An unusual carbon–carbon bond scission reaction with molecular oxygen under mild conditions; formation of piperidines from 1-azabicyclo[2.2.2]octanes

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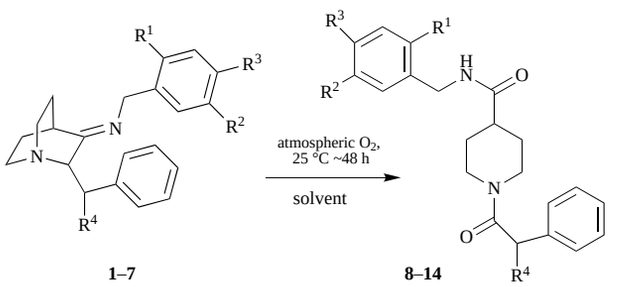
Molecular oxygen reacts with 2-(1-phenylethyl)- and 2-benzhydryl-3-alkylimino-1-azabicyclo[2.2.2]-octanes 1–7 in neutral solution at room temperature to form 1-acylpiperidine-4-carboxylic acid *N*-alkyl-amides 8–14. During the transformation two new carbonyl bonds are formed and a carbon–carbon bond is cleaved. The transformation is quite general provided the 2-substituent of the imine is of sufficient steric bulk, such as the 2-(1-phenylethyl) or 2-benzhydryl groups. No reaction is observed in the absence of a 2-substituent, as in the case of imine 15.

Introduction

We have observed that 2-(1-phenylethyl)- and 2-benzhydryl-3-alkylimino-1-azabicyclo[2.2.2]octanes **1**–**7** react with molecular oxygen when in neutral solution at room temperature to form 1,4-disubstituted piperidines **8**–**14** (Scheme 1). Oxygen is



1–7 **8–14**

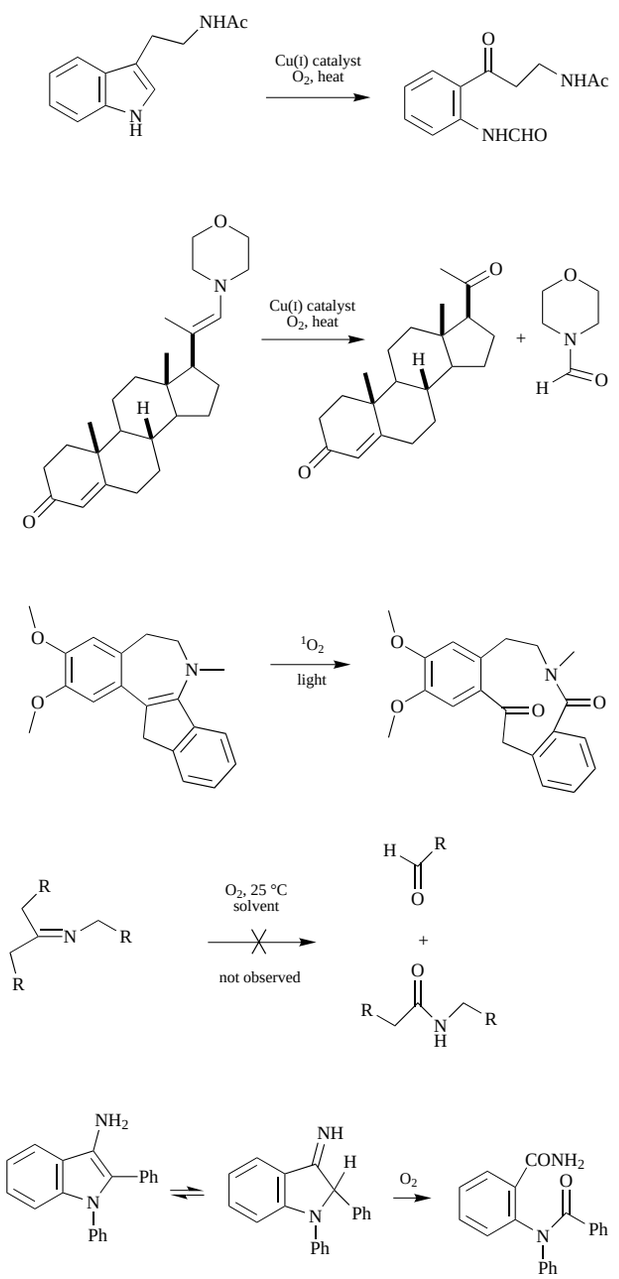
imine	piperidine	R^1	R^2	R^3	R^4
1	**8**	H	H	H	Ph
2	**9**	OMe	Pr^i	H	Ph
3	**10**	OMe	H	H	Ph
4	**11**	H	Me	H	Ph
5	**12**	H	H	H	Me
6	**13**	H	H	OMe	Ph
7	**14**	H	H	Me	Ph

Scheme 1

readily soluble in organic solvents but does not typically react with unsaturated organic substrates at room temperature. This is in sharp contrast to singlet oxygen where, in its excited state, molecular oxygen causes limited and specific oxidation of a wide variety of organic substrates.[1]

There are a few examples reported where singlet oxygen has been shown to add across the double bond of enamines in five and six membered rings in complex polycyclic systems to form the corresponding carbonyl compounds with carbon–carbon bond scission. Typically, light,[2] light and Rose Bengal on SiO_2,[3] or light and Rose Bengal[4] have been used for generation of singlet oxygen in these reactions. The simplest examples reported are the conversion of indol-3-ylacetic acid[5] or 2-(*N*-methylindol-3-yl)ethanol[6] to the corresponding aniline derivatives, using light and Rose Bengal in phosphate buffer as sensitizer. One example[7] is known where the ene bond of the enamine is *exo* to the ring system.

There are rare examples[8,9] where ground state triplet oxygen reacts directly with an enamine, but in these cases a copper catalyst is required (Scheme 2).



