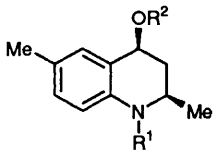
Microbiological Transformations. Part 12.[1] The Stereochemistry of some Derivatives of 2,6-Dimethyl-1,2,3,4-tetrahydroquinolin-4-ol. Single Crystal X-Ray Analyses of *cis*- and *trans*-1-Benzoyl-4-benzoyloxy-2,6-dimethyl-1,2,3,4-tetrahydroquinoline

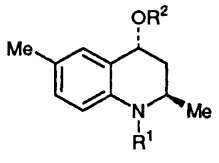
Trevor A. Crabb,[a] Lesley M. Canfield[a] and David Bowen[b]
[a] *Department of Chemistry, University of Portsmouth, Portsmouth, Hampshire PO1 2DT, UK*
[b] *Pfizer Central Research, Sandwich, Kent CT13 9NJ, UK*

Configurational and conformational assignments have been made on *cis*- and *trans*-2,6-dimethyl-1,2,3,4-tetrahydroquinolin-4-ol **1** and **2** and the *N*-benzoyl and *N,O*-dibenzoyl derivatives **3**–**6** from NMR spectroscopic measurements and single crystal X-ray crystallographic analyses of the dibenzoyl derivatives **5** and **6**. On the basis of this work, previously isolated products of the microbial transformations of certain *N*-substituted 2-methylated 1,2,3,4-tetrahydroquinolines with the fungi *Aspergillus niger* and *Cunninghamella elegans* were characterised. Subsequent incubation of 1-benzoyl-2-methyl-1,2,3,4-tetrahydroquinoline **7** with *A. niger* and *C. elegans* was determined to yield, predominantly, the *cis*-1-benzoyl-2-methyl-1,2,3,4-tetrahydroquinolin-4-ol **8**.

Oxygenated 1,2,3,4-tetrahydroquinoline and 1,2,3,4-tetrahydroisoquinoline systems are known to yield biologically active species; for example, 4-keto derivatives of tetrahydroquinolines possess analgesic properties[2,3] and 4-hydroxylated tetrahydroisoquinolines may be adrenergic agents.[4] In relation to this, the incubation of 1-acetyl-2-methyl- and 1-aroyl-1,2,3,4-tetrahydroquinolines with the fungi *Cunninghamella elegans* and *Aspergillus niger* reportedly gives[5] the *trans*-4-hydroxy-2-methyl derivatives. This stereochemical assignment was based on ^{1}H NMR vicinal coupling constants (J_{vic}) and the application of the Karplus relationship, but is open to objection due to uncertainty regarding the heterocyclic ring conformation. The problem is further complicated by the presence of the *N*-benzoyl substituent on the nitrogen (the electron-rich group is a necessary requirement for the binding of the fungal enzymes and hence the microbial transformation process),[6] which causes a degree of distortion to the B-ring and is expected to force the 2-methyl substituent into the axial orientation.[7]



1 R^1 = H, R^2 = H
3 R^1 = COPh, R^2 = H
5 R^1 = R^2 = COPh

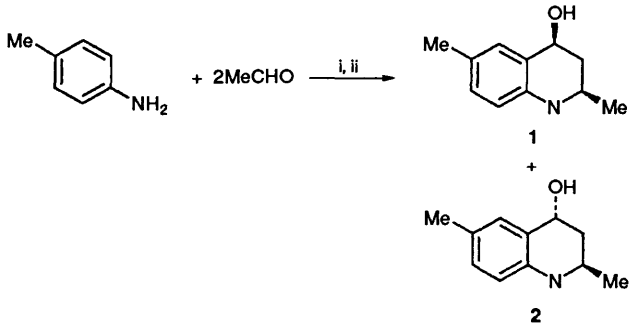


2 R^1 = H, R^2 = H
4 R^1 = COPh, R^2 = H
6 R^1 = R^2 = COPh

Accordingly, the corresponding 2-methyl-1,2,3,4-tetrahydroquinolines **1** and **2** were synthesised since the stereochemistry of these compounds has been determined previously[8,9] by X-ray crystallography. In this way the configurations of the derived *N*-benzoyl and *N,O*-dibenzoyl compounds **3**–**6** could then be assumed and the structural assignments of related microbially transformed 1,2,3,4-tetrahydroquinolines placed on a firm basis.

Results and Discussion

The 2,6-dimethyl-1,2,3,4-tetrahydroquinolin-4-ols **1** and **2** were obtained, in a ratio of approximately 2:1, from the reaction between 1 mole of *p*-toluidine and 2 moles of acetaldehyde in the presence of an excess of dilute hydrochloric acid[10,11]

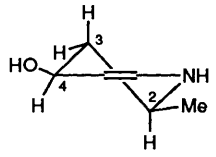


Scheme 1 Synthesis of the isomeric 2,6-dimethyl-1,2,3,4-tetrahydroquinolin-4-ols. *Reagents:* i, HCl; ii, NaOH–light petroleum (60–80 °C).

