Pyrazine Chemistry. Part VI.[1] Addition of Sulphur Nucleophiles across Dehydrocyclodipeptides

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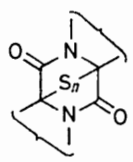
A mild method for the addition of sulphur nucleophiles across the double bonds of dehydrocyclodipeptides is described. The method involves the direct addition of thiols to dehydrocyclodipeptides in the presence of an acid catalyst. Kinetic control affords the α-addition products and this process competes with a slower equilibration leading to the β-adducts. The route to the dehydrocyclodipeptides is detailed.

CURRENT interest in the group of natural products containing the sulphur-bridged piperazinedione system (1), which includes compounds such as gliotoxin,[2] aranotin,[3] and the sporidesmins,[4] has been concerned with chemical



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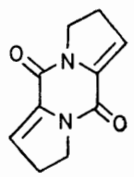

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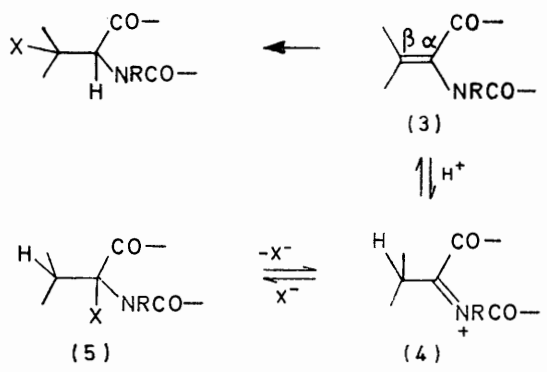
methods for the introduction of sulphur into the α-position of amino-acid derivatives. Although nucleophilic,[5] electrophilic,[6] and indirect oxidative routes,[7] have been utilised for the introduction of sulphur into piperazine-2,5-diones there is a need for a more general method.[8] One possible solution to this problem is to introduce sulphur into the amino-acids prior to formation of the piperazinedione ring. To this end methods for the introduction of sulphur into amino-acid derivatives have been reported,[9] including the indirect conversion of 2-acetamidoacrylic acid derivatives into *N*-acyl-α-mercaptoalanines,[10] but there remains the problem of piperazinedione ring formation. We now report a mild, general method for the introduction of sulphur into dehydrocyclodipeptides [*e.g.* (2)].

Under weakly acidic, neutral, or basic conditions β-addition is expected for the dehydro-system (3) (Scheme).[11] In the presence of strong acids, however, it is known that the weak enamine character of the enamide system (3) promotes β-protonation to produce the ion (4), which can react with nucleophiles to give the α-addition product (5).[12]

For example, monitoring the reaction of **1,3**-dimethyl-6-methylenepiperazine-2,5-dione (6; R = H) with thiolacetic acid in deuteriochloroform by ^{1}H n.m.r. spectroscopy showed that a quantitative yield of the β-addition adducts (7) was formed over 5 days at 25°;



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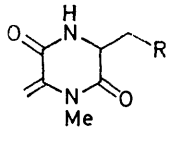
the two isomers were separated by preparative t.l.c. In contrast, when the reaction was repeated in the

[1] Part V, P. J. Machin, A. E. A. Porter, and P. G. Sammes, *J.C.S. Perkin I*, 1973, 404.
[2] M. R. Bell, J. R. Johnson, B. S. Wildi, and R. B. Woodward, *J. Amer. Chem. Soc.*, 1958, **80**, 1001.
[3] N. Nagarajan, L. L. Huckstep, D. H. Lively, D. L. DeLong, M. M. Marsh, and N. Neuss, *J. Amer. Chem. Soc.*, 1968, **90**, 2980.
[4] *Cf.* J. W. Ronaldson, A. Taylor, E. P. White, and R. J. Abraham, *J. Chem. Soc.*, 1963, 3172; W. D. Jamieson, R. Rahman, and A. Taylor, *J. Chem. Soc.* (*C*), 1969, 1564.
[5] P. W. Trown, *Biochem. Biophys. Res. Comm.*, 1968, **33**, 402.
[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] H. C. J. Ottenheym, T. F. Spande, and B. Witkop, *J. Amer. Chem. Soc.*, 1973, **95**, 1989.
[9] P. M. Pojer and I. D. Rae, *Tetrahedron Letters*, 1971, 3077.
[10] S. M. Patel, J. O. Currie, and R. K. Olsen, *J. Org. Chem.*, 1973, **38**, 126.
[11] F. W. Stacey and J. F. Harris, *Org. Reactions*, 1963, **13**, 150.
[12] G. Lucente and D. Rossi, *Chem. and Ind.*, 1973, 324.

