STEREOCHEMICAL AND HYDROGENOLYSIS STUDIES WITH SUBSTITUTED ISOXAZOLIDINES

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The use of ^{13}C n.m.r. and ^{1}H - ^{13}C decoupling to assign the chemical shifts to protons geminal to substituents at the 3,4 and 5 positions of a pair of stereoisomeric isoxazolidines allows determination of the ring stereochemistries. Catalytic hydrogenation of N-phenylisoxazolidines with a 5-methoxycarbonyl group leads readily to azolidin-2-ones, but C-N hydrogenolysis is not achieved if there is a dimethoxyphenyl substituent at the 3 position of the isoxazolidine.

In order to investigate the use of substituted isoxazolidines as possible intermediates in syntheses of the A ring of tetracycloxides eg. daunomycinone (1) we have prepared the model compounds (2) and (10) and studied their hydrogenolyses. The 1,3-dipolar addition[1,2] of C-(2',5'-dimethoxyphenyl)-N-phenylnitrone (15) to dimethyl fumarate (19) gave a 94:6 mixture of the isoxazolidines (2) and (3) which were separated by fractional crystallization. That the products were stereoisomeric isoxazolidines followed from combustion analysis, and i.r., u.v., ^{1}H and ^{13}C n.m.r. and mass spectra. Elucidation of the relative stereochemistry of the substituents on the isoxazolidine rings by utilizing the ^{1}H-^{1}H coupling constants $J_{3,4}$, required that the signals due to the protons at C-3 and C-5 be assigned unambiguously. This was achieved on the basis of ^{13}C n.m.r. and heteronuclear decoupling experiments.

Since no ^{13}C chemical shift data was available the reference compounds (4)[3] and (5) were prepared by addition of the nitrones (16) and (15) respectively to methyl methacrylate (20). The isoxazolidine (5) gave the expected combustion analysis and spectra. For compounds (4) and (5) the ^{13}C signals of the isoxazolidine carbons may be readily identified and assigned on the basis of signal multiplicities resulting from ^{1}H-^{13}C couplings. These assignments and the consequential assignments for the isoxazolidine (2) are summarized in Table 1.

	$\delta\ ^{13}C$			$\delta\ ^{1}H$			$J_{3,4}$ Hz
	3-C	4-C	5-C	3-H	4-H	5-H	
(4)	69.740(2)*	50.000(3)	83.248(1)	5.10	2.30 2.13	-	7.6 8.6
(5)	63.890(2)	55.842(3)	83.376(1)	5.15	2.23 2.00	-	7.7 8.8
(2)	67.658(2)	59.866(2)	78.570(2)	5.34	3.64	5.03	6.6
(3)	‡ -	-	-	5.60	3.83	5.17	8.4

Table 1

Specific ^{1}H-^{13}C decouplings then lead to the correlations between ^{1}H and ^{13}C signals which are shown. Finally ^{1}H-^{1}H decouplings allowed determination of the coupling constants $J_{3,4}$ (Table 1) from which it follows[2] that the protons and hence the substituents at C-3 and C-4 are cis in (3) and trans in (2), which, if the stereochemistry of the olefin is retained in both

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* Signal multiplicities. ‡ Insufficient of (3) was obtained for a ^{13}C spectrum.

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products, leads to the relative stereochemistries shown for (2) and (3). The stereochemical relationship between the C-3 and C-4 substituents is confirmed from a consideration of the positions in the ^{1}H n.m.r. spectrum of the signals due to the protons of the methoxycarbonyl groups. For (2) these appear at δ 3.72 and δ 3.77 and for (3) at δ 3.77 and δ 3.36. The upfield shift of this last signal indicates that one methoxycarbonyl group is strongly shielded relative to the others as would be expected for (3) where the dimethoxyphenyl and the 4-methoxycarbonyl groups are cis.

That the stereochemical relationship of the olefin substituents is retained in both isoxazolidines from such dipolar additions was confirmed when diethyl maleate was not isomerised to the more stable fumarate under the reaction conditions, and when the nitrone (16) reacted with dimethyl fumarate to give only (6) and (7) and with dimethyl maleate to give only (8) and (9).‡ These results support the view that such addition reactions are concerted.

Addition of C-(2',3'-dimethoxyphenyl)-N-phenylnitrone (17) to dimethyl fumarate (19) gave a 92:8 mixture of the isoxazolidines (10) and (11) from which only the former was isolated pure.

