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THE PHOTOCHEMICAL OR THERMAL REARRANGEMENT OF OXAZIRANES AS A METHOD IN ALKALOID SYNTHESIS

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Abstract—The conversion of cyclic ketones to β-arylethyl amine derived imines, their oxidation to oxaziranes and subsequent photochemical rearrangement to N-(β-arylethyl) lactams was probed as a potential method for alkaloid syntheses.

As a complement to the preceding paper,[1] we present some additional examples of photochemical rearrangements of oxaziranes,[2,3] which we obtained several years ago.[4] In order to ascertain the synthetic potential of this method for alkaloid syntheses, and particularly for a synthesis of vincamine, oxaziranes were prepared from Schiff bases derived from β-phenethylamine, 3,4-dimethoxy and 3,4-methylenedioxy-β-phenethylamine, tryptamine and ethanolamine. It was anticipated that the latter examples might serve in eventual β-arylations (particularly with an indole) of the ethyl amine chain.

Cyclic ketones with varying degree of α-substitution were condensed with these amines and the corresponding imines were obtained by azeotropic removal of water. The imines were subjected to oxidation with *m*-chloroperoxybenzoic acid. For a subsequent photochemical rearrangement, cyclohexane solutions of the resultant oxaziranes were irradiated with a 450 W Hanovia Hg lamp. Progress of the rearrangement was monitored by loss of the oxazirane IR absorption at 1375 cm^{-1}.

The yields of the oxaziranes and of the final lactam products, obtained by this reaction sequence, are shown in Table 1. It may be noted that the lactam obtained from tryptamine and 2-ethylcyclopentanone has, like the other examples given in the preceding paper, been used as an intermediate in the synthesis of vinamine,[5] and also in a synthesis of eburnamonine.[6]

A thermal rearrangement of oxazirane intermediates at 300° was also studied for comparison with the photochemical rearrangement leading to the the phenethyl and 3,4-dimethoxyphenethyl substituted valerolactams (entries 1 and 2, Table 1). It was found that the same products could thus be obtained in slightly, but not significantly, better yields (83 and 80% vs 75% for the oxazirane rearrangement step).

EXPERIMENTAL

General procedure for the preparation of Schiff bases. The imines were prepared by refluxing equimolar amounts of amine and ketone in benzene with a Dean Stark water separator until the expected amount of water had been produced. Upon drying over $MgSO_4$, filtration and evaporation of benzene, the resultant Schiff base was used without further purification as distillation was found to cause decomposition. Purity estimation was based upon IR spectra, observing disappearance of CO and amine bands and appearance of the imine band at ν_{max} 1660–1680 cm^{-1}. TLC provided another means of determining purity, by showing one major product spot on silica gel plates with diethyl ether.

General procedure for oxidation of the Schiff bases. The Schiff base in dry benzene, under N_2, was treated dropwise with an equimolar amount of *m*-chloroperoxybenzoic acid, dissolved in enough dry benzene to cause soln. After stirring at rt for 3 hr, $NaHCO_3$aq was added to neutralize the *m*-chlorobenzoic acid. Following extraction with dil HCl to remove any imine or amine produced by hydrolysis of the imine, the benzene soln was dried over $MgSO_4$, filtered and the benzene evaporated under vacuum. Any ketone produced from hydrolysis was removed by vacuum evaporation, leaving behind the oxazirane which was characterized by an IR adsorption near ν_{max} 1375 cm^{-1}. Relative purity was indicated by TLC on silica gel, using ether as solvent. Generally the oxazirane was used without further purification.

General irradiation procedure. The crude oxazirane, normally 2 g, was dissolved in 230 ml distilled cyclohexane (230 ml being the volume of a Pyrex reservoir surrounding the source of a photolysis apparatus). The soln was purged with N_2 and then irradiated with a 450 W Hanovia mercury lamp, occasionally removing aliquots of soln to monitor the loss of the osazirane band near ν_{max} 1375 cm^{-1}. Reaction times varied between 30 min and 12 hr. Workup after evaporation of the solvent varied with the experiment as indicated below.