presence of a small amount of hydrogen chloride, a rapid reaction ensued (*ca.* 2 h at 25°). ^{1}H N.m.r. analysis showed that none of the β-addition products were formed in this time and that a quantitative yield of the two α-adducts (8; R = H) was obtained and, again, these were isolated by preparative t.l.c.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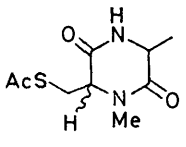
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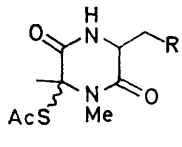
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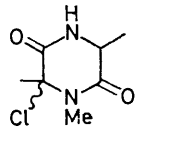
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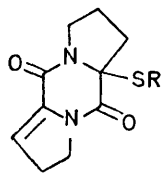
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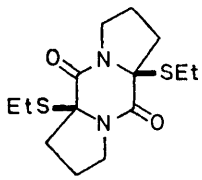
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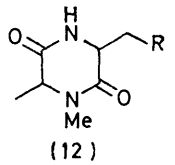
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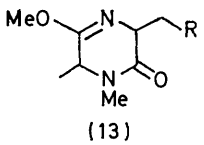
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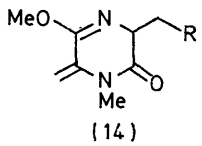
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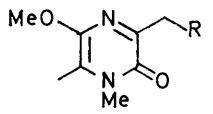
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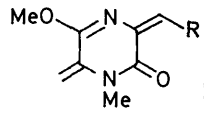
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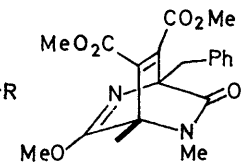
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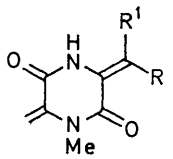
(18)

An attempt was made to preform the chloro-derivatives (9) by saturating a deuteriochloroform solution of the methylene compound (6; R = H) with hydrogen chloride. New resonances, attributed to the chloro-compounds, quickly appeared, but the ratio of these adducts (9) to the starting olefin (6; R = H) (ratio 1 : 4) subsequently remained constant at this value, indicating that an equilibrium had been attained. After 24 h addition of thiolacetic acid to this mixture rapidly consumed the remaining olefin without substantial reaction with the chloro-compounds. Thus, prior conversion of the dehydro-compound (6; R = H) to the chloro-compound before addition of the sulphur nucleophile is not essential.[12]

Similar results were obtained with the piperazinedione (6; R = Ph). In this case ^{1}H n.m.r. analysis showed that the reaction of thiolacetic acid in the presence of hydrogen chloride was complete within 90 min at 25°, giving a 1 : 1 mixture of the *cis*- and *trans*-adducts (8; R = Ph). On leaving the mixture for a further 20 h the ratio of the two isomers changed in favour of the *cis*-isomer (ratio 3 : 1), demonstrating the reversibility of the addition step to the ion (4). Configurational assignments in the phenylalanine series were aided by the observed shielding of the ring methyl substituent by the phenyl group in the ^{1}H n.m.r. spectrum of the *cis*-isomer.[13]

To test the generality of these α-addition reactions it was of interest to use 2,3,7,8-tetrahydrodipyrrolo-[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (bisdehydroproline anhydride) (2), since previous attempts at the α-addition of nucleophiles to this compound had failed.[14] Addition of ethanethiol to compound (2) in the presence of a small amount of hydrogen chloride gave an equilibrium mixture of the monoadduct (10; R = Et) (44%), as a non-crystalline foam, and the known[6] *cis*-bisadduct (11) (30%). When thiolacetic acid was used as reagent, a slower addition ensued to give the monothiolacetate (10; R = Ac). The second addition step was extremely slow and, after several days, a complex mixture of isomeric adducts formed. These results are readily explained in terms of the Scheme. Since thiolacetic acid is a better leaving group than ethanethiol, the set of equilibria only reach predominant formation of the monoadduct (10; R = Ac) before the onset of competing β-addition reactions.

The dehydrocyclodipeptides (6; R = H or Ph) were prepared by an extension of a method reported previously.[1] Alanine, or phenylalanine, was treated with 2-chloropropionyl chloride, followed by reaction with methylamine and heating in ethylene glycol[15] to give the piperazinediones (12; R = H or Ph). Both series afforded *cis–trans*-mixtures of the corresponding piperazinediones but, although the individual isomers could be separated, they were further employed without separation. Although specific structural assignments for the *cis*- and *trans*-isomers in the alanine series could not be readily made, the isomers from the phenylalanine series were again readily differentiated by the presence of the shielding effects caused by the phenyl substituent.[13] Reaction of both series of piperazinediones with trimethyloxonium fluoroborate produced the *cis–trans*-mixtures of the corresponding imino-ethers (13; R = H and Ph).

Oxidation of the freshly prepared alanine derivatives with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) in benzene afforded three products. Monitoring of the oxidation reaction showed that although the *cis*- and

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

[14] E. Ohler, F. Tataruch, and U. Schmidt, *Chem. Ber.*, 1973, **106**, 165.