Interestingly with both (15) and (17), which contain a methoxyl ortho to the nitrone substituent there is an increase in the stereoselectivity of reaction in favour of the isoxazolidine in which the methoxyphenyl and the 4-methoxycarbonyl groups are trans. This observation agrees with the findings of Masui et al.[4] that the favoured orientation for addition to a symmetrical olefin is that in which steric interactions between the olefin

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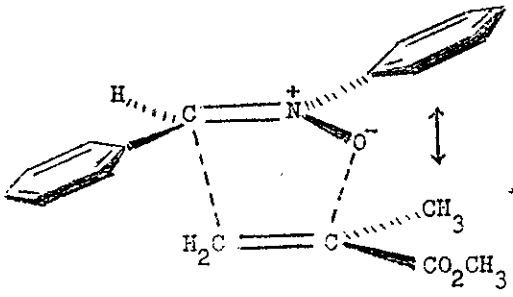
‡ After the completion of this phase of our work Joucla et al.[2] reported having reached similar conclusions for the isoxazolidines (6) (7) (8) and (9), after comparing the ^{1}H n.m.r. spectra with those of analoges deuterated at C-3.

and substituents on the carbon of the nitrone group are minimized, and suggested that the reactions might be made stereospecific by increasing this steric interaction. This proposal was confirmed when diethyl maleate (22) reacted with the nitrone (17) to give quantitatively only one product (12), and with the nitrone (16), in which the C-phenyl ring is unsubstituted, to give (13) and (14) in a 4:1 ratio similar to that obtained using the dimethyl ester (21).

The stereochemistries of the isoxazolidines (4) and (5) are proposed on the basis of similar arguments. It is known that aldonitrones exist in the more stable trans form[6] and two transition states I and II may be envisaged where interaction between the dipolarophile substituents and the C-aryl substituent of the nitrone is minimized during reaction[4]. If one assumes that the more abundant product will result from the transition state where the interaction between the N-phenyl group and the olefin substituents is least, then, because the methyl group is the smaller, reaction via transition state I will be favoured leading to the structures proposed for (4) and (5).



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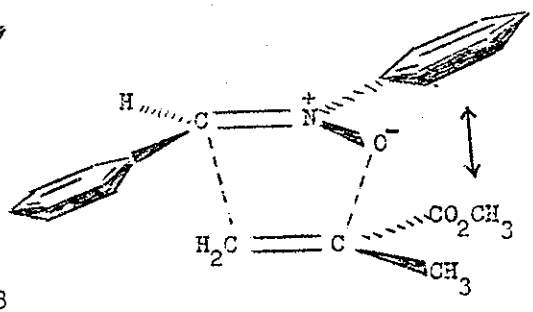


II

The nitrones (15), (16)[5], and (17) were prepared by condensation of

N-phenylhydroxylamine[7] with the appropriate aryl aldehyde in ethanol. Initially reactions were carried out at ambient temperatures, when reaction times of 48 h were required, and yields of 90% resulted. However, it was found that satisfactory yields (85%) could be obtained in 2 h in refluxing ethanol. Similarly a 75% yield of the nitrone (18) was obtained in 5 h, in contrast to a yield of 83% after 24 h at room temperature.[8]

Isoxazolidines were chosen as potential intermediates for the synthesis of the A ring of tetracycloxides on the basis of the observation[3] that catalytic hydrogenolysis of the isoxazolidine (4) gave the benzylic secondary amine (23), which hydrogenolysed further to the substituted methyl butanoate (28). However, on catalytic hydrogenation neither (2) nor (10) gave the desired butanoates (29) and (30) respectively, because cleavage of the carbon-nitrogen bond did not occur.

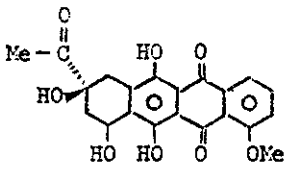
At atmospheric pressure over a 10% palladium-charcoal catalyst in absolute ethanol (2) took up 1.08 equivalents of hydrogen in 3 h to give the amino substituted methyl butanoate (24) as a colourless oil. Although it was not possible to obtain an acceptable microanalysis because (24) was converted to (31) on standing, the structure was supported by a high resolution mass spectrum, which included an ion at $\underline{m/e}$ 403.1621 corresponding to a molecular ion of composition $C_{21}H_{25}NO_7$, and by ^1H n.m.r. and i.r. spectra. On standing, or on silica gel chromatography, or on treatment with acid, (24) was converted to the azolidin-2-one (31), the structure of which followed from a combustion analysis, and i.r., ^1H n.m.r. and high resolution mass spectra. In the ^1H n.m.r. spectrum the 4-H signal appeared as a doublet of doublets centred on δ 3.58 ($\underline{J}_{4,3}$ 9.0 Hz, $\underline{J}_{4,5}$ 1.8 Hz), and the 3-H and 5-H doublets at δ 4.72 and δ 5.60 respectively. From measurements made on Dreiding models of the azolidinone (31) the Karplus equation predicts, for vicinal protons on the

ring, J_{cis} > 8.0 Hz and J_{trans} 1.0 to 3.5 Hz, whence it follows that the 4-methoxycarbonyl is *cis* to the 3-hydroxyl and *trans* to the 5-aryl substituent. The latter relationship is supported by the observation that the protons of the methoxycarbonyl group are not shielded by the aryl ring.

