Preparation and Reactions of 3-Phenyl-4a,5,6,8a-tetrahydro-4*H*-1,2-benz-[*e*]oxazines

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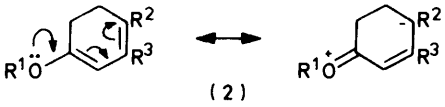
α-Nitrososstyrene (1) undergoes [4 + 2] cycloaddition reactions with cyclohexa-1,3-dienes (2) to give, in good yield, tetrahydro-4*H*-1,2-benzoxazines (3). In the case of 1,4-dimethoxycyclohexa-1,3-diene the regioisomeric adduct (4) is isolated. Hydrolysis of the adducts (3b—f) gives the ketone (5; R = H). This undergoes Beckmann rearrangement when heated in trifluoroacetic acid to give the dione (9). Pyrolysis of the oxazines (3b, c) and and (5; R = H) affords 3-(6-phenyl-3-pyridiyl)propionaldehyde (10) as the only product.

CYCLOADDITION reactions of nitroso- and azo-alkenes, obtained as intermediates,[1,2] to olefins, cyclic and alicyclic dienes, and enamines have already been described.[2,3] These intermediates are conveniently obtained by dehydrohalogenation of the appropriate oxime or hydrazone derivative of an α-halogeno-ketone with a non-nucleophilic base such as sodium carbonate in an aprotic solvent. They are hence generated at a slow rate which, in the presence of a high concentration of addend, allows for efficient trapping and reduces dimerisation and polymerisation.

We have investigated the addition reactions of α-nitrososstyrene (1; R = Ph) to cyclohexa-1,3-diene and its hydroxy- and alkoxy-derivatives (2) [4,5] in an attempt to utilise the adducts as precursors to other heterocyclic systems. Solutions containing α-chloroacetophenone oxime and an excess of the appropriate diene (2) were stirred with anhydrous sodium carbonate at 20—30 °C for 24 h. In most cases the adducts (3) isolated were stable crystalline solids (Table 1). However, no adducts were obtained from the dienes (2e, j). The isomeric adducts (4; R^3 = H), but excluding (4; $R^2 = R^3$ = OMe), may have been formed in low yield but were in fact not detected.

(1)



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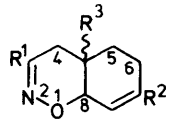

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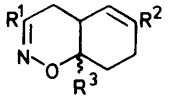
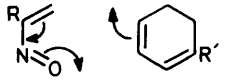


(4)

a ; R^1 = Ph , R^2 = H
b ; R^1 = Ph , R^2 = OMe
c ; R^1 = Ph , R^2 = OEt
d ; R^1 = Ph , R^2 = OPr^n
e ; R^1 = Ph , R^2 = OBu^n
f ; R^1 = Ph , R^2 = OCH_2OMe
g ; R^1 = $C_6H_4NO_2$-*p* , R^2 = OEt

For (3a—g), R^3 = H

The regioselectivity of the addition follows from the nitrosoalkene polarisation; its 4π-electron mode of addition [2] to the more nucleophilic double bond of the diene (Scheme 1) determines the periselectivity.



SCHEME 1

The ^{1}H n.m.r. spectra of the products (Table 2) provide support for the assigned structures. The adducts (3b—g) show a doublet at δ *ca.* 4.9—5.1 (*J* 7 Hz) for the allylic hydrogen at the bridgehead C-8a, whereas the corresponding C-4a proton at δ 2.98—2.86 [for (3a—g)] is a doublet of doublets. A long-range split multiplet at δ 4.2—4.3 is assigned to the proton at C-8.

The spectrum of the adduct obtained from 1,4-dimethoxycyclohexadiene is clearly incompatible with structure (3; $R^2 = R^3$ = OMe) but is consistent with structure (4; $R^2 = R^3$ = OMe); the absence of both a simple AB doublet of doublets for the C-4 proton and a signal at δ *ca.* 4.9 for the C-8a proton rules out structure (3) for this adduct; instead the signal for the C-5 proton is a singlet at δ 4.21, and the bridgehead C-4a proton occurs at higher field within the CH_2 signal region. It is probable that in the symmetrical diene there is little polarisation of the double bonds.

