Pyrazine Chemistry. Part VII.[1] Oxidations of Piperazine-2,5-diones and Derivatives

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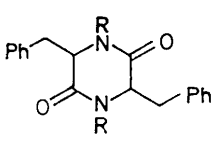
A solution of sulphur in dimethylformamide can act as an oxidant of certain *N*-blocked piperazine-2,5-dione derivatives, resulting in net dehydrogenation. The action of lead tetra-acetate on some representative derivatives of the title compounds has also been investigated, and affords acetoxylated products.

PREVIOUS work in this series has emphasised the importance of oxidised piperazine-2,5-diones as natural products.[1,2] Biosynthetic indications are that these compounds can arise from saturated precursors;[3] this paper summarises some initial oxidations on some model compounds.

Sulphur, which can act as a mild oxidant,[4] was selected because of the known incorporation of this element into the gliotoxin and sporidesmin families of piperazinediones. Simple piperazinediones were inert to the reagent, but activation of the system, by formation of the *NN'*-diacetyl derivative, was effective. Thus the system (1; R = Ac) (as a mixture of *cis*- and *trans*-isomers) reacted with sulphur in dimethylformamide



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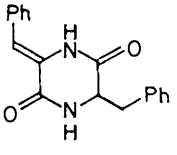

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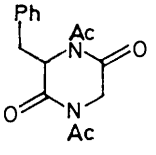

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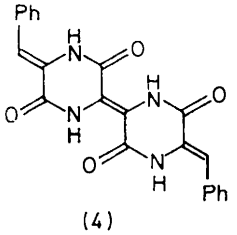

(4)

and triethylamine to form, after hydrolytic removal of the acetyl groups, the monobenzylidene derivative (2). A similar reaction with the acetylated monobenzylpiperazinedione (3) afforded a bright yellow precipitate as the major product. This material showed only the presence of aromatic and olefinic protons in its ^{1}H n.m.r. spectrum and was eventually characterised as the dimeric product (4) from its mass spectral properties (M^+ 400). The chemical shift of the methine protons was characteristic of the *Z*-configuration depicted.[5]

Although the monobenzylidene compound (2) was inert to the sulphur–dimethylformamide reagent, its isomer, the pyrazinediol (5), was rapidly oxidised to give the dibenzylidene derivative (6). In the absence of sulphur the pyrazinediol (5) was merely reconverted into its monobenzylidene derivative (2).

The above reactions complement the recent studies of Schmidt *et al.*,[6] who introduced sulphur into proline anhydride under strongly basic conditions. In our reactions, oxidation can be rationalised in terms of initial introduction of sulphur, for example by electrophilic attack by the enolic form of the substrate, followed by its elimination with net oxidation of the substrate (Scheme 1).

Schmidt *et al.* have also studied the oxidation of *cyclo*-Pro-Pro with lead(IV) acetate in benzene at 50—70 °C.[7] This provided the diacetate (7), a precursor of the tetradehydro-derivative (8). However, *cyclo*-Pro-Pro is particularly prone to oxidation: dichlorodicyanobenzoquinone, for example, reacts with it to form pyrocoll (9).[8] In order to study the scope of lead(IV) acetate oxidations, reactions with some other substrates have also been studied.

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[1] Part VI, P. J. Machin and P. G. Sammes, *J.C.S. Perkin I*, 1974, 698.

[2] P. G. Sammes, *Fortschr. Chem. org. Naturstoffe*, 1975, **32**, 51.

[3] B. W. Bycroft, *Nature*, 1969, **224**, 595; G. W. Kirby and S. Narayanaswami, *J.C.S. Chem. Comm.*, 1973, 322.

[4] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley–Interscience, New York, 1967, p. 1118; H. Wynberg, *J. Amer. Chem. Soc.*, 1958, **80**, 364; R. Mayer and J. Wehl, *Angew. Chem. Internat. Edn.*, 1964, **3**, 705.