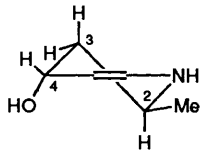
(Scheme 1) as a brown crystalline solid, m.p. 85–87 °C. Separation was achieved utilising the differing solubilities of the isomers in ethanol.

The 270 MHz ^{1}H NMR spectrum of the less soluble isomer, m.p. 167–169 °C exhibited resonances for the 3-methylene group protons at δ 1.62 and 2.22. These assignments were confirmed by a heteronuclear COSY experiment which showed correlation of both multiplets with the same carbon nucleus at δ 41.1. The downfield signals are assigned to 3-H_{eq} on the basis of one large geminal coupling ($J_{3ax,3eq}$ −12.3 Hz) and two smaller couplings ($J_{3eq,2}$ 2.6 and $J_{3eq,4}$ 6.2 Hz). The upfield proton, assigned to 3-H_{ax}, is strongly coupled to 4-H and 2-H ($J_{3eq,4}$ 11.6 and $J_{3eq,2}$ 11.0 Hz) indicating dihedral angles of about 180° between C-3–H_{ax} and the vicinal C-2–H_{ax} and C-4–H_{ax} bonds. This indicates that both the 4-OH and the 2-Me groups are equatorially placed and confirms the *cis* stereochemistry **1** assigned by X-ray analysis.[9]

The ^{1}H NMR spectrum of the more soluble isomer, m.p. 100–102 °C, shows resonances for the 3-methylene group protons at δ 1.52 and 1.97. Again, the upfield signals are assigned to 3-H_{ax} which, relative to the spectrum of **1**, show loss of one of the large vicinal couplings to the proton geminal to the hydroxy group. This indicates an axial orientation of one of the vicinal substituents and analysis of the 4-H signals shows a vicinal coupling between 3-H_{ax} and 4-H of 3.5 Hz confirming the axial orientation of the OH group and the *trans*-stereochemistry **2**. The couplings of the protons geminal to the 2-methyl are of very similar magnitude for both isomers.



1a

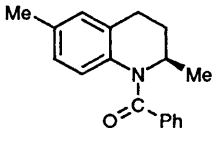


2a

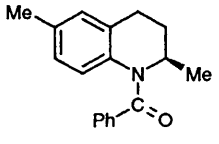
The ^{1}H NMR data permit assignment of the conformations **1a** and **2a** (in which the B-ring adopts a half-chair conformation) to **1** and **2**. Similar conformations have been reported[12] for other 2,4-disubstituted 1,2,3,4-tetrahydroquinoline systems. In addition, these conclusions are supported by both molecular modelling work and X-ray crystallography data.[8,9] The latter work shows the reduced ring of both *cis*- and *trans*-isomers as a distorted, flattened half-chair; the *cis*-isomer with the OH group on C-4 equatorial and the *trans*-isomer with a quasi-axial OH.

Preparation of the N- *and* N,O-*Dibenzoyl Derivatives of* cis- *and* trans-2,6-*Dimethyl*-1,2,3,4-*tetrahydroquinolin*-4-*ol*, **3–6**.—*cis*- and *trans*-*N*-benzoyl and *N*,*O*-dibenzoyl derivatives of **1** and **2** were prepared using the Schotten–Baumann procedure. It was observed that the *cis*-isomer yielded the *N*-benzoyl derivative preferentially, whereas under comparable conditions the *trans*-isomer gave a predominance of the dibenzoyl derivative. The configurations of these compounds are firmly based on the known stereochemistry of the precursors **1** and **2** since benzoylation does not affect the C-2 or C-4 configurations.

Stereochemical Study of the N- *and* N,O-*Dibenzoyl Derivatives of the* 2,6-*Dimethyl*-1,2,3,4-*tetrahydroquinolin*-4-*ols* **3–6** *by NMR Spectroscopy and X-Ray Crystallography*.—The ^{1}H NMR resonances of 2-H in the spectra of the benzoyl derivatives **3–6** are shifted markedly downfield (δ 4.8–5.0) relative to the resonances (δ 3.5) of 2-H in both parent free bases **1** and **2**. This is due to deshielding by the amide carbonyl group and indicates the predominant existence of the benzoylated derivatives as the *E*-rotamers.[7] In all of the compounds the 2-methyl group may be assumed to be pseudoaxially orientated to reduced unfavourable non-bonded interactions with the *N*-benzoyl group.[7,13]



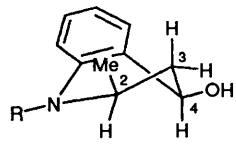
Z– Rotamer



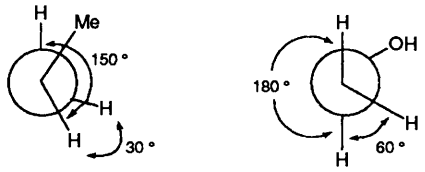
E–Rotamer

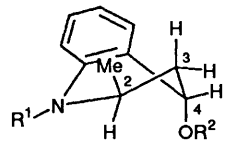
Comparison of the ^{1}H NMR coupling constants of the free bases **1** and **2** with those of the *N*-benzoyl derivatives **3** and **4** shows that marked differences between the $J_{2,3}$ vicinal couplings due to the change in orientation of the methyl substituent from pseudoequatorial in **1** and **2** to pseudoaxial in **3** and **4**.

