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THE PHOTOLYSIS OF BERBINE N-OXIDES

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Abstract—Photolysis of *trans*-canadine N-oxide (3) leads to lactam **5** and formamide **7**. Similarly, photolysis of *trans*-xylopinine N-oxide (**12**) supplies lactam **14** and amide **15**. Oxaziridine **4** is a probable intermediate in these transformations, so that selective oxidation of the berbine nucleus at C-6 has been achieved, accompanied by fission of the N-7–C-14 bond. LAH reduction of lactam **5** gives rise to dibenzazecine **8**, while similar treatment of amide **7** generates dibenzazonine **10**. Alternatively, acid hydrolysis of **7** furnishes dibenzazonine **11**.

As part of a program of investigation in the berbine series, we had occasion to study the photolysis of berbine N-oxides. The stereochemistry of two alkaloidal berbine N-oxides, corynoxidine (**1**) and epicorynoxidine (**2**), had previously been established using X-ray crystallography.[1] Additionally, it had been shown that the CMR chemical shifts of C-5, 6, 8, 13 and 14, listed in Table 1, were diagnostic in differentiating *trans* from *cis* berbine N-oxides.[1]

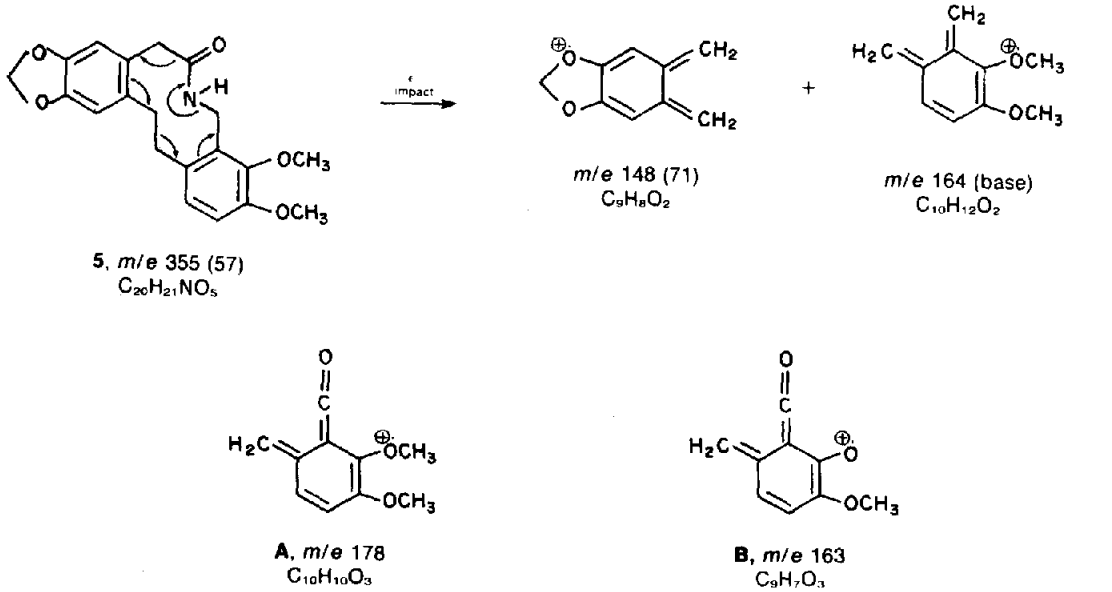
Presently, treatment of racemic canadine, obtained by sodium borohydride reduction of the readily available alkaloid berberine, with *m*-chloroperbenzoic acid followed by chromatography on alumina gave a stable and crystalline N-oxide, **3**, whose CMR spectrum with C-6 appearing at 64.5 ppm and C-13 at 29.7 ppm clearly established it to belong to the *trans* series (Table 1).

Irradiation of a methanolic suspension of *trans*-canadine N-oxide (**3**) under a nitrogen atmosphere, using a 450 watt Ace medium-pressure mercury lamp equipped with a quartz filter, for three hours furnished two products. The first proved to be a lactam which precipitates from chloroform upon work-up, ν_{max}^{KBr} 1640 and 3300 cm^{-1}, and was assigned structure **5**. The mass spectrum of **5**, Scheme 1, shows a molecular ion at *m/e* 355, and a base peak at *m/e* 164. Another intense peak is at *m/e* 148. The alternate structure **6** for the lactam could be eliminated since it would be expected to yield ions A (*m/e* 178) or B (*m/e* 163), Scheme 1, which were absent in the mass spectrum.

