Thermal Rearrangement of some Oxazolidine *N*-Oxides. 2-Alkyl-6-aryl-3,4-dihydro-2*H*-1,5,2-dioxazines[1]

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3-Alkyl-2-aryloxazolidines are oxidized with 3-chloroperoxybenzoic acid to produce the corresponding oxazolidine *N*-oxides. These *N*-oxides undergo thermal rearrangement to give 2-alkyl-6-aryl-3,4-dihydro-2*H*-1,5,2-dioxazines in 55–85% yield.

Nicotine *N*-oxide[2] as well as other *N*-methylpyrrolidine *N*-oxides[3] bearing aryl groups α- to the oxide function, undergo a thermal rearrangement resulting in the incorporation of the oxide function into the pyrrolidine ring leading to ring-expanded 6-aryl-2-methyl-tetrahydro-2*H*-1,2-oxazines. The applicability of this rearrangement to similarly substituted piperidine *N*-oxides has been examined and the conditions for the synthesis of a series of 7-aryl-2-methyl-hexahydro-1,2-oxazepines have been reported.[4]

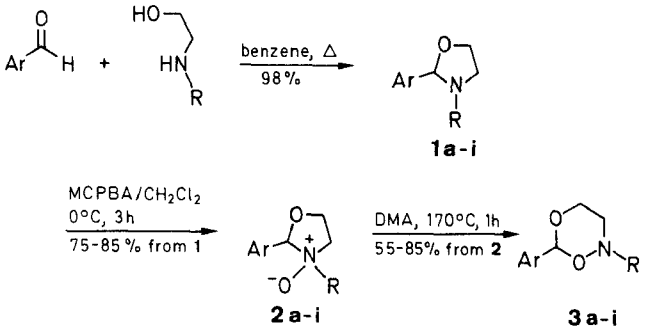
These thermal rearrangements are analogous to rearrangements of acyclic tertiary amine *N*-oxides bearing an allyl or benzyl group, to *O*-allyl- or *O*-benzylhydroxylamines discovered by Meisenheimer.[5] It is noteworthy that amine oxides bearing only alkyl groups exhibit different behavior, whereby an olefin and a hydroxylamine are obtained via a Cope elimination sequence.[6]

It was envisioned that heteroatom substitution of the ring CH_2 group of a 2-arylpyrrolidine *N*-oxide at the 3 position by an oxygen atom, could constitute a viable starting material for constructing 3,4-dihydro-2*H*-1,5,2-dioxazines and provide an efficient entry into such heterocyclic systems. We describe here the conditions for achieving the synthesis of a series of 2-alkyl-6-aryl-3,4-dihydro-2*H*-1,5,2-dioxazines **3a–i**, a previously unknown group of compounds.[7]

The starting materials for the synthesis are 3-alkyl-2-aryloxazolidines **1a–i**. These compounds were easily prepared by heating equimolar mixtures of commercially available 2-alkylaminoethanols and aromatic aldehydes in benzene in a Dean-Stark apparatus with azeotropic removal of the water formed.[8] The oxazolidine *N*-oxides **2a–i** were made by oxidation of **1a–i** with 3-chloroperoxybenzoic acid (MCPBA) using a general procedure for oxidation of tertiary amines.[9] The crude *N*-oxides **2**, obtained as viscous materials, were generally used without further purification in the subsequent rearrangement step. The *N*-oxide **2a** was purified by dissolving the crude material in the minimum quantity of dichloromethane, triturating it with petroleum ether, and cooling the solution at −20 °C giving rise to colorless crystals.

Attempts to oxidize the *N*-*tert*-butyloxazolidines gave rise to a number of minor products and did not afford the desired *N*-oxides.

The thermal rearrangement of *N*-oxides **2** was carried out by heating the *N*-oxides in dimethylacetamide at 170 °C for about 1 h. The course of the rearrangement was followed by thin-layer chromatography on silica gel ($MeOH/Et_2O$, 1:4) where the disappearance of the spot corresponding to the *N*-oxides (R_f 0) and appearance of the product (R_f 0.90) was monitored. Some decomposition ensued as was evident from darkening of the solution.



