# Oxidation of *N*-Acyl-Pyrrolidines and -Piperidines with Iron(II)–Hydrogen Peroxide and an Iron Complex–Molecular Oxygen

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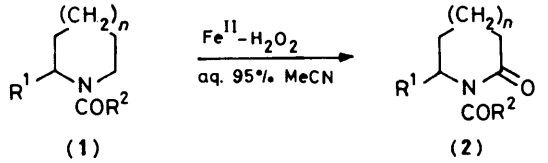
The reactions of *N*-acyl-pyrrolidines (**1a**—**c**) and -piperidines (**1d**—**f**) with $Fe^{II}$–hydrogen peroxide in aqueous 95% acetonitrile gave the corresponding pyrrolidin-2-ones (**2a**—**c**) and piperidin-2-ones (**2d**—**f**). The lactams (**2a**—**f**) were also the products in the oxidation of (**1a**—**f**) with molecular oxygen in the presence of an iron complex, either $[Fe^{II}Fe^{III}_2O(OAc)_6(py)_3]$ or $[\{Fe(salen)\}_2O]$, in aqueous 90% pyridine.

Because of their relevance to enzymatic *N*-dealkylation and as models for cytochrome P-450 and flavoprotein monooxygenases, there have been numerous studies of tertiary amine oxidation with a number of different systems.[1,2] The reactions are thought to involve as the initial step one-electron oxidation, hydrogen abstraction at the α-position to the nitrogen, and electrophilic attack by the oxidant on the nitrogen, depending on the nature of the systems. In contrast, and in spite of its biological importance, *N*,*N*-dialkylamide oxidation has been little studied,[3-5] perhaps because amides are relatively inert toward oxidation.

In the light of these results, we have undertaken the oxidation of *N*-phenylcarbamoyl- (**1a**) and *N*-benzoyl-pyrrolidines (**1b**—**c**) and *N*-phenylcarbamoylpiperidines (**1d**—**f**) with iron(II)–hydrogen peroxide in aqueous acetonitrile and with molecular oxygen in the presence of an Fe-complex (either $[Fe^{II}Fe^{III}_2O(OAc)_6(py)_3]$ or $[\{Fe(salen)\}_2O]$ in aqueous pyridine), these simple but potential model oxidizing systems being cited to be of importance in selective alkane oxidation.[6-8]

## Results and Discussion

*Oxidation with Iron(II)–Hydrogen Peroxide.*—When *N*-acyl-pyrrolidines (**1a**—**c**) and piperidines (**1d**—**f**) were oxidized with a mixture of iron(II) perchlorate (1 equiv.), hydrogen peroxide (5 equiv.), and acetic acid (10 equiv.) in acetonitrile containing 5% water, we obtained the corresponding pyrrolidin-2-ones (**2a**—**c**) and piperidin-2-ones (**2d**—**f**) in 52—75% yield based on the substrates (**1a**—**f**) consumed (Scheme 1 and Table 1). It was confirmed that in the absence of either hydrogen peroxide or iron(II) perchlorate the substrates were recovered quantitatively. On the basis of the results for the conversion of (**1a**—**f**), the order of reactivity of these substrates was found to follow the sequence (**1a**) ≃ (**1b**) > (**1c**) ≃ (**1d**) > (**1e**) ≃ (**1f**). These results may be interpreted in the following terms: (*a*) the methylene group at the α-position to the nitrogen rather than




(1) (2)

**a**; $n$ = 0, $R^1$ = H, $R^2$ = NHPh
**b**; $n$ = 0, $R^1$ = H, $R^2$ = Ph
**c**; $n$ = 0, $R^1$ = $CO_2Me$, $R^2$ = Ph
**d**; $n$ = 1, $R^1$ = H, $R^2$ = NHPh
**e**; $n$ = 1, $R^1$ = Me, $R^2$ = NHPh
**f**; $n$ = 1, $R^1$ = Ph, $R^2$ = NHPh

