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Oxidative Cleavage of a Tricyclic Pyridone to a Bicyclic Lactam-dione

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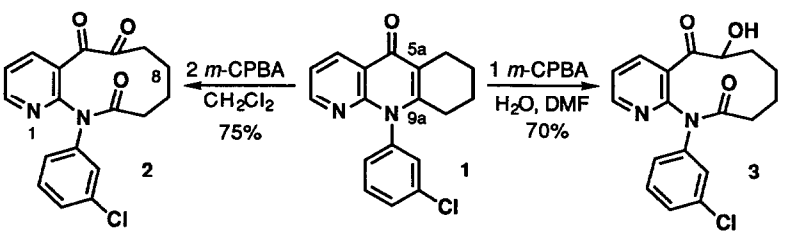
Abstract: *Two equivalents of anhydrous* m-*chloroperbenzoic acid* (m-*CPBA) cleaved the pyridone ring of 10-(3-chlorophenyl)-6,8,9,10-tetrahydrobenzo[b][1,8]naphthyridin-5(7H)-one, forming the ten-membered lactam α-diketone 12-(3-chlorophenyl)-7,8,9,10-tetrahydropyrido[2,3-b]azecine-5,6,11(12H)-trione. Under aqueous conditions, one equivalent of* m-*CPBA and the same pyridone formed the lactam α-ketol 12-(3-chlorophenyl)-7,8,9,10-tetrahydro-6-hydroxypyrido[2,3-b]azecine-5,11(6H, 12H)-dione, which partly confirmed the postulated mechanism of ring cleavage.*

During other work, we treated the fused tricyclic pyridone **1** with two equivalents of dry *m*-CPBA, hoping to form an N-oxide.[1] The product, however, was the lactam-dione **2**, not the desired pyridine N-oxide. As far as we know, this oxidative cleavage of a pyridone by a peracid to a lactam-dione is novel.[2] Thus, we report a structure proof, suggest a cleavage mechanism, and present a confirmatory experiment. In this experiment, one equivalent of *m*-CPBA in water containing N,N-dimethylformamide (DMF) sufficed to change pyridone **1** to lactam-ketol **3**.

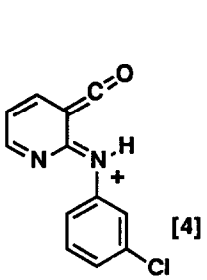


According to mass spectrometry and microanalysis, the empirical composition of product **2** was $C_{18}H_{15}ClN_2O_3$. The two added oxygen atoms composed lactam (δ 176 ppm, ν 1650 cm^{-1}) and ketone (δ 202 ppm, ν 1700 cm^{-1}) carbonyl groups. The appearance of these carbonyl groups in the product demonstrated that the pyridone double bond of the starting material had been oxidatively cleaved.

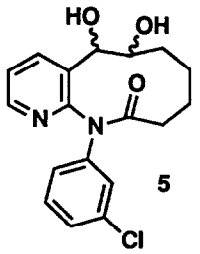
The 2-[(3-chlorophenyl)amino]-3-pyridinecarbonyl unit was intact in lactam-dione **2**. A third carbonyl group (δ 190 ppm, ν 1680 cm^{-1}) was present in **2**, its low-frequency absorption typifying a 2-(arylamino)-3-pyridyl ketone. Compound **2** fragmented to cation [**4**] (96%) on fast-atom bombardment. An exact measurement of the mass of [**4**] agreed (Δ = 0.0007) with the value expected for $[C_{12}H_8{}^{35}ClN_2O]^+$.

Lactam-dione **2** also comprised two $(CH_2)_2CO$ units. These units expressed the ^{13}C to ^{13}C connectivity established by a two-dimensional INADEQUATE experiment.[4] An APT experiment yielded the degrees of substitution of carbon atoms that structure **2** illustrates.[5]

The carbon atoms of two carbonyl groups were bound to one another in compound **2**. Reduction of lactam-dione **2** with sodium borohydride gave the diastereomeric diols **5**, which carbonyldiimidazole converted to the five-membered carbonates **6**. An infrared spectrum of diastereomers **6** showed ν_{CO} 1810 cm^{-1}, and so revealed the carbonate ring size.[6]



[4]



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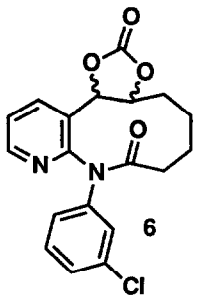