Scheme 2

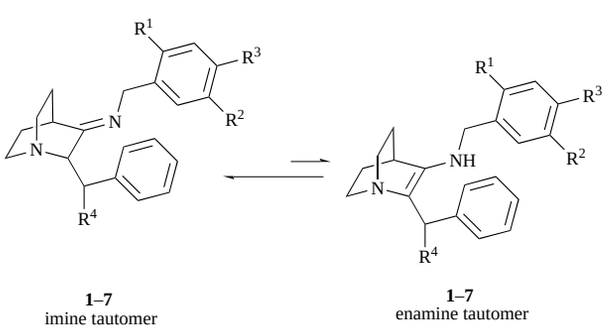
Table 1 Yield, reaction conditions and melting points for piperidines **8**–**14**

Compound[a]	Yield (%)	Reaction conditions	Mp/°C
8	95	CH_2Cl_2–hexane 2:1, 16 h, 25 °C	133–138
9	22[b]	hexane, 16 h, 25 °C	142–144
10	77	EtOAc, 24 h, 25 °C	oil
11	53	EtOAc, 60 h, 25 °C	123–125
12	91	EtOAc–hexane 1:2, 72 h, 25 °C	oil
13	78	EtOAc, 24 h, 25 °C	oil
14	65	EtOAc–hexane 2:1, 24 h, 25 °C	oil

[a] Satisfactory elemental analysis obtained for these compounds. [b] High mother liquor loss of **9**, HPLC analysis of reaction mixture indicated all of **2** had been consumed.

Examples where oxygen reacts directly with an imine causing scission between the α and β carbon atom, as depicted in Scheme 2, are not generally known. If, however, tautomerism between the imine and corresponding enamine occurs in solution, the result of the reaction we observed with 2-benzhydryl-3-alkylimino-1-azabicyclo[2.2.2]octanes **1**–**7** and molecular oxygen does bear a superficial resemblance, in terms of outcome, to the reaction of triplet oxygen and an enamine in the presence of a copper catalyst mentioned above, or with singlet oxygen and an enamine[10] (Scheme 2). The reaction we discovered is distinctly different, because the oxidation we have observed occurs at room temperature without the aid of a catalyst or singlet oxygen generator, unlike the literature examples noted above. The reactants are also different in the singlet oxygen and copper catalysed examples, as they are predominantly enamine systems.

In our reaction the starting substrate is predominantly in the imine form. We have found no direct evidence for the enamine tautomer in NMR spectra collected for the imines **1**–**7**, and the tendency to tautomerize from the imine into the enamine is disfavored by the molecular architecture of the azabicyclo-[2.2.2]octane ring system (Scheme 3). The enamine–imine



1–**7**
imine tautomer

1–**7**
enamine tautomer

Scheme 3

tautomer equilibrium is not necessarily an important factor in the reaction that we report. A long neglected observation by Bird[11] shows that 3-amino-1,2-diphenylindole undergoes very rapid autoxidation by atmospheric oxygen in diethyl ether solution to yield 2-(*N*-benzoyl-*N*-phenylamino)benzamide (Scheme 2). We believe the autoxidation studied by Bird is closely related to the reaction we have observed in the 2-imino-1-azabicyclo[2.2.2]octanes **1**–**7**. However, in the 3-aminoindole system enamine–imine tautomerism probably occurs readily compared to the 3-iminoazabicyclo[2.2.2]octane system.

Observations and discussion

The oxidation of 2-(1-phenylethyl)- and 2-benzhydryl-3-alkylimino-1-azabicyclo[2.2.2]octanes **1**–**7** with molecular oxygen is observed in neutral solution at room temperature to form 1,4-disubstituted piperidines **8**–**14**. The ring opening reaction is demonstrated by the conversions of **1**–**7** into **8**–**14** shown in Scheme 1. Typically the reaction proceeds to completion over

Table 2 Yield and melting points for imines **1**–**7**

Compound	Yield (%)	Mp/°C
1	90	158–159 (lit.,[16] 162–165)
2	95[a]	yellow oil
3 (ref. 17)	97	153–156
4	55	76–79
5	100[a]	oil
6	76	116–117
7	55	80–84

[a] Product reacted directly under oxygenation conditions.

48 h at room temperature and details are noted in Table 1. TLC and HPLC reaction monitoring indicates that all the starting material is consumed during reaction with oxygen and the main reaction product is the piperidine. Isolated yields observed so far range from 22–95%. The low yield of 22% observed for **9** is a result of mother liquor loss on crystallization, HPLC and TLC monitoring indicating that this reaction also went to completion.

The evidence for the piperidine structure, using **8** as an example, is supported by the characteristic ^{1}H NMR (300 MHz; $CDCl_3$) spectral resonances at δ 5.95 (1H, t, J 5.4 Hz) due to the amide NH proton and δ 4.36 (2H, d, J 5.7 Hz) due to the methylene protons of the benzyl group. The nine characteristic proton resonances of the 4-substituted piperidine ring are observed as follows: δ 1.33 (1H, qd, J 4.0 and 11.8 Hz), 1.53–1.67 (2H, m), 1.81 (1H, br d, J 11.4 Hz), 2.22 (1H, tt), 2.66 (1H, td, J 2.8 and 12.8 Hz), 2.92 (1H, td, J 2.8 and 12.8 Hz), 3.93 (1H, dm, J 13.8 Hz) and 4.62 (1H, dm, J 13.5 Hz). In the case of **8** and **9** the piperidine structure assignment is confirmed by a single crystal X-ray determination.

The starting materials, imines **1**–**7**, are prepared from the appropriate 2-substituted 1-azabicyclo[2.2.2]octan-3-one and benzylamine by heating at reflux in toluene in the presence of camphorsulfonic acid catalyst (Table 2). NMR spectral data indicates the imines **1**–**7** exist as *syn*:*anti* mixtures. An NMR study[12] has been reported on related compound **15**, which has no 2-substituent. We suspect that elongation along the C(2)–C(3) bond of the imines **1**–**7** may occur, caused by a combination of the introduction of an sp^2 carbon into the 1-azabicyclo[2.2.2]octane ring system and that of a 2-benzhydryl or 2-(1-phenylethyl) group. Both factors appear to be necessary for the reaction to proceed, see below. A weak σ carbon bond in the C(2)–C(3) position may be the cause of the unusual reactivity with molecular oxygen described below.

