 23.4; N, 9.2%).

(E) *Rearrangements leading to 6-Substituted Pyrazines.—Reactions with aluminium chloride.* (i) A mixture of the acylimine (19) and the chloro-compound (28) [from the hydroxy-acetate (146 g); see above] in dry nitromethane (8 ml) was treated with aluminium chloride (100 mg) with stirring at room temperature for 5 days. The solution was poured into dichloromethane (20 ml) and the resulting solution was washed with water (10 ml), dried, and evaporated to give, by preparative t.l.c. (1 : 19 MeOH–$CHCl_3$) the hydroxy-acetate (2) (33 mg, 16%) and (Z)-3-*benzylidene*-6-*hydroxy*-1-*methylpiperazine*-2,5-*dione* (35) (12 mg, 10%), m.p. 148—149° (ether), $\nu_{max.}$ 3 225, 1710, 1 680, 1 625, 1 452, 1 395, 1 360, 1 295, 1 262, 1 212, 1 030, 855, 765, and 692 cm^{-1}, τ 1.90br (1 H, s), 2.62br (5 H, s), 2.88 (1 H, s), 4.78br [2 H, s; collapsed to a sharp singlet (1 H) on exchange], and 6.85 (3 H, s), *m/e* 232 (M^+, 100%), 216 (6), 215 (4), 187 (14), 143 (8), 119 (22), 118 (14), 117 (41), 116 (8), 91 (8), 90 (14), and 89 (11).

(ii) A similar reaction with the chloro-acylimine (29) (125 mg) in nitromethane (3 ml) and aluminium chloride (40 mg), gave, after 3 days at room temperature, the chlorobenzylidene derivative (32) (24 mg, 20%), the hydroxychlorobenzyl compound (30) (16 mg, 12%), and the 3-benzylidene-6-hydroxypiperazinedione (35) (21 mg, 17%).

Reaction of the chloroacylimine (29) *with sodium methoxide.* The acylimine (250 mg) in dry tetrahydrofuran (10 ml) was stirred with sodium methoxide (54 mg) at room temperature for 2 h. The deep red solution was poured into 0.05N-hydrochloric acid (20 ml) and extracted with dichloromethane (2 × 30 ml), and the extracts were dried and evaporated to yield an orange oil. Preparative t.l.c. (1 : 19 MeOH–$CHCl_3$) gave (Z)-3-*benzylidene*-6-*methoxy*-1-*methylpiperazine*-2,5-*dione* (38) (93 mg, 38%), an oil, $\nu_{max.}$ (film) 3 220, 3 000—2 840, 1 710, 1 680, 1 450, 1 405, 1 350, 1 290, 1 255, 1 200, 1 020, 858, 765, and 690 cm^{-1}, τ 2.03br (1 H, s), 2.57br (5 H, s), 2.85 (1 H, s), 5.25 (1 H, s), 6.47 (3 H, s), and 6.83 (3 H, s), *m/e* 246 (M^+, 100%), 215 (8), 188 (11), 187 (78), 160 (11), 149 (23), 119 (9), 118 (25), 115 (13), 91 (9), 90 (32), and 89 (25).

The 6-methoxy-derivative (38) was also obtained by treatment of the methoxy-acetate (14) (206 mg) with methanolic 0.5N-hydrochloric acid (15 ml) for 2 days at room temperature. Work-up in the usual manner followed by preparative t.l.c. gave the 6-methoxy-compound (15 mg, 6%) as well as the hydrolysis product 3-(α-*hydroxybenzyl*)-3-*methoxy*-1-*methylpiperazine*-2,5-*dione* (37) (202 mg, 70%), m.p. 215—218° (decomp.) (from acetone), $\nu_{max.}$ 3 420, 3 200, 3 070, 1 690, 1 660, 1 455, 1 435, 1 415, and 1 380 cm^{-1}, τ 2.78 (5 H, s), 3.40br (1 H, s), 4.67 (1 H, s), 4.77 (1 H, s), 6.45 and 7.48 (2 H, ABq, *J* 19 Hz), 6.63 (3 H, s), and 7.27 (3 H, s) (Found: C, 59.2; H, 5.85; N, 10.6. $C_{13}H_{16}N_2O_4$ requires C, 59.1; H, 6.1; N, 10.6%).

We thank the S.R.C. and Lilly Research Centre Ltd., Windlesham, for a CAPS Studentship (to P. J. M.).

[5/1700 *Received*, 3*rd September*, 1975]