N-β-Phenethylvalerolactam.[7] A soln of 5.0 g (0.041 m) β-phenethylamine and 3.45 g cyclopentanone (0.040 m) in 50 ml benzene gave a quantitative yield of Schiff base.

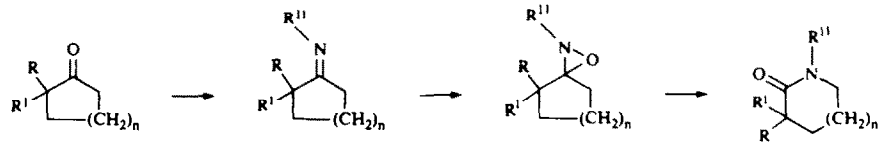
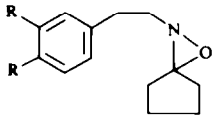
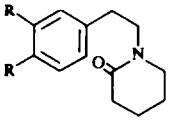
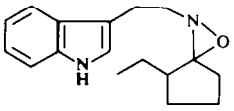
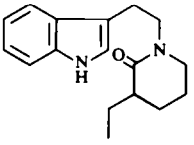
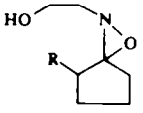
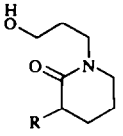
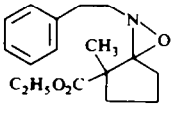
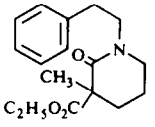
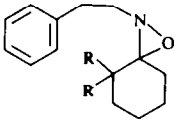
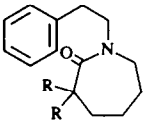
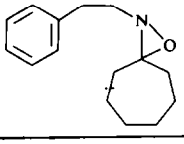
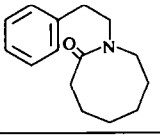


Table 1.

Oxaziranes, yields of imine oxidations	Lactams by photochemical rearrangement, yields, by thermal rearrangement,(yields)
 R = H, 95 % R = OCH_3, 90 % R-R = O-CH_2-O, 75 %	 R = H, 75 % (83 %) R = OCH_3, 75 % (80 %) R-R = O-CH_2-O, 60 %
	 25 % overall from ketone
 R = CH_3, 75 % R = C_2H_5, 66 %	 R = CH_3, 50 % R = C_2H_5, 25 %
 70 %	 50 %
 R = H, 75 % R-R = $(CH_2)_5$ 90 %	 R = H, 85 % R-R = $(CH_2)_5$, 95 %
 75 %	 89 %

To 3.00 g (0.0122 m) of the Schiff base in dry benzene was added 2.66 g (0.013 m) *m*-chloroperoxybenzoic acid and the soln was stirred for 7 hr. After usual workup a concentrated benzene soln of the product was diluted with petroleum ether, cooled to −5°, filtered and concentrated to 2.63 g oxazirane.

A soln of 920 mg oxazirane in 230 ml cyclohexane was irradiated for 10 hr to give, on evaporation and distillation, 700 mg of 1-(*β*-phenyethyl)-2-piperidone (75%), m.p. 38–40°.[7]

IR (KBr) ν_{max} 1647, 1488, 747, 695 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 7.3 (s, 5H), 3.6 (t, 2H), 3.1 (m, 2H), 2.9 (t, 2H), 2.4 (m, 2H) 1.7 (m, 4H); mass spectrum *m/z* 203 (M^+).[7]

Pyrolysis of the oxazirane was accomplished by injection of 200 mg of the compound, dissolved in 1 ml benzene, onto a glass column (1 m × 0.6 cm) packed with glass helixes, heated at 300° and maintained under a stream of N_2. Immediately after injection additional benzene was added to sweep the pyrolysis products from the column. Concentration gave 166 mg (83%) of the same 2-piperidone.