The oxazines (3b—f) were all easily hydrolysed to the oxazinone (5; R = H) with aqueous acid–ethanol at room temperature, thus establishing the presence of an enol-ether grouping at C-7. The CO group in compound (5) can be acetalised or reduced with no apparent cleavage of the N–O bond. A simple explanation for this kind of behaviour is not easily found since, in contrast, the adduct of cyclopentadiene was reported [2] to undergo cleavage with $LiAlH_4$ to afford the aminocyclopentenol (8).

The configurational isomers of the ethylene acetal (7a; *cis*) and (7a; *trans*), as well as the corresponding isomeric hydroxy-adducts (7b) obtained by $LiAlH_4$ reduction of the adduct (5; R = H), were isolated by preparative layer chromatography (p.l.c.). Indeed, the

TABLE 1

3-Phenyl-4a,5,6,8a-tetrahydro-4*H*-1,2-benz[*e*]oxazines (3) and the 3-phenyl-4a,7,8,8a-tetrahydro-4*H*-1,2-benz[*e*]oxazine (4)

Compound [a]	Yield (%)	M.p. (°C)	Formula	Analysis (%) [b] C	H	N	$\nu_{max.}$/cm^{-1} (Nujol)	*mz* (%)
(3a)	45.8	103—106	$C_{14}H_{15}NO$	78.4 (78.9)	7.0 (7.0)	6.6 (6.6)	710, 745, 770, 1 010, 1 045, 1 085, 1 105, 1 160, 1 655	213 (30), 194 (22), 117 (36), 104 (35), 103 (64), 39 (100)
(3b)	47	134—137	$C_{15}H_{17}NO_2$	73.7 (74.1)	7.0 (7.0)	6.0 (5.8)	700, 760, 800, 1 015, 1 175, 1 210, 1 665	343 (M^+, 28), 225 (45), 210 (73), 195 (14), 182 (14), 170 (15), 169 (14), 123 (61), 110 (34), 102 (30), 77 (100)
(3c)	49.2	147—149	$C_{16}H_{19}NO_2$	74.2 (74.7)	7.3 (7.4)	5.5 (5.45)	700, 730, 765, 1 050, 1 135, 1 205, 1 665	257 (M^+, 65), 240 (24), 229 (56), 210 (49), 183 (04), 172 (19), 156 (24), 104 (36), 103 (72), 78 (100)
(3d)	53.2	138—139	$C_{17}H_{21}NO_2$	75.3 (75.3)	7.8 (7.75)	5.3 (5.2)	700, 760, 800, 1 015, 1 195, 1 600	M^+ not observed, 263 (50), 251 (25), 210 (75), 211 (26), 151 (25), 109 (99), 104 (80), 96 (95), 50 (100)
(3e)	40	121—122	$C_{18}H_{23}NO_2$	75.6 (75.8)	7.9 (8.1)	5.4 (4.9)	700, 765, 805, 1 020, 1 170, 1 200, 1 660	
(3f)	46	114—115	$C_{16}H_{19}NO_3$	70.2 (70.3)	7.0 (7.0)	4.8 (5.1)	695, 730, 760, 800, 1 005, 1 025, 1 170, 1 200, 1 215, 1 235, 1 660	
(3g)	50	127—131	$C_{16}H_{18}N_2O_4$	63.5 (63.6)	5.8 (6.0)	9.4 (9.3)	700, 760, 800, 1 020, 1 035, 1 115, 1 200, 1 580, 1 600, 1 655	203 (M^+, 2), 191 (23), 180 (41), 164 (3), 118 (40), 117 (43), 102 (42), 103 (33), 91 (63), 43 (100)
(4; R^1 = Ph, R^2 = R^3 = OMe) [c]	48	114—116	$C_{16}H_{19}NO_3$	70.1 (70.3)	7.0 (7.0)	5.1 (5.1)	700, 760, 770, 1 050, 1 035 1 180, 1 670	