**Scheme 1.**

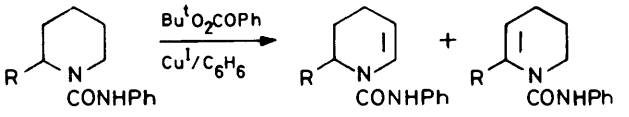
**Table 1.** Oxidation of *N*-acyl-pyrrolidines and -piperidines with $Fe^{II}$–hydrogen peroxide[a]

| Substrate | Conversion of substrate (%) | Lactam (% yield)[b] |
|---|---|---|
| (**1a**) | 44 | (**2a**) (75) |
| (**1b**) | 45 | (**2b**) (40) |
| (**1c**) | 34 | (**2c**) (61) |
| (**1d**) | 31 | (**2d**) (56) |
| (**1e**) | 22 | (**2e**) (52) |
| (**1f**) | 20 | (**2f**) (61) |

[a] The reaction was carried out in aqueous 95% acetonitrile at 0 °C for 50 min under nitrogen. [Substrate]:[$Fe(ClO_4)_2$]:[$H_2O_2$]:[AcOH] = 1:1:5:10. [b] Yield based on the substrate consumed.

the methine group is preferentially attacked by the oxidant; (*b*) the derivatives of pyrrolidine are more reactive than those of piperidine; and (*c*) the existence of an α-substituent decreases the substrate reactivity. These trends are very similar to those found in chemical tertiary amine oxidation involving one-electron oxidation in the initial reaction step[9] and also electrochemical oxidation of *N*,*N*-dialkylamides[5] and tertiary amines.[10]

*Oxidation with t-Butyl Perbenzoate–Copper(I) Chloride.*[11]—Treatment of (**1d**) with t-butyl perbenzoate (1 equiv.) in the presence of CuCl (0.1 equiv.) in refluxing benzene under nitrogen for 4.5 h yielded *N*-phenylcarbamoyl-1,2,3,4-tetrahydropyridine (**3**) (52%), the conversion of (**1d**) being 32% (Scheme 2 and Table 2). Benzoyloxylation at the α-position to the nitrogen in the piperidine moiety and subsequent




(1) (3) R = H (6) R = Ph
(4) R = Me
(5) R = Ph

**Scheme 2.**

elimination of benzoic acid could account for the formation of this compound.[11] Reaction of (**1e**) gave *N*-phenylcarbamoyl-2-methyl-1,2,3,4-tetrahydropyridine (**4**) (57%), suggesting that benzoyloxylation had, preferentially, occurred at the less substituted α-position. In contrast, reaction of (**1f**) gave a mixture (42% yield) of 1,2,3,4-(**5**) and 1,4,5,6-

**Table 2.** Oxidation of *N*-phenylcarbamoyl-pyrrolidine and -piperidines with t-butyl perbenzoate–CuCl[a]

| Substrate | Conversion of substrate (%) | Products (% yield)[b] |
|---|---|---|
| (**1a**) | 52 | (**7**) (11) |
| (**1d**) | 32 | (**3**) (52) |
| (**1e**) | 34 | (**4**) (57) |
| (**1f**) | 52 | (**5**) (18) |
| | | (**6**) (25) |

[a] The reaction was performed in refluxing benzene for 4.5 h under nitrogen. [Substrate]:[Peroxide]:[CuCl] = 1:1:0.1. [b] Yield based on the substrate consumed.

**Table 3.** Oxidation of *N*-acyl-pyrrolidines and -piperidines with molecular oxygen in the presence of an iron complex[a]

| Substrate | Fe-complex[b] | Conversion of substrate (%) | Lactam (% yield)[c] |
|---|---|---|---|
| (**1a**) | A | 51 | (**2a**) (34) |
| (**1b**) | A | 49 | (**2b**) (37) |
| (**1c**) | A | 34 | (**2c**) (30) |
| (**1d**) | A | 31 | (**2d**) (34) |
| (**1e**) | A | 30 | (**2e**) (49) |
| (**1f**) | A | 9 | (**2f**) (42) |
| (**1d**) | A[d] | 26 | (**2d**) (29) |
| (**1d**) | B | 25 | (**2d**) (29) |
| (**1e**) | B | 18 | (**2e**) (59) |
| (**1f**) | B | 3 | (**2f**) (18) |