In the spectrum of the *cis*-isomer **3** the magnitudes of the $J_{2,3}$ couplings ($J_{2,3ax}$ 8.1, $J_{2,3eq}$ 8.8 Hz) indicate dihedral angles of approximately 150 (2-H–C-2–C-3–3-H_{ax}) and 30° (2-H–C-2–C-3–3-H_{eq}). In addition, the large value of $J_{3ax,4}$ (10.8 Hz) indicates a dihedral angle (3-H_{ax}–C-3–C-4–4-H) of approximately 180° indicating equatorial orientation of the OH and the distorted half-boat conformation **3a** for the reduced ring. In the *trans*-isomer **4** the observed ^{1}H NMR coupling constants ($J_{2,3ax}$ 6.0, $J_{2,3eq}$ 7.3, $J_{3ax,4}$ 4.8 and $J_{3eq,4}$ 5.0 Hz) indicate a similar conformation **4a** with a pseudoaxially orientated hydroxy group on C-4. A similar boat type conformation has been suggested[14] for 1-(*p*-bromobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinoline following X-ray crystallographic analysis.

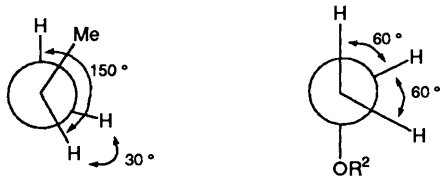


3a R = COPh





4a R^1 = COPh, R^2 = H
6a R^1 = R^2 = COPh



The $J_{2,3}$ and $J_{3,4}$ ^{1}H NMR coupling constants of the *trans*-*N*,*O*-dibenzoyl derivative **6** ($J_{3ax,2}$ 7.3, $J_{3eq,2}$ 7.9, $J_{3ax,4}$ 3.85, $J_{3eq,4}$ 4.2 Hz) are comparable to those of the monobenzoylated derivative **4** indicating a similar conformation **6a**. In contrast, the *cis*-*N*,*O*-dibenzoylate **5** exhibits marked differences in the J_{vic} values compared to those of the *cis*-*N*-benzoyl derivative **3**. In particular $J_{3ax,4}$ and $J_{2,3a}$ in **5** are 7.15 and 5.9 Hz respectively compared to corresponding values of 10.8 and 8.1 Hz in **3**.

Accordingly single crystal X-ray crystallographic analysis of the *cis*- and *trans*-*N*,*O*-dibenzoyl derivatives **5** and **6** was undertaken to provide further insight into the B-ring conformation. The refined molecular structures of **5** and **6**, plotted using the SHELXTL plotting package are shown in Figs. 1 and 2, respectively.

X-Ray analysis of the *trans* isomer **6** shows a comparable conformation to that indicated by solution NMR, with an axial methyl at C-2 and a pseudoaxial *O*-benzoyl substituent at C-4.

Using the dihedral angles between C-2–H, C-4–H and the C-3 methylene protons, provided by the X-ray analysis, permits a comparison (Table 1) between the calculated[15] and observed vicinal coupling constants. Whereas there is reasonable agreement in the case of the *trans*-isomer **6** there is considerable disparity in the values for **5**. X-Ray data show the conformation of the reduced ring in the *cis*-isomer as a half-chair **5a′** with both the C-2 and C-4 substituents axially situated. The ^{1}H NMR spectrum, in particular the vicinal coupling constants, of **5** does not correlate with either the distorted half-boat adopted by **6** or the half-chair indicated by the X-ray data but is consistent with an equilibrium between the two conformers in which the distorted half-boat predominates. This is confirmed by homonuclear ^{1}H NMR NOE studies on **5**, in which irradiation of the 4-H signals (δ 6.22) results in an enhancement of the 5-H signals (δ 7.17) consistent with the presence of **5a′**.