[a] The adducts (3b—f) were hydrolysed to the *oxazinone* (5; R = H), m.p. 151—153 °C (Found: C, 73.2; H, 6.7; N, 6.2. $C_{14}H_{15}NO_2$ requires C, 73.4; H, 6.6; N, 6.1%); $\nu_{max.}$ 1 170 cm^{-1}; δ 7.70 (2 H, m), 7.40 (3 H, m), 4.30 (1 H, s, 8a-H), 2.98 (1 H, dd, *J* 7 Hz, 4a-H), 2.90—2.30 (6 H, m), and 2.09—1.81 (2 H, m); *m/z* 229 (M^+, 43), 212 (8), 199 (9), 184 (7), 182 (6), 173 (5), 172 (11), 171 (11), 156 (15) 144 (17), 104 (45), 103 (63), and 43 (100%). [b] Required values in parentheses. [c] The adduct was hydrolysed to the *oxazinone* (6; R = OMe), m.p. 128—131 °C (Found: C, 69.5; H, 6.7; N, 5.3. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%); $\nu_{max.}$ 1 710 cm^{-1}; δ 7.75 (2 H, m), 7.43 (3 H, m), 3.38 (3 H, s, OMe), 3.06 (1 H, dd, *J* 7 Hz, 4a-H), and 2.80—1.74 (8 H, m); *m/z* 284 (16), 256 (16), 174 (4), 149 (5), 129 (12), and 41 (100%).

TABLE 2

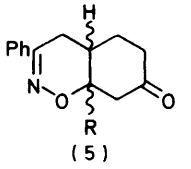
^{1}H N.m.r. chemical shifts (δ) and coupling constants (Hz) for adducts (3a—g) and (4); R′ = Ph, R² = R³ = OMe

Compound	Aromatic protons	8a-H	8-H	7-H or substituent	4a-H	Methylene protons; substituents
(3a)	7.72 (2 H, m), 7.38 (3 H, m)	6.05 (1 H, m, J 4)	4.20 (1 H, t, J 7 and 4)	5.90 (1 H, m)	2.86 (1 H, dd, $J_{4a,4ax'}$ $J_{4a,8a}$ 7)	2.40—1.52 (6 H, m)
(3b)	7.72 (2 H, m), 7.40 (3 H, m)	4.93 (1 H, d, J 7)	4.25 (1 H, m)	3.63 (3 H, s, OMe)	2.98 (1 H, dd, $J_{4a,4ax'}$ $J_{4a,8a}$ 7)	2.30—1.60 (6 H, m)
(3c)	7.73 (2 H, m) 7.40 (3 H, m)	4.90 (1 H, d, J 7)	4.25 (1 H, m)	3.80 (2 H, q, J 10, OCH_2)	2.95 (1 H, dd, $J_{4a,4ax}$ $J_{4a,8a}$ 7)	2.60—1.60 (6 H, m), 1.30 (3 H, J 10, Me)
(3d)	7.80 (2 H, m), 7.35 (3 H, m)	4.87 (1 H, d, J 7)	4.21 (1 H, m)	3.78 (2 H, q, $J_{vic.}$ 20 and $J_{gem.}$ 6, OCH_2)	2.92 (1 H, dd, $J_{4a,4ax'}$ $J_{4a,8a}$ 6)	2.50—1.50 (8 H, m), 0.95 (3 H, J 7, Me)
(3e)	7.70 (2 H, m), 7.38 (3 H, m)	4.88 (1 H, d, J 7)	4.22 (1 H, m)	3.70 (2 H, m, J 10, OCH_2)	2.90 (1 H, dd, $J_{4a,4ax'}$ $J_{4a,8a}$ 10)	2.50—0.90 (6 H, m), 1.63 (2 H, t, J 10, OCH_2CH_2)
(3f)	7.70 (2 H, m), 7.36 (3 H, m)	5.12 (1 H, d, J 7)	4.20 (1 H, m)	5.00 (2 H, dd, $J_{gem.}$ 17, OCH_2O, 3.43 (3 H, s, OMe)	2.90 (1 H, dd, J 10)	2.42—1.54 (6 H, m)
(3g)	8.20 (2 H, m), 7.83 (2 H, m)	4.90 (1 H, d, J 7)	4.30 (1 H, m)	3.80 (2 H, q, J 10, OCH_2)	2.98 (1 H, dd, $J_{4a,4ax.}$ $J_{4a,8a}$ 10)	2.58—1.60 (6 H, m), 1.30 (3 H, J 10, Me)

(4; R¹ = Ph, R² = R³ = OMe) 7.75 (2 H, m), 7.40 (3 H, m), 4.21 (1 H, s, 5-H), 3.48 (3 H, s, OMe), 3.38 (3 H, s, OMe), 3.02—1.61 (total 7 H; 3 H, ABX system, 4-H and 4a-H, and 4 H, m, 7-H_2 and 8-H_2).

corresponding oxazinones (3) themselves may be *cis*–*trans* mixtures, though this is not apparent from t.l.c.