[15] H. F. Schott, J. B. Larkin, L. B. Rockland, and M. S. Dunn, *J. Org. Chem.*, 1947, **12**, 490.

trans-isomers reacted at slightly different rates, both appeared to give the same products. The major oxidation product was the monodehydro-compound (14; R = H). On hydrolysis with 2N-hydrochloric acid in aqueous tetrahydrofuran this gave the dehydrocyclodipeptide (6; R = H). The other oxidation products were the pyrazinone (15; R = H) and the didehydro-derivative (16), both of which were unstable to storage and, consequently, could not be completely characterised.

A similar oxidation of the imino-ether derived from the phenylalanine series (13; R = Ph) gave rise to analogous oxidation products. The major product was the methylene derivative (14; R = Ph) which was hydrolysed with dilute acid to afford the dehydrocyclodipeptide (6; R = Ph). Also formed was the pyrazinone (15; R = Ph), which was characterised as its dimethyl acetylenedicarboxylate adduct (17).[1] The other product from the oxidation was the didehydro-derivative (16; R = H). That the benzylidene bond in the latter compound had the *E*-configuration was tentatively assigned as follows. Hydrolysis of the imino-ether (16; R = Ph) with dilute hydrochloric acid slowly (5 days) afforded pale yellow prisms of the substituted *E*-piperazinedione (18; R^1 = H, R^2 = Ph), which was only sparingly soluble in deuteriochloroform. Brief treatment with trifluoroacetic acid isomerised this compound into the more stable *Z*-isomer (18; R^1 = Ph, R^2 = H),[16] as colourless needles which were freely soluble in deuteriochloroform. The u.v. spectra of the two isomers, although similar, were consistent with the stereochemical formulation (see Experimental section) since the more stable *Z*-isomers absorb at slightly shorter wavelengths than the corresponding *E*-isomers.[17]

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 a Varian T60 instrument generally with deuteriochloroform as solvent containing tetramethylsilane as internal reference. Mass spectra were obtained on an A.E.I. MS 9 instrument. T.l.c. was carried out using Merck silica gel G, generally with acetone–light petroleum or methanol–chloroform as solvent. Light petroleum refers to the fraction of boiling range 40—60° unless otherwise stated. Thiolacetic acid was distilled directly before use.

Reaction of 1,3-*Dimethyl*-6-*methylenepiperazine*-2,5-*dione* (6; R = H) *with Thiolacetic Acid*.—(a) *Absence of acid catalyst*. The piperazinedione (50 mg) and thiolacetic acid (30 mg) dissolved in deuteriochloroform (1·0 ml) in a stoppered tube were kept at 25° for 4 days, after which no starting material remained. The two products were separated by preparative t.l.c. (1 : 19 MeOH–$CHCl_3$) to afford cis- and trans-6-*acetylthiomethyl*-1,3-*dimethylpiperazine*-2,5-*dione* (7). The more polar isomer afforded prisms (from acetone–light petroleum), m.p. 163—165° (29 mg, 38%), $\nu_{max.}$ (Nujol) 3310, 1690, 1640, 1470, 1460, 1420, 1330, 1320, 1300, 1165, 1135, 960, 765, 695, and 640 cm^{-1}, τ 2·4br (1H, s, NH), 5·80 (2H, m) 6·42 (2H, d, *J* 4 Hz, AcSCH_2), 6·98 (3H, s, NMe), 7·63 (3H, s, Ac), and 8·39 (3H, d, *J* 7 Hz, *Me*CH) (Found: C, 47·1; H, 6·2; N, 12·15; S, 14·2. $C_9H_{14}N_2O_3S$ requires C, 46·9; H, 6·1; N, 12·2; S, 13·9%). The less polar material was isolated as an oil (24 mg, 32%), τ 2·67br (1H, s, NH), 5·8 (2H, m), 6·43 (2H, m, AcSCH_2), 6·98 (3H, s, NMe), 7·63 (3H, s, Ac), and 8·51 (3H, d, *J* 7 Hz).

(b) *With acid catalyst*. The piperazinedione (60 mg) and thiolacetic acid (100 mg) were added to deuteriochloroform (1·0 ml) to which had been added several drops of solvent saturated with anhydrous hydrogen chloride. After 3 h at room temperature the solvent was removed by evaporation and the residue separated by preparative t.l.c. (1 : 19 MeOH–$CHCl_3$) to give cis- and trans-6-*acetylthio*-1,3,6-*trimethylpiperazine*-2,5-*dione* (8; R = H). The more polar material afforded prisms (from acetone–light petroleum) (17 mg, 19%), m.p. 140—143°, $\nu_{max.}$ (Nujol) 3200, 3080, 1685, 1655, 1500, 1460, 1432, 1384, 1370, 1330, 1298, 1270, 1178, 1120, 1070, 990, 954, 842, 790, 755, and 630 cm^{-1}, τ 3·55br (1H, s, NH), 5·73 (1H, q, *J* 6 Hz, MeC*H*), 6·98 (3H, s, NMe), 7·72 (3H, s, Ac), 8·18 (3H, s, Me), and 8·35 (3H, d, *J* 6 Hz, *Me*CH) (Found: C, 47·1; H, 6·2; N, 12·3. $C_9H_{14}N_2O_3S$ requires C, 46·9; H, 6·1; N, 12·2%).