The second product from the photolysis is the formamide **7** which was isolated upon preparative tlc of the reaction mother liquor, $\nu_{max}^{CHCl_3}$ 1655 cm^{-1}. The formyl proton in **7** diagnostically appeared as a singlet downfield at δ8.50, while the two sets of methylene protons adjacent to nitrogen were present as singlets at δ4.12 (2H) and δ4.27 (2H). Compounds **5** and **7** were obtained in 5 and 4% yields, respectively, along with 51% recovery of starting N-oxide. The corrected yields for **5** and **7** on the basis of N-oxide consumed are, therefore, 11 and 9%, respectively.

Lithium aluminum hydride reduction of lactam **5** provides the dibenzazecine **8** which can be N-acetylated with acetic anyhdride in pyridine to the amide **9**.

Turning now to the formamide **7**, reduction with LAH supplies the dibenzazonine **10** whose PMR spectrum shows an N-Me singlet at δ2.58 (3H), while the two sets of methylenes adjacent to nitrogen are present as singlets at δ3.40 (2H) and 3.45 (2H). Alternatively, acid hydroly-



5, *m/e* 355 (57)
$C_{20}H_{21}NO_5$

m/e 148 (71)
$C_9H_8O_2$

m/e 164 (base)
$C_{10}H_{12}O_2$

A, *m/e* 178
$C_{10}H_{10}O_3$

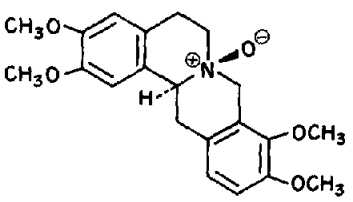
B, *m/e* 163
$C_9H_7O_3$

Scheme 1.

Table 1. CMR chemical shift assignments (ppm) for berbine N-oxides in $CDCl_3$

Compound	C-5	C-6	C-8	C-13	C-14
Corynoxidine (1)	25.1	65.4	67.8	30.4	68.9
Epicorynoxidine (2)	25.7	58.7	66.0	36.3	71.7
trans-Canadine N-oxide (3)	24.8	64.5	67.6	29.7	68.1
trans-Xylopinine N-oxide (12)	23.9	63.1	70.2	29.6	67.5
cis-Xylopinine N-oxide (13)	24.3	56.0	70.3	37.0	70.5
N-Oxide 17	-	66.6	70.3	31.4	68.1

The trivial numbering system adopted here for compound 17 corresponds to that for the berbines.



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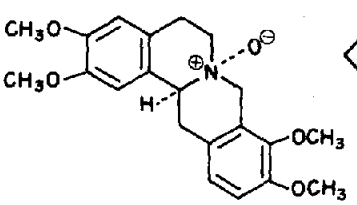

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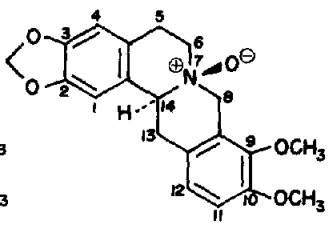

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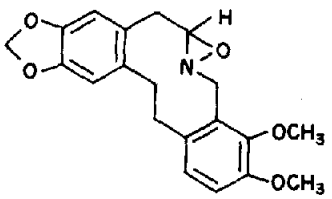

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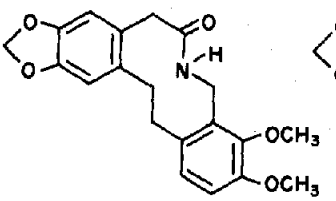

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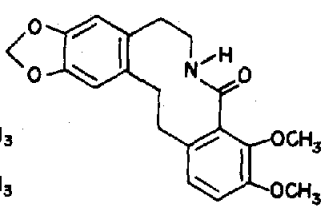

