Microbiological Transformations, Part 6.[1] Microbiological Transformations of Acyl Derivatives of Indoline, 1,2,3,4-Tetrahydroquinoline, 1,2,3,4-Tetrahydroisoquinoline and 2,3,4,5-Tetrahydro-1*H*-1-benzazepine with the Fungus *Cunninghamella elegans*

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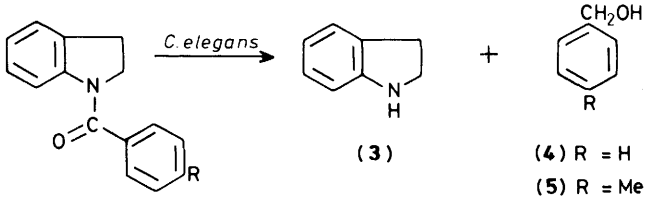
Incubation of *N*-benzoyl and *N*-(*p*-toluoyl)indoline with *Cunninghamella elegans* resulted in reductive cleavage with the formation of indoline and the corresponding benzyl alcohol. *N*-Acetylindoline underwent normal benzylic hydroxylation and open chain analogues of *N*-(*p*-toluoyl)indolines were hydroxylated at the aryl methyl group by *C. elegans*. The fungus effected benzylic oxidation at the 4-position in *N*-benzoyl-1,2,3,4-tetrahydroquinoline and in *N*-benzoyl-1,2,3,4-tetrahydroisoquinoline derivatives. *N*-(*p*-Toluoyl)-1,2,3,4-tetrahydroquinoline and *N*-(*p*-ethylbenzoyl)-1,2,3,4-tetrahydroisoquinoline were, however, hydroxylated at the alternative 4'-benzylic position. Incubation of *N*-(*p*-toluoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine with *C. elegans* gave 5-hydroxy-*N*-(*p*-toluoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine

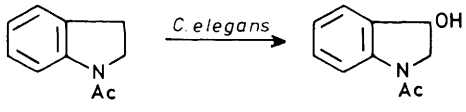
The microbiological transformations of saturated heterocycles have been well documented.[2] In contrast, transformations of partially reduced heterocyclic systems have received little attention. Since the presence of an amide grouping, presumably acting as a binding group to the enzyme surface,[3] was found to be essential for successful microbiological transformations of piperidine[4] and decahydroquinoline derivatives[5,6] it was decided to study *N*-benzoyl- and *N*-acetyl-derivatives of the simple partially reduced heterocycles indoline, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, and 2,3,4,5-tetrahydro-1*H*-1-benzazepine, rather than the parent secondary amines. In addition, indoline and 1,2,3,4-tetrahydroquinoline are expected to be sensitive to aerial oxidation which would occur at the same time as microbiological oxygenations.



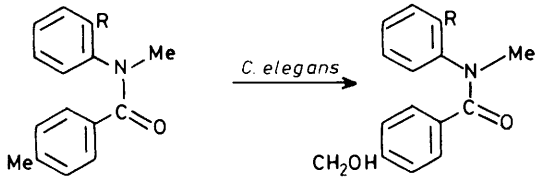
(1) R = H
(2) R = Me

(3)

(4) R = H
(5) R = Me



(6) (7)



(8) R = H
(9) R = Et

(10) R = H
(11) R = Et

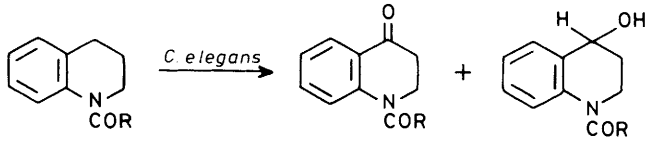
Cunninghamella elegans was chosen for study since incubations of yohimbine with this fungus had been shown[7] to result in hydroxylation of the aromatic ring. If such aromatic ring hydroxylations occurred in the indolines and quinolines this would provide a route to phenols of possible medicinal importance.