The less polar band gave prisms (from ethyl acetate–light petroleum) (28 mg, 30%), m.p. 114—115°, $\nu_{max.}$ (Nujol) 3200, 3080, 1685, 1665, 1455, 1420, 1390, 1375, 1330, 1320, 1265, 1170, 1160, 1125, 1100, 845, and 640 cm^{-1}, τ 3·45br (1H, s, NH), 5·41 (1H, q, *J* 7 Hz, MeC*H*), 6·98 (3H, s, NMe), 7·72 (3H, s, Ac), 8·12 (3H, s, Me), and 8·48 (3H, d, *J* 7 Hz, *Me*CH) (Found: C, 46·8; H, 6·25; N, 12·1%).

Reaction of 3-*Benzyl*-1-*methyl*-6-*methylenepiperazine*-2,5-*dione* (6; R = Ph) *with Thiolacetic Acid*.—The piperazinedione (58 mg) and thiolacetic acid (100 mg) in deuteriochloroform (1·0 ml) containing dry hydrogen chloride were left at 25° for 1 h, after which time no starting material remained. After a further 20 h the ratio of the two isomeric products had changed from *ca.* 1 : 1 to 3 : 1 (n.m.r. assay) and at this point tended to remain constant. (A complex array of products formed when a sample of the reaction mixture was left for several days, probably due to competing β-addition reactions.) Separation of the products by preparative t.l.c. afforded, as the more more polar band (1 : 19 MeOH–$CHCl_3$), cis-6-*acetylthio*-3-*benzyl*-1,6-*dimethylpiperazine*-2,5-*dione* (8; R = Ph) (37 mg, 49%), m.p. (from acetone–light petroleum) 181—182°, $\nu_{max.}$ (Nujol) 3190, 3060, 1695, 1685, 1665, 1500, 1460, 1390, 1370, 1270, 1245, 1215, 1120, 1095, 960, 868, 850, 792, 760, 720, 700, and 630 cm^{-1}, τ 2·67br (5H, s, Ph), 2·83br (1H, s, NH), 5·28 (1H, t, *J* 5 Hz, C*H*CH$_2$), 6·78 (2H, d, *J* 5 Hz, CHCH_2), 7·10 (3H, s, NMe), 7·75 (3H, s, Ac), and 8·70 (3H, s, Me) (Found: C, 58·6; H, 5·7; N, 9·1; S, 10·3. $C_{15}H_{18}N_2O_3S$ requires C, 58·8; H, 5·9; N, 9·1; S, 10·5%).

The less polar band gave the trans-*isomer* of (8; R = Ph) (18 mg, 23%), m.p. (from ethyl acetate–light petroleum) 124—126°, $\nu_{max.}$ (Nujol) 3190, 3060, 1695, 1685, 1655, 1500, 1450, 1380, 1270, 1120, 1095, 955, 742, 700, and 630 cm^{-1}, τ 2·60 (5H, s, Ph), 3·17br (1H, s, NH), 5·67 (1H, m), 6·30 (2H, m, PhCH_2), 6·92 (3H, s, NMe), 7·67 (3H, s, Ac), and 8·20 (3H, s, Me), *m/e* 306 (M^+, 16%), 305 (82), 263 (100), 231 (58), 203 (40), and 139 (38).

Reaction of 2,3,7,8-*Tetrahydrodipyrrolo*[1,2-a:1′,2′-d]*pyrazine*-5,10-*dione* (2) *with Ethanethiol*.—The proline anhydride (2) [14] (95 mg) and ethanethiol (0·1 ml) in dichloromethane (25 ml) containing dry hydrogen chloride were left at room temperature for 20 h. After evaporation of the solvent the

[16] K. W. Blake and P. G. Sammes, *J. Chem. Soc.* (*C*), 1970, 980.
[17] K. W. Blake, Ph.D. thesis, London University, 1970.

residue was separated by preparative t.l.c. (1 : 19 MeOH–$CHCl_3$). The less polar band was identified by its ^1H n.m.r. spectrum as the known *cis*-5a,10a-diethylthio-derivative (11) (39 mg, 30%). Recrystallisation from hexane afforded clusters of prisms, m.p. 98—100° (lit.,[7] m.p. 98—103°).

The more polar band gave the monoethylthio-adduct (10; R = Et) (47 mg, 44%) as an unstable, non-crystalline foam, $\nu_{max.}$ (film) (300—2860, 1670, 1642, 1420, 1370, 1205, 1010, 915, 735, and 675 cm^{-1}, τ 3·77 (1H, t, *J* 3 Hz), 5·67—6·40 (4H, m), 7·17 (2H, dt, *J* 3, 9 Hz), 7·41 (2H, q, *J* 7 Hz, SCH_2Me), 7·50—8·20 (4H, m), and 8·80 (3H, t, *J* 7 Hz, CH_2Me), *m/e* 252 (M^+, 2%) and 191 (100). All attempts to purify this material further led to its partial decomposition and hence a satisfactory microanalysis could not be obtained.

