75. Synthesis and Photo-oxygenation of Some Substituted 1-Benzyl-3,4-dihydroisoquinolines. Mechanism of Enamine Photo-oxygenation

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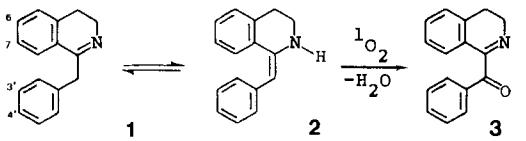
Summary

The synthesis of a series of substituted 1-benzyl-3,4-dihydroisoquinolines by *Bischler-Napieralski* cyclization is described. Competitive methylene blue sensitized photo-oxygenation experiments allowed the determination of relative rates of photo-oxygenation of 1-benzyl-3,4-dihydroisoquinolines. Substituents were shown to affect both the equilibrium concentration of the tautomeric enamine and the overall photo-oxygenation rate. After correcting for differences in enamine concentration, the relative rate data provided a diagnostic probe of the reaction mechanism, which involves transfer of charge in the rate-limiting step.

Introduction. – The autoxidation of substituted 1-benzyl-3,4-dihydroisoquinolines (**1**) to the corresponding 1-benzoyl derivatives **3** has been known for many years [1]. Although the transformation has been exploited synthetically [2], it is not efficient as reaction times are long and aromatization often occurs [3]. We have already shown that the process is a self-sensitized photo-oxygenation, the rate of which depends on light intensity [4]. Moreover, **1** can be converted to **3** faster and without side reactions by means of dye-sensitized photo-oxygenation [3] [4]. From the substituent effects on the relative rates of photo-oxygenation [5], the rate-limiting step is the transfer of charge from the enamine tautomer **2** to singlet oxygen. We now substantiate and enlarge on this conclusion and provide further evidence on the mechanism of this mild, selective oxidation.



Synthesis. – *Bischler-Napieralski* cyclization [6] of *N*-(2-phenylethyl)phenylacetamides (**4**) using either polyphosphoric acid (PPA) at 150° or phosphorous pentoxide in refluxing xylene afforded the corresponding 1-benzyl-3,4-dihydroiso-

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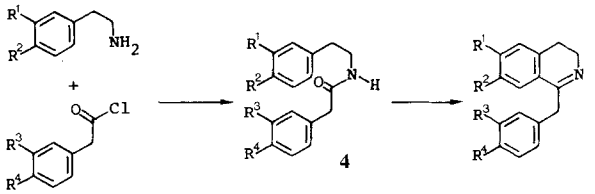
Table 1. Bischler-Napieralski *synthesis of 1-benzyl-3,4-dihydroisoquinolines* **1**



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	R^1	R^2	R^3	R^4	Yield of **4** [%]	M.p. of **4** [°C]	Yield of **1** %	M.p. of **1**-picrate [°C]
a	H	H	H	H	74	90[a])	65	175–176[b])
b	Cl	H	H	H	85	[c])	42	146–148
c	NO_2	H	H	H	77	[c])	[d])	
d	OCH_3	H	H	H	80	61– 62[e])	38	168–170[e])
e	H	Cl	H	H	75	102–102.5[f])	41	176–177[g])
f	H	NO_2	H	H	77	[c])	[d])	
g	H	CH_3	H	H	86	88– 89	51	170
h	H	OCH_3	H	H	71	103[h])	31	184–186[i])
i	H	H	Cl	H	80	80	67	183
j	H	H	NO_2	H	64	75	87	210–211
k	H	H	OCH_3	H	87	70[j])	52	157–158
l	H	H	H	Cl	73	107.5–108	57	198–201
m	H	H	H	NO_2	85	127.5–138[k])	75	213–214[l])
n	H	H	H	CH_3	85	104	56	197–198
o	H	H	H	OCH_3	86	97.5–98.5[m])	38	174–175[n])
p	OCH_3	OCH_3	OCH_3	OCH_3	93	122.5–123[o])	64	158.5–159[p])

[a]) [7]: 95°. [b]) [7]. [c]) Oil. [d]) No pure product could be isolated from this cyclization attempt. The difficulty of cyclizing amides bearing strongly electron-withdrawing groups in this ring has been previously noted [8]. [e]) [9]. [f]) [10]: 104.5–105.5°. [g]) [10]: 168–180°. [h]) [10]: 102.5–105°. [i]) [10]. [j]) [11]. [k]) [12]: 139–140°. [l]) [12]: Methiodide, m.p. 242–243°. [m]) [13]: 97.5–98.5°. [n]) [14]: 173–174°. [o]) [15]: 124°. [p]) [14]: 159–160°.

quinolines in 31–87% yield *(Table 1)*. For methoxy derivatives, P_2O_5 in xylene was used since PPA resulted in demethylation.

The starting amides were prepared by condensation of suitably substituted phenylacetyl chloride and 2-phenylethyl amines. The latter, when not commercially available, were obtained by converting the appropriate phenylacetic acid to the acid chloride, then to the corresponding amide which on reduction with lithium aluminium hydride gave the desired amine. The 1-benzyl-3,4-dihydroisoquinolines were stored under N_2 in the dark at $-20°$ to prevent oxidation.