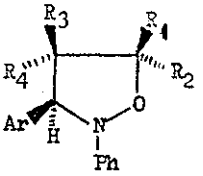
In an endeavour to achieve the desired carbon-nitrogen hydrogenolysis and remove the N-phenyl group, the more active Raney nickel (W-6)[10,11] and platinum dioxide catalysts were tried. Under a variety of conditions summarized in Table 2 (see experimental) the listed products resulted from hydrogenolysis of a 94:6 mixture of the isoxazolidines (2) and (3) in absolute ethanol at room temperature.

After 72 h over Raney nickel the major product was the tertiary amine (25) resulting from N-ethylation of (24). The ^{1}H n.m.r. spectrum of (25) was very similar to that of (24), differing in having only one exchangeable proton, and in containing a three proton triplet centred at δ 1.15, and a two proton quartet centred at δ 3.80. Similar N-ethylations over Raney nickel under both hydrogenating and non-hydrogenating conditions have been reported.[9]

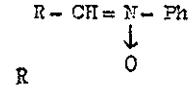
Over platinum dioxide after 24 h at 60 psi a new major product appeared. The ^{1}H n.m.r. spectrum included a broad eleven proton signal from δ 0 to 1.5, and the mass spectrum supported a molecular weight of 377, indicating that hydrogenation of the N-phenyl ring had occurred giving (32). The methyl aminobutanoate (24) is much more stable in the presence of platinum dioxide than in the presence of palladium-charcoal or Raney nickel. Thus its conversion to (31) was 50% complete after nine days over platinum dioxide, and fully completed after four days over the other two catalysts. It therefore appeared that the azolidinone (32) was formed by cyclisation of the hydrogenated benzylamine (26) rather than by hydrogenation of the azolidinone (31). Indeed hydrogenation of the azolidinone (31) using conditions which converted the



(1)



	Ar	R_1	R_2	R_3	R_4
(2)	2,5-dimethoxyphenyl	COOMe,	H,	H,	COOMe.
(3)	2,5-dimethoxyphenyl	H,	COOMe,	COOMe,	H.
(4)	phenyl	COOMe,	Me,	H,	H.
(5)	2,5-dimethoxyphenyl	COOMe,	Me,	H,	H.
(6)	phenyl	COOMe,	H,	H,	COOMe.
(7)	phenyl	H,	COOMe,	COOMe,	H.
(8)	phenyl	COOMe,	H,	COOMe,	H.
(9)	phenyl	H,	COOMe,	H,	COOMe.
(10)	2,3-dimethoxyphenyl	COOMe,	H,	H,	COOMe.
(11)	2,3-dimethoxyphenyl	H,	COOMe,	COOMe,	H.
(12)	2,3-dimethoxyphenyl	H,	COOEt,	H,	COOEt.
(13)	phenyl	H,	COOEt,	H,	COOEt.
(14)	phenyl	COOEt,	H,	COOEt,	H.

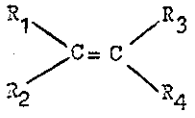


(15) 2,5-dimethoxyphenyl

(16) phenyl

(17) 2,3-dimethoxyphenyl

(18) n-propyl

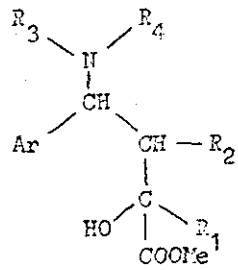


(19) $R_1 = R_4 = H$, $R_2 = R_3 =$ COOMe

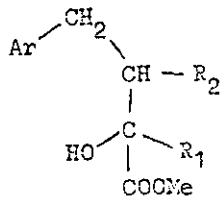
(20) $R_1 = R_2 = H$, $R_3 =$ Me, $R_4 =$ COOMe

(21) $R_1 = R_3 = H$, $R_2 = R_4 =$ COOMe

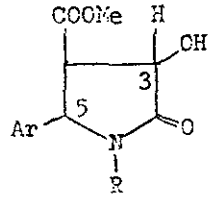
(22) $R_1 = R_3 = H$, $R_2 = R_4 =$ COOEt



	Ar	R_1	R_2	R_3	R_4
(23)	phenyl,	Me,	H,	H	phenyl
(24)	2,5-dimethoxyphenyl,	H,	COOMe,	H	phenyl
(25)	2,5-dimethoxyphenyl,	H,	COOMe,	Et	phenyl
(26)	2,5-dimethoxyphenyl,	H,	COOMe,	H	cyclohexyl
(27)	2,3-dimethoxyphenyl,	H,	COOMe,	H	phenyl



	Ar	R_1	R_2
(28)	phenyl,	Me,	H
(29)	2,5-dimethoxyphenyl,	H,	COOMe
(30)	2,3-dimethoxyphenyl,	H,	COOMe



	Ar	R
(31)	2,5-dimethoxyphenyl	phenyl
(32)	2,5-dimethoxyphenyl	cyclohexyl
(33)	2,3-dimethoxyphenyl	phenyl
(34)	2,3-dimethoxyphenyl	cyclohexyl

isoxazolidine (2) completely to (32) produced only 10% of (32), 90% of the (31) being recovered unchanged.