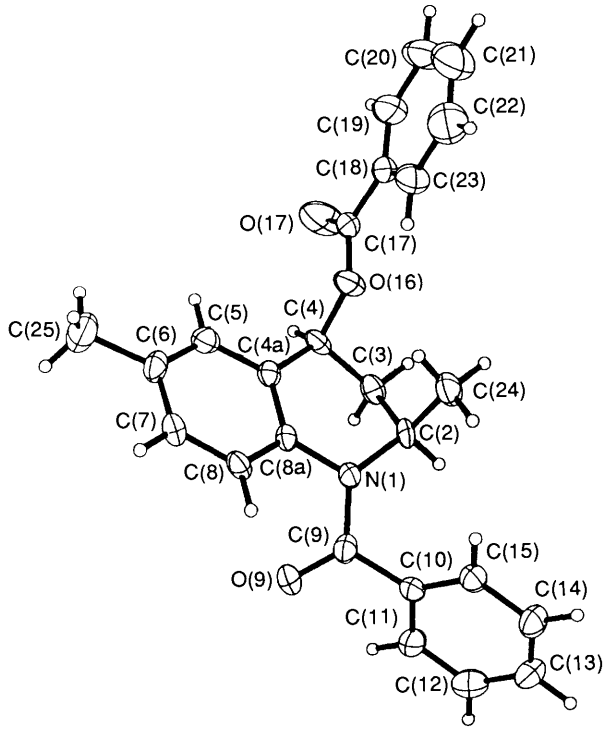


Fig. 1 Molecular structure of compound **5**

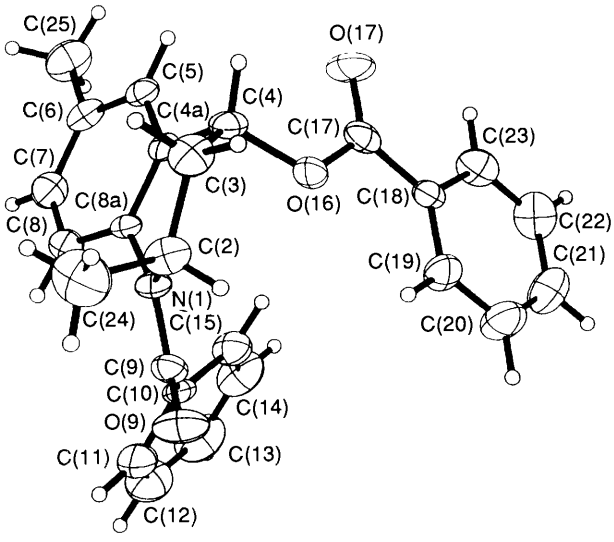
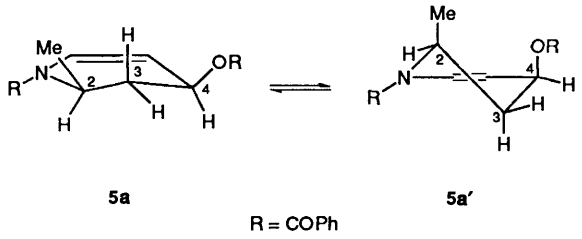


Fig. 2 Molecular structure of compound **6**



5a **5a'**

R = COPh

The X-ray structure of the *cis*-dibenzoyl derivative also indicates the *N*-benzoyl substituent to be in the *Z*-conformation, in direct contrast to solution NMR studies. This may be explained in terms of stacking/packing of molecules in the solid state.

Incubation of 1-*Benzoyl*-2-*methyl*-1,2,3,4-*tetrahydroquinoline* **7** *with* Cunninghamella elegans *and* Aspergillus niger.—Incubation of 1-benzoyl-2-methyl-1,2,3,4-tetrahydroquinoline **7** with both *C. elegans* and *A. niger*, was found to yield the *cis*-4-*ol* **8**, as the major product (average yield 5%). In the case of the *C. elegans* transformation, a trace of the *trans* product **9** (0.3%), was also detected. The configurations of these microbial products were assigned by reference to the spectral data of the synthesised monobenzoylated derivatives **3** and **4**.

In addition, the similarity in spectral parameters between *cis*-1-benzoyl-2,6-dimethyl-1,2,3,4-tetrahydroquinolin-4-ol **3**, and the product of the microbial transformation of 2-methyl-1-(*p*-toluoyl)-1,2,3,4-tetrahydroquinoline with *C. elegans* indicates an incorrect earlier assignment.[5]

Experimental

^{1}H and ^{13}C NMR spectra were measured in deuteriochloroform with tetramethylsilane as internal reference using a JEOL GSX spectrometer at 270.16 (^{1}H) and 67.97 (^{13}C) MHz. ^{1}H NMR parameters were determined by an NMR simulation/iteration program V2.10 (JEOL NMR COMIC program). *J* Values are given in Hz. M.p.s were measured on a hot-stage microscope apparatus and are uncorrected. Elemental analyses were performed by Butterworths' Microanalytical laboratory.