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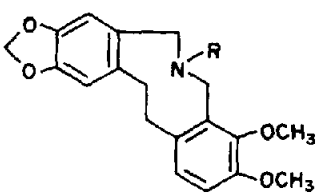
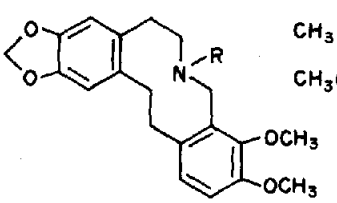
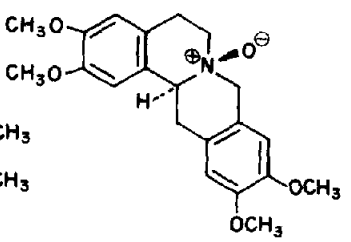


7: R = CHO
10: R = CH_3
11: R = H



8: R = H
9: R = Ac



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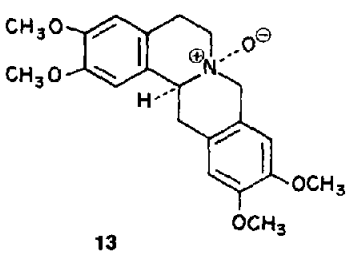

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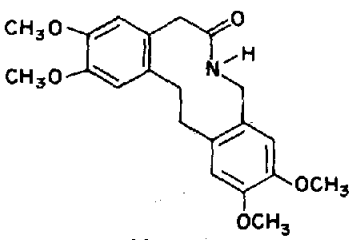

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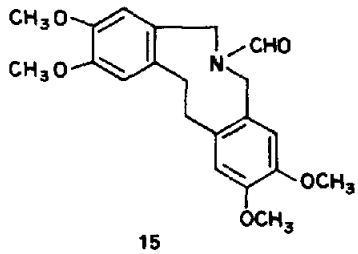

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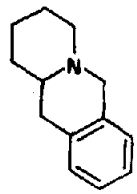

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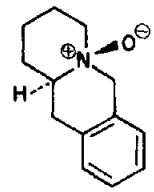
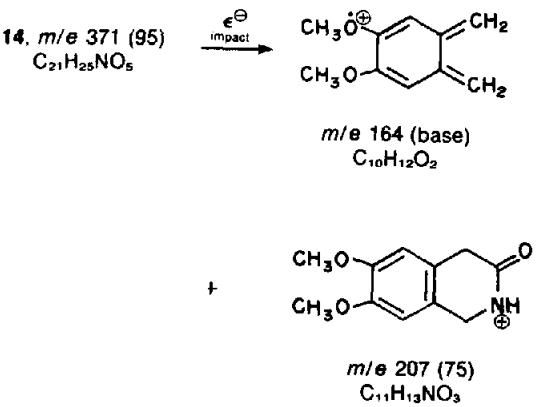


17

sis of 7 leads to the crystalline amine 11 whose methylene protons neighboring the N atom appear again as singlets at δ 3.42 (2H) and 3.52 (2H).

In order to test the generality of our photolytic transformation, the known racemic base xylopinine[2] was oxidized with *m*-chloroperbenzoic acid. Whereas only one stable N-oxide, namely the *trans* isomer, is produced from the oxidation of canadine under our conditions, two N-oxides, 12 and 13, were obtained in a 6:1 ratio from xylopinine, and were separated by careful tlc over silica gel. In the CMR spectrum of the major *trans*-N-oxide 12, C-6 appears characteristically downfield at 63.1 ppm, and C-13 is upfield at 29.6 ppm. On the other hand, the spectrum of the minor *cis*-N-oxide 13 shows C-6 at 56.0 ppm and C-13 at 37.0 ppm (Table 1).

Two products were isolated from the photolysis of *trans*-xylopinine N-oxide (12), together with 33% recovery of starting material. The two products are recognizable by partial analogy with those obtained from the photolysis of *trans*-canadine N-oxide (3). The first product is the lactam 14, $\nu_{max}^{CHCl_3}$ 1660 cm^{-1}, obtainable in 5% yield (8% corrected yield). The base peak in the mass spectrum of 14 is at *m/e* 164 which can obviously originate from either of the two aromatic rings. Another strong peak present, as indicated in Scheme 2 below, is at *m/e* 207. The second product from the photolysis of 12 is the formamide 15, $\nu_{max}^{CHCl_3}$ 1660 cm^{-1}, isolated in 4% yield (7% corrected).