Similarly, controlled hydrogenation of (10) for 2 h at 15 psi over palladium-charcoal afforded the methyl aminobutanoate (27), which on standing converted to the azolidin-2-one (33); while hydrogenation for 24 h at 15 psi resulted in the formation of some (34) as well as (33).

On the basis of mechanisms proposed for hydrogenolysis of benzylic amines[12] it is not obvious why the C-N bonds in (24) and (27) failed to cleave. Although it is known for hydrogenolysis of dibenzylamines that the presence of a methoxyl substituent at any position in one aryl ring results in preferential removal of the other ring,[13] when there are substituents on both rings, or indeed when there is only one ring and it is substituted, hydrogenolysis has been found to be inhibited but not prevented.[11,13]

Although these results suggest that substituted isoxazolidines will not prove to be useful intermediates in syntheses of tetracycloxides like (1) they clearly have potential for syntheses of analogues containing amino groups in the A ring, or of tetracyclines.

EXPERIMENTAL

Melting points were determined on a Reichert Kofler block and are uncorrected. I.r. spectra were measured for chloroform solutions on a Perkin-Elmer Infracord 237 or 337. U.v. spectra were measured for ethanol solutions on a Unicam S.P. 800A. ^{1}H n.m.r. spectra were measured for $CDCl_3$ solutions on a Varian T60, or a Jeol PFT-FX60. ^{13}C n.m.r. were measured for $CDCl_3$ solutions on a Jeol PFT-FX60. Low resolution mass spectra were determined on a Varian-MAT CH7 and high resolution spectra on an AEI-MS9 interfaced with a DS30 data system, and all spectra are recorded with nominal electron energy of 70eV

unless otherwise stated. Microanalyses were carried out by Dr. A.D. Campbell and associates, University of Otago. Hydrogenolyses were performed in a Parr hydrogenator.

Isoxazolidine Syntheses:

Isoxazolidines (2) and (3). A solution of the nitrone (15) (1.28 g, 5 x 10^{-2} mol) and dimethyl fumarate (0.72 g, 5 x 10^{-2} mol) in chloroform (100 ml) was heated under reflux for 40 h. Removal of the solvent and crystallization from ethanol gave 4-trans,5-cis-bismethoxycarbonyl-3-(2',5'-dimethoxyphenyl)-2-phenylisoxazolidine (2)* (1.46 g) as white grains m.p. 98°. (Found: $M^{+\cdot}$ 401 (mass spectrum); C, 62.6; H, 5.45; N, 3.5. $C_{21}H_{23}NO_7$ requires mol. wt. 401; C, 62.8; H, 5.7; N, 3.5%); $\lambda_{max.}$ 249 (ε, 7 850), 289 (ε, 5 175), 429 nm (ε, 232); $\nu_{max.}$ 3 040, 1 740 (C=O), 1 490, 1 270 (N→O), 1 040 cm^{-1}; ^1H n.m.r. δ 3.72 (s, 3,4-COOMe), 3.77 (s, 9,2'-OMe, 5'-OMe,5-COOMe), 3.78 (2d, $J_{4,3}$ 6.6 Hz, $J_{4,5}$ 5.0 Hz, 4-H), 5.01 (d, $J_{5,4}$ 5.0 Hz, 5-H), 5.34 (d, $J_{3,4}$ 6.6 Hz, 3-H), 6.75-7.40 (m, 8, ArH); ^{13}C n.m.r. δ 52.1, 55.71, 55.92, 56.62 (4q, 4, 2 x $COO\underline{C}H_3$, 2 x $O\underline{C}H_3$), 59.87 (d, 1, C4), 67.66 (d, 1, C3), 78.57 (d, 1, C5), 110-150 (m, 8, C2,C3,C4,C5 and C6 of N-phenyl, and C3',C4' and C6' of C-phenyl), 151.32, 156.04, 160.22 (3s, 4, C1 of N-phenyl and remainder of C-phenyl carbons), 173.62, 174.37 (2s, 2, $\underline{C}OOCH_3$), m/e 401, 371 ($M^{+\cdot}$-H_2C=O), 343 ($M^{+\cdot}$-H_2C=C=O), 325 ($M^{+\cdot}$-C_6H_4), 282 (20%, $M^{+\cdot}$-CO-NPh), 226 (100%).

4-cis,5-trans-bismethoxycarbonyl-3-(2',5'-dimethoxyphenyl)-2-phenylisoxazolidine (3), was crystallized from the concentrated mother liquors by seeding with crystals which had been manually separated, and recrystallized from ethanol as white needles (0.05 g) m.p. 122°. The i.r. and u.v. spectra of (3) were identical with those of (2); ^1H n.m.r. δ 3.36 (s, 3, 4-COOMe), 3.77 (s, 9, 2'-

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* Isoxazolidine stereochemistry is relative to the aryl group at C-3.