For compounds (3), normal *cis*-addition of the diene and nitrosoalkene must have occurred, but then the adduct would equilibrate by ring-opening and -closure



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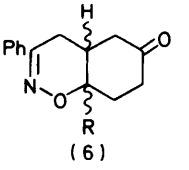

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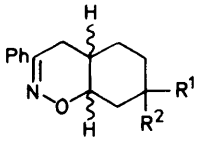

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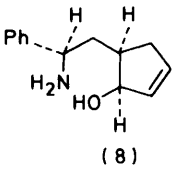
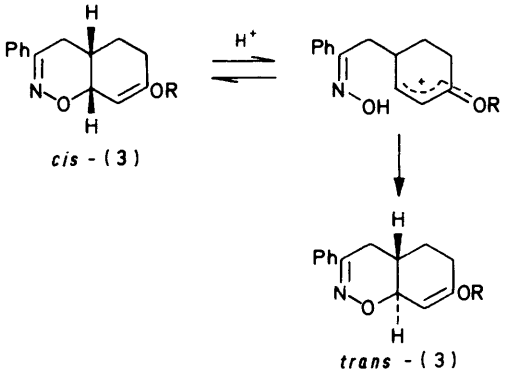


(8)

a ; $R^1 R^2$ = $-OCH_2CH_2O-$

b ; R^1 = OH , R^2 = H

through the allylic carbonium ion, possibly before hydrolysis of the enol-ether group, to give the thermodynamically more stable *trans*-isomer estimated to be present in the adduct (3) in *ca.* 20% by n.m.r.) (Scheme 2). The coupling constant between 8a-H and 4a-H was 7.0 Hz [δ (8a-H) 4.2] for *cis*-(7a) and 9.0 Hz [δ (8a-H) 3.6] for *trans*-(7a). In the latter isomer, the 8- and 8a-protons are perfectly eclipsed as is evident from a Dreiding model.



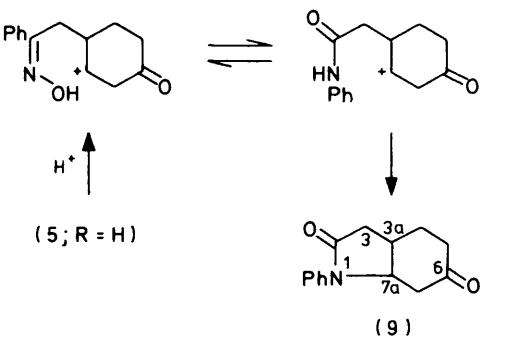
cis - (3)

trans - (3)

SCHEME 2

When the ketone (5; R = H) was heated with trifluoroacetic acid, the dione (9) was obtained in moderate yield; its structure follows from its physical data. The rearrangement probably results from protonation of the oxazinone oxygen atom, followed by a Beckmann rearrangement to give the product (Scheme 3). This type of reaction is not observed in similar bicyclic oxazines, though it was recently reported [3] for acyl-substituted monocyclic analogues.

Thermolysis.—The thermolysis of 3-arylcyclopent[*e*]-1,2-oxazines was found to give 2-arylpyridines and acetaldehyde as major products.[6] In our case, the thermal decompositon of the oxazines (3b, c) and the ketone

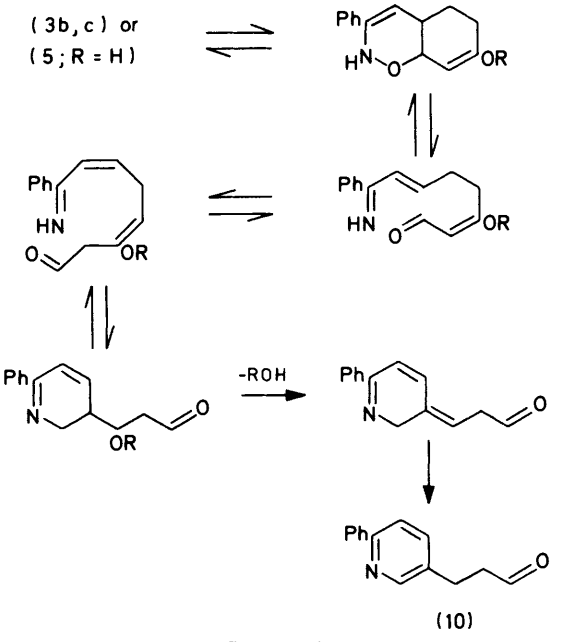


(5; R = H)

(9)

SCHEME 3

(5; R = H) in the melt at 265 °C for 10 min gave water as the only detectable volatile component, and a solid product isolated in low yield by p.l.c. was shown to be 3-(6-phenyl-3-pyridyl)propionaldehyde (10); a probable route is shown in Scheme 4. By analogy with other



(10)

SCHEME 4

findings [2,7] it is assumed that the adducts (3) or (5) rearrange initially to the 2*H*-isomers which can then undergo electrocyclic ring-opening.