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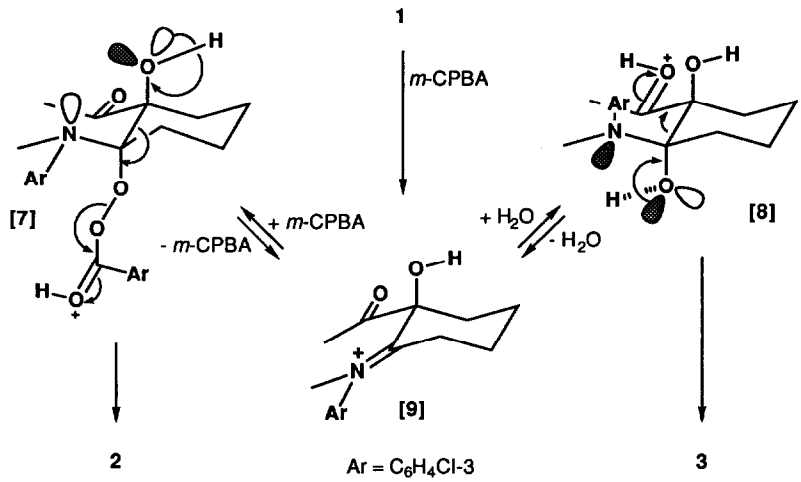
Taken altogether, the foregoing data implied that the product possessed structure **2**. The C (8) and C (9) methylene groups in **2** presumably linked one another as shown, although an INADEQUATE experiment did not detect this linkage.

A mechanism for the oxidative cleavage would begin with attack of C (5a) of pyridone **1** upon the hydroxyl oxygen of *m*-CPBA. Addition to the carbon terminus of the resulting iminium ion [9] would then consume the second equivalent of *m*-CPBA, giving [7]. Fragmentation of adduct [7] would then furnish the lactam and ketone carbonyl groups of the product **2**.



To devise an experiment confirming the intermediacy of iminium ion [9], we reasoned as follows. Ion [9] might form intermediate [8] in the presence of water and the absence of a second oxidant equivalent. Formally, intermediate [8] represents the (protonated) product of a hypothetical aldol reaction in which lactam-ketol **3** yields [8]. Because an amide carbonyl group would serve as the acceptor in such a reaction, the product should be unstable compared to the starting material. Intermediate [8] should undergo a reversed aldol reaction if it formed. Therefore, pyridone **1** in water containing only one equivalent of peracid should yield lactam-ketol **3**.

Treatment of pyridone **1** with one equivalent of *m*-CPBA in dimethylformamide containing 100 equivalents of water gave 70% of lactam-ketol **3**. The empirical composition of **3**, determined by microanalysis and mass spectroscopy, formally corresponded to addition of an oxygen atom and a water molecule to pyridone **1**. A new hydroxyl group (ν 3530 and 3460 cm^{-1}) was apparent in the infrared spectrum. The ketone group of **3** resonated at δ 198 ppm and absorbed at ν 1685 cm^{-1}. In its mass spectrum, lactam-ketol **3** fragmented efficiently to ion [4] (100% for ^{35}Cl), as did lactam-dione **2**.

EXPERIMENTAL[7]

12-(3-Chlorophenyl)-7,8,9,10-tetrahydropyrido[2,3-b]azecine-5,6,11(12H)-trione (2)

Pyridone **1** (3.11 g, 10 mmol), *m*-CPBA (4.32 g, 21 mmol; 80 – 90%) and CH_2Cl_2 (160 ml) were stirred at 25° C under N_2 for 40 h. The reaction mixture was washed with 1 M Na_2CO_3 and with H_2O, and aqueous washes were extracted with $CHCl_3$. Combined rganic phases were dried (Na_2SO_4), filtered, and concentrated. The combined solid residues crystallized from EtOH to give **2** (2.56 g, 75%): mp 173 – 175° C; IR (KBr) 1700 (C (6) carbonyl), 1680 (C (5) carbonyl), 1650 (C (11) carbonyl); UV (EtOH) 310 (3.18), 275sh (3.62), 230 (4.17), 209 (4.40); ^{1}H NMR (400 MHz, $CDCl_3$) 8.49 (dd, *J* (2 – 3) = 4.8, *J* (2 – 4) = 2.0, *H* (2)), 8.28 (dd, *J* (2 – 4) = 2.0, *J* (3 – 4) = 7.8, *H* (4)), 7.43 – 7.36 (m, 3H, *Ar*), 7.29 (dd, *J* (2 – 3) = 4.8, *J* (3 – 4) = 7.8, *H* (3)), 7.24 (br d, 1H, *Ar*), 3.29 (d of d, *J* = 2.7, *J* = 12.0, *J* (7a – 7b) = 15.4, 1H, *H* (7a)), 2.53 (ddd, *J* = 2.0, *J* = 7.5, *J* (7b – 7a) = 15.4, 1H, *H* (7b)), 2.43 – 2.38 (m, 1H, *H* (10)), 2.16 – 2.04 (m, 2H, *H* (9)*), 1.95 – 1.82 (m, 2H, *H* (8)*), 1.72 – 1.70 (m, 1H, *H* (10)); ^{13}C NMR (400 MHz, $CDCl_3$) 202 (*C* (6)), 190 (*C* (5)), 176 (*C* (11)), 152.9 (*C* (12a)), 152.5 (*C* (2)), 142 (*C* (1')), 139 (*C* (4)), 135 (*C* (3')), 130 (*C* (5')), 128.8 (*C* (6')=), 128.6 (*C* (4')=), 126.8 (*C* (2')), 125 (*C* (4a)), 122 (*C* (3)), 37 (*C* (7)), 36 (*C* (10)), 25.4 (*C* (9)), 25.1 (*C* (8)); FAB-MS (Gly-thio) 345 (48, [*M* +1]$^+$ for ^{37}Cl), 343 (100, [*M* + 1]$^+$ for ^{35}Cl), 233 (43, [$C_{12}H_8{}^{37}ClN_2O$]$^+$), 231 (96, [$C_{12}H_8{}^{35}ClN_2O$]$^+$ ([**4**])).