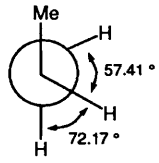
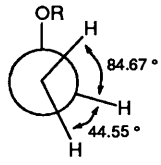
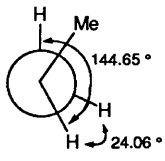
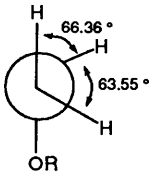
2,6-*Dimethyl*-1,2,3,4-*tetrahydroquinolin*-4-*ols* (*'Aldol Bases'*) **1** *and* **2**.—*p*-Toluidine (8.9 g, 0.08 mol) was placed in an Erlenmeyer flask containing twice the equivalent quantity of hydrochloric acid (16.5 cm^3 of 10 mol dm^{-3} hydrochloric acid, diluted with water to 120 cm^3). A slight excess of freshly distilled acetaldehyde (11 cm^3, 0.21 mol) was added and the resultant mixture maintained at room temperature in stoppered flasks for a minimum period of 18 h. Light petroleum (b.p. 60–80 °C; 40 cm^3) was then added, followed by the requisite amount of 30% aqueous sodium hydroxide (22.5 cm^3) to effect complete neutralisation. After a few minutes a light brown oil film formed at the interface of the two layers which quickly solidified to form a brown crystalline cake. The product, a mixture of the two isomers, was obtained by filtration as a fine, beige power (crude yield 13.5 g, 91.8%), m.p. 82–85 °C (lit.,[10] 84–87 °C); R_f(CH_2Cl_2–2% MeOH, SiO_2) 0.15 and 0.20.

The mixture of isomers (10 g) was placed in ethanol (50 cm^3) and shaken vigorously. After 30 min the insoluble *cis*-isomer, was filtered off and recrystallized from methylated spirits as a fine white powder (2.8 g, percentage recovery 28%), m.p. 167–169 °C (lit.,[10] 164–167 °C); R_f(CH_2Cl_2–2% MeOH, SiO_2) 0.20 (Found: C, 74.5; H, 8.8; N, 7.8. $C_{11}H_{15}NO$ requires C, 74.5; H, 8.5; N, 7.9%); δ(270 MHz; $CDCl_3$) 1.24 (3 H, d, 2-CH_3, $J_{CH_3,2}$ 6.2), 1.62 (1 H, q, 3-H_{ax}, $J_{3ax,2}$ 11.0, $J_{3ax,3eq}$ −12.3, $J_{3ax,4}$ 11.6), 2.21 (3 H, s, 6-CH_3) 2.22 (1 H, m, 3-H_{eq}, $J_{3eq,4}$ 6.2, $J_{3eq,2}$ 2.6), 3.51 (3 H, m, 2-H), 4.90 (1 H, m, 4-H), 6.41 (1 H, d, 8-H, $J_{8,7}$ 8.1), 6.85 (1 H, dd, 7-H, $J_{7,5}$ 2.1) and 7.20 (1 H, d, 5-H).

Evaporation of the filtrate gave the *trans*-isomer as a dark-brown solid which was recrystallized from light petroleum (b.p. 80–100 °C) and toluene (5%) as a fine cream coloured powder (5.4 g, percentage recovery 54%), m.p. 100–102 °C (lit.,[10] 108–110 °C); R_f(CH_2Cl_2–2% MeOH, SiO_2) 0.15 (Found: C, 74.7; H, 8.6; N, 7.7. $C_{11}H_{15}NO$ requires C, 74.5; H, 8.5; N, 7.9%); δ(270 MHz; $CDCl_3$) 1.25 (3 H, d, 2-CH_3, $J_{CH_3,2}$ 6.2), 1.52 (1 H, m, 3-H_{ax}, $J_{3ax,2}$ 11.9, $J_{3ax,3eq}$ −13.5, $J_{3ax,4}$ 3.5), 1.97 (1 H, dt, 3-H_{eq}, $J_{3eq,2}$ 2.4, $J_{3eq,4}$ 2.6), 2.22 (3 H, s, 6-CH_3), 3.50 (1 H, m, 2-H), 4.67 (1 H, t, 4-H), 6.47 (1 H, d, 8-H, $J_{8,7}$ 8.3), 6.89 (1 H, dd, 7-H, $J_{7,5}$ 1.95) and 7.01 (1 H, d, 5-H).

cis-1-*Benzoyl*-2,6-*dimethyl*-1,2,3,4-*tetrahydroquinolin*-4-*ol* **3**.—*cis*-2,6-Dimethyl-1,2,3,4-tetrahydroquinolin-4-ol **1** (1.01 g, 5.7 mmol) was dissolved in pyridine (10 cm^3) and a slight excess of benzoyl chloride (1.00 g, 7.1 mmol) was added dropwise. The reaction mixture was stirred for 2 h and then poured into ice-cold distilled water (approximately 25 cm^3). The pale pink solid