The imines **1**–**7** can be dissolved in any suitable neutral solvent such as ethyl acetate or mixtures of ethyl acetate and hexane, tetrahydrofuran, or mixtures of dichloromethane and hexane. The reaction does not occur to any appreciable extent in the solid phase. The imines **1**–**7**, when isolated as solids, are stable in dry air for several months and do not undergo significant reaction with molecular oxygen in air when stirred as a solid or crystal slurry in a solvent in which they are insoluble.

In order to demonstrate that the oxidation reaction is caused by atmospheric oxygen, the reaction was investigated under different conditions using imine **1** as a representative example. The conversion of imine **1** into piperidine **8** proceeded smoothly in 99.9% anhydrous tetrahydrofuran in the presence of air at room temperature in 16 h. When the experiment was repeated under the same conditions in an argon purged system, no detectable reaction was observed after 5 days.

When imines **3**, **5** and **7** were dissolved in dichloromethane no reaction was observed after stirring in air for 48 h at room temperature, even though the imines were completely in solution; however, addition of some hexane allowed the reaction to proceed. On the other hand, imine **2** is converted into piperidine **9** in dichloromethane alone. We have no simple explanation for this observation, since oxygen is readily soluble in dichloro-

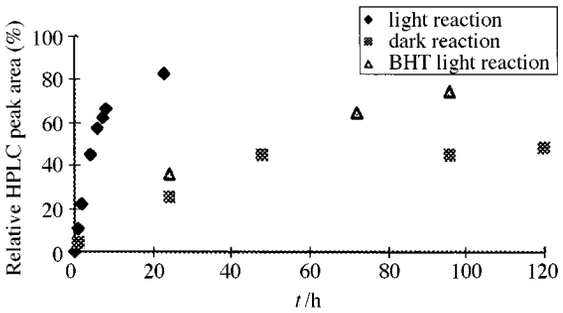
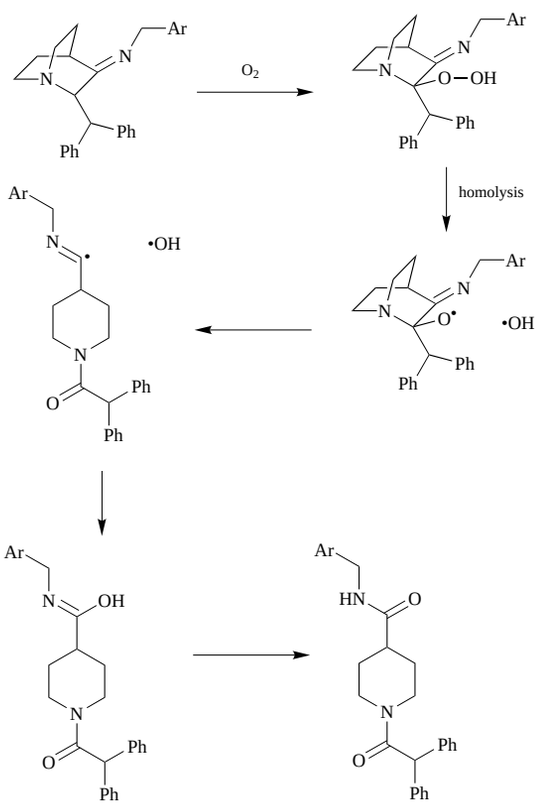


Fig. 1 Rate of formation of piperidine **8** in light, dark and the presence of BHT

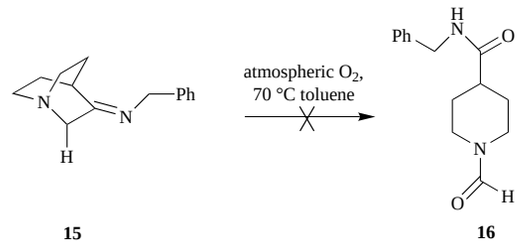
methane and should be available for reaction with the dissolved imine as in the case of imine **2**.

The reaction was investigated under different conditions using imine **1** as a representative example. Using dichloromethane–hexane (1:1) as a common reaction solvent, we compared the reaction with atmospheric oxygen at room temperature (~25 °C). The reaction proceeded both in normal laboratory light and in a reactor sealed from light with aluminium foil. The reaction progress was monitored using HPLC. The rate of reaction in the dark was significantly slower than the reaction carried out in normal laboratory light. When the reaction was repeated in light with the presence of a molar equivalent to 2,6-di-*tert*-butyl-4-methylphenol (BHT) to inhibit any radical processes that may be occurring, the reaction rate was intermediate between the light and dark reaction, see Fig. 1. These observations may implicate involvement of a radical process or an excited electronic state of **1**–**7** in the oxidation into **8**–**14** by molecular oxygen (see Scheme 4).



Scheme 4

The imine **15** was investigated to see if it would react with oxygen to yield piperidine **16** or a derived product. Imine **15** was prepared[12] by coupling 3-quinuclidone and benzylamine under Dean–Stark conditions for water removal in the presence of camphorsulfonic acid. In the case of imine **15**, no reaction was



15 **16**

observed when a solution in toluene was stirred in air at 25 °C overnight and then for 7 h at 70 °C, similar to conditions in which **1**–**7** were converted into **8**–**14**, respectively. When **15** was dissolved in toluene and held at reflux (110 °C) for 16 h with an air bleed through the reaction solution, still no conversion to the corresponding piperidine **16** was observed. Except for some slight coloration of the reaction solution the starting material **15** was recovered unchanged. This result appears to show that a bulky substituent at the 2-position of 1-azabicyclo-[2.2.2]octane is required for the scission of the C(2)–C(3) carbon bond to occur. When the 2-substituent is hydrogen, as in the case of imine **15**, no reaction is observed. This may indicate that the steric bulk of the 2-substituent contributes to the elongation of the C(2)–C(3) bond in imines **1**–**7**, and hence results in the unusual reactivity towards molecular oxygen. The following experiment supports this hypothesis.