EXPERIMENTAL

^{1}H n.m.r. spectra were obtained at 220 MHz in $CDCl_3$. Mass spectra were recorded at 70 eV using a direct-insertion probe. I.r. spectra were recorded as Nujol mulls on a Unicam SP 1000 spectrophotometer; u.v. spectra were recorded on a Unicam SP 800 model.

Dichloromethane was dried by distillation from calcium hydride, and tetrahydrofuran (THF) was distilled from $LiAlH_4$. Preparative layer chromatography (p.l.c.) was carried out with silica gel 60 $PF_{254+366}$ (Merck) as the stationary phase. Light petroleum refers to the fraction of boiling range 60—80 °C.

Alkoxybenzenes and Cyclohexa-1,3-dienes.—*m*-Methylphenetole, phenyl propyl ether, butyl phenyl ether, isopropyl phenyl ether, and methoxymethoxybenzene were prepared according to literature procedures.[4,8,9] The other substrates were commercial products (B.D.H.).

Reduction of the aromatic ethers with sodium and ethanol in liquid ammonia gave chiefly the corresponding cyclohexa-1,4-dienes which were isomerised smoothly to the conjugated 1,3-dienes in *ca.* 80—90% yield with sodium t-butoxide in dimethyl sulphoxide.[10]

Tetrahydro-4H-1,2-benzoxazines (3a—g) and (4; R^1 = Ph, R^2 = R^3 = OMe).—Anhydrous sodium carbonate (2 g) was added to a stirred solution of the α-chloroacetophenone oxime R'C(:NOH)CH_2Cl [11] and the diene (2) [4,5] in dichloromethane (25 cm^3) at room temperature. [Adduct (3a) was prepared from cyclohexa-1,3-diene.] After 24 h, the mixture was filtered through Celite, the solvent was removed under reduced pressure and the crude product was extracted with light petroleum, from which the adducts crystallised upon concentration and cooling. The analytical and ^1H n.m.r. data are summarised in Tables 1 and 2. The adducts (3b—f) and (4; R^1 = Ph, R^2 = R^3 = OMe), when dissolved in ethanol and treated with hydrochloric acid at room temperature, hydrolysed to the corresponding oxazinone (5; R = H) and (6; R = OMe), respectively.

The Oxazinone Ethylene Acetal (7a).—The ketone (5; R = H) was heated under reflux with a slight excess of dry ethylene glycol in benzene containing a trace of naphthalene-2-sulphonic acid using azeotropic separation of water. The product was extracted with ether, and the extract was washed with 1M NaOH and then with water, then dried (Na_2SO_4), and evaporated under reduced pressure to give the *acetal* (7a) (70%), m.p. 139—140 °C (from benzene–light petroleum) (Found: C, 70.3; H, 7.0; N, 5.1. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.0%); $\nu_{max.}$ 695, 705, 760, 770, 820, 990, 1 005, 1 030, 1 100, 1 130, 1 570, and 1 585 cm^{-1}; δ 7.70 (2 H, m), 7.38 (3 H, m), 3.60 (1 H, sextet, *J* 14 and 5 Hz, 8a-H, 3.98 (4 H, m, OCH_2CH_2O), and 2.98—1.24 (9 H, m); *m/z* 273 (M^+, 25), 256 (14), 103 (40), and 43 (100%). P.l.c. with chloroform–ethyl acetate (2 : 1) as developer gave two isomers: (a) cis-*isomer*, R_F 0.44, 30% yield, m.p. 120 °C (from benzene–light petroleum); $\nu_{max.}$ 695, 760, 820, 1 005, 1 040, 1 100, 1 570, and 1 595 cm^{-1}; δ 4.20 (1 H, m, 8a-H); (b) trans-*isomer*, R_F 0.61, 20% yield, m.p. 155—156 °C (from benzene–light petroleum); $\nu_{max.}$ 705, 770, 800, 1 030, 1 130, 1 565, and 1 590 cm^{-1}; δ 3.60 (1 H, m, 8a-H).