[a] The reaction was carried out in aqueous 90% pyridine at 20 °C for 20 h. [b] A: $[Fe^{II}Fe^{III}_2O(OAc)_6(py)_3]$, generated from a mixture of iron powder (10 equiv.), sodium sulphide (2 equiv.), and acetic acid (10 equiv.) in aqueous pyridine. B: $[\{Fe(salen)\}_2O]$ (0.1 equiv.) in the presence of sodium sulphide (2 equiv.) and acetic acid (10 equiv.). [c] Yield based on the substrate consumed. [d] The complex used was previously isolated.

tetrahydropyridine (**6**) derivatives in a ratio of 2:3, the conversion of (**1f**) being 52%. This contrasts with oxidation by the $Fe^{II}$–$H_2O_2$ system when the sole product (**2f**) arose from attack on the methylene group and the conversion of (**1f**) was lower than that for (**1d**). The pyrrolidine (**1a**) on oxidation gave *N*-phenylcarbamoylpyrrole (**7**) (11%).

*Oxidation with Molecular Oxygen in the Presence of an Iron Complex.*—Oxidation of (**1a**—**f**) with molecular oxygen was carried out in the presence of $[Fe^{II}Fe^{III}_2O(OAc)_6(py)_3]$ generated *in situ*, according to the Gif system,[7] at 20 °C for 20 h to give the corresponding pyrrolidin-2-ones (**2a**—**c**) and piperidin-2-ones (**2d**—**f**) in moderate yields as the sole characterizable products (Scheme 3 and Table 3).*

The reaction of (**1d**) in the presence of the iron complex previously isolated also afforded (**2d**) (29%). The order of reactivity for (**1a**—**f**) judged from the conversion of these

(1) $\xrightarrow[\text{aq. } 90\%\text{ pyridine}]{\text{Fe-Complex}^a\text{-}O_2}$ (2)

[a] $[Fe^{II}Fe^{III}_2O(OAc)_6(py)_3]$ or $[\{Fe(salen)\}_2O]$

**Scheme 3.**

* Although the by-products from each reaction could not be isolated in a pure state, mass spectroscopic analysis suggested that they contained more than two oxygen atoms. No evidence could, however, be obtained for the formation of the mono-oxygenated products other than (**2**).

**Table 4.** Kinetic isotope effect from the oxidation of *N*-phenylcarbamoyl[2,2-$^2H_2$]pyrrolidine (**8**) and the competitive reaction between (**8**) and (**1a**)

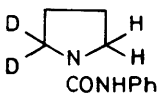
| Oxidizing system | Kinetic isotope effect[a] (A) | (B) |
|---|---|---|
| $Fe^{II}$–$H_2O_2$ | 1.9 | 1.8 |
| $[Fe^{II}Fe^{III}_2O(OAc)_6(py)_3]$–$O_2$ | 1.5 | 1.2 |
| $Cu^{I}$–Bu$^t$OOCOPh | — | 5.5 |

[a] From the oxidation of the [$^2H_2$]pyrrolidine (**8**); method (A) and from the competitive oxidation of (**8**) and (**1a**); method (B). The measurement was carried out by mass spectroscopy and $^1$H n.m.r. at the 20—30% conversion.

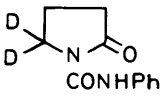
substrates was found to follow the sequence (**1a**) ≃ (**1b**) > (**1c**) ≃ (**1d**) ≃ (**1e**) > (**1f**), a trend similar to that observed in the oxidation with $Fe^{II}$–hydrogen peroxide system.

The reactions of (**1d**—**f**) with molecular oxygen in the presence of $[\{Fe(salen)\}_2O]$ (0.1 equiv.), also gave the piperidin-2-ones (**2d**—**f**) (Table 3).

*Isotope Effect.*—To obtain an insight into the initiation step of the reaction in each oxidizing system, the kinetic isotope effect was measured using *N*-phenylcarbamoyl[2,2-$^2H_2$]pyrrolidine (**8**) (Table 4). The intramolecular kinetic isotope effect ($k_H/k_D$) in the reaction of (**8**) with the $Fe^{II}$–hydrogen peroxide system evaluated from the product ratio of (**2a**) to *N*-phenylcarbamoyl[5,5-$^2H_2$]pyrrolidin-2-one (**9**) [method (A)]