N-*β*-(3,4-*Dimethoxyphenyl*)*ethylvalerolactam*.[7] A soln of 5.0 g of 3,4-dimethoxyphenethylamine and 2.65 g cyclopentanone in 50 ml benzene gave the Schiff base on evaporation. IR (neat) ν_{max} 1675, 1590, 1515, 1450, 1270, 1150, 1035, 815 cm^{-1}.

To 3.0 g of the imine was added 2.66 g *m*-chloroperbenzoic acid, giving on workup, a 90% yield of 2-(3, 4-dimethoxy-*β*-phenethyl)-3, 3-tetramethyleneoxazirane, IR (neat) ν_{max} 1600, 1500, 1450, 1375, 1275, 1175, 750 cm^{-1}.

The oxazirane (1.0 g) was irradiated 12 hr, giving on tube distillation and chromatography on silica gel with CH_2Cl_2 750 mg (75%) 2-(3,4-dimethoxy-*β*-phenethyl)piperidone, m.p. 204–206°; IR (KBr) ν_{max} 1625, 1500, 1450, 1270, 1240, 1150, 1030 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 6.9 (s, 3H), 3.6 (t, 2H), 3.2 (m, 2H), 2.9 (t, 2H), 2.4 (m, 2H), 1.8 (m, 4H), 3.9 (s, 6H); mass spectrum *m/z* 263 (M^+).[7]

Pyrolysis of 0.2 g of ozazirane in 1 ml benzene at 300°, under conditions described above, gave 177 mg, (80%), of the same 2-piperidone.

N-*β*-(3,4-*Methylenedioxyphenyl*)*ethylvalerolactam*.[7] The mixture obtained from 3 g 3,4-methylenedioxy-*β*-

phenethylamine, 1.53 g cyclopentanone and 40 ml benzene was concentrated to give the corresponding Schiff base, IR (neat) ν_{max} 1670, 1600, 1475, 1440, 1350, 1250, 1180, 1040, 940, 810 cm^{-1}.

To 3 g of the Schiff base was added 3.05 g *m*-chloroperbenzoic acid. After 4 hr and the usual workup a 75% yield of 2-(3,4-methylenedioxy-β-phenethyl)-3,3-tetramethylene oxazirane was obtained; IR (neat) ν_{max} 1600, 1500, 1440, 1375, 1250, 1190, 1040, 940, 810 cm^{-1}.

A cyclohexane soln of 700 mg of the oxazirane was irradiated for 10 hr. The resulting oil on evaporation of solvent and trituration with petroleum ether gave 510 mg (73%) of N-(3, 4-methylenedioxy-β-phenethyl-2-piperidone, m.p. 94–96°; IR (KBr) ν_{max} 1615, 1500, 1440, 1270, 1250, 1040, 940, 810 cm^{-1}; 100 MHz NMR δ ($CDCl_3$) 6.6 (m, 3H), 5.8 (s, 2H), 3.4 (t, 2H), 3.05 (m, 2H), 2.65 (t, 2H), 2.25 (m, 2H), 1.7 (m, 4H); mass spectrum *m/z* 247 (M^+).[7]

N-2-(3-*Indolyl*)*ethylvalerolactam*.[5] Oxidation of the Schiff base of tryptamine and 2-ethylcyclopentanone, dissolved in dry benzene, was obtained at 0–5°. Five min after addition of the peracid $NaHCO_3$aq was added, followed by the normal workup to give the oxazirane; IR (film) ν_{max} 3400, 3050, 2960, 1380, 1360, 1230, 1100 cm^{-1}.

A soln of 1 g crude oxazirane in cyclohexane and just enough abs EtOH to cause soln was irradiated for 45 min. The mixture was fractionally distilled, giving the lactam, b.p. 160–180° (0.01 mm), which crystallized and was recrystallized from ether and sublimed, to provide 0.23 g of product; m.p. 123–125°; IR 3260, 3050, 2915, 1615, 1490, 1455, 1260, 1100 cm^{-1}; 100 MHz NMR δ ($CDCl_3$), 8.4 (s, 1H), 7.55 (d, 1H), 6.9–7.3 (m, 4H), 3.6 (t, 2H), 2.9–3.3 (overlapping triplets, 4H), 1.2–2.4 (m, 7H), 0.95 (t, 3H); *m/z* 270 (M^+).[8]