Incubation of *N*-benzoylindoline (**1**) and of *N*-(*p*-toluoyl)-indoline (**2**) with *C. elegans* resulted in reductive cleavage to indoline (**3**) and benzyl alcohol (**4**) or *p*-methylbenzyl alcohol (**5**) respectively. Since the ease of the reductive cleavage of a compound of this type might be expected to be dependent upon the nature of the amide function, *N*-acetylindoline (**6**) was incubated for 4 days with *C. elegans* and instead of indoline, *N*-acetylindolin-3-ol (**7**) was produced.

Open-chain analogues of *N*-benzoylindoline, may adopt a different stereochemical relationship with the enzyme to that adopted by (**1**) and this may well influence the course of microbiological transformation. To investigate this possibility, *N*-methyl-*p*-toluanilide (**8**) and 2-ethyl-*N*-(*p*-toluoyl)aniline (**9**) were incubated with *C. elegans* and *N*-(4-hydroxymethylbenzoyl)-*N*-methylaniline (**10**) and 2-ethyl-*N*-(4-hydroxymethylbenzoyl)aniline (**11**) respectively, were produced.

Since the *N*-aroyl-derivatives of indoline (**1**) and (**2**) undergo the reductive cleavage to indoline and the corresponding aryl alcohols, it seemed of interest to investigate the six-membered ring analogue of (**1**). Accordingly, *N*-benzoyl-1,2,3,4-tetrahydroquinoline (**12**) was incubated with *C. elegans* when instead of the cleavage reaction benzylic oxidation occurred to give *N*-benzoyl-1,2-dihydroquinolin-4(3*H*)-one (**13**) and *N*-benzoyl-1,2,3,4-tetrahydroquinolin-4-ol (**14**).

Since benzylic attack by *C. elegans* had occurred with (**12**) as substrate, *N*-(*p*-toluoyl)-1,2,3,4-tetrahydroquinoline (**15**), which offers two positions (C-4 in the heterocyclic ring and the methyl



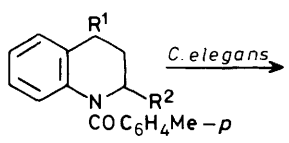
(12) R = Ph
(15) R = *p*-Tolyl
(17) R = Me

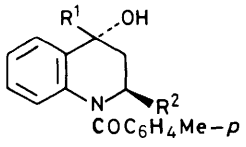
(13) R = Ph
(16) R = *p*-Tolyl
(18) R = Me

(14) R = Ph

group in the toluoyl moiety) to the fungus, was incubated with *C. elegans*. This resulted in oxidation at C-4 to give *N*-(*p*-toluoyl)-1,2-dihydroquinolin-4(3*H*)-one (**16**). Benzylic attack at C-4 to give *N*-acetyl-1,2-dihydroquinolin-4(3*H*)-one (**18**) also occurred when *N*-acetyl-1,2,3,4-tetrahydroquinoline (**17**) was incubated with *C. elegans*.

To evaluate the possible blocking effect of a 4-substituent on such benzylic oxidations 4-methyl-1-(*p*-toluoyl)-1,2,3,4-tetrahydroquinoline (**19**) was incubated with *C. elegans*. C-4 Hydroxylation was not inhibited as shown by the formation of 4-methyl-1-(*p*-toluoyl)-1,2,3,4-tetrahydroquinolin-4-ol (**20**) but 4-methyl-1-(*p*-hydroxymethylbenzoyl)-1,2,3,4-tetrahydroquinoline (**21**) was also produced as a result of hydroxylation at the alternative benzylic position.