1, 2, 3	Ar	R	1, 2, 3	Ar	R
a	Ph	Me	**f**	Ph	Et
b	4-MeC_6H_4	Me	**g**	4-MeC_6H_4	Et
c	4-ClC_6H_4	Me	**h**	4-ClC_6H_4	Et
d	4-$NO_2C_6H_4$	Me	**i**	4-$NO_2C_6H_4$	Et
e	1-naphthyl	Me			

Table 1. Dihydrodioxazines **3** Prepared

Product	Yield[a] (%)	mp (°C)[b] bp (°C)/mbar	Molecular Formula[c]	HRMS (*m/z*, M^+)[d] calc.	found
3a	62	79–80/0.24	$C_{10}H_{13}NO_2$ (179.2)	179.0946	179.0945
3b	55	88–90/0.50	$C_{11}H_{15}NO_2$ (193.2)	193.1103	193.1098
3c	65	83–85/0.47	$C_{10}H_{12}ClNO_2$ (213.6)	213.0557	213.0550
3d	85	103–105 (PE)[e]	$C_{10}H_{12}N_2O_4$ (224.2)		
3e	58	125/0.03	$C_{14}H_{15}NO_2$ (229.2)	229.1103	229.1108
3f	60	63–65/0.05	$C_{11}H_{15}NO_2$ (193.2)	193.1103	193.1104
3g	65	49–50/0.02	$C_{12}H_{17}NO_2$ (207.2)	207.1259	207.1253
3h	73	67–68/0.02	$C_{11}H_{14}ClNO_2$ (227.6)	227.0825	227.0824
3i	81	62–63 (PE)[e]	$C_{11}H_{14}N_2O_4$ (238.2)		

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained for **3d** and **3i**: C ±0.10, H ±0.11, N ±0.33.
[d] Obtained at 70 eV on a Kratos MS/50 double focusing spectrometer, Pennsylvania State University, University Park, PA.
[e] PE = petroleum ether.

Removal of dimethylacetamide and chromatography of the residue on basic alumina then gave the dihydrodioxazines **3a–i** which were eluted very quickly and were stable on silica gel TLC plates.

All new compounds were characterized by IR, ^{1}H-NMR, and MS or microanalysis (Tables 1 and 2). The IR spectra of the dioxazine derivatives **3a–i** show a band of medium intensity near $\nu = 930\,cm^{-1}$ indicative of the N–O bond.[10] The most diagnostic absorption in the ^{1}H-NMR spectra of **3a–i** is a sharp singlet near $\delta = 6–6.5$ for the benzylic hydrogen flanked by two oxygens. The same hydrogen appears as a singlet around $\delta = 5–5.5$ in the spectra of **1a–i**. This significant downfield shift of the signal is in accord with the proposed structure for **3a–i**. Further definitive evidence for the correctness of the assigned structure for the dihydrodioxazines came from an X-ray crystallographic analysis of **3i**.[11]

Table 2. Spectrometric Data of Compounds **3**

Compound	IR (Nujol or film)[a] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[b] δ, J(Hz)
3a	3200–2900, 1470, 1380, 1130, 1100–1080, 1040–990, 930, 760–700	2.82 (s, 3H, CH_3), 2.90–3.06 (m, 2H, NCH_2), 4.20–4.36 (m, 2H, OCH_2), 6.04 (s, 1H, OCHO), 7.52–7.84 (m, 5H$_{arom}$)
3b	3200–2850, 1380, 1130, 1100–1080, 1040–990, 930, 830	2.40 (s, 3H, CH_3), 2.80 (s, 3H, NCH_3), 2.88–3.04 (m, 2H, NCH_2), 4.18–4.34 (m, 2H, OCH_2), 6.00 (s, 1H, OCHO), 7.49 (q, 4H, $J = 8$, H$_{arom}$)
3c	3100–2800, 1500, 1380, 1130, 1100–1080, 1030, 930, 830	2.84 (s, 3H, CH_3), 2.92–3.10 (m, 2H, NCH_2), 4.22–4.38 (m, 2H, OCH_2), 6.00 (s, 1H, OCHO), 7.60 (q, 4H, $J = 8$, H$_{arom}$)
3d	3100–2800, 1480, 1380, 1100–1070, 1040, 930, 830	2.80 (s, 3H, CH_3), 2.88–3.02 (m, 2H, NCH_2), 4.16–4.32 (m, 2H, OCH_2), 6.01 (s, 1H, OCHO), 7.76, 8.35 (d, 4H, $J = 9$, H$_{arom}$)
3e	3150–2800, 1470, 1375, 1100–1080, 1040, 930	2.80 (s, 3H, CH_3), 2.90–3.14 (m, 2H, NCH_2), 4.18–4.46 (m, 2H, OCH_2), 6.54 (s, 1H, OCHO), 7.42–8.54 (m, 7H$_{arom}$)
3f	3150–2750, 1460, 1390, 1260–1120, 1060, 1040, 990, 930, 760–700	1.21 (t, 3H, $J = 7$, $CH_2\underline{CH_3}$), 2.60–3.14 (m, 4H, $\underline{CH_2}CH_3$, NCH_2), 4.14–4.32 (m, 2H, OCH_2), 5.94 (s, 1H, OCHO), 7.34–7.74 (m, 5H$_{arom}$)
3g	3100–2850, 1385, 1160–1060, 1040, 1020, 925, 830	1.20 (t, 3H, $J = 7$, $CH_2\underline{CH_3}$), 2.36 (s, 3H, CH_3), 2.66–3.04 (m, 4H, $\underline{CH_2}CH_3$, NCH_2), 4.10–4.28 (m, 2H, OCH_2), 5.90 (s, 1H, OCHO), 7.36 (q, 4H, $J = 8$, H$_{arom}$)
3h	3050–2850, 1620, 1520, 1400, 1180–1080, 1040, 930, 840	1.18 (t, 3H, $J = 7$, $CH_2\underline{CH_3}$), 2.66–3.14 (m, 4H, $\underline{CH_2}CH_3$, NCH_2), 4.14–4.28 (m, 2H, OCH_2), 5.90 (s, 1H, OCHO), 7.40 (q, 4H, $J = 8$, H$_{arom}$)
3i	3100–2850, 1480, 1390, 1100–1080, 1040, 935, 830	1.26 (t, 3H, $J = 7$, $CH_2\underline{CH_3}$), 2.64–3.20 (m, 4H, $\underline{CH_2}CH_3$, NCH_2), 4.16–4.36 (m, 2H, OCH_2), 6.00 (s, 1H, OCHO), 7.78, 8.36 (d, 4H, $J = 9$, H$_{arom}$)