The rates at which imines **1** and **5** were converted into piperidines **8** and **12**, respectively, were monitored by HPLC. In this experiment, **1** and **5** were stirred in air in a solution of dichloromethane and hexane (1:1) at room temperature and the growth of the peaks corresponding to **8** and **12** were monitored. The rate of reaction from **5** to piperidine **12** is much slower than for **1** to **8** under similar conditions (see Fig. 2). This observation is thought to be mainly an effect of the steric volume of the 2-substituent. It can be seen by comparing imines **1** and **5** that imine **1** has a benzhydryl group in the 2-position, while **5** has a 1-phenylethyl group, which has a lower steric volume; consequently, the 1-phenylethyl group exerts less of a contribution to the elongation of the C(2)–C(3) bond than does the benzhydryl group. This is consistent with the reduced rate of reaction observed for **5** with molecular oxygen relative to imine **1** under the same reaction conditions.

The effects of the substituents on the *N*-benzyl ring are generally not as pronounced compared with the 2-substituent effect. Thus piperidines **8**, **9**, **10** and **13** for example are formed from their corresponding imines **1**, **2**, **3** and **6** after about the same period of reaction (16–24 h) at room temperature and HPLC indicates that the reaction liquors contain very little residual starting material after this period of time.

The reaction of an enamine with singlet oxygen formed in the presence of UV light and a sensitizer is thought to proceed *via* either a 1,2-dioxetane intermediate[13] or possibly a four centered transition state, both of which give rise to the observed products, similar to the piperidine products **8**–**14**, by formation of two carbonyl bonds at the expense of breaking the C(2)–C(3) bond. However, this is only a superficial similarity with our reaction, which is more closely related to the rapid autoxidation of 3-aminoindoles studied by Bird,[11] where evidence is presented indicating that the first step of the autoxidation process is probably formation of a hydroperoxide at the 2-position of the indole ring. In our substrates **1**–**7** the required equilibrium in solution with the enamine tautomer of **1** is not energetically favored; this is different from the 3-aminoindole system, where tautomerism is more labile, but this does not appear to be an important factor in the autoxidation process. There is some provisional evidence that the C(2)–C(3) bond found in imines **1**–**7** may be abnormally long for a σ carbon single bond, which may explain why a bulky substituent is required at the 2-position of imines **1**–**7** in order for the reaction to proceed. Certainly, the lack of reac-

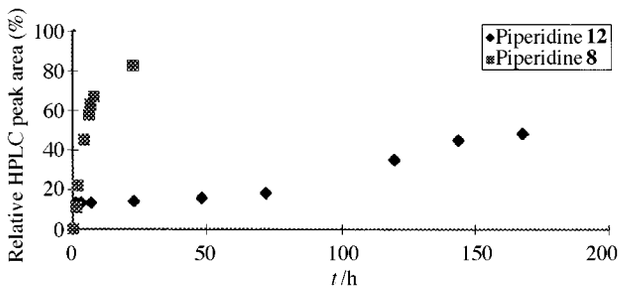


Fig. 2 Effect of 2-substituent on rate of piperidine formation

tion of the unsubstituted imine **15** and the decrease in reaction rate observed from imine **1** (2-benzhydryl) relative to imine **5** [2-(1-phenylethyl)] (Fig. 2) is consistent with this hypothesis.

We have no direct evidence for the nature of the intermediate or transition state formed during the course of our reaction, but we believe that it may be similar to 3-aminoindole autoxidation. A possible mechanistic pathway is noted in Scheme 4, which is consistent with the parallels that exist between our oxidation and the 3-aminoindole autoxidation. The first process step is formation of a hydroperoxide at the 2-position, followed by homolysis to form radicals which lead to the piperidine product as shown. The involvement of radicals is consistent with the reaction rate data noted in Fig. 1, observed for conversion of imine **1** into piperidine **8**.

Conclusions

Imines of the class **1**–**7** undergo an unusual oxidation reaction with molecular oxygen at the C(2)–C(3) carbon bond, resulting in the formation of piperidines **8**–**14**. The reaction sequence is most likely initiated by formation of a hydroperoxide at position 2 of the azabicyclo[2.2.2]octane ring system, which parallels observations reported[11] for 3-aminoindoles. It is postulated that the C(2)–C(3) bond in imines **1**–**7** is elongated, which facilitates reaction to the observed products. The reaction itself is of synthetic value, giving direct access to 4-substituted piperidines in good yields under very mild conditions, although other methods using piperidine based starting materials would more normally be used to gain access to compounds such as **8**–**14**. The real interest of this reaction is that it provides a novel and unexpected synthetic pathway that may be applied to other systems. The mechanism of the reaction is not strongly established and merits further investigation.

Experimental

Benzylamines and 1-azabicyclo[2.2.2]octan-3-one starting materials were obtained from commercial sources.

Formation of imines 1–7 and 15

Imines were prepared from either 2-(diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-one,[14] 2-(1-phenylethyl)-1-azabicyclo-[2.2.2]octan-3-one or 1-azabicyclo[2.2.2]octan-3-one, plus the corresponding benzylamine using camphorsulfonic acid as a catalyst. A typical procedure is noted for **4**.

N-[2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ylidene]-3-methylbenzylamine 4

A mixture of the ketone (2.0 g, 6.86 mmol), 3-methylbenzylamine (1.0 g, 8.84 mmol) and camphorsulfonic acid (3 mg) was added to toluene (7.2 cm^3) and heated at reflux under Dean–Stark conditions for 16 h to remove water. The solvent was removed by evaporation to give a mobile oil, which was treated with a small quantity of hexane to give a clear solution which solidified on standing to give a white solid. The total volume was made up to 30 cm^3 by addition of further hexanes, and the resultant slurry was stirred at room temperature for 1 h. The product was collected by filtration, washed with hexane (10 cm^3), and dried under vacuum to give **4** as a white solid (1.49 g, 55%). Yield and melting points are noted in Table 2. Analytical data collected for new compounds and unreported analytical data for known compounds are reported below. Compound **15** was consistent with previously reported data.[12]

Formation of piperidines 8–14

A typical procedure is noted for **8**.