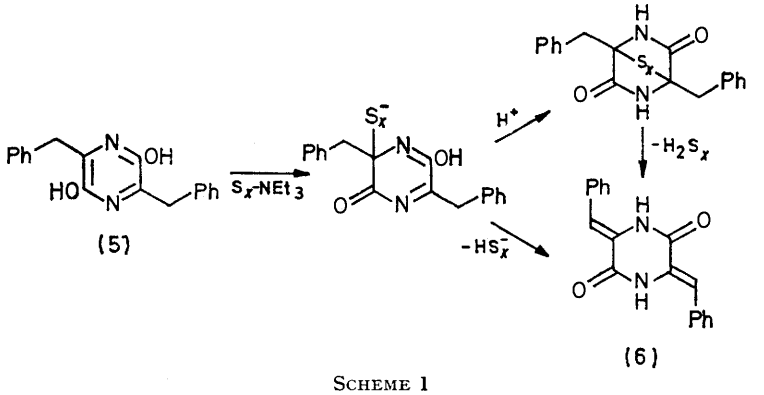
[5] K. W. Blake and P. G. Sammes, *J. Chem. Soc.* (*C*), 1970, 980.

[6] E. Ohler, H. Poisel, F. Tataruch, and U. Schmidt, *Chem. Ber.*, 1972, **105**, 635.

[7] E. Ohler, F. Tataruch, and U. Schmidt, *Chem. Ber.*, 1973, **106**, 396.

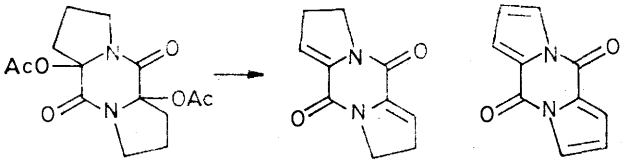
[8] W. J. Hale and W. V. Hoyt, *J. Amer. Chem. Soc.*, 1916, **38**, 1068.

Methylation of *cyclo*-Ala-Ala afforded the corresponding dimethylated product (10) (as a mixture of *cis*- and *trans*-isomers). The system (10) can also be prepared by dehydrative cyclisation of *N*-methylalanine in refluxing ethylene glycol.[9] In contrast to *cyclo*-Pro-Pro, isomeric material precluded a simple assignment of stereochemistry to the product. The structural assignment (11) was mainly based on n.m.r. properties, indicating one quaternary *C*-methyl group (τ 8.15) and an acetoxymethyl group (AB quartet, τ 5.10 and 5.50, J 12

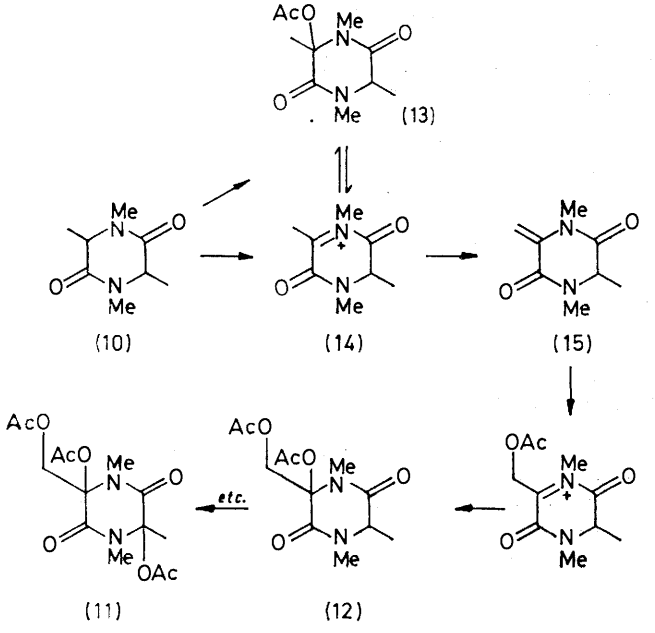


SCHEME 1

treatment of (10) with lead(IV) acetate in benzene gave two products, neither of which corresponded to a diacetate of type (7). The less polar material proved to be a



triacetate. The homogeneous nature of this compound was indicated both by exhaustive chromatographic tests and by its distinct ^{1}H n.m.r. spectrum, proving the presence of only one triacetate isomer. The absence of any