Scheme 2.

The formation of lactam 5 and formamide 7 from *trans*-canadine N-oxide (3) can be explained in terms of the oxaziridine intermediate 4 formed by attack of the N-oxide oxygen at the non-benzylic C-6 center, accompanied by cleavage of the N-7–C-14 bond. Oxaziridine 4 can then rearrange in either of two ways, through hydrogen migration to furnish lactam 5 or by alkyl migration to give rise to formamide 7. With *trans*-xylopinine N-oxide (12), the corresponding oxaziridine is also formed which accounts for the formation of lactam 14 and formamide 15. It is worth pointing out in this context that the intermediacy of oxaziridines in the photolysis of *aromatic* amines had previously been postulated.[4] However, in that case, no hydrogen shifts are required since the adjacent carbon is unsaturated.

The importance of the above transformations is twofold. Firstly, since canadine and xylopinine are inexpensive and readily available, we have here a practical route to certain dibenzazonines and dibenzazecines, and this in spite of the relatively low overall yields in the photolysis. In the second place, this is the first instance of *in vitro* oxidation of a berbine derivative at C-6, albeit accompanied by fission of the N-7–C-14 bond. Selective oxidation of a berbine at C-6 is of more than passing interest since this represents a key step in the *in vivo* transformation of berbine into benzophenanthridine alkaloids[5]—a transformation still remaining to be duplicated in the laboratory.

Irradiation of *cis*-xylopinine N-oxide (13), the minor product from the N-oxidation of xylopinine, gave no characterizable products. To complete our study, the known benzo[b]quinolizidine 16,[6] which incorporates rings B, C, and D, of the berbine skeleton, was prepared and oxidized with *m*-chloroperbenzoic acid. Only one N-oxide, 17, was produced whose CMR spectrum (Table 1) indicated it to incorporate the trans stereochemistry. Irradiation of this N-oxide provided only the corresponding free base 16 in 68% yield. It is, therefore, apparent that of the cases investigated, photolysis of only the *trans*-berbine N-oxides led to significant products.

EXPERIMENTAL

General procedures. PMR spectra are at 60 MHz with TMS as internal standard. Mass spectra are at 70 eV. Chemical ionization mass spectra were obtained using methane gas. All tlc was on Merck 254 silica gel plates. Solvent proportions quoted are v/v. Alkaloidal spots were visualized using uv light or by spraying either the chloroplatinate or the chromatropic acid spray reagents. All m.ps are uncorrected. Photolyses were performed using a 450 watts medium pressure Ace mercury lamp equipped with a quartz filter. A steady stream of N_2 gas was continuously passed through the reaction vessel.

Canadine N-oxide (3). Racemic canadine (1.0 g, 3 mmol) was dissolved in 25 ml CH_2Cl_2 to which 1 g (6 mmol) *m*-chloroperbenzoic acid was then added. The mixture was stirred 1 hr. The soln was washed with $NaHCO_3$ aq, and the organic layer was dried (K_2CO_3) and the solvent evaporated. The crude product was chromatographed on a neutral alumina column (Brockmann Activity 1, 80–200 mesh) in $CHCl_3$. The fraction eluted with $CHCl_3$ proved to be unreacted canadine. The fraction eluted with 1% MeOH–$CHCl_3$ yielded 3 which crystallized from MeOH (0.76 g, 75%), m.p. 203–204°; λ_{max}^{EtOH} 283 nm (log ϵ 3.81); PMR ($CDCl_3$) δ3.77 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.50 (1H, t,

J = 15 Hz, H-14), 5.82 (2H, s, OCH_2O), 6.55 (1H, s, H-4), 6.60 (1H, s, H-1), and 6.73 and 6.88 (ABq, 2H, J = 8.5 Hz, H-11 and H-12); CMR ($CDCl_3$) ppm 24.8, 29.7, 55.9, 60.3, 64.5, 67.6, 68.1, 101.1, 105.6, 108.5, 111.9, 122.9, 123.7, 124.9, 125.3, 125.8, 145.6, and 150.6; ms *m/e* 355 (2) $(M)^+$ ($C_{20}H_{21}NO_5$), 339 (54), 338 (38), 337 (29, 174 (21), and 164 (base).