(**19**) R^1 = Me R^2 = H (**20**) R^1 = Me R^2 = H
(**22**) R^1 = H R^2 = Me (**23**) R^1 = H R^2 = Me

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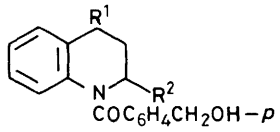
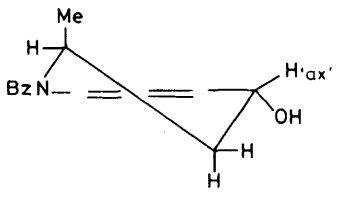


(**21**) R^1 = Me R^2 = H
(**24**) R^1 = H R^2 = Me

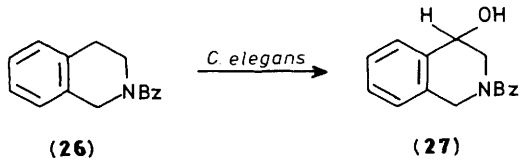
Incubation of 2-methyl-1-(*p*-toluoyl)-1,2,3,4-tetrahydroquinoline (**22**) with *C. elegans*, followed a similar pattern to give *trans*-2-methyl-1-(*p*-toluoyl)-1,2,3,4-tetrahydroquinolin-4-ol (**23**) ($[\alpha]_D^{25°}$ +42.5°) and 2-methyl-1-(*p*-hydroxymethylbenzoyl)-1,2,3,4-tetrahydroquinoline (**24**).

The 270 MHz n.m.r. spectrum of (**23**) showed the C-2 methyl doublet at δ 1.25 and the benzylic methyl singlet at δ 2.31. The C-2 proton multiplet and an ArC*H*OH multiplet overlapped at δ 4.80. First-order analysis of the 3ax-H eight line multiplet at δ 1.45 (assigned to 3ax-H rather than 3eq-H on the basis of line width of signals) gave $J_{3ax,3eq}$ 12.5 Hz, $J_{3ax,4'ax'}$ 10 Hz and $J_{3ax,2eq}$ 7.5 Hz. Similarly, analysis of the 3eq-H signals (δ 2.69) gave $J_{3eq,2eq}$ 5 Hz and $J_{3eq,4'ax'}$ 7.5 Hz. These vicinal couplings are in accordance with a pseudoequatorial hydroxy substituent at C-4 as shown in (**25**). The C-2-methyl group in (**25**) is assigned the axial orientation from the known [3] preferences of 2-alkyl groups in 2-alkylpiperidine benzamides.

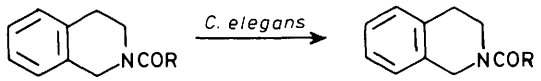


(**25**)

The effect of a change in ring nitrogen position on the course of the microbiological transformation was investigated by incubation of *N*-benzoyl-1,2,3,4-tetrahydroisoquinoline (**26**) with *C. elegans*. This gave *N*-benzoyl-1,2,3,4-tetrahydro-



(**26**) (**27**)

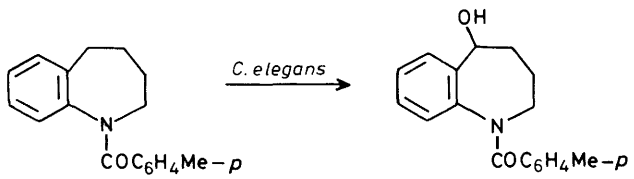


(**28**) R = *p*-MeC_6H_4 (**30**) R = *p*-$HOCH_2C_6H_4$
(**29**) R = *p*-$MeCH_2C_6H_4$ (**31**) R = *p*-$MeCH(OH)C_6H_4$
(**32**) R = *p*-$MeC_6H_4CH_2$ (**33**) R = *p*-$HOCH_2C_6H_4CH_2$

isoquinoline-4-ol (**27**) ($[\alpha]_D^{25°}$ +3.53°) resulting from C-4 hydroxylation as observed for the 1,2,3,4-tetrahydroquinoline analogue (**12**). *N*-(*p*-Toluoyl)-1,2,3,4-tetrahydroisoquinoline (**28**) however on incubation with *C. elegans* gave *N*-(*p*-hydroxymethylbenzoyl)-1,2,3,4-tetrahydroisoquinoline (**30**) as a result of hydroxylation at the alternative benzylic position.