Photo-oxygenation rates. – Relative rates of photo-oxygenation were determined from competition experiments in which a solution containing equimolar amounts of the substituted and the unsubstituted 1-benzyl-3,4-dihydroisoquinoline(**1a**)was photo-oxygenated using methylene blue in oxygen-saturated chloroform. Aliquots were analyzed by gas-liquid chromatography; butyl phthalate was used as internal standard. The results were plotted as the natural logarithm of the relative concentration of each 1-benzyl-3,4-dihydroisoquinoline remaining *vs.* time. Straight lines were obtained, thereby confirming pseudo-first order kinetics. The ratio of the slope

Table 2. *Relative rates of photo-oxygenation of some 1-benzyl-3,4-dihydroisoquinolines* **1** → **3**

R	k_{rel}	σ_m[a])	R	k_{rel}	σ_p[a])
3′-Cl	1.35	0.37	4′-Cl	1.2	0.23
3′-NO_2	1.5	0.71	4′-NO_2	2.5	1.27[2])
3′-OCH_3	1.15	0.12	4′-OCH_3	0.85	−0.27
			4′-CH_3	0.95	−0.17
7-Cl	2.2	0.37			
7-OCH_3	1.2	0.12	6-Cl	1.65	0.23
7-CH_3	0.9	−0.07	6-OCH_3	0.57	−0.27

[a]) [16].

of the line obtained for each substituted compound to that for the unsubstituted one gave the relative rate constants (k_{rel}) *(Table 2)*.

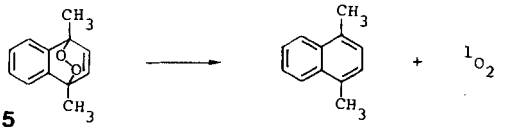
Confirmation of the intermediacy of singlet oxygen. – Verification that the photo-oxygenations proceed *via* singlet oxygen was obtained from the following evidence.

1. The rate of oxidation in the light is unaffected by the radical inhibitor 2,6-di-(*t*-butyl)-*p*-cresol (1 mM), but is retarded considerably by addition of diazabicyclo-octane (1–10 mM), a known quencher of singlet oxygen [18].

2. Oxidation ceases immediately when irradiation is stopped.

3. Pseudo-first order kinetics are observed.

4. The same oxidation products and relative oxidation rate constants (k_{rel}) are observed when 1,4-dimethylnaphthalene endoperoxide (**5**) is used to generate singlet oxygen thermally in the dark [19].



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5. The rate is enhanced by a factor of 4.5 when the photo-oxygenation is performed in deuteriochloroform rather than chloroform. Such rate enhancements are due to the longer lifetime of singlet oxygen in the deuteriated solvent, and are diagnostic of the involvement of singlet oxygen [20].

6. The same product is obtained regardless of the sensitizer/solvent combination used, *viz.* methylene blue/chloroform, *meso*-tetraphenylporphine/carbon tetrachloride, rose bengal/methanol and methylene blue/acetonitrile.

Correlation of substituent effects. – When the logarithms of the relative rate constants were plotted against *Hammett* σ-values[2]), straight lines were obtained *(Fig. 1)*. The slopes calculated by least-squares analysis were $\rho = +0.29$ ($r = 0.992$) for the 3′ and 4′-substituted compounds, and $\rho = +0.89$ ($r = 0.996$) for the 6- and 7-substituted compounds. The positive values obtained for ρ in both cases seem to

[2]) The constant σ_A designed for anilinium ion acidity [16] and used for β-arylenamines [17] gives the best fit for the experimental data for the 4′-nitro compound.

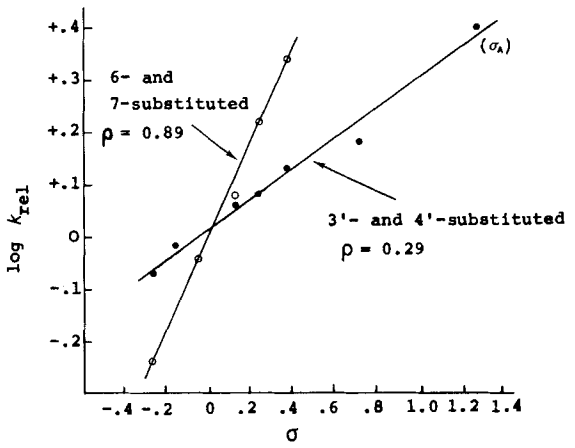


Fig. 1. *Logarithm of relative photo-oxygenation rates of some 1-benzyl-3,4-dihydroisoquinolines* **1** vs. Hammett *σ-constants*

be inconsistent with the mild electrophilic nature of singlet oxygen, but are understandable in terms of the greater equilibrium concentration of the enamine tautomer of those compounds bearing electron-withdrawing substituents [21].

The UV./VIS. spectra of the substituted 1-benzyl-3,4-dihydroisoquinolines *(Table 3)* permit the determination of the amount of enamine **2** present in the equilibrium **1** ⇌ **2** since all of these compounds have an *α*-aminostilbene chromophore absorbing near 355 nm[3]). The molar extinction coefficients (*ε*) of substituted *α*-aminostilbenes are essentially independent of substituent effects[4]); consequently, *ε* is proportional to the enamine concentration. The logarithms of *ε* correlate well with *Hammett σ*-constants for the two series of substituted compounds, giving slopes of +0.79 ($r = 0.991$) for the 3′- and 4′-substituted compounds and +0.38 ($r = 0.981$) for the 6′- and 7′-substituted compounds *(Fig. 2)*. Consequently, the enamine concentration is a linear free-energy function, and the UV./VIS. spectral measurement provides a valid index of the enamine concentration.