Photolysis of **3**. N_2 gas was bubbled into a suspension of **3** (300 mg, 0.85 mmol) in MeOH for 30 min. The mixture was irradiated under N_2 for 3 hr. The solvent was evaporated, and the residue triturated with $CHCl_3$. The white solid was filtered and washed with ether to provide lactam **5** (16 mg, 5%) (11% corrected) which was recrystallized from MeOH, m.p. > 250°; λ_{max}^{EtOH} 285 nm (log ε 3.28); λ_{max}^{KBr} 1640 and 3300 cm^{-1}; PMR (TFA) δ3.98 (6H, s, 2 × OCH_3), 5.93 (2H, *m*, OCH_2O), 6.85 (2H, s, H-1 and H-4), and 7.05 and 7.23 (2H, ABq, J = 8 Hz, H-11 and H-12); ms *m/e* 355 (57) *(M)*$^+$, 164 (base), and 148 (71).

Anal. by high res ms, calcd. for $C_{20}H_{21}NO_5$: 355.1419. Fd.: 355.1406.

The above mother liquor was subjected to preparative tlc using 2% MeOH in $CHCl_3$. The higher band (R_f 0.55) was **7** (13 mg, 4%) (9% corrected), m.p. 228–230° (MeOH); λ_{max}^{EtOH} 288 nm (log ε 3.47); $\nu_{max}^{CHCl_3}$ 1655 cm^{-1}; PMR ($CDCl_3$) δ2.90 (4H, s, $ArCH_2CH_2Ar$), 3.88 (6H, s, 2 × OCH_3), 4.12 (2H, s, $ArCH_2N$), 4.27 (2H, s, $ArCH_2N$), 5.98 (2H, s, OCH_2O), 6.68 (1H, s, ArH), 6.95 (2H, s, ArH), 6.98 (1H, s, ArH), and 8.50 (1H, s, HCO); ms *m/e* 355 (base) $(M)^+$, 326 (10), 310 (90), 165 (70), and 149 (70).

Anal. by high res ms, calcd. for $C_{20}H_{21}NO_5$: 355.1419. Fd.: 355.1443.

The band remaining at the origin of the preparative tlc plate proved to be **3** (154 mg, 51%).

Reduction of **5**. LAH reduction of **5** (10 mg, 0.03 mmol) in hot THF (10 ml) provided an oil which was purified by tlc using 10% MeOH in $CHCl_3$. The major band (R_f 0.10) provided amorphous amine **8** (4 mg, 42%); PMR ($CDCl_3$) δ3.05 (4H, s, $ArCH_2CH_2Ar$), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.92 (2H, s, OCH_2O), 6.62 (1H, s, H-4), 6.65 (1H, s, H-1), and 6.73 and 6.95 (2H, ABq, J = 8 Hz, H-11 and 12); ms *m/e* 341 (86) $(M)^+$, 310 (57), 178 (base), and 149 (50).

Anal. by high res ms, calcd. for $C_{20}H_{23}NO_4$: 341.1626. Fd.: 341.1599.

A few mg of **8** were acetylated using Ac_2O in pyridine. Work-up provided **9** as an oil, ms *m/e* 383 (base).

Anal. by high res ms, calcd. for $C_{22}H_{25}NO_5$: 383.1732. Fd.: 383.1761.

Reduction of **7**. Compound **2** (10 mg; 0.03 mmol) was reduced with excess LAH in hot THF. Work-up gave colorless needles of **10** (6 mg, 62%), m.p. 170–171° (MeOH); PMR ($CDCl_3$) δ2.58 (3H, s, NCH_3), 2.87 (4H, s, $ArCH_2CH_2Ar$), 3.40 (2H, s, $ArCH_2N$), 3.45 (2H. s, $ArCH_2N$), 3.88 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 5.98 (2H, s, OCH_2O), 6.70 (1H, s, ArH), 6.83 (1H, s, ArH), and 6.90 (2H, s, ArH); ms *m/e* 341 (base) $(M)^+$, 310 (80), 176 (50), 164 (60), and 148 (60).