OMe, 5'-OMe, 5-COOMe), 3.83 (2d, $J_{4,3}$ 8.4 Hz, $J_{4,5}$ 7.8 Hz, 1, 4-H), 5.17 (d, $J_{5,4}$ 7.8 Hz, 1, 5-H), 5.60 (d, $J_{3,4}$ 8.4 Hz, 1, 3-H), 6.75-7.40 (m, 8, ArH).

Isoxazolidine (5). 5-cis-methoxycarbonyl-5-trans-methyl-3-(2',5'-dimethoxyphenyl)-2-phenylisoxazolidine was prepared using a procedure similar to the above with methyl methacrylate as the dipolarophile. Crystallization gave lustrous white plates (87% yield) m.p. 96°. (Found: $M^{+\cdot}$ 357 (mass spectrum); C, 67.2; H, 6.35; N, 3.7. $C_{20}H_{23}NO_5$ requires mol. wt. 357; C, 67.2; H, 6.5; N, 3.9%); $\lambda_{max.}$ 250 (ε, 8 250), 293 (ε, 5 025), 429 nm (ε, 220); $\nu_{max.}$ 3 030, 1 745 (C=O), 1 490, 1 275 (N→O), 1 050, 950 cm^{-1}; ^1H n.m.r. δ 1.56 (s, 3, Me), 1.96-2.30 (2d, $J_{4,3}$ 7.7 Hz, $J_{4,4}$ 12.8 Hz, 1, 4-H), 3.23 (2d, $J_{4,3}$ 8.8 Hz, $J_{4,4}$ 12.8 Hz, 1, 4-H), 3.42, 3.65, 3.75 (3s, 9, OMe), 5.15 (2d, $J_{3,4}$ 7.7 Hz, $J_{3,4}$ 8.8 Hz, 1, 3-H), 6.75-7.50 (m, 8, ArH); ^{13}C n.m.r. δ 21.92 (q, 1, $\underline{C}H_3$), 50.95 (q, 1, COO$\underline{C}H_3$), 47.85, 55.83 (2q, 2, O$\underline{C}H_3$), 55.84 (t, 1, C4), 63.89 (d, 1, C3), 83.38 (s, 1, C5), 132.14 (s, 1, C 1' of C-phenyl), 110-130 (m, 8, aryl carbons), 150.98, 152.03, 154.63 (3s, 3, C 1 of N-phenyl and C2', C5' of C-phenyl), 173.17 (s, 1, $\underline{C}OOCH_3$); m/e 357 (100%, $M^{+\cdot}$), 298 (7%, $M^{+\cdot}$-COOMe), 226 (35%), 189 (75%).

Isoxazolidine (4)[3]. ^{13}C n.m.r. δ 22.42 (q, 1, $\underline{C}H_3$), 50.00 (t, 1, C4), 53.28 (q, 1, COO$\underline{C}H_3$), 69.74 (d, 1, C3), 141.54 (s, 1, C 1' of C-phenyl), 151.16 (s, 1, C 1 of N-phenyl), 110-145 (m, 10, aryl carbons), 173.83 (s, 1, $\underline{C}OOCH_3$).

Isoxazolidine (10). Dimethyl fumarate (1.80 g, 1.24×10^{-2} mol) was added to a solution of the nitrone (17) (3.21 g, 1.24×10^{-2} mol) and the resulting solution was left at room temperature for 16 days. Removal of the solvent afforded a brown oil (4.95 g) which was shown to contain two compounds of nearly identical R_f. The ^1H n.m.r. spectrum indicated that the mixture contained (10) and (11) in a ratio of 92:8. Crystallization from warm (45°) ethanol gave 4-trans,5-cis-bismethoxycarbonyl-3-(2',3'-dimethoxyphenyl)-2-

phenylisoxazolidine as pale green plates m.p. 64-5°. (Found: C, 62.55; H, 5.75; N, 3.5. $C_{21}H_{23}O_7N$ requires C, 62.8; H, 5.8; N, 3.5%); $\nu_{max.}$ 2 950 1 725, 1 585, 1 475, 1 430, 1 260, 1 070, 995 cm^{-1}; ^1H n.m.r. δ 3.67, 3.73, 3.79, 3.85 (4s, 12, OMe and CO_2Me), 3.97 (2d, 1, J 6.5 Hz, J 5.5 Hz), 5.10 (d, 1, J 5.5 Hz, 3-H or 5-H), 5.23 (d, 1, J 6.5 Hz, 5-H or 3-H), 6.75-7.40 (m, 8, ArH).