Reaction of Dipyrrolopyrazine (2) *with Thiolacetic Acid.*—The piperazinedione (190 mg) and thiolacetic acid (200 mg), in deuteriochloroform (2 ml) containing hydrogen chloride, were stirred at room temperature for 4 h. Unchanged starting material (45 mg) was filtered off, the filtrates evaporated, and the residue recrystallised from ethyl acetate to give the major reaction product, 5a-*acetylthio*-2,3,5a,6,7,8-*hexahydrodipyrrolo*[1,2-a:1′,2′-d]*pyrazine*-5,10-*dione* (10; R = Ac) (29 mg, 15%), m.p. 138—141° (decomp.), $\nu_{max.}$ (Nujol) 1690, 1670, 1655, 1460, 1430, 1375, 1358, 1338, 1200, 1115, 1090, 1010, 958, 915, 725, and 630 cm^{-1}, τ 3·72 (1H, t, *J* 3 Hz), 5·93 (2H, t, *J* 9 Hz), 5·68—6·55 (2H, m), 7·18 (2H, dt, *J* 3, 9 Hz), 7·46—8·04 (4H, m), and 7·73 (3H, s, Ac) (Found: C, 54·4; H, 5·5; N, 10·4; S, 11·7. $C_{12}H_{14}N_2O_3S$ requires C, 54·1; H, 5·3; N, 10·5; S, 12·0%). Prolonged reaction times gave lower yields of the monoadduct. ^1H N.m.r. examination of the reaction mixtures indicated the formation of a complex array of products.

Preparation of 1,3,6-*Trimethylpiperazine*-2,5-*dione* (12; R = H).—Alanine (17·8 g) was dissolved in aqueous 1N-NaOH (200 ml) and the solution treated at 0° with 2-chloropropionyl chloride (32 g) and more 1N-NaOH (250 ml) simultaneously over 30 min. After a further 90 min at 0—5° the solution was acidified with 1N-HCl (210 ml). The solution was evaporated to give a sticky white solid which was extracted with acetone, filtered, dried (Na_2SO_4), and evaporated to give a solid (25 g). The crude product was stirred with aqueous methylamine (250 ml, 25% w/w) and stirred at room temperature for 5 days. After removal of water under reduced pressure, the residue was triturated with acetone and then methanol and the resulting solid (10 g) dried. Heating this dipeptide in ethylene glycol at reflux for 16 h, followed by cooling and extraction with dichloromethane (3 × 100 ml), drying ($CaCl_2$) of the extract, filtration, and evaporation gave the piperazinedione (6·7 g, 22% overall) as a colourless solid. A sample was separated by preparative t.l.c. (1 : 9 MeOH–$CHCl_3$). The least polar isomer was assigned as trans-1,3,6-*trimethylpiperazine*-2,5-*dione*, m.p. (from tetrahydrofuran) 96—97°, $\nu_{max.}$ (Nujol) 3190, 3050, 1675, 1635, 1365, 1325, 1300, 1250, 1160, 840, and 770 cm^{-1}, τ 2·78br (1H, s, NH), 5·93 (1H, q, *J* 7 Hz, C*H*Me), 6·11 (1H, q, *J* 7 Hz, MeC*H*), 7·02 (3H, s, NMe), and 8·51 (6H, d, *J* 7 Hz, 2 × *Me*CH) (Found: C, 53·9; H, 7·7; N, 18·2. $C_7H_{12}N_2O_2$ requires C, 53·8; H, 7·7; N, 17·9%).

The more polar material was recrystallised from acetone–light petroleum to give the cis-*isomer*, m.p. 132°, $\nu_{max.}$ (Nujol) 3170, 3080, 1680, 1660, 1375, 1370, 1320, 1250, 1150, 1090, 1050, 835, 820, and 770 cm^{-1}, τ 2·68br (1H, s, NH), 5·89 (1H, dq, *J* 2, 7 Hz, MeC*H*NH), 6·09 (1H, q, *J* 7 Hz), 7·02 (3H, s, NMe), 8·44 (3H, d, *J* 7 Hz, *Me*CH), and 8·49 (3H, d, *J* 7 Hz, *Me*CH) (Found: C, 53·7; H, 7·7; N, 18·1%).

The crude mixture of isomers could be recrystallised from tetrahydrofuran to give a *ca.* 1 : 1 mixture as large prisms.