To extend these results, additional derivatives of 1,2,3,4-tetrahydroisoquinoline were prepared and used as substrates for *C. elegans* to assess its differing modes of attack. Since the microbiological transformation of (**28**) with *C. elegans* resulted in attack at the *p*-methyl position, it was decided to incubate *N*-(*p*-ethylbenzoyl)-1,2,3,4-tetrahydroisoquinoline (**29**) with this fungus to see whether attack would occur at the same position. This in fact occurred to give *N*-[*p*-(1-hydroxyethyl)-benzoyl]-1,2,3,4-tetrahydroisoquinoline (**31**).

The distance from the point of attachment of the enzyme (postulated [4] to be the amide carbonyl group) to the position of hydroxylation was extended by introducing a methylene group between the carbonyl function and the aromatic ring as in *N*-(*p*-tolylacetyl)-1,2,3,4-tetrahydroisoquinoline (**32**). Incubation of (**32**) with *C. elegans* gave *N*-(*p*-hydroxymethylphenylacetyl)-1,2,3,4-tetrahydroisoquinoline (**31**).



(**34**) (**35**)

Incubation of *N*-(*p*-toluoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (**34**), the seven-membered ring analogue of (**15**) with *C. elegans* gave 5-hydroxy-*N*-(*p*-toluoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (**35**) by a similar benzylic hydroxylation.

Discussion of Results.—The most unexpected microbiological transformation described in this paper is the conversion of *N*-benzoylindoline (**1**) to indoline (**3**) and benzyl alcohol (**4**) by *C. elegans*. Unlike *N*-benzoylindoline (**1**) and *N*-(*p*-toluoyl)indoline (**2**), *N*-acetylindoline (**6**) does not undergo the reductive cleavage but instead, hydroxylation at the C-3 benzylic position. The open-chain analogue (**9**) undergoes alternative benzylic hydroxylation of the *p*-methyl group.

In contrast to the transformation of *N*-aroylindolines, the six-membered ring analogues (*i.e.* the tetrahydroquinolines) undergo benzylic hydroxylation with *C. elegans* and no cleavage products are detected. All the oxygenations occurred at the C-4 position even when an alternative benzylic position [*e.g.* as in (**15**)] was available.

Whereas *N*-benzoyl-1,2,3,4-tetrahydroisoquinoline (**26**) undergoes C-4 hydroxylation the *N*-(*p*-alkylaroyl)-derivatives (**28**) and (**29**) are hydroxylated at the alternative *p*-alkyl benzylic sites. Increasing the distance between the amide function and the methyl group in the aryl substituent as in (**32**) did not affect the preference for hydroxylation at the methyl substituent.

Experimental

General experimental details and incubation procedures are as given previously.[8] Heterocyclic starting materials were obtained from Aldrich Chemical Co. Ltd. Light petroleum refers to that fraction b.p. (40—60 °C).

N-*Benzoyl- and* N-(p-*Toluoyl*) *Derivatives: General Procedure.*—*p*-Toluoyl chloride was obtained by heating *p*-toluic acid (10 g) with thionyl chloride under reflux for 1 h. The excess thionyl chloride was removed by distillation and the residual oil distilled under reduced pressure to give *p*-toluoyl chloride (8.2 g, 72%) as an oil, b.p. 80 °C at 7 mmHg (lit.,[9] 94—95 °C/11 mm Hg). The amine suspended in 10% sodium hydroxide solution was shaken for 20 min with an excess of benzoyl chloride or *p*-toluoyl chloride. The solid product was filtered and recrystallised from ethanol. If an oil formed, it was extracted with ether, dried over sodium sulphate, and distilled.