Table 1

	Dihedral angle from X-ray (°)		Calculated[15] J_{vic} from Karplus/Hz	Observed J_{vic} from ^{1}H NMR/Hz
cis-Dibenzoyl derivative **5**	2,3ax = 72.17		1–2	5.9
	2,3eq = −57.41		2–3	7.0
	3ax,4 = −44.55		4–5	7.15
	3eq,4 = 84.67		< 1.0	5.8
trans-Dibenzoyl derivative **6**	2,3ax = −144.65		6	7.3
	2,3eq = 24.06		7	7.9
	3ax,4 = 66.26		2	3.85
	3eq,4 = −63.55		2	4.2

R = COPh

which formed was filtered and recrystallized from methylated spirits to give the *title compound* **3**, as a fine white powder (1.33 g, 83.1%), m.p. 178–180 °C (Found: C, 76.7; H, 6.7; N, 4.9. $C_{18}H_{19}NO_2$ requires C, 76.9; H, 6.5; N, 5.0%); δ(270 MHz; $CDCl_3$), 1.23 (3 H, d, 2-CH_3, $J_{CH_3,2}$ 6.4), 1.41 (1 H, m, 3-H_{ax}, $J_{3ax,2}$ 8.1, $J_{3ax,3eq}$ −12.45, $J_{3ax,4}$ 10.8), 1.62 (1 H, br d, OH), 2.29 (3 H, s, 6-CH_3), 2.69 (1 H, m, 3-H_{eq}, J_{3eq}, $J_{3eq,2}$ 8.8, $J_{3eq,4}$ 5.1), 4.76 (1 H, m, 4-H, $J_{4,OH}$ 5.5), 4.79 (1 H, m, 2-H) and 6.40–7.35 (8 H, aryl H); δ(C_6D_6) 4.80 (1 H, m, 2-H) and 4.27 (1 H, m, 4-H).

cis-1-*Benzoyl*-4-*benzoyloxy*-2,6-*dimethyl*-1,2,3,4-*tetrahydroquinoline* **5**.—*cis*-2,6-Dimethyl-1,2,3,4-tetrahydroquinolin-4-ol **1** (1.0 g, 5.7 mmol) was dissolved in pyridine (25 cm^3) and an excess of benzoyl chloride (1.98 g, 14.1 mmol) was added dropwise. The mixture was stirred for about 3 h and then left overnight. The stirring was then resumed, the mixture warmed to *ca.* 60 °C and a second aliquot (2.0 g, 14.2 mmol) of benzoyl chloride added. After *ca.* 3 h the mixture was allowed to return to room temperature and aqueous sodium hydroxide (2.5 mol dm^{-3}; 20–30 cm^3) was added. The required *N*,*O*-dibenzoyl derivative crystallized after cooling the mixture in an ice bath. The product was filtered under vacuum and recrystallized from 50:50 light petroleum (b.p. 40–60 °C)–diethyl ether to give the *title compound* **5**, as a fine white powder (1.40 g, 63.8%), m.p. 138–140 °C (Found: C, 78.0; H, 6.0; N, 3.5. $C_{25}H_{23}NO$ requires C, 77.9; H, 6.0; N, 3.6%); δ(270 MHz; $CDCl_3$), 1.37 (3 H, d, 2-CH_3, $J_{CH_3,2}$ 6.6), 1.89 (1 H, m, 3-H_{ax}, $J_{3ax,2}$ 5.9, $J_{3ax,3eq}$ −13.6, $J_{3ax,4}$ 7.15), 2.26 (3 H, s, 6-CH_3), 2.79 (1 H, m, 3-H_{eq}, $J_{3eq,2}$ 7.0, $J_{3eq,4}$ 5.8), 4.96 (1 H, m, 2-H), 6.22 (1 H, t, 4-H) and 6.60–8.20 (aryl H).

trans-1-*Benzoyl*-2,6-*dimethyl*-1,2,3,4-*tetrahydroquinolin*-4-*ol* **4**.—*trans*-2,6-Dimethyl-1,2,3,4-tetrahydroquinolin-4-ol **2** (1.01 g, 5.7 mmol) was dissolved in pyridine (100 cm^3) and benzoyl chloride (0.80 g, 5.7 mmol) was added dropwise. The mixture was stirred for *ca.* 1 h and then poured into dilute aqueous sodium hydroxide (20 cm^3). The organic layer was separated and evaporated to yield a mixture of a brown gum and colourless star-like needles. TLC of the mixture showed two spots, R_f(CH_2Cl_2–3% MeOH, SiO_2) 0.16 and 0.79, which, by comparison with the TLC of the previously synthesised *cis* compounds **3** and **5**, appeared to be both the mono- and di-benzoylated derivatives, in an approximate ratio of 7:3. Satisfactory separation was achieved by triturating the gum with a little diethyl ether to produce a crystalline solid. Recrystallization from light petroleum (b.p. 60–80 °C)–diethyl ether (1:1), gave the *title compound* **4**, as a fine white powder (0.37 g, 23.31%), m.p. 112–114 °C (Found: C, 76.7; H, 6.5; N, 4.8. $C_{18}H_{19}NO_2$ requires C, 76.9; H, 6.5; N, 5.0%); δ(270 MHz; $CDCl_3$), 1.24 (3 H, d, 2-CH_3, $J_{CH_3,2}$ 6.40), 1.84 (1 H, m, 3-H_{ax}, $J_{3ax,3eq}$ −13.9, $J_{2,3ax}$ 6.0, $J_{3ax,4}$ 4.8), 2.25 (3 H, s, 6-H_3), 2.46 (1 H, m, 3-H_{eq}, $J_{3eq,2}$ 7.3, $J_{3eq,4}$ 5.0), 4.85 (1 H, t, 4-H), 4.85 (1 H, m, 2-H) and 6.50–7.20 (13 H, aryl H).