Anal. by high res ms, calcd. for $C_{20}H_{23}NO_4$: 341.1626. Fd.: 341.1609.

Hydrolysis of **7**. Formamide **7** (15 mg, 0.04 mmol) was refluxed with 10% HCl for 16 hr. The mixture was cooled, basified with NH_4OH, and extracted with $CHCl_3$. The organic soln was dried and evaporated. The residue crystallized from MeOH to provide needles of **11** (9 mg, 65%), m.p. 183–184°; PMR ($CDCl_3$) δ2.60 (1H, s, NH), 2.83 (4H, s, $ArCH_2CH_2Ar$), 3.42 (2H, s, NCH_2), 3.52 (2H, S, NCH_2), 3.90 (6H, s, 2 × OCH_3), 5.95 (2H, s, OCH_2O), 6.65 (1H, s, ArH), 6.88 (2H, s, ArH), and 6.93 (1H, s, ArH); ms *m/e* 327 (base) $(M)^+$, and 310 (90).

Anal. by high res ms, calcd. for $C_{19}H_{21}NO_4$: 327.1470. Fd.: 327.1459.

trans- *and* cis-*Xylopinine* N-*oxides* (**12** *and* **13**). Racemic xylopinine (200 mg, 0.5 mmol) was oxidized using *m*-chloroperbenzoic acid (200 mg, 1.2 mmol) in CH_2Cl_2. Preparative tlc using 10% MeOH in $CHCl_3$ supplied two major bands. The lower band (R_f 0.17) crystallized from MeOH–$CHCl_3$ to afford *trans-* **12** (95 mg, 45%), m.p. 167–168°; PMR ($CDCl_3$) δ3.77 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.00 (6H, s, 2 × OCH_3), 6.50 (1H, s, ArH), 6.60 (1H, s, ArH), 6.65 (1H, s, ArH), and 6.70 (1H, s, ArH); CMR ($CDCl_3$) ppm 23.9, 29.6, 55.6 and 55.9 (4 × OCH_3), 63.9, 67.5, 70.2, 108.7, 109.2, 111.0, 111.1, 120.4, 123.8, 124.2, 124.4, 147.6, 147.9, and 148.0; chem. ion. ms *m/e* 372 (15) $(M+H)^+$.

Anal. by high res ms, calcd. for $C_{21}H_{25}NO_5$: 371.1732. Fd.: 371.1755.

The band with R_f 0.21 gave the *cis* isomer **13** (17 mg, 8%), m.p. 130–135° (MeOH–$CHCl_3$); PMR ($CDCl_3$) δ3.80 (6H, s, 2 × OCH_3), 3.83 (6H, s, 2 × OCH_3), 6.53 (1H, s, ArH), 6.60 (2H, s, ArH), 6.70 (1H, s, ArH); CMR ($CDCl_3$) ppm 24.3, 37.0, 55.5 (4 × OCH_3), 56.0, 70.3, 70.5, 108.4, 109.6, 110.0, 111.5, 120.9, 121.2, 121.4, 126.5, 147.3, 148.0 and 148.6.

Photolysis of **12**. The photolysis of **12** (300 mg, 0.8 mmol) was carried out for 4 hr as described for **3** above. The methanolic soln was evaporated and the residue subjected to preparative tlc using 2% MeOH in $CHCl_3$. The band with R_f 0.70 crystallized from MeOH and consisted of formamide **15** (13 mg, 4%; 7% adjusted), m.p. 202–203°; $\nu_{max}^{CHCl_3}$ 1660 cm^{-1}; PMR ($CDCl_3$) δ2.95 (4H, s, $ArCH_2CH_2Ar$), 3.90 (6H, s, 2 × OCH_3), 3.95 (6H, s, 2 × OCH_3), 4.03 (2H, s, NCH_2Ar), 4.23 (2H, s, NCH_2Ar), 6.78 (3H, s, ArH), 7.02 (1H, s, ArH) and 8.55 (1H, s, CHO).

