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CHARACTERIZATION OF NEW OXIDATION PRODUCTS OF THE PERCHLORATE SALT OF THE METHADONE METABOLITE, (±)-2-ETHYLIDENE-1,5-DIMETHYL-3,3-DIPHENYLPYRROLIDINE (EDDP)

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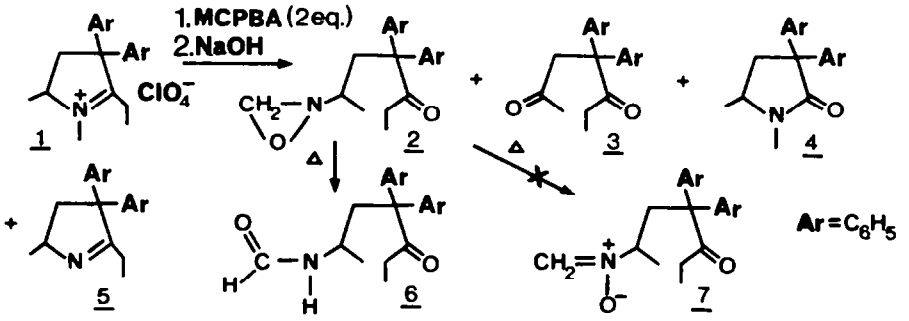
Abstract: The oxidation of (±)-2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium perchlorate (1, EDDP) with m-chloroperbenzoic acid (MCPBA) afforded diastereomeric 2-(4',4'-diphenylheptan-5'-one-2'-yl)-oxaziridine (2), 4,4-diphenyl-2,5-heptanedione (3), and the known compounds 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (5, EMDP) and 1,5-dimethyl-3,3-diphenylpyrrolidone (4, DDP). ^{13}C and ^{1}H NMR results for the new compounds and mechanisms for their formation are discussed.

Lusinchi and coworkers have shown that peroxidation of N-methylpyrrolidine derivatives of the alkaloid conanine can lead to open chain keto-oxaziridines, dicarbonyl compounds, cyclic oxaziridinium salts, lactams, pyrrolines and related compounds[2a-c]. During a study on the synthesis of deuterium labelled (±)-methadone (6-dimethylamino-4,4-diphenyl-3-heptanone) and its metabolites[3a], we observed a similar array of products when the MCPBA oxidation of the salt of the methadone major metabolite, (±)-2-ethyl-1,5-dimethyl-3,3- diphenylpyrrolinium perchlorate (EDDP)[3b,c] (1), was investigated as a source of potential noncyclic metabolites.

RESULTS AND DISCUSSION

Two new oxidation products were characterized, the oxaziridine, 2-(4',4'-diphenylheptan-5'-one-2'-yl)-oxaziridine (2) and the 1,4-diketone, 4,4-diphenyl-2,5-heptanedione (3). The expected oxidation product, 1,5-dimethyl-3,3-diphenylpyrrolidone (DDP) (4), a known metabolite, 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (EMDP) (5) and minor byproducts were detected by GLC-mass spectrometry (GCMS). The oxaziridine 2 underwent a facile thermal isomerization to 6-formamido-4,4-diphenyl-3-heptanone (6), which was identical by GCMS to a conjugated biliary methadone metabolite of rats[4].



There are very few examples of methylene oxaziridines that have protons alpha to the ring nitrogen. These include 2-n-butyloxaziridine[5a] and 2-cyclohexyloxaziridine[5b]. Both compounds were synthesized by peracid oxidation of the 1,3,5-triazane obtained when the corresponding primary amine was condensed with formaldehyde. These oxaziridines isomerized to the formamide on heating or standing. Emmons noted that bulkier N-alkyl groups stabilized the oxaziridine ring[5a], which may account for the stability of the oxaziridine described here.

The best yield of the oxaziridine 2 was obtained with two equivalents of MCPBA and a NaOH wash during workup. The ratio of products in the mixture varied, with two N,C-diastereomeric oxaziridines accounting for up to 36% of the product. These were separated by silica gel flash chromatography[6]. This separation is similar to that achieved for RR and SR diastereomers of the oxaziridine, 2-[(R)-α-phenylethyl]-3,3-dimethyloxaziridine[7]. The diastereoisomerism that allows this separation is due to the high inversion barrier of the oxaziridine nitrogen[8a,b].