Table 3. *Long-wavelength absorption spectra of some 1-benzyl-3,4-dihydroisoquinolines* **1** *in acetonitrile*

R	λ_{max} (nm)	log*ε*	R	λ_{max}	log*ε*
3′-Cl	360	2.65	4′-Cl	360	2.63
3′-NO_2	350	2.87	4′-NO_2	455	3.49
3′-OCH_3	350	2.48	4′-OCH_3	350	2.21
			4′-CH_3	360	2.31
7-Cl	360	2.57			
7-OCH_3	360	2.45	6-Cl	352	2.54
7-CH_3	360	2.42	6-OCH_3	352	2.33

[3]) The 4′-nitro compound absorbs at 455 nm, owing to additional conjugation.

[4]) When a strong mesomeric electron-withdrawing substituent is conjugated with the ring N-atom, as exemplified by the 4-nitro derivative, then the *ε* value in the *α*-aminostilbene structure is altered [17] [21c]. Correcting for this effect does not alter appreciably the slope or correlation coefficient of the lines concerned.

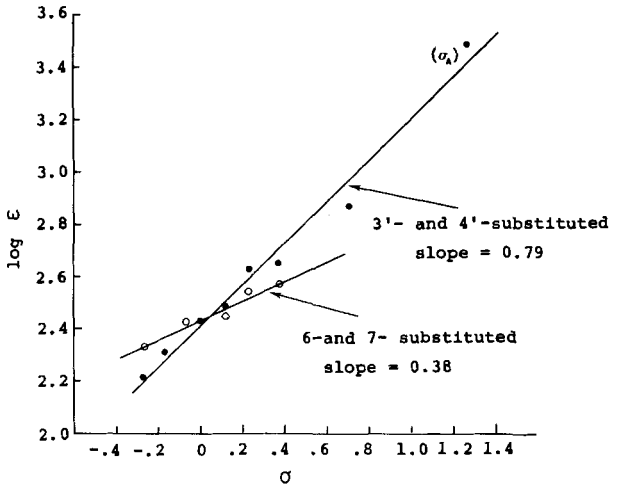


Fig. 2. *Logarithm of molar extinction coefficients (ε) of some 1-benzyl-3,4-dihydroisoquinolines* **1** vs. Hammett *σ-constants*

Additional evidence for tautomerism to the enamine form is provided by the observation of deuterium exchange at the imino-benzylic position when 1-benzyl-3,4-dihydroisoquinoline (**1a**) is dissolved in D_4-methanol as revealed by ^{1}H-NMR. The possibility that the rate of photo-oxygenation was limited by the rate of tautomerism to the more reactive enamine form can be discounted since deuterium

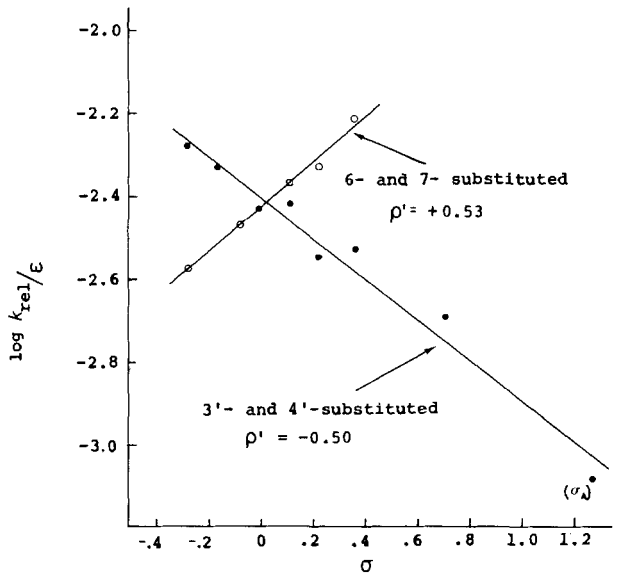
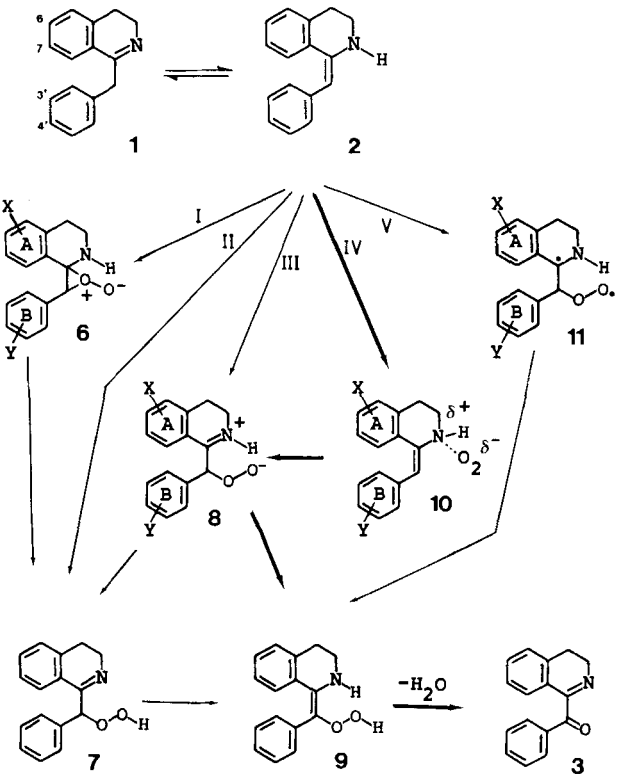


Fig. 3 *Logarithm of the ratio of relative photo-oxygenation rates to ε* vs. Hammett *σ-constants*

Scheme 1



exchange at the imino-benzylic position proceeds more rapidly than photo-oxygenation under similar conditions.