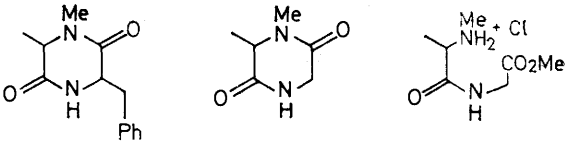
SCHEME 2

Hz). The more polar product was the diacetate (12), again isolated as a single stereoisomer and hence of unknown relative configuration.

The products (11) and (12) must be produced *via* an initial monoacetoxylated product, *e.g.* (13), itself arising either by a free-radical process or, more likely, by oxidation of the corresponding enol, to generate an acyliminium species (14) (Scheme 2) and then the didehydrodipeptide species (15) which are known to be rapidly oxidised by lead(IV) acetate.[10]

Attempts to influence the reaction, either by changing the solvent to acetic acid, or by using acid scavengers, such as anhydrous calcium carbonate or pyridine, resulted in lower yields and, sometimes, even complete inhibition of the acetoxylation.

In an attempt to extend the application of this reaction, the dibenzyl analogue (1; R = Me) was treated



with the oxidant, but no reaction occurred even in 4 days at 80 °C. Mono-*N*-methyl derivatives, such as (16) and (17), also failed to react with lead(IV) acetate.

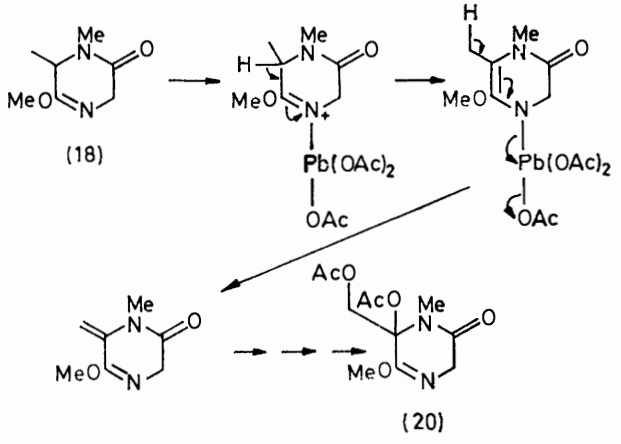
Oxidation of various imino-ether derivatives was also attempted. Earlier work[11] had shown that the presence of this grouping does favour oxidations involving dichlorodicyanobenzoquinone. The mono-(imino-ether) (18), prepared by cyclisation of the ester (19) to give the piperazinedione (17) and then alkylation with

[9] K. D. Kopple and H. C. Ghazarian, *J. Org. Chem.*, 1968, **33**, 862.

[10] P. J. Machin, Ph.D. Thesis, London, 1974; P. J. Machin and P. G. Sammes, following paper.

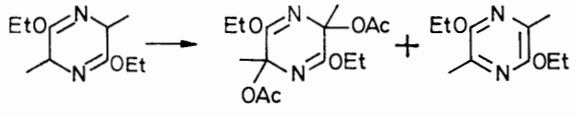
[11] K. W. Blake, A. E. A. Porter, and P. G. Sammes, *J.C.S. Perkin I*, 1972, 2494.

trimethyloxonium tetrafluoroborate, reacted smoothly with lead(IV) acetate at 80 °C to produce, as the major product, the diacetate (20). No evidence for the expected monoacetate, or for oxidation at position 3 could be obtained. Scheme 3 summarises one possible reaction path.



SCHEME 3

The bis-imidate (21) could also be oxidised with the reagent to give two products (ratio 1 : 4). The major product, after recrystallisation from hexane, was a single isomer of the diacetate (22); the minor component was the known diethoxypyrazine (23).