Preparation of 2-*Benzyl*-1,6-*dimethylpiperazine*-2,5-*dione* (12; R = Ph).—In an analogous manner to that described for the alanine analogue, phenylalanine (33·2 g) was converted into the title compound (13·1 g, 30% overall), obtained as an oily solid, which could be recrystallised from acetone–light petroleum to give a *ca.* 1 : 1 mixture of the *cis*- and *trans*-isomers. A sample was separated by preparative t.l.c. (1 : 19 MeOH–$CHCl_3$). The least polar material was assigned as trans-2-*benzyl*-1,6-*dimethylpiperazine*-2,5-*dione*, m.p. (from acetone–light petroleum) 132—133°, $\nu_{max.}$ (Nujol) 3190, 3060, 1675, 1655, 1400, 1370, 1340, 1310, 1205, 1180, 1078, 1040, 868, 860, 760, 747, and 700 cm^{-1}, τ 2·68br (5H, s, Ph), 3·32br (1H, s, NH), 5·70 (1H, m), 6·28—7·20 (3H, m), 7·07 (3H, s, NMe), and 8·56 (3H, d, *J* 7 Hz, *Me*CH) (Found: C, 67·1; H, 6·8; N, 12·0. $C_{13}H_{16}N_2O_2$ requires C, 67·2; H, 6·9; N, 12·1%).

The more polar compound was recrystallised from acetone–light petroleum to give the cis-*isomer*, m.p. 161—162°, $\nu_{max.}$ (Nujol) 3230, 3080, 1680, 1640, 1400, 1340, 1330, 1320, 1300, 1205, 1084, 1070, 1045, 745, and 700 cm^{-1}, τ 2·70br (6H, s, Ph and NH), 6·24 (1H, q, *J* 7 Hz), 6·82 (2H, double ABq, $PhCH_2$), 7·12 (3H, s, NMe), 9·18 (3H, d, *J* 7 Hz, *Me*CH) (Found: C, 67·05; H, 6·8; N, 12·0%).

Preparation and Oxidation of 5-*Methoxy*-1,3,6-*trimethyl*-3,6-*dihydropyrazin*-2(1H)-*one* (13; R = H).—The mixture of *cis*- and *trans*-piperazinediones (12; R = H) (3·0 g) was treated with trimethyloxonium fluoroborate (4·4 g) in dichloromethane (60 ml) at room temperature for 4 h with vigorous stirring. The resulting solution was poured onto cold, saturated, aqueous sodium hydrogen carbonate (25 ml) and the organic layer separated. The aqueous soluton was re-extracted with dichloromethane before washing the organic extracts with water, drying (Na_2SO_4), and evaporating to yield a colourless oil (2·63 g, 81%). T.l.c. examination indicated the presence of only two compounds in similar proportions, corresponding to the *cis*- and *trans*-isomers of the title compound. The mixture had $\nu_{max.}$ 1695, 1650, 1490, 1375, 1350, 1315, 1260, 1095, 990, 960, and 755 cm^{-1}, τ 5·58—6·22 (2H, m), 6·27 (3H, s) 7·03 (3H, s), and 8·40—8·65 (6H, m).

A sample (0·78 g) of the imidate was oxidised with DDQ (1·05 g) in refluxing benzene (100 ml) with stirring for 24 h. The mixture was cooled, precipitated quinol was filtered off, and the filtrates evaporated. The residue was chromatographed through alumina (100 g; grade III), eluting with benzene and then with 1 : 19 acetone–benzene. Three fractions were obtained. The first product was the unstable bismethylenepyrazinone (16; R = H), obtained as a yellow solid (94 mg, 12%). In deuteriochloroform this compound initially dissolved but rapidly precipitated an amorphous precipitate. The n.m.r. spectrum of the initial compound had τ 3·85 (1H, d, *J* 1·5 Hz), 4·38 (1H, d, *J* 1·5 Hz), 4·62 (1H, d, *J* 2 Hz), 5·20 (1H, d, *J* 2 Hz), 6·08 (3H, s, MeO), and 6·75 (3H, s, NMe).

The second compound eluted from the column was 5-*methoxy*-1,3-*dimethyl*-6-*methylene*-3,6-*dihydropyrazin*-2(1H)-*one* (14; R = H) (98 mg, 12%), isolated as a pale yellow oil, $\nu_{max.}$ (film) 3000—2840, 1680, 1615, 1355, 1278, 1180, 1110, 1030, 980, and 865 cm^{-1}, τ 4·78 (1H, d, *J* 2 Hz), 5·35 (1H, d, *J* 2 Hz), 5·71 (1H, q, *J* 7 Hz), 6·28 (3H, s,

MeO), 6·88 (3H, s, NMe), and 8·59 (3H, d, *J* 7 Hz, *Me*CH). Hydrolysis of the imidate (14; R = H) was accomplished as follows. The imidate (182 mg) was stirred with 60% v/v aqueous tetrahydrofuran (10 ml) containing 2N-HCl (1 ml) at room temperature for 16 h. The solution was basified with aqueous sodium hydrogen carbonate and extracted with dichloromethane. After drying (Na_2SO_4), evaporation of the organic extract gave 1,3-*dimethyl*-6-*methylenepiperazine*-2,5-*dione* (6; R = H) (134 mg, 80%), m.p. (from acetone–light petroleum) 117—119°, $\nu_{max.}$ (Nujol) 3190, 3040, 1690, 1455, 1428, 1382, 1374, 1365, 1340, 1295, 1150, 1025, 875, 855, and 755 cm^{-1}, $\lambda_{max.}$ 227 nm (ε 14,500), τ 2·43br (1H, s, NH), 4·20 (1H, d, *J* 1·5 Hz, $=CH_2$), 5·05 (1H, d, *J* 1·5 Hz, $=CH_2$), 5·73 (1H, dq, *J* 2, 7 Hz, MeC*H*NH), 6·78 (3H, s, NMe), and 8·44 (3H, d, *J* 7 Hz, *Me*CH) (Found: C, 54·7; H, 6·6; N, 18·0. $C_7H_{10}N_2O_2$ requires C, 54·5; H, 6·5; N, 18·2%).