trans-1-*Benzoyl*-4-*benzoyloxy*-2,6-*dimethyl*-1,2,3,4-*tetrahydroquinoline* **6**.—*trans*-2,6-Dimethyl-1,2,3,4-tetrahydroquinolin-4-ol **2** (1.01 g, 5.7 mmol) was dissolved in pyridine (10 cm^3) and an excess of benzoyl chloride (2.02 g, 14.4 mmol) was added dropwise. The reaction mixture was stirred for *ca.* 3 h and then left overnight. Evaporation of the pyridine yielded a white crystalline material which was recrystallized from light petroleum (b.p. 60–80 °C)–diethyl ether (1:1), to give the *title compound* **6**, as fine white crystals (1.31 g, 60.0%), m.p. 146–148 °C (Found: C, 77.9; H, 5.8; N, 3.6. $C_{25}H_{23}NO_3$ requires C, 77.9; H, 6.0; N, 3.6%); δ(270 MHz; $CDCl_3$), 1.37 (3 H, d, 2-CH_3, $J_{CH_3,2}$ 6.6), 1.90 (1 H, m, 3-H_{ax}, $J_{3ax,2}$ 7.3, $J_{3ax,3eq}$ −14.3, $J_{3ax,4}$ 3.85), 2.25 (3 H, s, 6-CH_3), 2.84 (1 H, m, 3-H_{eq}, $J_{3eq,2}$ 7.9, $J_{3eq,4}$ 4.2), 5.00 (1 H, m, 2-H), 6.18 (1 H, t, 4-H) and 6.40–8.10 (13 H, aryl H).

Microbiological Procedures.—*Cunninghamella elegans* and *Aspergillus niger* were obtained as freeze-dried cultures from I.M.I. at Kew, Surrey.

The 1,2,3,4-tetrahydroquinoline substrate (1.5 g) was dissolved in acetone (50 cm^3) and added to 25, 500 cm^3, shake-flasks containing the fungus growing in a 0.5% (weight per volume) malt extract broth–0.5% glucose nutrient medium (200 cm^3). Incubation was continued, with swirling, for 3 days at 28 °C. The contents of the flasks were then combined and filtered under vacuum. The filtrate was saturated with sodium chloride and extracted with dichloromethane (3 × 1 dm^3). The combined extracts were dried over sodium sulfate and evaporated to yield the broth extract residue.

Incubation of 1-*Benzoyl*-2-*methyl*-1,2,3,4-*tetrahydroquinoline* **7** *with* Cunninghamella elegans.—1-Benzoyl-2-methyl-1,2,3,4-tetrahydroquinoline **7** (1.50 g) was dissolved in acetone (50 cm^3), added to the fungus in the nutrient medium (5 dm^3, 25 flasks) and incubated for 3 days at 28 °C. TLC [50% light petroleum (b.p. 40–60 °C)–50% ethyl acetate, SiO_2] of the broth extract residue (0.47 g) showed three spots, R_f 0.82, 0.47 and 0.38. Flash column chromatography, using the TLC solvent system, with silica gel (mesh 230–400, particle size 0.004 → 0.063 mm^3) as the stationary phase yielded in decreasing order of R_f value, unchanged starting material (150 mg, 14.2%), m.p. 117–118 °C, R_f 0.82; cis-1-*benzoyl*-2-*methyl*-1,2,3,4-*tetrahydroquinolin*-4-*ol* **8** (50 mg, 3.3%), m.p. 157–158 °C (Found: C, 76.35; H, 6.4; N, 5.3. $C_{17}H_{17}NO_2$ requires C, 76.4; H, 6.4; N, 5.2%); R_f 0.47; δ(270 MHz; $CDCl_3$), 1.27 (3 H, d, 2-CH_3, $J_{CH_3,2}$ 6.4), 1.50 (1 H, m, 3-H_{ax}, $J_{3ax,2}$ 7.7, $J_{3ax,3eq}$ −12.6, $J_{3ax,4}$ 10.3), 2.50 (1 H, s, OH), 2.78 (1 H, m, 3-H_{eq}, $J_{3eq,2}$ 8.3, $J_{3eq,4}$ 5.3), 4.93 (1 H, m, 4-H) and 4.93 (1 H, m, 2-H); trans-1-*benzoyl*-2-*methyl*-1,2,3,4-*tetrahydroquinolin*-4-*ol* **9** (5 mg, 0.3%), m.p. 155–156 °C (Found: C, 76.5; H, 6.5; N, 5.05. $C_{17}H_{17}NO_2$ requires C, 76.4; H, 6.4; N, 5.2%); R_f 0.38; δ(270 MHz; $CDCl_3$), 1.28 (3 H, d, 2-CH_3, $J_{CH_3,2}$ 6.4), 1.90 (1 H, m, 3-H_{ax}, $J_{3ax,2}$ 5.9, $J_{3ax,3eq}$ −13.9, $J_{3ax,4}$ 4.8), 2.52 (1 H, m, 3-H_{eq}, $J_{3eq,2}$ 7.1, $J_{3eq,4}$ 6.0), 4.80 (1 H, m, 4-H) and 4.80 (1 H, m, 2-H).