An APT experiment helped us assign ^{13}C chemical shifts.[5]

Anal. Calcd. for $C_{18}H_{15}ClN_2O_3$: C, 63.06; H, 4.41; Cl, 10.34; N, 8.17. Found: C, 62.94; H, 4.32; Cl, 9.98; N, 8.14.

Exact mass measurement. Calcd. for [$C_{12}H_8{}^{35}ClN_2O$]$^+$ ([**4**]): *m/z* 231.0325; found (FAB-MS): *m/z* 231.0318.

12-(3-Chlorophenyl)-7,8,9,10-tetrahydro-6-hydroxypyrido[2,3-b]azecine-5,11(6H,12H)-dione (3)

A solution of pyridone **1** (2.00 g, 6.44 mmol) in N,N-dimethylformamide (60 ml) was diluted with H_2O (11.6 ml). *m*-CPBA (1.31 g, nominally 85% pure, 6.48 mmol) was added, and dissolved. The resulting solution was kept 94 h at 25° C, and progress of the oxidation was periodically monitored by starch-iodide tests. The resulting mixture was poured into H_2O (600 ml) and extracted with EtOAc. Combined extracts were washed with H_2O, 1 M $NaHCO_3$ solution, and with brine. The dried (Na_2SO_4), filtered solution was concentrated to give an oil (2.06 g) containing the starting **1** and the desired lactam-ketol **3**, according to TLC.

Chromatography over silica gel under N_2 pressure and elution with MeOH – CH_2Cl_2 (99 : 1 by vol.) furnished **1** (0.32 g) as the more polar and the desired **3** (1.30 g, 59% conversion and 70% yield) as the less polar components. Recovered pyridone **1** was identified by side-by-side TLC. Lactam-ketol **3**, which crystallized from Et_2O containing a little CH_2Cl_2, formed colorless crystals yellowing on exposure to air: FAB-MS 347 (32, [*M* + 1]$^+$ for ^{37}Cl), 345 (91, [*M* + 1]$^+$ for ^{35}Cl), 329 (36, [*M* + 1 – H_2O]$^+$ for ^{37}Cl), 327 (100, [*M* + 1 – H_2O]$^+$ for ^{35} Cl).

Anal. Calcd. for $C_{18}H_{17}ClN_2O_3$: C, 62.70; H, 4.97; Cl, 10.28; N, 8.12. Found: C, 62.70; H, 4.97; Cl, 10.26; N, 8.11.

12-(3-Chlorophenyl)-5,7,8,9,10,12-hexahydro-5,6-dihydroxypyrido[2,3-b]azecin-11(6H)-one (5)

A solution of $NaBH_4$ (0.587 g, 15 mmol) in H_2O (22 ml) was added to a suspension of **2** (5.32 g, 13 mmol) and EtOH (110 ml). After 20 min the solution was warmed (steam bath) for 5 min, cooled, and poured onto ice. After 1 h, the EtOH was evaporated and the residue was extracted with $CHCl_3$. Combined extracts were dried (Na_2SO_4) and concentrated to give a colorless foam (4.3 g). Chromatography over silica gel (400 g) and elution with MeOH – $CHCl_3$ (1 : 99, by vol.), followed by crystallization from MeCN, gave the diol as a mixture of diastereomers (1.77 g, 34%): mp 181 – 196° C; IR (KBr) 3410 (OH), 3280 (OH), 1650 (lactam CO); ^{1}H NMR (79.5 MHz, $CDCl_3$) 8.52 (dd, *J* (2 – 3) = 5, *J* (2 – 4) = 2, *H* (2)), 8.12 (dd, *J* (4 – 3) = 7, *J* (4 – 2) = 2, *H* (4)), 7.92 (dd, *J* (4 – 3) = 8, *J* (4 – 2) = 2, *H* (4)), 7.48 – 6.94 (m, 5 H, *Ar* and *H* (3)), 5.08 (dd (collapsed to a d with *J* = 5 on exchange with D_2O), *J* (5 – O*H*) = 5, *J* (5 – 6) = 3, *H* (5)), 4.93 (dd (collapsed to