The final product from the oxidation of the imino-ether (13; R = H), eluted from the column as an oil, using the acetone–benzene eluant, was assigned as the pyrazinone (15; R = H) (120 mg, 16%), but this compound rapidly reacted with oxygen on exposure to air.[1] The freshly isolated material exhibited τ 6·17 (3H, s, MeO), 6·47 (3H, s, NMe), and 7·60 and 7·70 (6H, s × Me).

Preparation and Oxidation of 3-*Benzyl*-5-*methoxy*-1,6-*dimethyl*-3,6-*dihydropyrazin*-2(1H)-*one* (13; R = Ph).—The mixture of *cis*- and *trans*-piperazinediones (12; R = Ph) (5·8 g) was stirred vigorously with trimethyloxonium fluoroborate (5·9 g) in dichloromethane (100 ml) at room temperature for 3 h. The solution was worked-up in the usual manner, extracted with dichloromethane, dried (Na_2SO_4), and evaporated to give a crystallising oil (6·1 g, 99%). T.l.c. examination of the product indicated the presence of two compounds only. A sample was separated by preparative t.l.c. (1 : 1 acetone–light petroleum). The more polar product was identified as cis-3-*benzyl*-5-*methoxy*-1,6-*dimethyl*-3,6-*dihydropyrazin*-2(1H)-*one* (13; R = Ph), isolated as a solid, m.p. 92—94°, $\nu_{max.}$ (Nujol) 1700, 1630, 1490, 1445, 1310, 1265, 1240, 1090, 1000, 850, 745, and 695 cm^{-1}, τ 2·80 (5H, s, Ph), 5·52 (1H, m), 6·27 (3H, s, MeO), 6·33—7·10 (3H, m), 7·20 (3H, s, NMe), and 9·58 (3H, d, *J* 7 Hz, *Me*CH) (Found: C, 68·4; H, 7·4; N, 11·6. $C_{14}H_{18}N_2O_2$ requires C, 68·3; H, 7·4; N, 11·4%).

The less polar material was the corresponding *trans*-isomer, isolated as an oil, $\nu_{max.}$ (film) 3080, 1695, 1645, 1495, 1450, 1430, 1400, 1260, 1235, 1090, 745, and 700 cm^{-1}, τ 2·80 (5H, s, Ph), 5·72 (1H, m), 6·30 (3H, s, MeO), 6·47—6·93 (3H, m), 7·17 (3H, s, NMe), and 8·64 (3H, d, *J* 7 Hz), *m/e* 246 (100%, M^+), 231 (20), 189 (5·5), 174 (6·5), 155 (44), 127 (73), and 91 (40).

Oxidation. The *cis*- and *trans*-imidate mixture (2·0 g) was oxidised with DDQ (1·0 g) in benzene (100 ml) at reflux for 24 h. After cooling, the precipitated quinol was removed, the filtrates evaporated to small bulk, and then chromatographed through alumina (150 g, grade III), using benzene as eluant. The separated products, in order of elution, were as follows. 3,1′-E-3-*Benzylidene*-5-*methoxy*-1-*methyl*-6-*methylene*-3,6-*dihydropyrazin*-2(1H)-*one* (16; R = Ph) (336 mg, 17%), was eluted first as orange needles, m.p. 103—105°, $\nu_{max.}$ (Nujol) 3050, 1673, 1630, 1592, 1492, 1460, 1445, 1430, 1340, 1272, 1175, 1123, 1063, 990, 835, 768, 755, 740, and 690 cm^{-1}, $\lambda_{max.}$ 231, 236, 244, 322, 335, and 348 nm (ε 6800, 7900, 7300, 21,000, 25,000, and 23,000), τ 1·85 (2H, m), 2·60 (4H, m), 4·65 (1H, d, *J* 2 Hz), 5·20 (1H, d, *J* 2 Hz), 5·98 (3H, s, MeO), and 6·70 (3H, s, NMe) (Found: C, 69·2; H, 5·8; N, 11·6. $C_{14}H_{14}N_2O_2$ requires C, 69·4; H, 5·8; N, 11·6%).