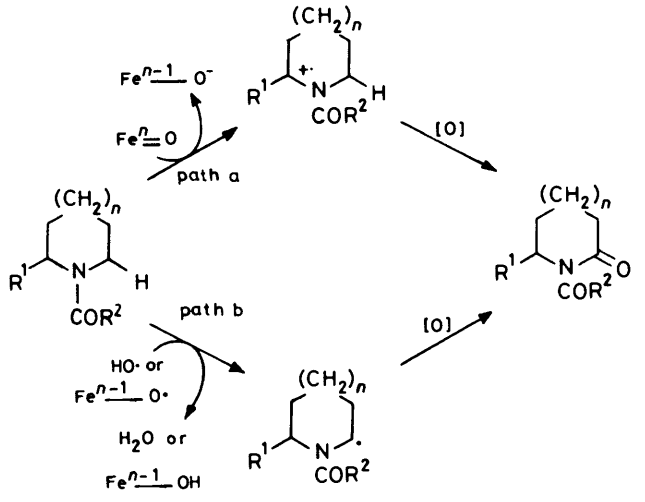
(**8**)



(**9**)

was found to be 1.9. A value of 1.8 calculated from the recovered substrate ratio of (**1a**) to (**8**) in the competitive reaction between (**8**) and (**1a**) [method (B)] was also obtained, assuming that the reactivity of the $CH_2$ group in (**8**) is equal to that in (**1a**). The isotope effect observed in the reaction of (**8**) with molecular oxygen in the presence of $[Fe^{II}Fe^{III}_2O(OAc)_6(py)_3]$ was 1.5 by method (A) and 1.2 by method (B). These values of 1.2—1.9 are comparable with the reported isotope effects of 1.84 in the electrochemical oxidation of *N*-methoxycarbonyl[2,2-$^2H_2$]-pyrrolidine[5] and 1.3 in the reaction of *N*,*N*-dimethylbenzylamine with $[Fe^{III}(TPP)Cl]$–iodosylbenzene,[1e] these reactions being believed to involve one-electron oxidation in the initiation steps. In contrast, the observed isotope effect in the reaction of (**8**) with t-butyl perbenzoate–CuCl was 5.5 measured by method (B), suggesting that the reaction proceeded *via* initial hydrogen abstraction by a t-butoxy radical.[11]

*Reaction Scheme.*—The kinetic isotope effect observed in the reaction with $Fe^{II}$–$H_2O_2$ and the consistency of the order of reactivity of (**1a**—**f**) with the reported trends in both chemical tertiary amine oxidation involving initial one-electron oxidation[9] and electrochemical oxidation of *N*,*N*-dialkylamides[5] and tertiary amines[10] lead us to deduce that the first step of the reaction involves one-electron oxidation. These results also suggest that the active species generated from a mixture of iron(II) ion and hydrogen peroxide under the present reaction conditions employed is $Fe^{IV}$–O rather than hydroxyl radical



Scheme 4.

(Scheme 4).* On the basis of the observed isotope effect and the order of reactivity of (**1a**—**f**) in the oxidation with molecular oxygen in the presence of $[Fe^{II}Fe^{III}_2O(OAc)_6(py)_3]$, the reaction is thought to proceed *via* initial one-electron transfer from the substrate to the active species generated in the reaction medium (probably an iron-oxo complex)[7] (path **a** in the Scheme).

## Experimental

$^1H$ N.m.r. spectra were obtained with a Hitachi JNM-PS-100 spectrometer for $CDCl_3$ solutions. Mass spectra were obtained with a Hitachi RMU-6M spectrometer and i.r. spectra with a Shimazu IR-400 spectrometer.

*Materials.*—The pyrrolidines (**1a**),[12] (**1b**),[13] and (**1c**)[14] and the piperidines (**1d**)[12] and (**1e**)[12] were prepared by the reported methods.

*N*-Phenylcarbamoyl-2-phenylpiperidine (**1f**) was prepared by the reaction of 2-phenylpiperidine[15] with phenyl isocyanate in dichloromethane at 20 °C. The piperidine had m.p. 117—119 °C (from ethanol), $\delta_H$ 1.45—2.39 (6 H, m), 2.84—3.24 (1 H, m), 3.80—4.17 (1 H, m), 5.30 (1 H, t, *J* 6.0 Hz), 6.36 (1 H, br s), and 6.90—7.50 (10 H, m).