***N*-Benzyl-1-(diphenylacetyl)piperidine-4-carboxamide 8.** A solution of imine **1** (5.0 g, 13.14 mmol) in hexane (50 cm^3) and dichloromethane (100 cm^3) was stirred in air for 48 h at 25 °C. The reaction mixture was concentrated by evaporation, dissolved in dichloromethane (150 cm^3) and ethyl acetate (20 cm^3), filtered and concentrated to give a white solid which was washed with ethyl acetate, and dried under vacuum to give **8** (5.18 g, 95%). Yields, reaction details of other examples and melting points are noted in Table 2.

The following spectral and analytical data was collected for imines **1**–**7** and piperidines **8**–**14**.

N-[2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ylidene]-benzylamine 1

δ_H(300 MHz; $CDCl_3$) 1.70–1.76 (2H, m), 1.80–1.86 (2H, m), 2.39–2.79 (2H, m), 3.04–3.09 (3H, m), 4.28 (1H, d, *J* 8.1), 4.48 (1H, d, *J* 17.8), 4.61 (1H, d, *J* 15.9), 4.71 (1H, d, *J* 8.1), 7.02 (2H, d, *J* 7.2), 7.12–7.48 (13H, m); δ_C($CDCl_3$; 75.5 MHz) 25.7, 26.3, 27.9, 41.9, 49.7, 52.0, 54.3, 69.0, 125.8, 126.2, 126.3, 127.0, 128.1, 128.3, 129.0, 129.1, 140.6, 143.4, 144.6, 177.7; ν_{max}(KBr)/cm^{-1} 1667 (s); *m*/*z* 380 (M^+) [HRMS (FAB$^+$) found 381.2304. $C_{27}H_{28}N_2$ Calc. for $(M + H)^+$ 381.2324].

N-[2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ylidene]-5-isopropyl-2-methoxybenzylamine 2

δ_H(300 MHz; $CDCl_3$) 1.27 (3H, d, *J* 6.8), 1.28 (3H, d, *J* 6.9), 1.66–1.72 (2H, m), 1.80–1.85 (2H, m), 2.45–2.50 (2H, m), 2.89 (1H, septet, *J* 6.9), 3.03–3.13 (2H, m), 3.17 (1H, pentet, *J* 3.1), 3.83 (3H, s), 4.26 (1H, d, *J* 6.9), 4.57 (2H, ABq, *J* 16.0, 30.0), 4.87 (1H, d, *J* 6.8), 7.02–7.48 (13H, m); δ_C($CDCl_3$; 75.5 MHz) 21.5, 24.3, 24.4, 26.0, 26.1, 27.9, 28.9, 29.3, 30.4, 33.3, 69.2, 109.7, 124.5, 125.9, 126.1, 126.5, 127.3, 127.4, 128.1 (2), 128.2, 128.3, 128.4, 128.5, 128.6, 129.0, 129.1, 129.2, 140.9, 143.4, 144.7, 146.5, 155.0, 177.9; ν_{max}(KBr)/cm^{-1} 1663 (s); *m*/*z* 453 $(M + H)^+$ [HRMS (FAB$^+$) found 453.2911. $C_{31}H_{36}N_2O$ Calc. for $(M + H)^+$ 453.2906].

N-[2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ylidene]-2-methoxybenzylamine 3

δ_H(300 MHz; $CDCl_3$) 1.71–1.87 (4H, m), 2.43–2.70 (2H, m), 3.07 (2H, t, *J* 7.5), 3.15 (1H, t, *J* 3.0), 4.30 (1H, d, *J* 7.9), 4.48 (1H, d, *J* 16.5), 4.59 (1H, d, *J* 16.5), 4.72 (1H, d, *J* 8.1), 6.75–6.89 (3H, m), 7.15–7.48 (11H, m); δ_C($CDCl_3$; 75.5 MHz) 25.7, 26.4, 27.9, 41.9, 48.7, 49.8, 50.6, 52.0, 55.2, 69.0, 109.5, 120.4, 125.8, 126.1, 127.1, 128.1, 128.3, 128.7, 128.8, 128.9, 129.0, 177.7; ν_{max}(KBr)/cm^{-1} 1667 (s); *m*/*z* 410 $(M)^+$ [HRMS (FAB$^+$) found 411.2435. $C_{28}H_{30}N_2O$ Calc. for $(M + H)^+$ 411.2429].

N-[2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ylidene]-3-methylbenzylamine 4

δ_H(300 MHz; $CDCl_3$) 1.69–1.89 (5H, m), 2.31 (1.5H, s), 2.33 (1.5H, s), 2.42–2.75 (2H, m), 3.01–3.06 (2H, m), 4.36 (1H, d, *J* 8.0), 4.48 (2H, ABq, *J* 15.9, 33.3), 7.01–7.42 (14H, m); δ_C($CDCl_3$; 75.5 MHz) 21.4, 21.5, 25.7, 26.2, 27.9, 28.7, 41.7, 41.9, 42.9, 43.5, 45.5, 49.7, 50.5, 51.9, 54.4, 54.9, 69.0, 124.6, 124.8, 125.9, 126.1, 127.0, 127.1, 128.0, 128.1, 128.2 (2), 128.4, 128.5, 128.7, 128.9, 129.0 (2), 137.7, 138.1, 140.4, 143.3, 144.6, 173.6, 177.6; ν_{max}(KBr)/cm^{-1} 1660 (s); *m*/*z* 394 (M^+) [HRMS (FAB$^+$) found 395.2459. $C_{28}H_{30}N_2$ Calc. for $(M + H)^+$ 395.2480].