The above oxidations demonstrate the lability of the piperazinedione ring system under appropriate conditions. The enhanced reactivity of the imino-ether derivatives and (with sulphur) the acetylated products, as compared with the relative inertness of the free amide groups, suggests that *in vivo* oxidations of compounds, such as the piperazinediones could involve enzyme-bound intermediates of similar type.

EXPERIMENTAL

M.p.s were recorded with a Kofler hot-stage apparatus. I.r. spectra were recorded with a Unicam SP 200 spectrometer and u.v. spectra with a Unicam SP 800 instrument for solutions in ethanol. ^{1}H N.m.r. spectra were obtained with a Varian T60 instrument, with deuteriochloroform as solvent, unless otherwise stated, and tetramethysilane as internal reference. Mass spectra were obtained with an A.E.I. MS9 instrument. T.l.c. was carried out on Merck silica gel G, generally with acetone–light petroleum or methanol–chloroform. Light petroleum refers to the fraction of boiling range 40—60 °C. All amino-acids used were racemates.

(a) *Oxidations with Sulphur.*—(i) (cis–trans)-1,4-*Diacetyl-3,6-dibenzylpiperazine-2,5-dione.* L-Phenylalanine (10 g) was heated in refluxing ethylene glycol (20 ml) for 24 h. The mixture was cooled in ice and filtered, and the colourless needles were washed with methanol and ether, and then dried to give *cis*-3,6-dibenzylpiperazine (1; R = H) (7.3 g, 82%).[12] A portion (2 g) was suspended in acetic acid (10 ml) and acetic anhydride (10 ml) and then heated to reflux for 5 h. The yellow solution was poured onto ice (100 g) and the precipitate was collected and recrystallised from ether to give a mixture of the *cis*- and *trans*-isomers of the title compound (1; R = Ac), m. range 145—151°, $\nu_{max.}$ 1 712, 1 460, 1 380, 1 222, 1 140, 752, 736, and 694 cm^{-1}, τ 2.60—2.93 (10 H, m), 4.65 (2 H, m), 7.20—7.45 (4 H, m), and 7.48 (6 H, s).

The diacetyl derivative (1; R = Ac) (0.57 g) and sulphur (0.09 g) in dimethylformamide (4 ml) and triethylamine (1 ml) were stirred at 60 °C for 2 h, and then at room temperature overnight. The solution was evaporated to dryness under reduced pressure and the residue treated with methanolic N-potassium hydroxide (25 ml) for 2 h at room temperature. The resulting suspension was acidified and the precipitate collected, washed with water and methanol, and dried, to yield 3-benzyl-6-benzylidenepiperazine-2,5-dione (2) (0.21 g, 48%), identical (m.p. and spectra) with an authentic sample.[13]

(ii) 1,4-*Diacetyl*-3-*benzylpiperazine*-2,5-*dione.* 3-Benzylpiperazine-2,5-dione [14] (16.4 g) was suspended in acetic anhydride (100 ml) and heated to reflux for 2 h. The cooled solution was poured into ice and kept at 0 °C for 4 h. The crude product was filtered off, treated with decolourising charcoal, and recrystallised from aqueous ethanol to give compound (3) (17.7 g, 77%), m.p. 85°, $\nu_{max.}$ 1 725, 1 690, 1 465, 1 405, 1 385, and 1 372 cm^{-1}, τ 2.5—3.0 (5 H, m), 4.52 (1 H, t, *J* 5 Hz), 5.46 and 7.46 (2 H, ABq, *J* 19 Hz), 6.73 (2 H, m), 7.40 (3 H, s), and 7.42 (3 H, s).