Isoxazolidine (12). A solution of nitrone (17) (0.77 g, 3 x 10^{-3} mol) and diethyl maleate (0.516 g, 3 x 10^{-3} mol) in chloroform and benzene (20 ml: 15 ml) was refluxed for 4.5 days. Removal of the solvents gave 4-trans,5-trans-bismethoxycarbonyl-3-(2',3'-dimethoxyphenyl)-2-phenylisoxazolidine as a golden brown oil which was homogeneous on t.l.c. $\nu_{max.}$ 1 740, 1 595, 1 480, 1 370, 1 260, 1 180, 970, 895 cm^{-1}; ^1H n.m.r. δ 1.13 (t, 3, J 7.4 Hz, $-OCH_2CH_3$), 1.19 (t, 3, J 7.4 Hz, $-OCH_2CH_3$), 3.91, 3.94 (2s, 6, OMe), 4.13, 4.16 (2q, 4, $-OCH_2CH_3$), 4-H signal multiplicity is obscured by these resonances, 5.03 (d, 1, J 7.8 Hz, 3-H or 5-H), 5.27 (d, 1, J 6.4 Hz, 5-H or 3-H), 6.80-7.37 (m, 8, ArH).

Isoxazolidines (13) and (14). Modification of the preceding procedure by using nitrone (16) gave a golden oil which contained two products of nearly identical R_f. Dry-column chromatography (silicagel S deactivated by tumbling for 3 h with 15% (W/W) water, $CHCl_3$ eluant) afforded a pure sample of the major product 4-trans,5-trans-bisethoxycarbonyl-2,3-diphenylisoxazolidine (13). (Found: C, 68.25, H, 6.5; N, 3.9. $C_{21}H_{23}O_5N$ requires C, 68.3; H, 6.3; N, 3.8%); $\nu_{max.}$ 2 995, 1 735, 1 595, 1 485, 1 370, 1 340, 1 295, 1 220, 1 195, 1 020 cm^{-1}; ^1H n.m.r. δ 1.13 (t, 3, J 7.2 Hz, $-OCH_2CH_3$), 1.17 (t, 3, J 7.2 Hz, $-OCH_2CH_3$), 3.82 (3 lines, 1, $J_{4,3}$ 8.0 Hz, $J_{4,5}$ 8.0 Hz, 4-H), 4.08 (q, 2, J 7.2 Hz, $-OCH_2CH_3$), 4.10 (q, 2, J 7.2 Hz, $-OCH_2CH_3$), 5.03 (d, 2, J 8.0 Hz, 3-H and 5-H, having identical δ and identical coupling with 4-H), 6.90-7.65 (m, 10, ArH). The minor product was shown to be isomeric from a combustion analysis of the

reaction mixture, and was assigned the structure 4-cis,5-cis-bisethoxycarbonyl-2,3-diphenylisoxazolidine (14) on the basis of spectra. I.r. spectrum identical with that of (13). ^{1}H n.m.r. δ 0.83 (t, 3, J 7.2 Hz, 4-OCH$_2$CH$_3$), 1.30 (t, 3, J 7.2 Hz, 5-OCH$_2$CH$_3$), 3.61 and 3.63 (2q, 2, J 7.2 Hz, 4-OCH$_2$CH$_3$), 4.12 (2d, 1, J 9.2 Hz, J 7.2 Hz, 4-H), 4.26 (q, 2, J 7.2 Hz, 5-OCH$_2$CH$_3$), 4.86 (d, 1, J 7.2 Hz, 3-H or 5-H), 5.18 (d, 1, J 9.2 Hz, 5-H or 3-H), 6.90-7.70 (m, 10, ArH).

Nitrone Syntheses:

Nitrone (17). Freshly prepared phenylhydroxylamine (2.0 g, 1.83 x 10^{-2} mol) was added to 2,3-dimethoxybenzaldehyde (3.0 g, 1.81 x 10^{-2} mol) in absolute ethanol (20 ml). After standing at room temperature for 48 h C-(2',3'-dimethoxyphenyl)-N-phenylnitrone crystallized out (4.4 g, 90%) m.p. 133-4°. (Found: C, 69.9; H, 6.0; N, 5.35. $C_{15}H_{15}O_3N$ requires C, 70.0; H, 5.9; N, 5.4%); $\nu_{max.}$ 2 985, 1 595 (C=N), 955 cm^{-1}; ^{1}H n.m.r. δ 3.90 (s, 6, OMe), 7.07-8.00 (m, 7, N-phenyl, C 4'-H and C 5'-H ArH), 8.36 (s, 1, ArCH=N) 9.03 (2d, 1, $J_{6',5'}$ 7.0 Hz, $J_{6',4'}$ 2.6 Hz, 6'-H).