[a] Recorded on a Perkin-Elmer 710B spectrometer.
[b] Recorded at 100 MHz on a Varian XL 100 spectrometer.

3-Alkyl-2-aryloxazolidines (1); General Procedure:
A stirred mixture of a 2-alkylaminoethanol (0.05 mol) and an aldehyde (0.05 mol) in benzene (100 mL) is heated in a Dean–Stark apparatus. Water is continuously removed from the mixture by azeotropic distillation with the benzene. After collection of the theoretical amount of water, the benzene is removed on the rotary evaporator and the residue is purified by distillation or crystallization as appropriate. Oxazolidines **1a,c,d,f–i** are known compounds.

1b: yield: 96%; bp 67–68°C/0.065 mbar

$C_{11}H_{15}NO$	calc.	C 74.54	H 8.53	N 7.90
(177.2)	found	74.50	8.55	7.89

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.30$ (s, 3H, CH_3), 2.37 (s, 3H, NCH_3); 2.54–2.86, 3.24–3.46 (m, 2H, NCH_2), 3.98–4.27 (m, 2H, OCH_2), 4.68 (s, 1H, OCHN), 7.18–7.46 (q, 4H$_{arom}$).

1e: yield: 95%; bp 120°C/0.030 mbar

$C_{14}H_{15}NO$	calc.	C 78.84	H 7.09	N 6.57
(213.3)	found	78.79	7.00	6.68

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.36$ (s, 3H, CH_3), 2.76–3.08, 3.31–3.57 (m, 2H, NCH_2), 4.08–4.35 (m, 2H, OCH_2), 5.54 (s, 1H, OCHN), 7.34–8.58 (m, 7H$_{arom}$).

2-Alkyl-6-aryl-3,4-dihydro-2*H*-1,5,2-dioxazines (3); General Procedure:
To a stirred ice-bath cooled solution of the oxazolidine **1** (10 mmol) in anhydrous CH_2Cl_2 (10 mL) under N_2, a solution of MCPBA (Aldrich 80–85%; 2.14 g, 10 mmol) in anhydrous CH_2Cl_2 (90 mL) is added dropwise. The mixture is stirred for a total of 3 h during which time the ice bath is allowed to warm up to room temperature. The solution is then passed through a dry column containing basic alumina (about 20 times the total weight of starting materials). Chloroform (100 mL) is then added to remove trace amounts of unreacted **1**, followed by MeOH/$CHCl_3$ (1:3; v/v; 300 mL) to elute the *N*-oxide **2**. Evaporation of the solvents on the rotary evaporator affords the crude *N*-oxide as a viscous residue in 75–85% yield. The *N*-oxide is then dissolved in anhydrous DMA (20 mL) and the solution is heated in an oil bath at 170°C for 50 min. The solution is then cooled to r.t. and DMA is removed under reduced pressure at a bath temperature of about 40°C. The dark brown residue is chromatographed on basic alumina. Elution with anhydrous Et_2O followed by evaporation of the solvent yields the dihydrodioxazine **3**. With the exception of **3d** and **3i**, the dihydrodioxazines are pale yellow oils. The liquid products obtained from several chromatographic separations were combined and distilled under vacuum (Table 1).

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