The oxaziridine was also observed by GCMS when the enamine free base of EDDP was oxidized with MCPBA. However oxidation of EDDP in the presence of two equivalents of suspended K_2CO_3 did not afford oxaziridine, and cyclized the diketone to a cyclopentenone.

The ^{1}H NMR chemical shifts of 3.17 and 3.62 (major diastereomer) and 3.42 and 3.94 (minor diastereomer) for the oxaziridine ring protons (J_{AB} = 10Hz) were similar to 3.66 and 3.77 ppm resonances reported for 2-t-butyloxaziridine[9]. The upfield doublet is normally presumed to be the proton trans to the lone pair of the oxaziridine nitrogen atom[10a,b]. The ^{13}C NMR oxaziridine ring carbon resonance was at 72.54 ppm and SFORD revealed a doublet of doublets. The alpha carbon resonance was at 64 ppm. The ring and alpha carbon resonances of t-butyloxaziridine were at 65.5 and 58.1 ppm, respectively[9]. Small differences in chemical shifts (0.04, 0.00, 0.04 ppm for aromatic CH, 0.15 ppm for aromatic C-C) were present between corresponding resonances of the two aromatic rings. The non equivalence of aromatic ring resonances has been observed in the mesityl ring of 3,3-diphenyl-2-(1-mesitylethyl)oxaziridine, but was attributed to a sterically dominated rotational barrier, due to the bulky phenyl substituents of the oxaziridine ring[11a,b].

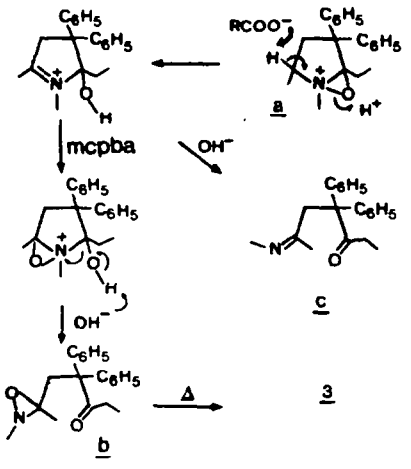
Thermal isomerization of oxaziridines to formamides is well known[5a, 11c]. The oxaziridine isomerized in the GC inlet to give the secondary formamide 6[4]. The formamide was also obtained as an 8:6 mixture of rotamers (NMR results) by refluxing the oxaziridine overnight in m-xylene. High resolution mass spectrometry of the oxaziridine at a low inlet temperature (120°C) shows that CHN containing fragments are enhanced relative to peaks characteristic of the formamide.

Following isolation of the oxaziridine 2, the flash chromatography column was stripped with ethyl acetate to elute any of the isomeric methylene nitrone 7, since this was also a potential breakdown product of the oxaziridines and a possible thermolabile drug metabolite[12a,b]. The nitrone was not a product of the oxidation. Attempted synthesis of the nitrone using the diketone as a starting material failed. A nitrone has been described as a possible intermediate in the MCPBA acid oxidation of L-acetylmethadol[13].

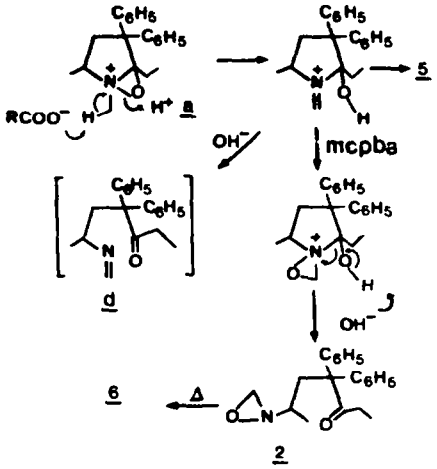
The other major product of the peroxidation of EDDP perchlorate was the diketone 3 which has been mentioned as a potential synthetic precursor for methadone[14]. We have also obtained this product in low yield via Jones oxidation of 4,4-diphenyl-2,5-heptanediol[15]. The diketone was separated from the major product, 2,2-diphenyl-4-valerolactone[16] by recrystallization. Aldol condensation of 1,4-diketones results in cyclopentenone formation[17]. Reflux of the diketone in 0.75 M methanolic sodium hydroxide afforded only 2,3-dimethyl-5,5-diphenylcyclopent-2-enone 8. NMR results show that none of the regioisomeric 3-ethyl-4,4-diphenyl-cyclopent-2-enone was formed.