The diacetyl compound (3) (1.73 g) and sulphur (0.38 g) in dimethylformamide (14 ml) and triethylamine (4 ml) were stirred at 60 °C for 4 h. The yellow precipitate was filtered off, washed with methanol and chloroform, and dried to give 5,5′-dibenzylidene-2,2′-bipiperazinylidene-3,3′,6,6′-tetraone (4) (0.3 g, 25%), m.p. >320°, $\nu_{max.}$ 3 285, 3 160, 1 660, 1 625, 1 456, 1 390, 985, 760, and 690 cm^{-1}, *m/e* 400 (*M*$^+$, 26%), 399 (100), 371 (10), 228 (12), 227 (10), 118 (40), 117 (28), 91 (24), 90 (14), and 89 (10), τ (CF_3·CO_2H) 2.93—3.21 (m). Yellow needles crystallised from the n.m.r. solution as a *solvate* (Found: C, 56.2; H, 3.9; N, 11.3. $C_{22}H_{16}N_4O_4$,CF_3CO_2H requires C, 56.0; H, 3.3; N, 10.9%).

(iii) 3,6-*Dibenzylpyrazine*-2,5-*diol* (5). The pyrazine (1.0 g) and sulphur (0.22 g) in dimethylformamide (40 ml) containing triethylamine (10 ml) were heated at 60 °C for 2 h with stirring, followed by stirring at room temperature overnight. After cooling, the yellow precipitate was filtered off, washed well with water, and dried *in vacuo* to yield 3,6-dibenzylidenepiperazine-2,5-dione (6) (0.59 g, 60%), m.p. 294—297° (lit.,[13] 298—300°), τ (CF_3·CO_2H) 2.7—3.25 (m), *m/e* 290 (*M*$^+$, 100), 118 (87), 117 (49), 116 (13), 91 (27), 90 (28), and 89 (20). When the reaction was repeated in the absence of sulphur the product isolated was the benzylidene derivative (2).

(b) *Reaction of* cyclo-*Pro-Pro with Dichlorodicyanobenzoquinone* (*DDQ*).—The anhydride (190 mg) and DDQ (227 mg) in benzene (20 ml) were heated at reflux for 5 days. The precipitated quinol was removed and the filtrate evaporated.

[12] K. Bleiku, *Coll. Czech. Chem. Comm.*, 1969, **34**, 4000.
[13] R. Brown, C. Kelly, and S. E. Wibberley, *J. Org. Chem.*, 1965, **30**, 277.
[14] P. J. Machin, A. E. A. Porter, and P. G. Sammes, *J.C.S. Perkin I*, 1973, 404.

The residue was triturated with dichloromethane (5 ml) and the residual crystals (146 mg, 100%) recrystallised from benzene to give yellow plates of pyrocoll (9), m.p. 272° (lit.,[8] 272.5°), $\nu_{max.}$ 3 130, 1 705, 1 560, and 1 460 cm^{-1}, $\lambda_{max.}$ (H_2O) 235, 276, 308, and 322 nm (ε 26 000, 16 000, 14 000, and 15 000).

(c) *Oxidation with Lead*(IV) *Acetate.*—(i) 1,3,4,6-*Tetramethylpiperazine*-2,5-*dione* (10). 3,6-Dimethylpiperazine-2,5-dione (12 g) and dimethyl sulphate (50 ml) were stirred vigorously in water (500 ml) containing potassium hydroxide (20 g) for 16 h. The solution was extracted with dichloromethane (3 × 300 ml), and the extract dried and evaporated to yield a white crystalline solid (5.76 g, 40%), shown by ^1H n.m.r. analysis to be a 1 : 1 mixture of *cis*- and *trans*-isomers of compound (10); m.p. 116°; $\nu_{max.}$ 1 650 and 1 490 cm^{-1} (Found: C, 56.7; H, 8.55; N, 16.4. Calc. for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.3; N, 16.5%).