N-*Benzoylindoline.* This compound was obtained from indoline (10 ml) and benzoyl chloride (15 ml) as colourless crystals (12.9 g, 69%), m.p. 116—117 °C (lit.,[10] 118 °C).

N-(p-*Toluoyl*)*indoline.* This compound was obtained from indoline (10 ml) and *p*-toluoyl chloride (15 ml) as colourless *needles* (7.3 g, 37%), m.p. 101—102 °C (Found: C, 80.8; H, 6.6; N, 6.1. $C_{16}H_{15}NO$ requires C, 81.0; H, 6.4; N, 5.9%).

N-*Methyl*-p-*toluanilide.* This compound was obtained from *N*-methylaniline (10 ml) and *p*-toluoyl chloride (15 ml) as colourless crystals, m.p. 67—68 °C (lit.,[11] 69.5—71.0 °C).

2-*Ethyl*-N-(p-*toluoyl*)*aniline.* This compound was obtained from *o*-ethylaniline (10 ml) and *p*-toluoyl chloride (12 ml) as colourless needles (13.5 g, 68.3%), m.p. 129 °C (Found: C, 80.4; H, 7.05; N, 5.7. $C_{16}H_{17}NO$ requires C, 80.3; H, 7.2; N, 5.85%).

N-*Benzoyl*-1,2,3,4-*tetrahydroquinoline.* This compound was obtained from 1,2,3,4-tetrahydroquinoline (10 ml) and benzoyl chloride (15 ml) as colourless crystals (4.9 g, 28%), m.p. 75—76 °C (lit.,[12] 75 °C).

N-(p-*Toluoyl*)-1,2,3,4-*tetrahydroquinoline.* This compound was obtained from 1,2,3,4-tetrahydroquinoline (10 ml) and *p*-toluoyl chloride (15 ml) as colourless *crystals* (8 g, 42%), m.p. 93 °C (Found: C, 81.1; H, 6.95; N, 5.7. $C_{17}H_{17}NO$ requires C, 81.2; H, 6.8; N, 5.6%).

N-*Benzoyl*-1,2,3,4-*tetrahydroisoquinoline.* This compound was obtained from 1,2,3,4-tetrahydroisoquinoline (13.3 g) and benzoyl chloride (15 ml) as crystals (15.3 g, 64.5%), m.p. 128 °C (lit.,[13] 129 °C).

N-(*p*-*Toluoyl*)-1,2,3,4-*tetrahydroisoquinoline.* This compound was obtained from 1,2,3,4-tetrahydroisoquinoline (10 ml) and *p*-toluoyl chloride (15 ml) as crystals (6.1 g, 32%), m.p. 83 °C (Found: C, 81.1; H, 6.9; N, 5.6. $C_{17}H_{17}NO$ requires C, 81.2; H, 6.8; N, 5.6%).

N-(p-*Ethylbenzoyl*)-1,2,3,4-*tetrahydroisoquinoline.* This compound was obtained from 1,2,3,4-tetrahydroisoquinoline (10 g) and *p*-ethylbenzoyl chloride (15 g) as colourless crystals, (12.5 g, 68.8%), m.p. 49—50 °C (Found: C, 81.3; H, 7.4; N, 6.1. $C_{18}H_{19}NO$ requires C, 81.5; H, 7.2; N, 6.0%).

N-(p-*Methylphenylacetyl*)-1,2,3,4-*tetrahydroisoquinoline.* This compound was obtained from 1,2,3,4,-tetrahydroisoquinoline (6.7 g) and *p*-methylphenylacetyl chloride (9.25 g) as colourless crystals (8.5 g, 64%), m.p. 102 °C (Found: C, 81.3; H, 7.4; N, 5.4. $C_{18}H_{19}NO$ requires C, 81.5; H, 7.2; N, 5.3%).