Nitrone (15). Freshly prepared phenylhydroxylamine (7.8 g, 6.5 x 10^{-2} mol) and 2,5-dimethoxybenzaldehyde (2 g, 1.20 x 10^{-2} mol) were refluxed in absolute ethanol (20 ml) for 2 h. On cooling the nitrone crystallized out. Recrystallization from aqueous ethanol gave C-(2',5'-dimethoxyphenyl)-N-phenylnitrone (2.7 g, 85%) m.p. 88°. (Found: M^+ 257 (mass spectrum); C, 70.0; H, 5.8; N, 5.45. $C_{15}H_{15}O_3N$ requires mol. wt.257; C, 70.0; H, 5.9; N, 5.4%); $\lambda_{max.}$ 225 (ε, 10 900), 288 (ε, 8 480), 334 nm (ε, 9 640); $\nu_{max.}$ 3 030, 1 580 (C=N), 1 190, 1 175, cm^{-1} (N→O); ^{1}H n.m.r. δ 3.81, 3.82 (2s, 6, OMe), 6.80-8.00 (m, 7, ArH), 8.30 (s, 1, ArCH=N), 9.10 (d, 1, J, 4 Hz, 6'-H); mass spectrum (12 eV); m/e 257, 241 ($M^{+\cdot}$-O), 226 ($M^{+\cdot}$-MeO$^{\cdot}$), 166 ($M^{+\cdot}$-C_6H_5N), 149 ($M^{+\cdot}$-$C_6H_6NO^{\cdot}$).

C,N-Diphenylnitrone (16) was obtained in 90% yield after 48 h at room temperature,

and in 82% yield using refluxing ethanol for 2 h, m.p. 112° (lit. 112-113°[5]); $\nu_{max.}$ 3 100, 3 020, 1 595 (C=N) cm^{-1}; ^1H n.m.r. δ 7.30-7.63 (m, 6, ArH), 7.65-7.93 (m, 2, 2-H and 6-H of N-phenyl), 7.97 (s, 1, ArCH=N), 8.33-8.57 (m, 2, 2'-H and 6'-H of C-phenyl).

Hydrogenolyses: The isoxazolidine (0.4 g, 1 x 10^{-3} mol) was dissolved in ethanol (20 ml), catalyst (0.20 g) was added and hydrogenation was carried out for the times and at the pressures listed in Table 2. The courses of all reactions were followed by analytical t.l.c. Filtration followed by removal of the solvent gave the products as colourless oils.

Catalyst	Palladium-Charcoal 10%		Raney Nickel		Platinum Dioxide	
Pressure psi	15	60	15	60	15	60
3 h	(24)	(24)	(24)	(24)	(24)	(24)
24 h	(24) (31)	(24) (31)	(24) (31) (25)	(24) (31) (25)	(24) (31)	(32)
48 h	(24) (31)	(24) (31)	(24) (31) (25)	(31) (25)	(24) (31)	(32)
72 h	(24) (31)	(24) (31)	(31) (25)	(31) (25)	(24) (31)	(32)

Table 2

Methyl 2-hydroxy-3-methoxycarbonyl-4-(2',5'-dimethoxyphenyl)-4-N-phenylaminobutanoate (24). (Found: $M^{+\cdot}$ 403.1621 (mass spectrum). $C_{21}H_{25}NO_7$ requires mol. wt. 403.1621); $\nu_{max.}$ 3 450 (N-H), 3 500-2 850 (O-H), 1 725 (C=O), 1 425, 1 040 cm^{-1}; ^1H n.m.r. δ 3.62, 3.68 (2s, 6, COOMe), 3.74 (2d, $J_{3,4}$ 8.0 Hz, $J_{3,2}$ 3.0 Hz, 1, 3-H), 3.90, 4.05 (2s, 6, OMe), ca 3.90 (b, 2,

OH and NH), 4.68 (d, $J_{2,3}$ 3.0 Hz, 1, 2-H), 5.15 (d, $J_{4,3}$ 8.0 Hz, 1, 4-H), 6.80-7.25 (m, 8, ArH); mass spectrum, m/e 403.1621, 242.1180 (100%, $C_{15}H_{16}NO_2$), no other peaks of greater than 15% relative abundance.

Methyl 2-hydroxy-3-methoxycarbonyl-4-(2',5'-dimethoxyphenyl)-4-(N-ethyl-N-phenylamino)butanoate (25) was purified by p.l.c.; $\nu_{max.}$ 3 500-2 850 (O-H), 1 725 (C=O), 1 420, 1 045 cm^{-1}; ^1H n.m.r. δ 1.15 (t, 3, $-NCH_2CH_3$), 3.68 and 3.73 (2s, 6, COOMe), 3.75 (2d, $J_{3,2}$ 3.1 Hz, $J_{3,4}$ 8.0 Hz, 1, 3-H), 3.80 (q, 2, $-NCH_2CH_3$), 3.95 (b, 1, OH), 3.92, 4.05 (2s, 6, OMe), 4.70 (d, $J_{2,3}$ 3.1 Hz, 1, 2-H), 5.15 (d, $J_{4,3}$ 8.0 Hz, 1, 4-H), 6.80-7.25 (m, 8, ArH).