N-(*β-Hydroxyethyl*)-3-*methyl*-2-*piperidone*. The oily N-(2-methylcyclopentylidene-β-ethanolamine, IR (film) ν_{max} 3400, 1650, 1455, 1075, 1050 cm^{-1}, was oxidized according to the general procedure to provide 2-(β-hydroxyethyl)-3,3-(2-methyltetramethylene)oxazirane in 75% yield; IR (film) ν_{max} 3400, 1470, 1375, 1075 cm^{-1}.

Irradiation of 3.0 g of the oxazirane in cyclohexane for 1 hr and chromatography of the concentrated mixture on alumina, eluting with ether and MeOH and distillation at 120° (0.2 mm) gave 1.36 g (50%) of the N-alkylpiperidone as a very hygroscopic oil; IR (film) ν_{max} 3400, 2950, 1615, 1500, 1360, 1290, 1060 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 4.5 (s, 1H), 3.2–3.8, (3 overlapping t, 6H), 2.4 (d, 1H), 1.8 (m, 4H), 1.3 (d, 3H); mass spectrum *m/z* 157 (M^+). (Found: C, 61.13; H, 9.86; N, 8.64. Calc for $C_8H_{15}NO_2$: C, 61.15; H, 9.55; N, 8.92%).

N-(*β-Hydroxyethyl*)-3-*ethyl*-2-*piperidone*. Oxidation of N-(2-ethylcyclopentylidene)-β-ethanolamine gave 2-(β-hydroxyethyl)-3,3-(2-ethyltetramethylene) oxazirane in 66% yield; IR (film) ν_{max} 3400, 1470, 1380, 1075 cm^{-1}. Photochemical rearrangement of 1 g of the oxazirane and workup as in the preceding example gave 0.25 g of the very hygroscopic piperidone product, b.p. 120° (0.05 mm); IR (film) ν_{max} 3400, 2950, 1620, 1500, 1475, 1360, 1300, 1075 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 4.5 (s, 1H), 3.2–4.0 (m, 6H), 2.3 (s, 1H), 1.9 (m, 6H), 1.0 (t, 3H); mass spectrum *m/z* 171 (M^+). (Found: N, 8.15. Calc for $C_9H_{17}NO_2$: N, 8.19%).

N-(*β-Phenethyl*)-3-*carboethoxy*-3-*methyl*-2-*piperidone*. A mixture of 5.0 g (29 mmol) 2-carboethoxy-2-methylcyclopentanone and 3.66 g (30 mmol) β-phenethylamine was stirred under vacuum for 10 hr. Gas chromatography of the resultant oil indicated it to be a single product and showed total reaction of the starting ketone. The N-(2-carboethoxy-2-methylcyclopentylidene)-β-phenethylamine, IR (film) ν_{max} 1735, 1675, 1600, 1460, 1375, 1165, 1100, 1040 cm^{-1}, was oxidized according to the general procedure to provide 2-(β-phenethyl)-3,3-(2-carboethoxy-2-methyl) tetramethylene-oxazirane in 70% yield. Irradiation of 3.3 g of the oxazirane in cyclohexane for 6 hr, column chromatography on silica, eluting with ether and chloroform and distillation gave 1.5 g (50%) of the piperidone, b.p. 195–198° (1 × 10 $^{-4}$ mm); IR (film) ν_{max} 1735, 1640, 1490, 1460, 1360, 1260, 1180, 1160, 1135, 1025 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 7.2 (s, 5H), 4.1 (q, 2H), 3.5 (t, 2H), 3.05 (t, 2H), 2.8 (t, 2H), 1.7 (m, 4H), 1.4 (s, 3H), 1.2 (t, 3H); mass spectrum *m/z* 289 (M^+). (Found: C, 70.55; H, 8.15; N, 4.62. Calc for $C_{17}H_{23}NO_3$: C, 70.59; H, 7.96; N, 4.84%).