In order to determine the substitutent effects on the relative rates of photo-oxygenation of the reactive enamine tautomer[5]), the logarithm of the ratio of k_{rel} to ε for each compound was plotted against σ^2). Significantly, the result *(Fig. 3)* is two straight lines of different slopes. The plot for the 3′- and 4′-substituted compounds has a negative slope ($\rho' = -0.50$, $r = 0.986$), whereas the one for the 6- and 7-substituted compounds shows a positive slope ($\rho' = +0.53$, $r = 0.995$). Thus, electron-withdrawing groups (X) in ring A *(Scheme 1)* stabilize the transition state, enhancing the rate while electron-donating groups (Y) in ring B cause the same effect.

To reconcile these results with a single mechanism for the reaction of singlet oxygen with the secondary enamine, we now consider five possible mechanisms *(Scheme 1)*[6]).

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[5]) A preliminary study [3] demonstrated that the ease of oxidation of 1-substituted-3,4-dihydroisoquinolines paralleled the stability of the enamine tautomer.

[6]) Dioxetane formation, usually the predominant reaction of enamines with singlet oxygen [22], is not considered as it does not lead to the observed product, except in special cases *(vide infra)*.

I) Singlet oxygen could react with the electron-rich double bond generating the *perepoxide* **6** which could subsequently abstract a proton to give the hydroperoxide **7** which on prototropy and dehydration gives the iminoketones **3**;

II) A concerted *ene mechanism* could occur to give the hydroperoxide **7** directly, which leads as before to the products **3**;

III) An intermediate *zwitterionic peroxide* **8** could form initially which then leads to **3** *via* either hydroperoxide **7** or **9**.

IV) Transfer of charge from the enamine to the electrophilic singlet oxygen would form a *charge-transfer* complex **10**, which could collapse to the zwitterionic peroxide **8** and then to the iminoketone **3**.

V) Addition could produce the peroxy *diradical* **11** which could collapse by H-atom transfer to either hydroperoxide **7** or **9**, and eventually undergo dehydration to **3**.

We now consider the substituent effects.

I) Electron-donating X and Y should equally stabilize the perepoxide **6** and exhibit negative ρ-values.

II) Electron-donating substituents X and Y would lower the energy of the transition state for the ene-type mechanism, as the energy of the enamine HOMO would be raised. Negative ρ-values would be predicted.

III) The zwitterionic intermediate **8** should be stabilized when X is an electron-donating substituent. Ring A substituents should correlate better with σ^+ than σ. The nature of the substituent Y should have little effect on the stability of the intermediate as ring B is essentially insulated from the positive and negative centers.

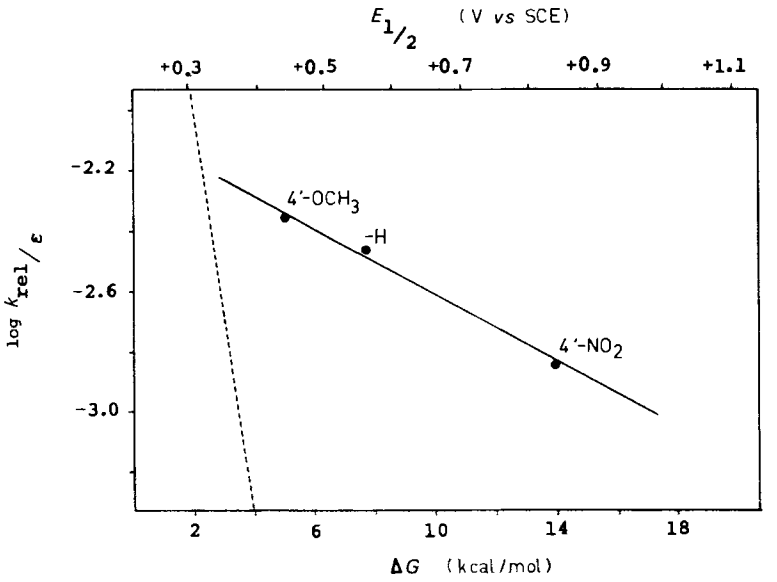


Fig. 4. *Logarithm of the ratio of relative photo-oxygenation rates to* ε vs. *oxidation half-wave potential for some 4'-substituted 1-benzyl-3,4-dihydroisoquinolines* **1** *and free energy of electron transfer from* **1** *to* $^1O_2$. The broken line indicates the expected relationship for full electron transfer [23].

Table 4. *Predicted ρ-values for the mechanisms* I–V

Mechanism		Signs of ρ predicted for substituents	
		X	Y
I)	Perepoxide	–	–
II)	Concerted (ene)	–	–
III)	Zwitterionic peroxide	–	0
IV)	Charge-transfer	+	–
V)	Diradical	–	0
	Observed	+	–

A negative ρ-value is therefore expected for the X substituent and a zero value for substituent Y.

IV) An electron-attracting substituent X should stabilize the charge-transfer complex **10** in much the same way as it stabilizes the enamine **2**, although the effect may be moderated owing to partial positive charge on the N-atom. On the other hand, when Y is electron-donating, the cationic center on the N-atom should be stabilized. Opposing this effect is the destabilizing influence of electron-donating substituents on the enamine. A small positive ρ-value is predicted for substituent X while a small negative value is expected for substituent Y. If the amount of charge transferred is great, better agreement of log k_{rel}/ε with σ^+-constants rather than with σ might be expected for substituents Y in the 4′-position. This is not observed[7]). For the extreme case of complete electron transfer in the rate-limiting step which is endothermic by at least 5 kcal/mol, the logarithm of the relative photooxygenation rate (corrected for substituent effects on the enamine concentration) plotted against the free energy of activation for electron transfer[8]) would be expected to yield a line having a maximal value of -0.73 mol/kcal for its slope. As the slope of the line actually obtained is only -0.063 mol/kcal *(Fig. 4)*, clearly an electron is not transferred in the rate-limiting step.