There followed 3-*benzyl*-5-*methoxy*-1-*methyl*-6-*methylene*-3,6-*dihydropyrazin*-2(1H)-*one* (14; R = Ph) (264 mg, 13%), as a yellow oil, τ 2·8 (5H, s), 5·05 (1H, d, *J* 2 Hz), 5·32 (1H, t, *J* *ca.* 5 Hz), 5·62 (1H, d, *J* 2 Hz), 6·20 (3H, s, MeO), 6·77 (2H, d, *J* 5 Hz), and 7·00 (3H, s, NMe). This compound was further characterised after hydrolysis with dilute hydrochloric acid in aqueous tetrahydrofuran, in the manner described above. The hydrolysis occurred quantitatively to give 3-*benzyl*-1-*methyl*-6-*methylenepiperazine*-2,5-*dione* (6; R = Ph), m.p. (from acetone–light petroleum) 133—137°, $\nu_{max.}$ (Nujol) 3190, 3060, 1690, 1608, 1425, 1380, 1340, 1155, 875, and 698 cm^{-1}, $\lambda_{max.}$ 233 nm (ε 14,000), τ 2·20br (1H, s, NH), 2·80 (5H, m, Ph), 4·50 (1H, d, *J* 1·5 Hz, $=CH_2$), 5·38 (1H, d, *J* 1·5 Hz), 5·67 (1H, dt, *J* 2, 5 Hz, CH_2CHNH), 6·97 (2H, d, *J* 5 Hz, $PhCH_2$), and 6·98 (3H, s, NMe) (Found: C, 67·7; H, 6·1; N, 12·2. $C_{13}H_{14}N_2O_2$ requires C, 67·8; H, 6·1; N, 12·2%). 3-*Benzyl*-5-*methoxy*-1,6-*dimethylpyrazin*-2(1H)-*one* (15; R = Ph) (305 mg, 15%), was obtained finally as an oil, contaminated with starting material. The diene was characterised by reaction of the freshly obtained material (150 mg) with dimethyl acetylenedicarboxylate (200 mg) in dichloromethane (20 ml) at reflux for 40 h. The solvent was removed and the residue purified by preparative t.l.c. to give *dimethyl* 5,7-*diaza*-4-*benzyl*-6-*methoxy*-1,7-*dimethyl*-8-*oxobicyclo*[2.2.2]*octa*-2,5-*diene*-2,3-*dicarboxylate* (17) (150 mg), m.p. (from acetone–light petroleum) (131—132°, $\nu_{max.}$ (Nujol) 1742, 1725, 1692, 1638, 1620, 1500, 1450, 1435, 1420, 1390, 1375, 1368, 1275, and 1230 cm^{-1}, τ 2·43 (2H, m), 2·73 (3H, m), 6·15, 6·28, and 6·50 (3 × MeO), 6·30 (2H, s, $PhCH_2$), 7·18 (3H, s, NMe), and 8·17 (3H, s) (Found: C, 62·5; H, 5·7; N, 7·2. $C_{20}H_{22}N_2O_6$ requires C, 62·2; H, 5·7; N, 7·25%).

Hydrolysis of the Imidate (16; R = Ph).—The imidate (52 mg) in 60% v/v aqueous tetrahydrofuran containing 2N-HCl (2 ml) was stirred at room temperature for 5 days. Work-up of the mixture in the usual manner gave 3,1′-E-3-*benzylidene*-1-*methyl*-6-*methylenepiperazine*-2,5-*dione* (18; R^1 = H, R^2 = Ph) (50 mg, 100%), m.p. (from acetone) 145—154° (decomp.), as yellow prisms, $\nu_{max.}$ (Nujol) 3290, 3200, 1680, 1625, 1605, 1500, 1450, 1370, 1230, 1185, 1140, and 905 cm^{-1}, $\lambda_{max.}$ 232, 236, and 316 nm (ε 23,000, 8400, and 8200) (Found: C, 68·25; H, 5·5; N, 12·0. $C_{13}H_{12}N_2O_2$ requires C, 68·4; H, 5·3; N, 12·3%). The material was too insoluble in deuteriochloroform to record a n.m.r. spectrum. The material was dissolved in trifluoroacetic acid and then recovered by evaporation to give a colourless compound, which was isomeric to the starting compound (less polar on t.l.c. with 1 : 19 MeOH–$CHCl_3$). The new compound was recrystallised from ethanol to give colourless needles of the 3,1′-Z-*isomer* (18; R^1 = Ph, R^2 = H), m.p. 115—117°, $\nu_{max.}$ (Nujol) 3260, 1690, 1625, 1605, 1480, 1430, 1400, 1320, 1355, 1200, 1140, and 905 cm^{-1}, $\lambda_{max.}$ 231, 235, and 313 nm (ε 30,000, 13,000, and 13,000), τ 1·80br (1H, s, NH), 2·53 (5H, s, Ph), 2·83 (1H, s, =CH), 4·12 (1H, d, *J* 1·5 Hz, $=CH_2$), 4·97 (1H, d, *J* 1·5 Hz, $=CH_2$), and 6·65 (3H, s, NMe) (Found: C, 68·3; H, 5·3; N, 12·2%).

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

[3/2238 *Received*, 31*st October*, 1973]