The peracid oxidation of imines proceeds by a two step Baeyer-Villiger type mechanism, with oxidant addition to the C=N bond as the rate determining step[18]. Ring closure with loss of MCBA follows in the second step to give an intermediate of type a. Lusinchi and coworkers[2a-c] have incorporated this type of intermediate into their proposals for the mechanism of peroxidation of N-methylpyrrolinium salts and free bases. They propose that elimination of the ring proton alpha to nitrogen in a accounts for their observation of keto-imine, C-disubstituted keto-oxaziridine and diketone oxidation products. Their mechanism, modified to EDDP in Scheme 1 accounts for the diketone 3 possibly by thermolysis of oxaziridine b. We speculate that elimination of the alpha proton on the N-methyl carbon of a in a similar manner accounts for both EMDP 5 (in accord with the results of Milliet), as well as the methylene oxaziridine 2 (Scheme 2). Milliet *et al*[2a] have also shown that oxidation of structurally related pyrrolidines with a single equivalent of MCPBA followed by alkaline workup should result in an open chain keto-imine of type c. Compound c or its Scheme 2 homologue d would be the conventional imine precursors of oxaziridines b and 2 respectively, but were not observed. The methylene imine d is presumably unstable and could form a variety of cyclic and non cyclic polymers[20], themselves amenable to peroxidation[5a].

Milliet *et al*.[2a] have indicated that the initial addition of MCPBA is a reversible reaction unaffected by oxidant concentration. This accounts for the presence of unreacted EDDP with MCPBA in excess of two equivalents. The diphenylpyrrolidone (DDP) 4 arises from oxidation of the enamine tautomer of EDDP by known mechanisms[2a,21], although the endocyclic double bond position is preferred in acid solution[22].



Scheme 1



Scheme 2

CONCLUSION

Peracid oxidation of (±)-EDDP gives rise to a mixture of cyclic and non cyclic compounds according to variations of known mechanisms. Two new compounds have been characterized, a methylene oxaziridine and a 1,4-diketone. The oxaziridine converted to an isomeric secondary formamide on heating. The diketone cyclized in alkali to 2,3-dimethyl-5,5-diphenylcyclopent-2-enone.

EXPERIMENTAL

(±)-EDDP perchlorate 1 was synthesized in this laboratory[3a]. All ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at the Department of Chemistry, University of British Columbia. Infrared spectra were recorded as liquid films or nujol mulls on sodium chloride discs on a Unicam SP-1000. GCMS analysis was performed on a Hewlett-Packard 5700A gas chromatograph interfaced to a Varian MAT-111 mass spectrometer. Electron impact spectra were recorded at 70eV, ion source pressure 5.0×10^{-6} torr, source temp. 250°C, emission current 300 μA. A glass column (2m x 2 mm i.d.) packed with 3% OV-17 on 100-120 mesh Gas chrom Q was used with helium carrier gas (20 mL/min). Column temp.; 150 to 280°C at 4° per min., inlet temp. 250°C. Ultraviolet spectra were recorded on a Beckman Model 24 UV-Visible spectrometer in 1 cm path length cells. Elemental analyses were done by the Canadian Microanalytical Service Ltd., 5704 University Blvd., Vancouver, B.C., V6T 1K6. High resolution mass spectra were recorded with a source temp. of 120° on a Kratos MS-50 high performance mass spectrometer with an ionizing voltage of 70eV at the Department of Chemistry, University of British Columbia.