3-Hydroxy-4-methoxycarbonyl-5-(2',5'-dimethoxyphenyl)-1-cyclohexylazolidin-2-one (32). (Found: $M^{+\cdot}$ 377 (mass spectrum). $C_{20}H_{27}NO_6$ requires mol. wt. 377); $\nu_{max.}$ 3 450-2 900 (O-H), 2 950 (aliphatic C-H), 1 742 (azolidin-2-one C=O), 1 700 (methoxycarbonyl C=O), 1 435, 1 055, 1 000, 910 cm^{-1}; ^1H n.m.r. δ 0-1.5 (b, 11 cyclohexyl protons), 3.22 (2d, $J_{4,3}$ 1.6 Hz, $J_{4,5}$ 8.4 Hz, 1, 4-H), 3.76, 3.77 and 3.81 (3s, 9, COOMe and OMe), 3.80 (b, 1, OH), 4.72 (d, $J_{5,4}$ 8.4 Hz, 1, 5-H), 5.12 (d, $J_{3,4}$ 1.6 Hz, 1, 3-H), 6.50-7.50 (m, 3, ArH); mass spectrum, m/e 377, 350 ($M^{+\cdot}$-HO·), 248 ($M^{+\cdot}$-$C_5H_5O_4$·).

Methyl 2-hydroxy-3-methoxycarbonyl-4-(2',3'-dimethoxyphenyl)-4-phenylaminobutanoate (27). (Found: $M^{+\cdot}$ 403 (mass spectrum). $C_{21}H_{25}O_7N$ requires mol. wt. 403); $\nu_{max.}$ 3 460 (N-H), 3 550-2 930 (O-H), 1 725 (C=O), 1 595, 1 470, 1 420, 1 260, 1 210, 1 110, 1 060, 990 cm^{-1}; ^1H n.m.r. δ 3.59 and 3.63 (2s, 6, COOMe), 3.85 (2d, $J_{3,4}$ 8.0 Hz, $J_{2,3}$ 3.0 Hz, 1,3-H), 3.80, 4.01 (2s, 6, OMe), 4.25 (b, 2, OH and NH), 4.70 (d, $J_{2,3}$ 3.0 Hz, 1, 2-H), 5.40 (d, $J_{4,3}$ 8.0 Hz, 4-H), 6.50-7.25 (m, 8, ArH).

Azolidinone (31). The butanoate (24) (0.2 g, 5 x 10^{-4} mol) dissolved in methanol (10 ml) containing 10% aqueous hydrochloric acid (2 drops) was

heated (steam bath) for 4 h. Removal of the solvent gave a colourless oil which crystallized on standing. Recrystallization from diethyl ether-hexane gave 3-hydroxy-4-methoxycarbonyl-5-(2',5'-dimethoxyphenyl)-1-phenylazolidin-2-one as colourless needles m.p. 43°. (Found: $M^{+\cdot}$ 371.1368 (mass spectrum); C, 68.45; H, 5.9; N, 3.7. $C_{20}H_{21}NO_6$ requires mol. wt. 371.1368; C, 68.7; H, 5.7; N, 3.8%); $\nu_{max.}$ 3 500 - 2 800 (O-H), 1 740 (azolidine C=O), 1 700 (methoxycarbonyl C=O), 1 430, 1 055, 910 cm^{-1}; ^1H n.m.r. δ 3.58 (2d, $J_{4,3}$ 9.0 Hz, $J_{4,5}$ 1.8 Hz, 1, 4-H), 3.80 (b, 1, OH), 3.82 (s, COOMe), 3.90 and 3.98 (2s, 6, OMe), 4.72 (d, $J_{3,4}$ 9.0 Hz, 1, 3-H), 5.60 (d, $J_{5,4}$ 1.8 Hz, 1, 5-H), 6.50-7.80 (m, 8, ArH); mass spectrum m/e 371.1368, 242,1180 (100%, $C_{15}H_{16}NO_2$).

Azolidinone (33). Was obtained (25%) by silicagel/chloroform p.l.c. of the butanoate (27). (Found: $M^{+\cdot}$ 371 (mass spectrum). $C_{20}H_{21}NO_6$ requires mol. wt. 371); $\nu_{max.}$ 3 550, 3 600 - 3 100, 2 940 (O-H), 1 738 (azolidinone C=O) 1 705 (methoxycarbonyl C=O), 910 cm^{-1}; ^1H n.m.r. δ 3.52 (2d, $J_{4,3}$ 8.2 Hz, $J_{4,5}$ 2.0 Hz, 1, 4-H), 3.80 (b, 1, OH), 3.80 (s, 3, COOMe), 3.90, 3.95 (2s, 6, OMe), 4.83 (d, $J_{3,4}$ 8.2 Hz, 1, 3-H), 5.75 (d, $J_{5,4}$ 2.0 Hz, 1, 5-H), 6.60-7.65 (m, 8, ArH).

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