*N*-Phenylcarbamoyl[2,2-$^2H_2$]pyrrolidine (**8**) was prepared by the reaction of [2,2-$^2H_2$]pyrrolidine[16] with phenyl isocyanate in ether; $\delta_H$ 1.76—1.96 (4 H, m), 3.39 (2 H, t, *J* 7.5 Hz), 6.64 (1 H, br s), and 6.80—7.54 (5 H, m).

*Oxidation of the Pyrrolidine* (**1a**) *with Iron*(II)*–Hydrogen Peroxide.*—A solution of 10% hydrogen peroxide (10 mmol) in acetonitrile (15 ml) was added to a stirred solution of (**1a**) (2 mmol), $Fe(ClO_4)_2 \cdot 6H_2O$ (2 mmol), and acetic acid (20 mmol) in acetonitrile (20 ml) over a period of 20 min at 0 °C under nitrogen. The mixture was stirred for a further 30 min, and then poured into ice-cold water, and the products were extracted with dichloromethane. Work-up of the extracts and column chromatography of the product on silica gel (elution with hexane–ethyl acetate) afforded first *N*-phenylcarbamoylpyrrolidin-2-one (**2a**), m.p. 98—100 °C (from ethanol) (lit.,[17] 98 °C); $\delta_H$ 1.83—2.22 (2 H, m), 2.66 (2 H, t, *J* 7.5 Hz), 3.92 (2 H, t, *J* 7.5 Hz), and 6.90—7.66 (6 H, m). From the second fraction the starting material (**1a**) was recovered.

* Participation of such a high-valent iron-oxo species has been already proposed to explain the stereoselective oxidation of cyclohexanol to *cis*-cyclohexane-1,4-diol with $Fe^{II}$–$H_2O_2$ in aqueous acetonitrile.[6]

*Oxidation of the Piperidine* (**1f**) *with t-Butyl Perbenzoate–Copper*(I) *Chloride.*—A solution of t-butyl perbenzoate (2 mmol) in benzene (30 ml) was added to a refluxing benzene (30 ml) containing (**1f**) (2 mmol) and copper(I) chloride (0.2 mmol) over a period of 1 h, after which the mixture was refluxed for a further 3.5 h with stirring. The products were isolated by column chromatography on silica gel using hexane–ethyl acetate as eluant. The first fraction contained a viscous oily mixture of *N*-phenylcarbamoyl-2-phenyl-1,2,3,4-(**5**) and 1,4,5,6-(**6**) tetrahydropyridines. Repeated column chromatography of the products on silica gel resulted in a partial separation, (**6**) being less polar than (**5**); *m/z* 278 ($M^+$) [a mixture of (**5**) and (**6**), (**5**)/(**6**) = 2:3]; (**5**), $\delta_H$ 1.64—2.48 (4 H, m), 4.90—5.15 (1 H, m), 5.25 (1 H, t, 6.0 Hz), 6.54 (1 H, br s), and 6.60—8.00 (11 H, m); (**6**), $\delta_H$ 1.63—2.48 (2 H, m), 3.98 (2 H, t, *J* 6.0 Hz), 5.61 (1 H, t, *J* 5.0 Hz), 6.17 (1 H, br s), and 6.80—7.60 (10 H, m). From the second fraction was recovered (**1f**).

*Oxidation of the Piperidine* (**1e**) *by Molecular Oxygen in the Presence of* $[Fe^{II}Fe^{III}_2O(OAc)_6(py)_3]$.—Iron powder (10 mmol) and $Na_2S \cdot 9H_2O$ (4 mmol) were added to a solution of (**1e**) (2 mmol) in pyridine (20 ml) containing acetic acid (20 mmol) and water (1.5 ml). The resulting mixture was stirred at 20 °C for 20 h under oxygen after which it was poured into dilute hydrochloric acid and extracted with dichloromethane. After work-up of the organic extract, products were column chromatographed on silica gel using hexane–ethyl acetate as eluant. The first fraction contained the piperidin-2-one (**2e**), m.p. 85—87 °C (from benzene–hexane) (Found: C, 67.3; H, 7.0; N, 12.0. $C_{13}H_{16}N_2O_2$ requires C, 67.2; H, 6.9; N, 12.1%); *m/z* 218 ($M^+$); $\delta_H$ 1.28 (3 H, t, *J* 7.5 Hz), 1.75—2.18 (4 H, m), 2.66 (2 H, t, *J* 7.5 Hz), 4.80—5.04 (1 H, m), and 7.05—7.60 (6 H, m). From the second fraction was recovered the piperidine (**1e**). The third fraction (52 mg) was a mixture containing at least two components; the mass spectrum showed the peaks at *m/z* 248 and 264.