The product (10) (0.72 g) and lead(IV) acetate (3.78 g) in benzene (50 ml) were heated at reflux for 20 h. The cooled mixture was filtered and the filtrate washed with water (50 ml). Drying and evaporation afforded oily crystals which were triturated with ether to give a white solid (0.2 g). This was separated by preparative t.l.c. (1 : 19 MeOH–$CHCl_3$). The least polar material crystallised from carbon tetrachloride as needles of 3,6-*diacetoxy*-3-*acetoxymethyl*-1,4,6-*trimethylpiperazine*-2,5-*dione* (11) (95 mg, 9%) (single isomer), m.p. 163°, $\nu_{max.}$ 1 768, 1 747, 1 690, 1 452, 1 428, 1 390, 1 372, 1 325, 1 285, 1 218, 1 130, 1 095, 1 076, 992, and 776 cm^{-1}, τ 5.10 and 5.50 (2 H, ABq, *J* 12 Hz), 6.95 (3 H, s), 7.02 (3 H, s), 7.88 (6 H, s), and 8.15 (3 H, s) (Found: C, 48.8; H, 5.8; N, 8.1. $C_{14}H_{20}N_2O_8$ requires C, 48.8; H, 5.9; N, 8.1%).

The more polar band gave 3-*acetoxy*-3-*acetoxymethyl*-1,4,6-*trimethylpiperazine*-2,5-*dione* (12) (80 mg, 9%) as needles, m.p. 166—167° (from light petroleum–acetone), $\nu_{max.}$ 1 740, 1 680, 1 460, 1 395, 1 375, 1 335, 1 315, 1 262, 1 225, 1 155, 1 059, 1 012, 870, and 778 cm^{-1}, τ 5.32 and 5.63 (2 H, ABq, *J* 12 Hz), 5.91 (1 H, q, *J* 7 Hz), 6.97 (3 H, s), 7.10 (3 H, s), 7.88 (3 H, s), 7.93 (3 H, s), and 8.39 (3 H, d, *J* 7 Hz) (Found: C, 50.55; H, 6.4; N, 9.8. $C_{12}H_{18}N_2O_6$ requires C, 50.35; H, 6.3; N, 9.7%).

(ii) 3,6-*Dibenzyl*-1,4-*dimethylpiperazine*-2,5-*dione* (1; R = Me).[15] 3,6-Dibenzylpiperazine-2,5-dione (0.88 g) and sodium hydride (0.28 g of 50% w/w oil dispersion) were stirred in dimethylformamide (5 ml) at room tempeerature for 15 min. The suspension was then cooled and methyl iodide (2 ml) slowly added. The solution was allowed to warm to room temperature before adding water (50 ml) and extraction with dichloromethane (2 × 50 ml). The extract was washed with water, dried, and evaporated to give a solid mixture of the *cis*- and *trans*-isomers (0.72 g, 75%) (ratio 1 : 2) which was used later without further separation. Fractional crystallisation afforded pure *trans*-isomer, m.p. 161° (from acetone–light petroleum), $\nu_{max.}$ 1 645, 1 610, 1 500, 1 460, 1 400, 1 355, 1 340, 1 255, 1 050, and 930 cm^{-1}, τ 3.75 (10 H, m), 5.93 (2 H, dd, *J* 4.5 and 6 Hz), 7.07 (2 H, dd, *J* 4.5 and 15 Hz), 7.25 (6 H, s), and 7.76 (2 H, dd, *J* 6 and 15 Hz). The *cis*-isomer had τ 2.75 (10 H, m), 6.60 (2 H, m), 6.90 (4 H, m), and 7.15 (6 H, s).

Treatment of the mixture of methylated piperazines (1; R = Me) (0.71 g) with lead(IV) acetate (3.5 g) in dry benzene (50 ml) at reflux for 4 days gave, after work-up, mainly starting material (>80%).

(iii) cis- *and* trans-3-*Benzyl*-1,6-*dimethylpiperazine*-2,5-*dione* (16). Prepared by the literature method, the *cis*–*trans*–mixture was essentially unaffected by treatment with lead(IV) acetate in refluxing benzene over 20 h.