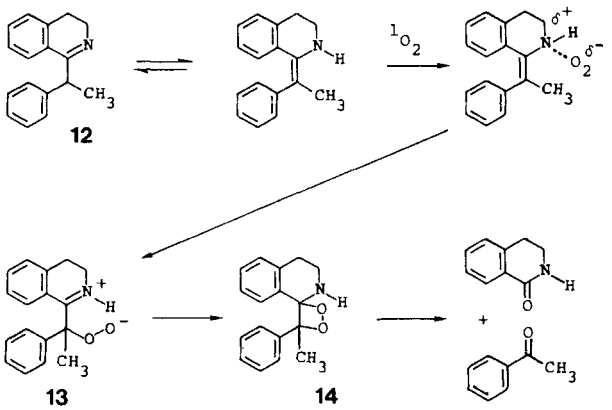
V) The diradical intermediate **11** ought to be stabilized by an electron-donating substituent X, whereas the nature of Y would have little effect since both radical sites are insulated. A negative ρ-value is expected for X and a negligible value is predicted for Y. Of these mechanisms, the charge-transfer process is the one which fits the substituent effects the best *(Table 4)*.

Enamines normally react with singlet oxygen to give dioxetanes, which then cleave to dicarbonyl products [14]. This is observed in the 1-benzyl-3,4-dihydroisoquinoline series when prototropy from the imino-benzylic position of the intermediate zwitterionic peroxide is prevented by alkyl substitution, as in **12** [3] *(Scheme 2)*. The intermediate zwitterionic peroxide **13**, unable to lose a proton, collapses to the dioxetane **14**, which is subsequently cleaved. A similar fate is observed for the tertiary enamine **16** *(Scheme 3)* [25], obtained from the methiodide

[7]) A better correlation is obtained between log k_{rel}/ε and σ ($r = 0.986$) than with σ^+ ($r = 0.948$) for 4′-substituents.

[8]) The free energy of electron transfer for the enamine to singlet oxygen can be calculated using the *Weller* equation [23] from oxidation potentials determined by cyclic voltammetry. For a similar treatment see [24].

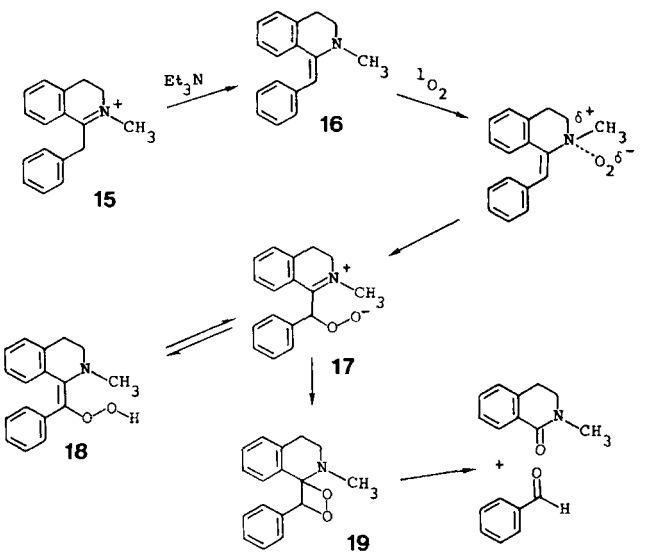
Scheme 2



salt **15**. This time, however, the zwitterionic peroxide **17** can undergo prototropy to give **18** on the one hand, or can collapse to dioxetane **19**, ultimately cleaving to the carbonyl products. The latter process is preferred, probably because **18** does not have a low energy pathway for dehydration available as does its secondary enamine counterpart **9** *(Scheme 1)*.

All the foregoing results may be accounted for by a single unifying mechanism. In summary, photo-oxygenation of 1-benzyl-3,4-dihydroisoquinolines passes through a rate-limiting charge-transfer complex which subsequently collapses to a

Scheme 3



short-lived zwitterionic peroxide[9]). Rearrangement by prototropy to the tautomeric enaminohydroperoxide **9**[10]) then occurs which readily loses a molecule of water, probably *via* a 6-membered ring transition state, giving the oxidized product[11]) (bold arrows, *Scheme 1*).

We are grateful to Dr. *P. Tissot* and Mrs. *H. Lartigue* for measuring the oxidation potentials.

Experimental Part

General remarks. Solvents were redistilled prior to use. Other reagents were used as supplied by *Fluka* or *Aldrich*. Melting points (m.p.) were determined in capillary tubes and are uncorrected. IR. spectra were recorded as $CHCl_3$ solutions using 0.2 mm cells on a *Pye Unicam SP-1100* spectrophotometer. UV./VIS. spectra were determined using a *Beckman Acta III* UV./VIS. spectrophotometer. ^{1}H-NMR. spectra were recorded as $CDCl_3$ solutions using a *Varian T-60A* spectrometer; chemical shifts (δ) are expressed relative to internal TMS. Elemental analyses were performed by Mr. *K.I. Jones*, Department of Organic Chemistry, Imperial College of Science and Technology, London. Cyclic voltammetry was carried out on acetonitrile solutions containing 0.1M tetrabutylammonium tetrafluoroborate as supporting electrolyte using a platinum working electrode and Ag/Ag^+ as reference. Oxidation half-wave potential values are corrected to a saturated calomel reference potential.