META-CHLOROPERBENZOIC ACID OXIDATION OF EDDP PERCHLORATE

To a solution of 100 mg (2.6×10^{-4} mol) (±) EDDP perchlorate in 5 mL $CHCl_3$ at 0°C was added 100 mg (5.2×10^{-4} mol) MCPBA in 5 mL of 0°C $CHCl_3$. After 12 hours, the solution was filtered and washed twice with cold 1.5 M NaOH solution, twice with water then dried over K_2CO_3 and evaporated. The yellow oil was analyzed by GLC-mass spectrometry. Major products were: EMDP 5, t_R = 18.2 min; EDDP 1, t_R = 20.0 min; diketone 3, t_R = 21.8 min; DDP 4, t_R = 24.2 min; oxaziridine 2 (as the formamide), t_R = 29.5 min. The residue was flash chromatographed in 1:9 ethyl acetate, pet. ether (30°-60°) on a 1 x 15 cm column. The diastereomeric oxaziridines gave partially resolved black spots when visualized by Dragendorf's Reagent on TLC plates. The clear oil deposited cubic crystals from $CDCl_3$ which melted at 80°C and decomposed at 150-160°C. CHN anal, calc.for $C_{20}H_{23}NO_2$ (309.411): C, 77.64; H, 7.49; N, 4.52; O, 10.34. Found: C, 77.61; H, 7.45; N, 4.52; O, 10.42. NMR (400 MHz): δppm (major diast.) 0.85, t(3H, CH_3-CH_2); 0.84 d (3H, CH_3-CH); 1.8, m (1H,-CH-CH_3); 2.27, q buried (2H,-CH_2-CH_3); 2.32, dd (1H, CH_aH_b-CH); 2.80, dd (1H CH_bH_a); 3.17, d (J =10 Hz, 1H; oxaziridine ring); 3.62, d (1H, oxaz. ring); 7.3 (10H, Arom.). (100 MHz) δppm (minor diast.) 0.56, d(3H, CH_3-CH), 0.85, t(3H, CH_3-CH_2); 1.8, m (1H, CH_3-CH-); 2.45 q buried (2H, -CH_2-CH_3); 2.35, dd(1H, -CH_aH_bCH); 3.2 dd(1H, CH_bH_a-CH), 3.42 d(1H, oxaz. ring), 3.92, d(1H, oxaz. ring, J = 10 Hz), 7.3, (10H, Arom.). IR (film): νmax 3000 cm^{-1}, (m), 1710 (s, C = O str), 1600 (m-w) 1585 (w), 1495 (s), 1448 (m), 1380 (w-m), 1350 (w-m), 1250 (m) oxaz. ring, 1150 (w-m), 1110 (m-s), 1050 (m), 935 (w) oxaz. ring; 770 (s, Ar), 757 (m-s, Ar), 702 (s, Ar). UV (Methanol): λmax 296 mμ (ε = 502); 265 (ε = 548); 254.5 (ε = 480, π-π *Ar); 207.5 (ε = 21, 168 π-π *Ar). ^{13}CNMR: (Major Diast.) (Broad Band and SFORD at 100.6 MHz) δppm 9.18, q(CH_3-CH_2; 21.29, q(CH_3-CH); 33.04, t(CH_2-CH_3); 211.26, s(weak C=O); 65.46, s(weak R_2-C-Ar_2); 42.6 t(CH_2-CH);64.00, d(CH-CH_2); 72.54, dd(CH_2-oxaz.); 127.42, 127.46 (ArCH-); 128.55 (ArCH-); 129.32, 129.37 (Ar-CH); 141.52, 141.69 (Ar.C-C, weak). Mass Spectrum: By GCMS; (identical to formamide 6) m/z 309 (M^+3%), 72(100), 207(72), 73(60), 208(50), 44(46), 253(42), 129(30), 57(22), 291(8). High Resolution (Source Temperature 120°); m/z 309 ($C_{20}H_{23}NO_2$, M^+, 1.5%); 56(C_3H_6N;80%); 222 ($C_{16}H_{16}N$ 28%). The formamide dominates the mass spectrum, 72 m/z (C_3H_6NO, 100%), 253 ($C_{17}H_{19}NO$, 60%); 207 ($C_{16}H_{15}$, 80%), etc.