4-*Methyl*-1-(p-*toluoyl*)-1,2,3,4-*tetrahydroquinoline.*—4-Methylquinoline (50 g) in glacial acetic acid (150 ml) was hydrogenated in the presence of Adams platinum oxide catalyst (1 g). The catalyst was filtered off and the filtrate basified with 30% aqueous sodium hydroxide. The basic solution was extracted with ether and the extract dried over sodium sulphate. Evaporation of the ether followed by distillation of the residue gave 4-methyl-1,2,3,4-tetrahydroquinoline as an oil, b.p. 80 °C at 0.5 mmHg. 4-*Methyl*-1-(p-*toluoyl*)-1,2,3,4-*tetrahydroquinoline* was obtained from 4-methyl-1,2,3,4-tetrahydroquinoline (7.35 g) and *p*-toluoyl chloride (8.5 g) as colourless crystals (9.9 g, 75%), m.p. 64—65 °C (Found: C, 81.4; H, 7.3; N, 5.25. $C_{18}H_{19}NO$ requires C, 81.5; H, 7.2; N, 5.3%).

2-*Methyl*-1-(p-*toluoyl*)-1,2,3,4-*tetrahydroquinoline.* This compound was obtained from 2-methyl-1,2,3,4-tetrahydroquinoline (7.35 g) (prepared by catalytic hydrogenation of quinaldine as described above for reduction of 4-methylquinoline) and *p*-toluoyl chloride (8.4 g) as colourless crystals (9.6 g, 72.7%), m.p. 106—107 °C (Found: C, 81.4; H, 7.5; N, 5.1. $C_{18}H_{19}NO$ requires C, 81.5; H, 7.2; N, 5.3%).

N-*Acetyl Derivatives: General Procedure.*—A mixture of equal volumes of acetic anhydride (40 ml) and glacial acetic acid (40 ml) was boiled under reflux with the amine (20 ml). The mixture was poured into water and the solution basified (NaOH) and extracted with ether. The ether solution was dried ($NaSO_4$), evaporated and the residue distilled.

N-*Acetylindoline.* This compound was formed from indoline (20 ml) as colourless needles (12 g, 44%), m.p. 103 °C (lit.,[14] 105 °C).

N-*Acetyl*-1,2,3,4-*tetrahydroquinoline.* This compound was formed from 1,2,3,4-tetrahydroquinoline (20 ml) as a colourless oil (12.4 g, 47%), b.p. 141 °C at 0.45 mmHg (lit.,[15] 295 °C).

N-(p-*Toluoyl*)-2,3,4,5-*tetrahydro*-1H-1-*benzazepine.*—2,3,4,5-Tetrahydro-1*H*-2-oxo-benzo[*b*]azepine, prepared by the Beckmann rearrangement[16] of the oxime of 3,4-dihydronaphthalen-1(2*H*)-one,[17] (7 g) in dry ether (100 ml) was added with stirring to a suspension of lithium aluminium hydride (2 g) in dry ether (50 ml). When addition was complete, the mixture was boiled under reflux overnight. Ice was then cautiously added until a white precipitate had formed. This was filtered off, washed with ether, and the filtrate combined with the ethereal solution of reduction products. The ethereal solution was dried over sodium sulphate and evaporated. The residual oil was distilled to give 2,3,4,5-tetrahydro-1*H*-1-benzazepine as an oil, b.p. 88 °C/ at 0.25 mmHg, which crystallised to give a white solid, m.p. 32 °C (lit.,[18] 32 °C). N-(p-*Toluoyl*)-2,3,4,5-*tetrahydro*-1H-1-*benzazepine* was obtained from 2,3,4,5-tetrahydro-1*H*-1-benzazepine[18] (4.6 g) and *p*-toluoyl chloride (5.3 g) as colourless crystals (5.2 g, 63%), m.p. 128 °C (Found: C, 81.7; H, 7.3; N, 5.1. $C_{18}H_{19}NO$ requires C, 81.5; H, 7.2; N, 5.3%).