N-(*β-Phenethyl*)-*perhydroazepin*-2-*one*. The Schiff base (3 g) of cyclohexanone and β-phenethylamine, IR (film) ν_{max} 1655, 1600, 1490, 1475, 1450, 1350, 1230, 1030, 900 cm^{-1}, was oxidized to the oxazirane, IR (film) ν_{max} 1600, 1490, 1380, 1340, 1230, 1070 cm^{-1}, by the general procedure, with a 75% yield. Irradiation of 1.0 g of 2-(β-phenethyl)-3,3-pentamethyleneoxazirane in 220 ml cyclohexane for 10 hr, column chromatography on silica, eluting with CH_2Cl_2, and distillation gave 0.59 g (60%) of the lactam, b.p. 160° (0.025 mm); IR (film) ν_{max} 1640, 1480, 1450, 1360, 1200 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 7.6 (s, 5H), 3.7 (t, 2H), 3.35 (m, 2H), 2.9 (t, 2H), 2.6 (m, 2H), 1.7 (m, 6H); mass spectrum *m/z* 217 (M^+). (Found: C, 77.14; N, 8.89; N, 6.23. Calc for $C_{14}H_{19}NO$: C, 77.41; H, 8.76; N, 6.45%).

N - (*β-Phenethyl*) - 3,3 - *pentamethyleneperhydroazepin* - 2 - *one*. By the general procedure 2,2-pentamethylenecyclohexanone[8] and β-phenethylamine were converted to the corresponding imine; IR (film) ν_{max} 1650, 1600, 1500, 1455, 1080, 1035 cm^{-1}. Oxidation of 5.5 g (24 mmol) of the Schiff base with 4.2 g (24 mmol) of *m*-chloroperoxybenzoic acid in benzene for 8 hr gave 5.3 g (90%) of the oxazirane; IR (film) ν_{max} 1600, 1455, 1380, 1325, 1150, 1050, 875 cm^{-1}. Irradiation of 1.51 g 2-(β-phenethyl)-3, 3-(2,2-pentamethylene) pentamethylene oxazirane in cyclohexane for 8 hr and concentration and crystallization of the residue from petroleum ether, gave 1.43 g of the 7-membered ring lactam, m.p. 86–88°. IR (KBr) ν_{max} 1625, 1500, 1465, 1420, 1275, 1170 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 7.2 (s, 5H), 3.55 (t, 2H), 3.20 (m, 2H), 2.75 (t, 2H). 1.5 (m, 14H); mass spectrum *m/z* 285 (M^+). (Found: C, 79.79; H, 9.49; N, 4.63. Calc for $C_{19}H_{27}NO$: C, 80.00; H, 9.47; N, 4.91%).

N-(*β-Phenethyl*)*perhydroazocine*-2-*one*. N-Cycloheptylidene-β-phenethylamine was prepared by the general procedure; IR (film) ν_{max} 1635, 1600, 1500, 1450, 1350, 1100, 750 cm^{-1}. Its oxidation by the general procedure gave 2-(β-phenethyl)-3, 3-hexamethyleneoxazirane in 75% yield; IR (film) ν_{max} 1600, 1500, 1450, 1390, 1350, 1255 cm^{-1}. Irradiation of 2.2 g of the oxazirane in 230 ml cyclohexane for 8 hr, concentration and column chromatography of the product on silica, eluting with CH_2Cl_2, gave, after distillation, 1.95 g (89%) of the 8-membered ring lactam, b.p. 150–155° (0.25 mm); IR (film) ν_{max} 1630, 1470, 1455, 1425, 1370, 1140 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 7.5 (s, 5H), 3.6 (t, 2H), 3.4 (m, 2H), 2.9 (t, 2H), 2.5 (t, 2H), 1.4–1.9 (m, 8H); mass spectrum *m/z* 231 (M^+). (Found: C, 77.65; H, 9.27; N, 5.84. Calc for $C_{15}H_{21}NO$: C, 77.92; H, 9.09; N, 6.06%).

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