a d with $J = 8$ on exchange with D_2O), J (5 – O*H*) = 3, *H* (5)), 4.20 – 3.62 (m, *H* (6)), 2.77 (br d, J (5 – OH) = 5, overlapping signals of 2 –O*H*), 2.62 (br d, J (5 – OH) = 3, overlapping signals of 2 –O*H*), 2.38 – 1.04 (7 H) and 0.88 – 0.38 (1 H) (overlapping signals of 2 *H* (10), 2 *H* (9), 2 *H* (8), and 2 *H* (7)); ^{13}C NMR (100 MHz, $CDCl_3$ – Me_2SO-d_6) 174.1 (N*C*=O), 173.9 (N*C*=O), 152.1, 151.9, 149.1, 148.9, 142.0, 141.9, 140.7, 138, 136, 134.6, 133.8, 133.7, 129, 126.0, 125.7, 125.6, 124.9, 124.1, 123.8, and 123.7 (*Ar*), 77 (*C* (5)), 70 (*C* (6)), 67 (*C* (6)), 32 (*C* (10)), 29 (*C* (7)), 27 (*C* (7)), 26.1 (*C* (9)), 25.6 (*C* (9)), 20 (*C* (8)), 19 (*C* (8)); EI-MS 348 (7, M^+ for ^{37}Cl), 346 (20, M^+ for ^{35}Cl), 235 (39, $[M - C_6H_4Cl]^+$), 233 (100), 113 (2, $[C_6H_4{}^{37}Cl]^+$), 111 (5, $[C_6H_4{}^{35}Cl]^+$).

Anal. Calcd. for $C_{18}H_{19}ClN_2O_3$: C, 62.33; H, 5.52; Cl, 10.22; N, 8.08. Found: C, 62.27; H, 5.40; Cl, 9.99; N, 7.73.

*9-(3-Chlorophenyl)-3a,4,5,6,7,13b-hexahydro-2H-1,3-dioxolo[4,5-*d*]pyrido[2,3-*b*]azecin-2,8(9H)-dione (6)*

A mixture of carbonyl diimidazole Im_2CO (0.73 g, 4.5 mmol), the foregoing diol (1.04 g, 3.0 mmol), and CH_2Cl_2 (50 ml) was stirred at 24° C for 3h. The resulting solution was washed with H_2O and brine, and was dried (Na_2SO_4) and concentrated. The residue (1.18 g of a colorless foam) crystallized from EtOAc to give **6** (0.496 g, 44%): mp 132 – 142° C; IR (KBr) 1810 (carbonate CO), 1680 (lactam CO); UV (EtOH) 266 (3.72), 238 (3.88), 209 (4.38), 207 (4.38); ^{13}C NMR (400MHz, $CDCl_3$) 174 (*C* (8)), 154 (C (2)), 152 (*C* (9a)), 151 (*C* (11)), 140 (*C* (1')), 138 (*C* (13)), 135 (*C* (3')), 130 (*C* (5')), 128 (*C* (13a)), 127 (*C* (4')*), 125.3 (*C* (6')*), 124.9 (*C* (2')), 123 (*C* (12)), 81 (*C* (13b)), 76 (*C* (3a)), 32 (*C* (7)), 26 (*C* (4)), 24 (*C* (6)$^=$), 21 (*C* (5)$^=$); EI-MS 374 (35, M^+ for ^{37}Cl), 372 (100, M^+ for ^{35}Cl), 330 (2, $[M - CO_2]^+$ for ^{37}Cl, 328 (7, $[M - CO_2]^+$ for ^{35}Cl), 113 (15, $[C_6H_4{}^{37}Cl]^+$, 111 (31, $[C_6H_4{}^{35}Cl]^+$).

Anal. Calcd. for $C_{19}H_{17}ClN_2O_4$: C, 61.21; H, 4.60; Cl, 9.51; N, 7.52. Found: C, 60.95; H, 4.58; Cl, 9.49; N, 7.43.

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