SYNTHESIS OF (±) 6-FORMAMIDO-4,4-DIPHENYL-3-HEPTANONE (6)

The oxaziridine 2 (100 mg, 3.2 x 10^{-4} mol) was dissolved in 10 mL dry, m-xylene, and refluxed under nitrogen overnight. The yellow solution was evaporated and flash chromatographed. After a 50 mL prerun of 50% pet. ether (30-60°) in ethyl acetate, the amide was eluted with ethyl acetate. The column was stripped with 25 mL methanol but no nitrone, was recovered. Mass Spectrum: By GCMS: Identical to 2. NMR (400 MHz): Major Rotamer: δppm 0.85, t(3H, CH_3-CH_2); 1.11, d(3H, CH_3-CH); 2.1-2., q buried (2H, CH_2CH_3); 2.4-2.5, dd buried (1H, CH_aH_b-CH); 2.8-2.9, dd(1H, CH_bH_aCH); 3.25, m(1H, CH_2-CH- CH_3); 5.98, bs(1H, NH); 7.1-7.4, m(10H, Ar) 7.75, s(1H, C(=O)H). Minor Rotamer: δppm 0.85, t(3H, CH_3-CH_2); 1.12, d(3H, CH_3-CH); 2.14-2.3, q buried (CH_3-CH_2); 2.3-2.4, dd(1H, CH_aH_b-CH-); 2.7-2.8, dd(1H, CH_aH_b-CH); 2.9-3.0, m(CH_3-CH); 5.52, bs(1H, NH); 7.1-7.4, s(10H, Ar); 7.45, d(1H, C(=O)H). IR (film): νmax: 3360 cm^{-1}, (m), 3260 (m, broad, H-bond N-H), 1710 (s, C=O str), 1670 (s, C=O Str, Amide I), 1535(m), 1495(m), 1445(m), 1380(mw), 1140(mw), 1100(wm-doublet), 1035(m), 915(w-m broad), 755(m), 730(m), 700(s).

SYNTHESIS OF 4,4-DIPHENYL-2,5-HEPTANEDIONE (3)

Jones reagent was added dropwise to 4,4-diphenyl-2,5-heptanediol[15] in acetone, on an ice bath. The solution was diluted with water and isopropanol, then extracted with ether. The yellow oil crystallized upon trituration with pet. ether (30-60°). Crystallization from ether/pet. ether (30°-60°) separated 5% diketone, from the major product, 2,2-diphenyl-4-valerolactone[16]. Elemental Analysis, Calculated for $C_{19}H_{20}O_2$ (mol. wt. 280.37): C, 81.39%; H, 7.19%; O, 11.43%. Found: C, 81.14%; H, 7.1%, O, 11.76%.
Mass Spectrum: m/z 262 (M^+-18, 2%), 43(100), 57(15), 223(12), 181(10), 206(8), 29(10). ^1H NMR (80MHz): δppm, 0.94 t (3H, CH_3-CH_2); 2.0 s(3H CH_3 -C=O); 2.39 q (2H, CH_3-CH_2); 3.58 s (2H, CH_2-C -Ar_2) 7.3 (10H, Aromatic). IR (mull): ν max 1710 cm^{-1}, and 1705 cm^{-1}, (s, C=O str), 1490(m) 1460(s, CH_3 bend) 1370, 1360 (m-s) 1180 (m) 1120(m) 770, 750 (m, Ar), 700 (s, Ar). ^{13}CNMR (20 MHZ): (0-200 ppm), 8.8 (CH_3-CH_2); 31.24 (-CH_2-CH_3); 33.04 (CH_3-C(=O)); 52.6 (CAr_2-CH_2-C(=O)); 63.92 (Ar_2CR_2); 127.07, 128.23, 129.16 (Arom CH); 142.34 (Arom C-C).

The diketone was refluxed in 0.75 M methanolic sodium hydroxide solution then diluted with water and extracted with ether. The clear hygroscopic aldol product was exclusively 2,3-dimethyl--5,5-diphenylcyclopent-2-enone 8, Mass Spectrum: m/z 262 (M^+, 100%), 185(80), 247(52), 233(52), 219(22), 165(22). ^{1}H NMR (270 MHz): δppm, 1.78 s(3H, CH_3-C-CH_2); 2.13 s(3H, CH_3-C-C=C); 3.32 s(2H, -CH_2-); 7.12-7.32 M (10 H, Arom.). The singlets were broadened by long range couplings. UV Spectrum: (CH_3CN) λmax (ε); 316(419, R band cyclopentenone); 240(8122, K band cyclopentenone); 204 (17,819, Arom.) 256(buried). IR (film): ν max 1697 (s, C=O Str); 1655 (s, C=C str).

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