(iv) 1,6-*Dimethylpiperazine*-2,5-*dione* (17). *N*-Methylalanylglycine was prepared from glycine and 2-chloropropionyl chloride, followed by amination with methylamine, according to the method previously described for dipeptides.[1] The product (33 g) was esterified with methanol, in the presence of hydrogen chloride. The resulting hydrochloride (19) was liberated with ammonia in dichloromethane and left for 20 h at room temperature to give the piperazinedione (17) (26.7 g, 93%), m.p. 102° (lit.,[16] 105°). Heating this compound with lead(IV) acetate in refluxing benzene gave no reaction during 30 h.

(v) 1,6-*Dimethyl*-5-*methoxy*-3,6-*dihydropyrazin*-2(1H)-*one* (18). The piperazinedione (17) (4.26 g) and trimethyloxonium tetrafluoroborate (6.66 g) were stirred together in dichloromethane (100 ml) at room temperature for 20 h. Work-up in the normal manner afforded the imidate (18) as a mobile oil (2.74 g, 59%), $\nu_{max.}$ (film) 3 000—2 820, 1 700, 1 690, 1 650, 1 500, 1 450, 1 355, 1 275, 1 240, 1 095, and 1 075 cm^{-1}, τ 5.85 (2 H, s), 6.09 (1 H, q, *J* 7 Hz), 6.28 (3 H, s), 7.02 (3 H, s), and 8.58 (3 H, d, *J* 7 Hz). The imidate (0.39 g) and lead(IV) acetate (2.66 g) in benzene (15 ml) were heated under reflux for 20 h. After filtering, the solution was washed with water (25 ml), dried, and evaporated to give 6-*acetoxy*-6-*acetoxymethyl*-1-*methyl*-5-*methoxy*-3,6-*dihydropyrazin*-2(1H)-*one* (20) (134 mg, 25%), m.p. 146—147° (from acetone–light petroleum), $\nu_{max.}$ 1 760, 1 745, 1 715, 1 670, 1 380, 1 280, 1 140, and 1 090 cm^{-1}, τ 5.52 and 5.60 (2 H, ABq, *J* 11 Hz), 5.73 (2 H, s), 6.28 (3 H, s), 7.12 (3 H, s), 7.91 (3 H, s), and 7.98 (3 H, s) (Found: C, 48.8; H, 5.8; N, 10.7. $C_{11}H_{16}N_2O_6$ requires C, 48.5; H, 5.9; N, 10.3%).

(vi) 2,5-*Diethoxy*-3,6-*dihydro*-3,6-*dimethylpyrazine* (21). The imidate (0.9 g) and lead(IV) acetate (5.6 g) in dry benzene (30 ml) were heated under reflux for 20 h. Work-up gave a 1 : 4 mixture (1.22 g) of the known 2,5-diethoxy-3,6-dimethylpyrazine (23),[17] m.p. 77°, and a new diacetate. Recrystallisation from hexane gave needles of 3,6-*diacetoxy*-2,5-*diethoxy*-3,6-*dimethyl*-3,6-*dihydropyrazine* (22) as a discrete isomer, m.p. 136—137°, $\lambda_{max.}$ 1 750, 1 690, 1 460, 1 378, 1 320, 1 265, 1 215, 1 190, 1 090, 960, 920, and 840 cm^{-1}, τ 5.83 (4 H, q, *J* 7 Hz), 7.98 (6 H, s), 8.33 (6 H, s), and 8.77 (6 H, t, *J* 7 Hz) (Found: C, 53.4; H, 6.9; N, 8.8. $C_{14}H_{22}N_2O_6$ requires C, 53.5; H, 7.1; N, 8.9%).

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

[5/1699 *Received*, 3rd *September*, 1975]

[15] M. O. Forster and W. B. Saville, *J. Chem. Soc.*, 1922, 816.
[16] L. Birkofer, A. Ritter, and P. Neuhausen, *Annalen*, 1965, **659**, 190.
[17] R. A. Baxter, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1958, 1859.