Photo-oxygenations were performed in one of two ways: *a)* In an apparatus previously described [26], using a $CHCl_3$ solution 1.0×10^{-1}M in each of the two substrates being compared, and containing 2.6×10^{-3}M methylene blue, 2.0×10^{-2}M 2,6-di-*t*-butyl-*p*-cresol, and 5.4×10^{-2}M di-butyl phthalate (internal standard).

b) Employing a 40 W 'mini' spot light placed 5 cm from a 25 ml two-neck flask partially immersed in a water bath maintained at 10–12°, and using a $CHCl_3$ solution 2.0×10^{-2}M in each substrate being compared, and containing 5.0×10^{-3}M 2,6-di(*t*-butyl)-*p*-cresol and 1.0×10^{-2}M dibutyl phthalate.

Samples were removed periodically and analyzed by GC. on a 0.3 mm I.D. $\times$2 m glass column packed with 3% OV-17 on gas chrom Q (80–100 mesh, base washed) at 210–240° on a *Carlo Erba* model *2350* gas chromatograph equipped with a flame ionization detector. Peak areas were measure using an *Autolab* model *6300* digital integrator.

Synthesis of phenylacetamides *4*. – *General procedure.* A solution of the phenylacetyl chloride in $CHCl_3$ was added dropwise to a stirred solution of the phenylethylamine and triethylamine in $CHCl_3$ at 0°. The mixture was allowed to warm to RT., then it was diluted with $CHCl_3$, washed successively with 10% HCl- and sated, aqueous $NaHCO_3$,-solution, and dried ($MgSO_4$). The solvent was removed under vacuum.

Preparation of N-*[2(3-chlorophenyl)ethyl]phenylacetamide* (**4b**). Reaction of phenylacetyl chloride (6.7 mmol) in $CHCl_3$ (10 ml), with 3-chlorophenylethylamine [27] (1.0 g, 6.4 mmol) and triethylamine (0.6 ml) in $CHCl_3$ (10 ml) then dilution with $CHCl_3$ (20 ml), ($MgSO_4$), ion gave 1.49 g (85%) as a pale oil. – IR. ($CHCl_3$): 3425*m*, 1672*s*. – ^{1}H-NMR. ($CDCl_3$): 7.3 (*m*, 9H, Ar-H); 5.6 (br., 1H, NH); 3.6 (*s*, 2H, CH_2CO); 3.5 (*qa*, 2H, CH_2NH); 2.7 (*t*, 2H, CH_2Ar).

$C_{16}H_{16}ClNO$	Calc.	C 70.20	H 5.89	Cl 12.95	N 5.12%
(273.75)	Found	„ 69.99	„ 5.90	„ 12.81	„ 5.90%

Preparation of N-*[2-(*p*-tolyl)ethyl]-2-phenylacetamide* (**4g**). Reaction of phenylacetyl chloride (8.3 mmol) in 10 ml of $CHCl_3$, with 2-(*p*-tolyl)ethylamine [28] (8.3 mmol) and triethylamine (0.6 ml) in

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[9]) Attempts to trap this intermediate using nucleophilic solvents (*e.g.* methanol or aqueous acetonitrile) have been unsuccessful thus far.

[10]) Prior formation of the iminohydroperoxide **7** cannot be ruled out.

[11]) An alternative to this pathway involves a *Criegee*-type rearrangement of an intermediate iminohydroperoxide **7**; however, no product of phenyl migration is observed, which casts doubt on this possibility.

$CHCl_3$ (15 ml) gave 1.80 g (86%) as a pale solid. Recrystallization from ethanol gave white crystals, m.p. 88–89°. – IR. ($CHCl_3$): 3430*m*, 1670*s*. – ^{1}H-NMR. ($CDCl_3$): 7.3–7.0 (*m*, 9H, arom.); 5.7 (br., 1H, NH); 3.55 (*s*, 2H, CH_2CO); 3.5 (*qa*, 2H, CH_2NH); 2.7 (*t*, 2H, $ArCH_2$); 2.2 (*s*, 3H, CH_3).

$C_{17}H_{19}NO$ (253.33) Calc. C 80.59 H 7.56 N 5.53% Found C 80.75 H 7.56 N 5.55%

Preparation of N-*(2-phenylethyl)(3-chlorophenyl)acetamide* (**4i**). Reaction of 3-chlorophenylacetyl chloride (2.5 g, 14.6 mmol) in $CHCl_3$ (15 ml), with 2-phenylethylamine (1.9 ml, 14.6 mmol) and triethylamine (1.2 ml) in $CHCl_3$ (15 ml), then dilution with $CHCl_3$ (20 ml), yielded 3.19 g (80%) of a yellow semi-solid. Recrystallization from ethanol gave colorless needles, m.p. 80°. – IR. ($CHCl_3$): 3430*m*, 3330*w*, 1672*s*. – ^{1}H-NMR. ($CDCl_3$): 7.3 (*m*, 9H, arom.)H); 5.8 (br., 1H, NH); 3.55 (*qa*, 2H, CH_2NH); 3.5 (*s*, 2H, CH_2CO); 2.8 (*t*, 2H, CH_2Ar).