_N_-[2-(1-Phenylethyl)-1-azabicyclo[2.2.2]octan-3-ylidene]benzylamine 5

δ_H(300 MHz; $CDCl_3$) 1.41–1.58 (3H, m), 1.65–1.99 (5H, m), 2.62–3.01 (3H, m), 3.08–3.30 (3H, m), 3.55 (1H, t, *J* 10.4), 4.39 (0.8H, ABq, *J* 16.4, 44.5), 4.68 (1.2H, ABq, *J* 15.2, 35.2), 7.15–7.39 (10H, m); δ_C($CDCl_3$; 75.5 MHz) 21.5, 22.2, 24.2, 24.6, 26.9, 27.4, 27.9, 41.3, 41.5, 41.6, 42.2, 49.6, 49.7, 53.9, 54.7, 71.3, 125.7, 126.0, 126.1, 126.6, 127.1, 127.2, 127.4, 127.5, 127.7, 128.0, 128.1, 128.2, 128.5, 140.6, 146.2, 177.5, 179.6 [HRMS (FAB$^+$) found 319.2162. $C_{22}H_{26}N_2$ Calc. for $(M + H)^+$ 319.2174].

_N_-[2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ylidene]-4-methoxybenzylamine 6

δ_H(300 MHz; $CDCl_3$) 1.66–1.69 (2H, m), 1.75–1.84 (2H, m), 2.42–2.63 (2H, m), 3.00–3.04 (3H, m), 3.79 (3H, s), 4.22 (1H, d, *J* 8.0), 4.43 (2H, ABq, *J* 16.0, 36.1), 4.65 (1H, d, *J* 8.1), 6.76 (2H, d, *J* 8.7), 6.88 (2H, d, *J* 8.2), 7.08–7.41 (10H, m); δ_C($CDCl_3$; 75.5 MHz) 25.7, 26.3, 27.8, 41.9, 49.7, 51.9, 53.6, 55.3, 69.0, 113.5, 125.8, 126.1, 128.1, 128.2, 128.4, 128.6, 128.7, 128.8, 129.0 (2), 132.8, 143.3, 144.6, 177.4; ν_{max}(KBr)/cm^{-1} 1669 (s); *m*/*z* 410 $(M)^+$ [HRMS (FAB$^+$) found 411.2458. $C_{28}H_{30}N_2O$ Calc. for $(M + H)^+$ 411.2429].

_N_-[2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ylidene]-4-methylbenzylamine 7

δ_H(300 MHz; $CDCl_3$) 1.66–1.83 (5H, m), 2.32 (3H, s), 2.42–2.66 (2H, m), 3.01–3.06 (2H, m), 4.23 (0.6H, d, *J* 7.8), 4.36 (0.4H, d, *J* 5.6), 4.48 (2H, ABq, *J* 15.6, 34.7), 4.69 (1H, d, *J* 7.8), 6.84–6.89 (1.4H, m), 7.04–7.44 (12.6H, m); δ_C($CDCl_3$; 75.5 MHz) 21.1, 25.8, 26.2, 27.8, 41.9, 43.0, 49.8, 50.5, 51.8, 54.0, 54.9, 69.0, 125.8, 126.1, 127.4, 127.5, 127.8, 128.1, 128.2, 128.5, 128.7, 128.8, 128.9, 129.0, 129.4, 135.7, 137.5, 143.3, 144.6, 177.5; ν_{max}(KBr)/cm^{-1} 1668 (s); *m*/*z* 394 $(M)^+$ [HRMS (FAB$^+$) found 395.2462. $C_{28}H_{30}N_2$ Calc. for $(M + H)^+$ 395.2480].

_N_-Benzyl-1-(diphenylacetyl)piperidine-4-carboxamide 8

δ_H(300 MHz; $CDCl_3$) 1.33 (1H, qd, *J* 4.0, 11.8), 1.53–1.67 (2H, m), 1.81 (1H, br d, *J* 11.4), 2.22 (1H, tt, *J* 3.9, 11.2), 2.66 (1H, td, *J* 2.8, 12.8), 2.92 (1H, td, *J* 2.8, 12.8), 3.93 (1H, dm, *J* 13.8), 4.36 (2H, d, *J* 5.7), 4.62 (1H, dm, *J* 13.5), 5.19 (1H, s), 5.95 (1H, br t, *J* 5.4), 7.17–7.35 (15H, m); δ_C($CDCl_3$; 75.5 MHz) 28.5, 28.6, 41.7, 42.8, 43.5, 45.5, 54.9, 126.9, 127.0, 127.6, 127.7, 128.5, 128.6, 128.7, 128.9, 129.0, 138.2, 139.4, 139.5, 170.1, 173.7; ν_{max}(KBr)/cm^{-1} 3246 (s), 1642 (s), 1633 (s); *m*/*z* 413 $(M + H)^+$ (Found: C, 78.36; H, 6.64; N, 6.94. $C_{27}H_{28}N_2O_2$ requires C, 78.61; H, 6.84; N, 6.79%).

_N_-(5-Isopropyl-2-methoxybenzyl)-1-(diphenylacetyl)piperidine-4-carboxamide 9

δ_H(300 MHz; $CDCl_3$) 1.21 (1H, d, *J* 6.9), 1.33 (1H, qd, *J* 4.0, 12.5), 1.54–1.66 (2H, m), 1.82 (1H, br d, *J* 13.2), 2.21 (1H, tt, *J* 3.8, 11.2), 2.69 (1H, tm, *J* 13.7), 2.84 (1H, septet, *J* 6.9), 2.93 (1H, tm, *J* 14.3), 3.81 (3H, s), 3.94 (1H, br d, *J* 13.7), 4.39 (2H, d, *J* 5.7), 4.64 (1H, br d, *J* 13.5), 5.20 (1H, s), 6.04 (1H, br t, *J* 5.5), 6.81 (1H, d, *J* 8.3), 7.08 (1H, d, *J* 2.2), 7.12 (1H, dd, *J* 2.3, 8.3), 7.16–7.33 (10H, m); δ_C($CDCl_3$; 75.5 MHz) 24.2, 28.5, 28.7, 33.3, 39.7, 41.7, 43.0, 45.5, 54.9, 55.5, 110.3, 125.8, 126.5, 126.9, 127.0, 128.1, 128.5, 128.6, 128.9, 129.0, 139.4, 139.5, 141.2, 155.7, 170.1, 173.3; ν_{max}(KBr)/cm^{-1} 3359 (s), 1654 (s), 1640 (s); *m*/*z* 484 (M^+) (Found: C, 76.80; H, 7.40; N, 5.87. $C_{31}H_{36}N_2O_3$ requires C, 76.83; H, 7.49; N, 5.78%).