Incubation of N-Benzoylindoline with C. elegans.—A solution of *N*-benzoylindoline (1.5 g) in acetone (25 ml) was incubated with *C. elegans* grown in the nutrient medium (5 l, 25 flasks) for 3 days. The material extracted* was chromatographed over neutral alumina (100 g, activity IV). Elution with 5% ether in light petroleum gave indoline and in addition elution with a 20% solution of ether in light petroleum gave benzyl alcohol (20 mg). The i.r. and n.m.r. spectra were identical to those of authentic samples.

Incubation of N-(p-*Toluoyl*)*indoline* (**2**) *with* C. elegans.—*N*-(*p*-Toluoyl)indoline (1.5 g) in acetone (25 ml) was incubated

* Extractions are as described in the Experimental section of ref. 8.

with *C. elegans* in the nutrient medium (5 l, 25 flasks) for 3 days. Extraction, followed by chromatography over neutral alumina (100 g, activity IV) and elution with light petroleum gave indoline. Elution with a 10% solution of ether in light petroleum gave p-*methylbenzyl alcohol* (**5**) (35 mg) as needles, m.p. 58 °C. $\nu_{max.}$ 3 610 and 3 450 cm^{-1}; δ 7.30 (4 H, m, ArH), 4.65 (2 H, m, $ArCH_2$), 2.03 (3 H, s, Me), and 1.68 (1 H, m, $ArCH_2OH$).

Incubation of N-*Acetylindoline with* C. elegans.—*N*-Acetylindoline (1.5 g) in acetone (25 ml) was added to *C. elegans* in the nutrient medium (5 l, 25 flasks) and incubation carried out for 4 days. The extract was dissolved in the minimum amount of chloroform and chromatographed over neutral alumina (100 g, activity IV). The product (35 mg) was characterised as N-*acetylindolin*-3-*ol* (**7**), m.p. 127 °C (Found: C, 67.6; H, 6.0; N, 7.7. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.3; N, 7.9%); $\nu_{max.}$ 3 560, 3 380, and 1 643 cm^{-1}; δ 8.33—8.00 (1 H, d, 7-*H*), 7.41—7.00 (3 H, m, ArH), 5.23 (1 H, m, ArC*H*OH), 4.33—3.83 (2 H, m), 2.98 (1 H, m, ArCHO*H*) and 2.11 (3 H, s, Me).

Incubation of N-*Methyl*-p-*toluanilide* (**18**) *with* C. elegans.—A solution of *N*-methyl-*p*-toluanilide (1.7 g) in acetone (25 ml) was added to *C. elegans* grown in the nutrient medium (5 l, 25 flasks). After incubation for 3 days, extraction was followed by chromatography over neutral alumina (100 g, activity IV). The product (15 mg) was characterised as N-(p-*hydroxymethylbenzoyl*)-N-*methylbenzanilide* (**10**) (Found: C, 74.45; H, 6.5; N, 5.6. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.3; N, 5.8%); $\nu_{max.}$ 3 582, 3 367, and 1 634 cm^{-1}; δ 7.28—6.83 (9 H, m, ArH), 4.50 (2 H, s, $ArCH_2OH$), 3.43 (3 H, s, Me), and 3.32 (1 H, s, $ArCH_2OH$).

Incubation of 2-*Ethyl*-N-(p-*toluoyl*)*aniline* (**9**) *with* C. elegans.—A solution of 2-ethyl-*N*-(*p*-toluoyl)aniline (1.8 g) in acetone (25 ml) was incubated with *C. elegans* grown in the nutrient medium (5 l, 25 flasks) for 3 days. Extraction followed by chromatography over neutral alumina (100 g, activity IV) gave N-(p-*hydroxymethylbenzoyl*)-2-*ethylanilide* (**11**) (155 mg), m.p. 115 °C (Found: C, 75.6; H, 6.5; N, 5.8. $C_{16}H_{17}NO_2$ requires C, 75.3; H, 6.7; N, 5.5%); $\nu_{max.}$ 3 620, 3 440, and 1 660 cm^{-1}; δ 7.87 (2 H, d, ArH), 7.52—7.22 (6 H, m, ArH), 4.75 (2 H, d, $ArCH_2OH$), 2.67 (2 H, q, CH_2Me), 2.47 (1 H, s, $ArCH_2OH$), and 1.30 (3 H, t, CH_2Me).