Anal. by high res ms, calcd. for $C_{21}H_{25}NO_5$: 371.1732. Fd.: 371.1742.

The band with R_f 0.43 was collected and crystallized from MeOH thus providing lactam **14** (16 mg, 5%; 8% adjusted), m.p. 238–240°; λ_{max}^{EtOH} 283 nm (log ε 4.19); $\nu_{max}^{CHCl_3}$ 1660 cm^{-1}; PMR ($CDCl_3$) δ3.88 (9H, s, 3 × OCH_3), 3.92 (3H, s, OCH_3), 6.68 (1H, s, ArH), 6.73 (1H, s, ArH) and 6.80 (2H, s, ArH); ms *m/e* 371 (95) $(M)^+$, 207 (75) and 164 (base).

Anal. by high res ms, calcd. for $C_{21}H_{25}NO_5$: 371.1732. Fd.: 371.1739.

The band at the origin consisted of starting N-oxide **12** (100 mg, 33%).

Reduction of **15**. Formamide **15** (10 mg, 0.03 mmol) was reduced using excess LAH in hot THF. Work-up provided the corresponding N-methyl tertiary amine (5 mg, 52%), m.p. 173–174° (MeOH); PMR ($CDCl_3$) δ2.62 (3H, s, NCH_3), 2.87 (4H, s, $ArCH_2CH_2Ar$), 3.37 (4H, s, $ArCH_2NCH_2Ar$), 3.95 (12H, s, 4 × OCH_3), 6.77 (2H, s, ArH) and 6.93 (2H, s, ArH); ms *m/e* 357 (40) $(M)^+$, 326 (90) and 164 (base).

Anal. by high res ms, calcd. for $C_{21}H_{27}NO_4$: 357.1940. Fd.: 357.1910.

Reduction of **14**. Lactam **14** (15 mg, 0.04 mmol) was reduced with excess LAH in hot THF. Work-up followed by preparative tlc using 10% MeOH in $CHCl_3$ (R_f 0.23) provided the corresponding oily secondary amine (8 mg, 55%); PMR ($CDCl_3$) δ3.02 (4H, s, $ArCH_2CH_2Ar$), 3.82 (12H, s, 4 × OCH_3), 4.55 (1H, br s, NH), 6.60 (2H, s, ArH), 6.67 (1H, s, ArH), and 6.75 (1H, s, ArH); ms *m/e* 357 (base) $(M)^+$ ($C_{21}H_{27}NO_4$), 328 (50) and 192 (50).

trans-*Benzo[b]quinolizidine* N-*oxide* (**17**). Free base **16** (1 g, 5 mmol) was oxidized using *m*-chloroperbenzoic acid (2 g, 12 mmol) in CH_2Cl_2 for 90 min. The mixture was extracted with 10% $NaHCO_3$ aq. The organic layer was dried (K_2CO_3) and the solvent evaporated. The crude product was chromatographed on an alumina column (Brockmann Activity I, 80–200 mesh) in $CHCl_3$. The fraction eluting with 1% MeOH in $CHCl_3$ crystallized from ether to provide **17** (0.73 g, 67%), m.p. 170–171°; PMR ($CDCl_3$) δ4.43 (2H, s, NCH_2Ar) and 6.92–7.20 (4H, m, ArH); ms *m/e* 203 (20) $(M)^+$, 187 (base), 186 (40), 185 (80) and 104 (80).

Anal. by high res ms, calcd. for $C_{13}H_{17}NO$: 203.1309. Fd.: 203.1321.

Photolysis of **17**. Photolysis of N-oxide **17** (100 mg, 0.5 mmol) for 4 hr under N_2 supplied an oil which contained only one major spot on tlc, R_f 0.50, using 10% MeOH in $CHCl_3$. Preparative tlc provided free base **16** (63 mg, 68%; PMR ($CDCl_3$) δ3.34 and 3.88 (2H, ABq, J = 15 Hz, NCH_2Ar), and 7.08 (4H, br s, ArH); ms *m/e* 187 (base) (M^+) ($C_{13}H_{17}N$), 146 (20) and 105 (40).

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