_N_-(2-Methoxybenzyl)-1-(diphenylacetyl)piperidine-4-carboxamide 10

δ_H(300 MHz; $CDCl_3$) 1.33 (1H, m), 1.64–1.52 (2H, m), 1.80 (1H, br d, *J* 13.5), 2.20 (1H, m), 2.67 (1H, tm, *J* 14.1), 2.92 (1H, tm, *J* 14.0), 3.82 (3H, s), 3.92 (1H, dm, *J* 13.3), 4.39 (2H, d, *J* 5.7), 4.62 (1H, dm, *J* 13.3), 5.19 (1H, s), 6.07 (1H, br s), 6.91 (1H, dd, *J* 0.8, 7.5), 7.18–7.32 (12H, m); δ_C($CDCl_3$; 75.5 MHz) 28.5, 28.7, 39.3, 41.7, 42.9, 45.5, 54.9, 55.4, 110.4, 120.7, 126.2, 127.0, 127.1, 128.5, 128.6, 129.0 (2C), 129.7, 139.5 (2C), 157.5, 170.1, 173.5; ν_{max}($CHCl_3$)/cm^{-1} 3448 (s), 1639 (s); *m*/*z* 443 $(M + H)^+$ (Found: C, 76.06; H, 6.74; N, 5.99. $C_{28}H_{30}N_2O_3$ requires C, 75.99; H, 6.83; N, 6.33%).

_N_-(3-methylbenzyl)-1-(diphenylacetyl)piperidine-4-carboxamide 11

δ_H(300 MHz; $CDCl_3$) 1.25–1.38 (1H, m), 1.62–1.68 (2H, m), 1.85 (1H, br d, *J* 12.0), 2.21–2.29 (1H, m), 2.33 (3H, s), 2.70 (1H, br t, *J* 11.3), 2.95 (1H, br t, *J* 11.7), 3.96 (1H, dm, *J* 13.2), 4.35 (2H, d, *J* 5.6), 4.66 (1H, dm, *J* 13.0), 5.19 (1H, m), 5.69 (1H, br s), 7.00–7.31 (14H, m); δ_C($CDCl_3$; 75.5 MHz) 21.4, 28.5, 28.6, 41.7, 42.8, 43.4, 45.5, 54.9, 124.7, 127.0, 127.1, 128.3, 128.5, 128.5, 128.6, 128.9, 129.0, 138.2, 138.4, 139.4, 139.5, 170.1, 173.7; ν_{max}($CHCl_3$)/cm^{-1} 3322 (s), 1644 (s), 1628 (s); *m*/*z* 426 $(M)^+$ (Found: C, 79.10; H, 7.70; N, 6.61. $C_{28}H_{30}N_2O_2$ requires C, 78.84; H, 7.09; N, 6.57%).

_N_-Benzyl-1-(2-phenylpropanoyl)piperidine-4-carboxamide 12

NMR spectra of two diastereomers in 1 : 1 ratio: δ_H(300 MHz; $CDCl_3$) 0.78 (0.5H, qd, *J* 3.6, 12.6), 1.38–1.50 (3.5H, m), 1.62–1.65 (1H, m), 1.72–1.77 (1H, m), 1.86–1.97 (1H, m), 2.17–2.25 (1H, m), 2.50–2.71 (2H, m), 2.82–2.97 (1H, m), 3.81–3.86 (2H, m), 4.31 (1H, d, *J* 5.6), 4.38 (1H, d, *J* 5.6), 4.51 (0.5H, br d, *J* 12.9), 4.64 (0.5H, br d, *J* 13.3), 5.99 (0.5H, br s), 6.21 (0.5H, br s), 7.14–7.28 (10H, m); δ_C($CDCl_3$, 75.5 MHz) 20.8, 21.6, 28.2, 28.4, 28.6, 28.8, 40.5, 41.1, 41.4, 41.6, 42.8, 43.0, 43.4, 44.9, 45.0, 49.3, 126.7, 126.9, 127.1, 127.5, 127.6, 127.9, 128.3, 128.4, 128.7, 128.9, 129.0, 138.2, 142.0, 141.9, 173.7; ν_{max}($CHCl_3$)/cm^{-1} 3444 (s), 3331 (br), 1664 (s), 1633 (s); *m*/*z* 351 $(M + H)^+$ (Found: C, 75.25; H, 7.67; N, 7.72. $C_{22}H_{26}N_2O_2$ requires C, 75.44; H, 7.48; N. 8.00%).

_N_-(4-Methoxybenzyl)-1-(diphenylacetyl)piperidine-4-carboxamide 13

δ_H(300 MHz; $CDCl_3$) 1.34 (1H, m), 1.55–1.68 (2H, m), 1.82 (1H, br d, *J* 11.3), 2.18–2.26 (1H, m), 2.67 (2H, tm, *J* 11.4), 3.78 (3H, s), 3.94 (1H, dm, *J* 13.8), 4.31 (2H, d, *J* 5.5), 4.64 (1H, dm, *J* 13.0), 5.19 (1H, s), 5.74 (1H, br t), 6.84 (2H, d, *J* 8.6), 7.13–7.32 (12H, m); δ_C($CDCl_3$; 75.5 MHz) 28.6, 28.7, 41.7, 42.9, 43.0, 45.5, 54.9, 55.3, 114.1, 126.9, 127.1, 128.5, 128.6, 129.0, 129.1, 130.5, 139.4, 139.5, 159.2, 170.1, 173.6; ν_{max}(KBr)/cm^{-1} 3443 (s), 1639 (br); *m*/*z* 443 $(M + H)^+$ (Found: C, 75.60; H, 6.68; N, 6.05. $C_{28}H_{30}N_2O_3$ requires C, 75.99; H, 6.83; N, 6.33%).