*Oxidation of the Piperidine* (**1d**) *by Molecular Oxygen in the Presence of* $[\{Fe(salen)\}_2O]$.—The oxidation of (**1d**) (2 mmol) was carried out in the presence of $[\{Fe(salen)\}_2O]$[18] (0.1 equiv.), $Na_2S \cdot 9H_2O$ (4 mmol), and acetic acid (20 mmol) in 90% aqueous pyridine (20 ml) at 20 °C for 20 h under oxygen. The products were column chromatographed on silica gel using hexane–ethyl acetate as eluant. The first fraction contained the piperidin-2-one (**2d**), m.p. 98—100 °C (from ethanol) (lit.,[19] m.p. 96—97 °C), $\delta_H$ 1.72—2.04 (4 H, m), 2.62 (2 H, t, *J* 7.5 Hz), 3.88 (2 H, t, *J* 7.5 Hz), and 6.96—7.66 (6 H, m). From the second fraction was recovered the piperidine (**1d**).

*Products.*—The pyrrolidin-2-one (**2b**) had m.p. 85—87 °C (from ethanol) (lit.,[20] 85 °C), $\delta_H$ 1.98—2.36 (2 H, m), 2.48—2.72 (2 H, m), 3.96 (2 H, t, *J* 7.5 Hz), and 7.24—7.72 (5 H, m). The pyrrolidin-2-one (**2c**) had m.p. 162—164 °C (from ethanol) (Found: C, 63.1; H, 5.3; N, 5.6. $C_{13}H_{13}NO_4$ requires C, 63.2; H, 5.3; N, 5.7%); $\delta_H$ 1.87—2.90 (4 H, m), 3.78 (3 H, s), 4.80—5.03 (1 H, m), and 7.24—7.80 (5 H, m). The piperidin-2-one (**2f**) had m.p. 117—119 °C (from benzene–hexane) (Found: C, 73.5; H, 6.2; N, 9.4. $C_{18}H_{18}N_2O_2$ requires C, 73.5; H, 6.2; N, 9.5%); $\delta_H$ 1.50—1.84 (2 H, m), 2.04—2.30 (2 H, m), 2.69 (2 H, t, *J* 7.5 Hz), 5.98 (1 H, t, *J* 6.0 Hz), and 7.00—7.60 (6 H, m). The tetrahydropyridine (**3**) was an oil (Found: C, 71.4; H, 7.0; N, 14.0. $C_{12}H_{14}N_2O$ requires C, 71.3; H, 7.0; N, 13.9%); *m/z* 202 ($M^+$); $\delta_H$ 1.76—2.20 (4 H, m), 3.65 (2 H, t, *J* 7.5 Hz), 4.84—5.08 (1 H, m), 6.51 (1 H, br s), 6.80 (1 H, d, *J* 5.0 Hz), and 6.90—7.50 (5 H, m). The tetrahydropyridine (**4**) had m.p. 117—118 °C (from benzene–hexane) (Found: C, 73.4; H, 7.4; N, 12.5. $C_{13}H_{16}N_2O$ requires C, 72.2; H, 7.5; N, 13.0%); *m/z* 216 ($M^+$); $\delta_H$ 1.24 (3 H, d, *J* 7.5 Hz), 1.59—2.30 (4 H, m), 4.30—4.63 (1 H, m), 4.90—5.15 (1

H, m), 6.55 (1 H, br s), 6.73 (1 H, d, *J* 9.0 Hz), and 7.00—7.70 (5 H, m). The pyrrole (**7**) had m.p. 155—157 °C (from benzene–hexane) (lit.,[21] 154—155 °C); $\delta_H$ 6.24—6.40 (2 H, m), and 7.04—7.78 (8 H, m).

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