Incubation of 1-*Benzoyl*-2-*methyl*-1,2,3,4-*tetrahydroquinoline* **7** *with* Aspergillus niger.—1-Benzoyl-2-methyl-1,2,3,4-tetrahydroquinoline **7** (1.50 g) in acetone (50 cm^3) was added to the fungus in the nutrient medium (5 dm^3, 25 flasks) and incubation continued for 3 days at 28 °C. TLC [50% light petroleum (b.p. 40–60 °C)–50% ethyl acetate, SiO_2] of the broth extract residue (0.41 g) showed two spots, R_f 0.80 and 0.45. Flash column chromatography, using the above solvent system, with silica gel (mesh 230–400, particle size 0.004 → 0.063 mm^3) as the stationary phase, yielded, in decreasing order of R_f value, unchanged starting material (150 mg, 14.2%), R_f 0.80 and *cis*-1-benzoyl-2-methyl-1,2,3,4-tetrahydroquinolin-4-ol **8** (100 mg, 6.7%), m.p. 157–158 °C (Found: C, 76.5; H, 6.4; N, 5.3. $C_{17}H_{17}NO_2$ requires C, 76.4; H, 6.4; N, 5.2%); R_f 0.45; δ(270 MHz; $CDCl_3$), 1.27 (3 H, d, 2-CH_3, $J_{CH_3,2}$ 6.4), 1.50 (1 H, m, 3-H_{ax}, $J_{3ax,2}$ 7.7, $J_{3ax,3eq}$ −12.6, $J_{3ax,4}$ 10.3), 2.50 (1 H, s, OH), 2.78 (1 H, m, 3-H_{eq}, $J_{3eq,2}$ 8.3, $J_{3eq,4}$ 5.3), 4.93 (1 H, m, 4-H) and 4.93 (1 H, m, 2-H).

Crystal Data for cis-1-*Benzoyl*-4-*benzoyloxy*-2,6-*dimethyl*-1,2,3,4-*tetrahydroquinoline* **5**.—$C_{25}H_{23}NO_3$, M = 385.4. Cell dimensions: a = 13.649(2), b = 10.353(2), c = 14.329(2) Å, α = 90.0, β = 98.78(1), γ = 90.0°, V = 2001.0(5) Å^3, space group $P2_1/c$, number of molecules per unit cell = 4, D_c = 1.279 g cm^{-3}. Crystal dimensions/mm 0.26 × 0.30 × 0.48.

Crystal Data for trans-1-*Benzoyl*-4-*benzoyloxy*-2,6-*dimethyl*-1,2,3,4-*tetrahydroquinoline* **6**.—$C_{25}H_{23}NO_3$, M = 385.4. Cell dimensions: a = 9.951(1), b = 10.590(1), c = 10.825(1) Å, α = 77.17(1), β = 77.15(1), γ = 74.63°, V = 1056.1(2) Å^3, space group $P\bar{1}$, number of molecules per unit cell = 2, D_c = 1.212 g cm^{-3}. Crystal dimensions/mm 0.28 × 0.30 × 0.52.

Data Collection and Processing/Structure Analysis and Refinement.—A representative crystal was surveyed and a 1 Å data set (maximum sin θ/λ = 0.5) was collected on a Siemens R3RA/v diffractometer. Atomic scattering factors were taken from the *International Tables for X-ray Crystallography*.[16] All crystallographic calculations were facilitated by the SHELXTL[17] system. All diffractometer data were collected at room temperature.

A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. A final difference Fourier revealed no missing or misplaced electron density.

Tables of atomic coordinates, bond lengths and angles, and thermal parameters have been desposited at the Cambridge Crystallographic Data Centre.*

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* For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1994, Issue 1.