$C_{16}H_{16}ClNO$	Calc.	C 70.20	H 5.90	Cl 12.95	N 5.12%
(273.75)	Found	„ 70.45	„ 5.93	„ 12.96	„ 5.14%

Preparation of N-*(2-phenylethyl)(3-nitrophenyl)acetamide* (**4j**). Reaction of 3-nitrophenylacetyl chloride (5.5 mmol) in $CHCl_3$ (10 ml), with 2-phenylethylamine (1 ml, 8 mmol) and triethylamine (0.6 ml, 9 mmol) in $CHCl_3$ (20 ml), then dilution with $CHCl_3$ (20 ml) gave a pale oil, 1.04 g (66%). Recrystallization from benzene gave fine white needles, m.p. 75°. – IR. ($CHCl_3$): 3480*m*, 1675*s*. – ^{1}H-NMR. ($CDCl_3$): 8.2 (*m*, 2H, arom.H *o* to NO_2); 7.6 (*m*, 2H, arom.H *m* and *p* to NO_2); 7.3 (*m*, 5H, arom.H); 6.1 (br., 1H, NH); 3.6 (*s*, 2H, $ArCH_2CO$); 3.5 (*qa*, 2H, CH_2N); 2.8 (*t*, 2H, $ArCH_2$).

$C_{16}H_{16}N_2O_3$ (284.31) Calc. C 67.59 H 5.67 N 9.86% Found C 67.52 H 5.66 N 9.79%

Preparation of N-*(2-phenylethyl)(4-chlorophenyl)acetamide* (**4l**). Reaction of 4-chlorophenylacetyl chloride (65.6 mmol) in $CHCl_3$ (20 ml), and 2-phenylethylamine (8.5 ml, 66 mmol) and triethylamine (5 ml, 66 mmol) in $CHCl_3$ (20 ml) then dilution with $CHCl_3$ (30 ml) gave a pale solid, 13.2 g (73%). Recrystallization from ethanol gave colorless plates, m.p. 107.5–108°. – IR. ($CHCl_3$): 3430*m*, 3330*w*, 1670*s*. – ^{1}H-NMR. ($CDCl_3$): 7.3 (*m*, 9H, arom.H); 5.8 (br., 1H, NH), 3.5 (*qa*, 2H, CH_2NH); 3.45 (*s*, 2H, CH_2CO); 2.8 (*t*, 2H, CH_2Ar).

$C_{16}H_{16}ClNO$	Calc.	C 70.20	H 5.90	Cl 12.95	N 5.12%
(273.75)	Found	„ 69.96	„ 5.88	„ 13.24	„ 5.05%

N-*(2-phenylethyl)(*p-*tolyl)-acetamide* (**4n**). Reaction of *p*-tolylacetyl chloride (33 mmol) in $CHCl_3$ (15 ml), with 2-phenylethylamine (4.3 ml, 34 mmol) and triethylamine (2.5 ml, 34 mmol) in $CHCl_3$ (15 ml) yielded a white solid, 7.1 g (85%). Recrystallization from ethanol gave white flakes, m.p. 104°. – IR. ($CHCl_3$): 3530*m*, 1670*s*. – ^{1}H-NMR. ($CDCl_3$): 7.4–7.2 (*m*, 9H, arom.H); 5.8 (br., 1H, NH); 3.55 (*s*, 2H, CH_2CO); 3.5 (*qa*, 2H, CH_2NH); 2.8 (*t*, 2H, $ArCH_2$); 2.4 (*s*, 3H, CH_3).

$C_{17}H_{19}NO$ (253.33) Calc. C 80.59 H 7.56 N 5.53% Found C 80.72 H 7.54 N 5.54%

Preparation of 3,4-dihydroisoquinolines 1[12]. – *1-benzyl-6-chloro-3,4-dihydroisoquinoline* (**1b**). A mixture of **4b** (1.47 g, 5.37 mmol), PPA (21 g) and P_2O_5 (1.5 g) was heated to 170° with mechanical stirring for 6 h, then it was cooled to 80° and water (150 ml) was added cautiously. After cooling with ice, the mixture was washed with ether, then basified to pH 9 with cold (0°) conc. aq. NH_3 and extracted with ether. The combined ether extract was dried ($CaSO_4$) and evaporated under reduced pressure to provide an oil, 1.72 g (42%). – IR. ($CHCl_3$): 1629*s*. – ^{1}H-NMR. ($CDCl_3$): 7.4–7.3 (*m*, 8H, arom.H); 4.1 (*s*, 2H, $ClArCH_2$); 3.8 (*t*, 2H, CH_2N); 2.7 (*t*, 2H, $ArCH_2$).

$C_{22}H_{17}ClN_4O_7$	Calc.	C 54.5	H 3.5	Cl 7.3	N 11.6%
(484.856)	Found	„ 54.7	„ 3.6	„ 7.6	„ 11.5%

Preparation of 1-benzyl-7-methyl-3,4-dihydroisoquinoline (**1g**). A mixture of **4g** (1.34 g, 5.3 mmol) and PPA (14 g) was stirred at 150° for 4.5 h, then cooled to 80° and diluted with water (100 ml). After washing with ether, the aqueous phase was cooled with ice, basified with cold conc. aq. NH_3-solution, and extracted with ether. The ether extract was dried ($CaSO_4$) and concentrated in vacuum to give a

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[12]) All elemental analyses were done with picrates of the corresponding dihydroisoquinolines as can be seen in the formulae.

pale oil, 0.64 g (51%). – IR. ($CHCl_3$); 1625*s*. – ^{1}H-NMR. ($CDCl_3$): 7.5–7.2 (*m*, 8 H, arom. H); 4.2 (*s*, 2 H, $ArCH_2$); 3.8 (*t*, 2 H, CH_2N); 2.7 (*t*, 2 H, $ArCH_2$); 2.3 (*s*, 3 H, CH_3).