Attempted Reduction of the Ethylene Acetal (7a).—The acetal resisted attempted reduction with $LiAlH_4$ in dry ether at room temperature or in dry THF under reflux for 24 h, or with aluminium amalgam [12] in wet ether at room temperature.

Reduction of the Oxazinone (5; R = H).—The oxazinone was reduced with $LiAlH_4$ in dry THF at room temperature. P.l.c. [chloroform–ethyl acetate (2 : 1) as developer] of the *product* (7b) gave two isomers: (a) cis-*isomer* (73%), m.p. 102—105 °C (from ethyl acetate–light petroleum) (Found: C, 72.7; H, 7.5; N, 6.0. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%); $\nu_{max.}$ 700, 770, 930, 960, 1 095, 1 110, and 3 420 cm^{-1}; δ 7.70 (2 H, m), 7.34 (3 H, m), 4.13—3.85 (1 H, m), 3.02 (1 H, s), 2.75 (1 H, dd, *J* 7 Hz each, 4a-H), and 2.40—1.35 (8 H, m); (b) trans-*isomer* (27%), m.p. 182—185 °C (from ethyl acetate–light petroleum) (Found: C, 72.5; H, 7.4; N, 5.9. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%); $\nu_{max.}$ 700, 770, 930, 960, 1 075, 1 0105, and 3 340 cm^{-1}; δ 7.67 (2 H, m), 7.34 (3 H, m), 4.15—3.96 (2 H, m), 2.78 (1 H, dd, *J* 7 Hz each, 4a-H), and 2.50—1.20 (9 H, m).

Beckmann Rearrangement of the Ketone (5; R = H).—A solution of the ketone (0.5 g) in trifluoroacetic acid (3 cm^3) was heated under reflux for 5 h, after which the acid was removed under reduced pressure. P.l.c. [chloroform–diethyl ether (5 : 1) as developer] of the residue afforded the *rearrangement product* (9) (0.35 g, 70%) as needles, m.p. 169—172 °C (from ethanol) (Found: C, 72.9; H, 6.6; N, 6.2. $C_{14}H_{15}NO_2$ requires C, 73.2; H, 6.55; N, 6.1%); $\nu_{max.}$ 710, 730, 775, 820, 1 150, 1 170, 1 235, 1 280, 1 565, 1 600, 1 715, and 1 720 cm^{-1}; δ 7.70 (2 H, m), 7.40 (3 H, m), 3.60 (1 H, m, 7a-H), 2.91 (2 H, m, 3-H_2), 2.47 (2 H, m, 7-H_2), 2.23 (2 H, m, 5-H_2), 2.05 (1 H, m, 3a-H), and 1.21 (2 H, m, 4-H_2); *m/z* 229 (M^+, 8), 199 (14), 172 (14), 141 (17), 119 (20), 118 (31), and 77 (100%).

Thermolysis of the Oxazine Adducts (3b, c) and (5; R = H).—Each adduct (0.5 g) was heated at 265 °C for 10 min in a microdistillation apparatus. For the ketone (5; R = H) case it was observed that water condensed on the upper end of the apparatus. The residue was purified by p.l.c. [chloroform–ethyl acetate (3 : 1) as developer] to give 3-(6-*phenyl*-3-*pyridyl*)*propionaldehyde* (10) (0.2 g, 40%), m.p. 61—62 °C (from light petroleum) (Found: C, 79.4; H, 6.2; N, 6.4. $C_{14}H_{13}NO$ requires C, 79.6; H, 6.2; N, 6.6%); $\nu_{max.}$ 1 585, 1 600, 1 680, 1 720, and 3 030 cm^{-1}; δ 9.75 br. (1 H, s, CHO), 8.6 (1 H, s, pyridine), 7.6—7.15 (3 H, m), 7.4—7.0 (4 H, m), 2.45 (2 H, t, *J* 10 Hz, CH_2CHO), and 1.63 (2 H, t, *J* 10 Hz, Py-CH_2).

The authors express their thanks to Dr. T. L. Gilchrist, University of Liverpool, for useful comments and valuable criticisms of this work. Thanks are also extended to the technical staff, University of Liverpool, for carrying out the mass-spectral analyses.

[1/1530 *Received*, 2nd *October*, 1981]

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