_N_-(4-Methylbenzyl)-1-(diphenylacetyl)piperidine-4-carboxamide 14

δ_H(300 MHz; $CDCl_3$) 1.26–1.38 (1H, m), 1.52–1.66 (2H, m), 1.79 (1H, br d, *J* 13.2), 2.20 (1H, tt, *J* 3.8, 11.2), 2.33 (3H, s), 2.64 (1H, tm, *J* 14.0), 2.90 (1H, tm, *J* 14.1), 3.93 (1H, br d, *J* 13.6), 4.31 (2H, d, *J* 5.6), 4.60 (1H, br d, *J* 13.4), 5.19 (1H, s), 6.02 (1H, br t, *J* 5.3), 7.00–7.39 (14H, m); δ_C($CDCl_3$; 75.5 MHz) 21.1, 28.5, 28.6, 41.7, 42.8, 43.2, 45.5, 54.9, 127.0, 127.1, 127.7, 128.5, 128.6, 128.9, 129.0, 129.4, 135.2, 137.2, 139.4, 139.5, 170.1, 173.7; ν_{max}(KBr)/cm^{-1} 3313 (br), 1643 (br); *m*/*z* 427 $(M + H)^+$ (Found: C, 78.52; H, 7.18; N, 6.44. $C_{28}H_{30}N_2O_2$ requires C, 78.84; H, 7.09; N, 6.57%).

2-(1-Phenylethyl)-1-azabicyclo[2.2.2]octan-3-one

A 3 M solution of methylmagnesium chloride in tetrahydrofuran (100 cm^3, 0.3 M), under nitrogen, was cooled in an ice–water bath and treated with copper(I) bromide–dimethyl sulfide complex (1.25 g, 6.08 mmol). The mixture was stirred for 5 min and treated slowly with a solution of 2-benzylidene-1-azabicyclo[2.2.2]octan-3-one[15] (53.3 g, 0.25 M) in tetrahydrofuran (480 cm^3). The resultant solution was stirred at 0 °C for 15 min. A solution of ammonium chloride (40.1 g, 0.75 M) in water (260 cm^3) was added slowly. The resultant mixture was stirred at room temp. for 1 h. The organic layer was removed,

filtered through a short pad of Celite and concentrated by evaporation to give a yellow oil, which was treated with propan-2-ol (200 cm^3) and concentrated by evaporation to give a clear yellow oil which solidified on standing overnight. The solid was washed with propan-2-ol (30 cm^3), collected by filtration, washed with propan-2-ol (50 cm^3) and dried *in vacuo* at 55 °C for 12 h to afford the product (31.62 g, 55%) as a white solid (mp 114–116 °C). δ_H(300 MHz; $CDCl_3$) 1.45 (3H, d, *J* 6.9), 1.88–2.01 (4H, m), 2.44 (1H, quintet, *J* 3.0), 2.53–2.64 (1H, m), 2.74–2.85 (1H, m), 2.88–3.04 (2H, m), 3.13 (1H, dq, *J* 6.8, 9.7), 3.28 (1H, d, *J* 9.7), 7.16–7.37 (5H, m); δ_C($CDCl_3$; 75.5 MHz) 21.6, 25.1, 27.1, 40.0, 41.1, 41.2, 49.3, 74.2, 126.4, 127.2, 127.8, 128.4, 145.2, 221.3; ν_{max}(KBr)/cm^{-1} 1721 (s); *m*/*z* 230 $(M + H)^+$ (Found: C, 78.80; H, 8.37; N, 6.01. $C_{15}H_{19}NO$ requires C, 78.56; H, 8.35; N, 6.11%).

Crystal data collected for compounds 8 and 9

Compound **8**. $C_{27}H_{28}N_2O_2$, $M = 412.5$, orthorhombic, $a = 17.717(3)$, $b = 81.77(1)$, $c = 6.269(1)$ Å, $V = 9082(3)$ Å^3, space group *Fdd*2 (no. 43), $Z = 16$, $D_x = 1.207$ g cm^{-3}, colorless plates, crystal dimensions 0.08 × 0.44 × 0.50 mm, μ(Cu-Kα) = 5.99 cm^{-1}.

Compound **9**. $C_{31}H_{36}N_2O_3$, $M = 484.6$, triclinic, $a = 9.193(1)$, $b = 9.441(1)$, $c = 16.654(1)$ Å, $\alpha = 83.81(1)$, $\beta = 80.47(1)$, $\gamma = 67.69(1)°$, $V = 1317.2(2)$ Å^3, space group $P\bar{1}$ (no. 2), $Z = 2$, $D_x = 1.222$ g cm^{-3}, colorless needles, crystal dimensions 0.03 × 0.06 × 0.16 mm, μ(Cu-Kα) = 6.18 cm^{-1}.

Data collection and processing

Siemens R3m/v diffractometer, $\omega/2\theta$ mode with ω scan width = 1.2° plus Kα-separation, ω scan speed 4 deg per min, graphite monochromated Cu-Kα ($\lambda = 1.541\,78$ Å) radiation; for $C_{27}H_{28}N_2O_2$ (**8**), 1032 reflections measured with 798 ($I > 3.0\sigma$), for $C_{31}H_{36}N_2O_3$ (**9**), 2711 reflections measured with 1631 ($I > 3.0\sigma$).

Structure analysis and refinement

Trial structures were obtained using direct methods. These trial structures were refined in a full-matrix least-squares fashion ultimately using anisotropic temperature factors for the non-hydrogen atoms. All crystallographic calculations were facilitated by the Siemens SHELXTL PLUS computer programs. The hydrogen positions were calculated wherever possible. Methyl hydrogens were located by difference Fourier techniques and then idealized by calculation. The hydrogen atoms were added to the structure factor calculations but were not refined. The final data fit criteria were as follows: for $C_{27}H_{28}N_2O_2$ (**8**), final difference map, +0.39 to −0.45 e Å^{-3}, $R = 9.37\%$, GOF = 1.22; for $C_{31}H_{36}N_2O_3$ (**9**), final difference map, +0.20 to −0.20 e Å^{-3}, $R = 5.72\%$, GOF = 1.02.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web pages (http://chemistry.rsc.org/rsc/p1pifa.htm). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/161.

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