$C_{23}H_{20}N_4O_7$ (464.438) Calc. C 59.48 H 4.34 N 12.06% Found C 59.74 H 4.40 N 11.89%

Preparation 1-(3-chlorobenzyl)-3,4-dihydroisoquinoline (**1i**). A mixture of **4i** (2.65 g, 9.76 mmol) and PPA (24 g) was heated to 150° with mechanical stirring for 4 h. The reaction mixture was then cooled to 80° and water (150 ml) was added cautiously. The resulting suspension was washed with ether, then cooled to 0° and basified with cold conc. aq. NH_3-solution. The product was extracted with ether, which after drying ($CaSO_4$) was evaporated under vacuum to leave a pale oil, 1.69 g (67%). – IR. ($CHCl_3$): 1628*s*. – ^{1}H-NMR. ($CDCl_3$): 7.5–7.2 (*m*, 8H, arom.H); 4.1 (*s*, 2H, $ArCH_2$); 3.8 (*t*, 2H, CH_2N); 2.7 (*t*, 2H, $ArCH_2$).

$C_{22}H_{17}ClN_4O_7$	Calc.	C 54.50	H 3.53	Cl 7.31	N 11.56%
(484.856)	Found	„ 54.46	„ 3.53	„ 7.39	„ 11.47%

Preparation of 1-(3-nitrobenzyl)-3,4-dihydroisoquinoline (**1j**). A mixture of **4j** (1.0 g, 3.75 mmol) PPA (43 g) was heated with stirring to 165° for 4 h, then cooled to 80° and treated with water (100 ml) added dropwise with stirring. After washing with ether, the aqueous phase was cooled with ice, basified with cold conc. aq. NH_3-solution, and extracted with ether. Removal of the solvent after drying ($CaSO_4$) gave an orange colored oil, 0.81 g (87%). – IR. ($CHCl_3$): 1628*s*. – ^{1}H-NMR. ($CDCl_3$): 8.4–8.2 (*m*, 2H, arom.H *o* to NO_2); 7.7–7.3 (*m*, 6H, arom.H); 4.2 (*s*, 2H, $ArCH_2$); 3.8 (*t*, 2H, CH_2N); 2.7 (*t*, 2H, $ArCH_2$).

$C_{22}H_{17}N_5O_9$ (495.409) Calc. C 53.34 H 3.46 N 14.14% Found C 53.43 H 3.47 N 14.02%

Preparation of 1-(3-methoxybenzyl)-3,4-dihydroisoquinoline (**1k**). P_2O_5 (2.4 g) was added in 4 portions over 1 h to a mechanically stirred refluxing solution of **4k** (1.66 g, 6.2 mmol) in dry xylene (35 ml), then the mixture was stirred at reflux for an additional 2 h. After cooling, the xylene was decanted, and methanol (15 ml) and water (150 ml) were added, and the mixture was washed with ether. The aqueous phase was then cooled with ice, basified with cold conc. aq. NH_3-solution, and extracted with ether. After drying (Na_2SO_4) the ether was evaporated to leave a pale yellow oil, 0.81 g (52%). – IR. ($CHCl_3$): 1628*s*. – ^{1}H-NMR. ($CDCl_3$): 7.4 (*m*, 8H, arom.H); 4.2 (*s*, 2H, $ArCH_2$); 3.85 (*t*, 2H, CH_2N); 3.8 (*s*, 3H, OCH_3); 2.7 (*t*, 2H, $ArCH_2$).

$C_{23}H_{20}N_4O_8$ (480.438) Calc. C 57.50 H 4.20 N 11.66% Found C 57.39 H 4.39 N 11.48%

Preparation of 1-(4-chlorobenzyl)-3,4-dihydroisoquinoline (**1l**). A mixture of **4l** (3.25 g, 13.1 mmol) and PPA (35 g) was heated to 170° for 4 h with mechanical stirring. The reaction mixture was then cooled to 80° and water (250 ml) was added slowly. The resulting suspension was washed with ether, then cooled with ice, basified to pH 9 with cold conc. aq. NH_3-solution, and extracted with ether. The combined ether extract was dried ($CaSO_4$) and concentrated under vacuum to give an oil which partially solidified on standing. Yield 1.72 g (57%). – IR. ($CHCl_3$): 1628*s*. – ^{1}H-NMR. ($CDCl_3$): 7.4–7.2 (*m*, 8H, arom.H); 4.1 (*s*, 2H, $ArCH_2$); 3.8 (*t*, 2H, CH_2N); 2.7 (*t*, 2H, $ArCH_2$).

$C_{22}H_{17}ClN_4O_7$	Calc.	C 54.50	H 3.53	Cl 7.31	N 11.56%
(484.856)	Found	„ 54.35	„ 3.44	„ 7.49	„ 11.53%

Preparation 1-(4-methylbenzyl)-3,4-dihydroisoquinoline (**1n**). A mixture of **4n** (2.1 g, 8.8 mmol) and PPA (23 g) was heated to 150° with stirring for 4 h, then cooled to 80°, and diluted with water (100 ml). The resulting suspension was washed with ether, then cooled with ice, basified with cold conc. aq. NH_3-solution, and extracted with ether. The ether phase was dried ($CaSO_4$) and concentrated under vacuum to yield 1.16 g (56%) of a yellow oil. – IR. ($CHCl_3$): 1630*s*. – ^{1}H-NMR. ($CDCl_3$): 7.4–7.2 (*m*, 8H, arom.H); 4.1 (*s*, 2H, $ArCH_2$); 3.8 (*t*, 2H, CH_2N); 2.7 (*t*, 2H, $ArCH_2$); 2.3 (*s*, 3 H, CH_3).

$C_{23}H_{20}N_4O_7$ (464.438) Calc. C 59.48 H 4.34 N 12.06% Found C 59.78 H 4.36 N 12.01%

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