Incubation of N-*Benzoyl*-1,2,3,4-*tetrahydroquinoline with* C. elegans.—*N*-Benzoyl-1,2,3,4-tetrahydroquinoline (1.5 g) was dissolved in acetone (25 ml) and added to the fungus in the nutrient medium (5 l, 25 flasks) and incubation continued for 3 days. The extracted material was chromatographed over alumina (100 g, activity IV). Elution with 20% ether in light petroleum gave N-*benzoyl*-1,2-*dihydroquinolin*-4(3H)-*one* (**13**) (150 mg), m.p. 116—117 °C (Found: C, 76.3; H, 5.1; N, 5.6. $C_{16}H_{13}NO_2$ requires C, 76.5; H, 5.2; N, 5.6%); $\nu_{max.}$ 1 688 and 1 647 cm^{-1}; δ 7.90 (1 H, m, 5-H), 7.70—7.00 (8 H, m, ArH), 4.50 (2 H, t, CH_2), and 3.05 (2 H, t, CH_2); *m/z* 251 (M^+). Elution with ether gave *N*-benzoyl-1,2,3,4-tetrahydroquinolin-4-ol (**14**) (25 mg), m.p. 119—120 °C (lit.,[19] 118—119 °C) (Found: C, 75.7; H, 6.1; N, 5.8. Calc. for $C_{16}H_{15}NO_2$: C, 75.9; H, 6.0; N, 5.5%); $\nu_{max.}$ 3400 and 1 640 cm^{-1}; δ 6.66—7.33 (9 H, m, ArH), 4.83 (1 H, m, ArC*H*OH), 3.90 (2 H, m, CH_2, 2-H), 2.80 (1 H, d, ArCHO*H*), and 2.16 (2 H, m, 3-H); *m/z* 253 (M^+).

Incubation of N-(p-*Toluoyl*)-1,2,3,4-*tetrahydroquinoline* (**15**) with C. elegans.—*N*-(*p*-Toluoyl)-1,2,3,4-tetrahydroquinoline (4.4 g) in acetone (75 ml) was added to *C. elegans* in the nutrient medium (15 l, 75 flasks). Incubation was continued for 3 days. The extracts were chromatographed over neutral alumina (200 g, activity IV) giving N-(p-*toluoyl*)-1,2-*dihydroquinolin*-4(3H)-*one* (**16**) (40 mg), m.p. 109 °C (Found: C, 79.7; H, 5.9; N, 5.1. $C_{17}H_{15}NO_2$ requires C, 80.0; H, 5.7; N, 5.3%); $\nu_{max.}$ 1 688 and 1 667 cm^{-1}; δ 7.93 (1 H, m, ArH), 7.50—6.83 (7 H, m, ArH), 4.33 (2 H, t, CH_2), 2.87 (2 H, t, CH_2), and 2.38 (3 H, s, Me).

Incubation of N-(*Acetyl*)-1,2,3,4-*tetrahydroquinoline with* C. elegans.—A solution of *N*-acetyl-1,2,3,4-tetrahydroquinoline (3.0 g) in acetone (50 ml) was added to *C. elegans* in the nutrient medium (10 l, 50 flasks) and incubation continued for 4 days. Extraction followed by chromatography over alumina (150 g, activity IV), gave, on elution with 50% ether in light petroleum, N-*acetyl*-1,2-*dihydroquinolin*-4(3H)-*one* (**18**) (80 mg), m.p. 90 °C (Found: C, 69.5; H, 5.7; N, 7.3. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.9; N, 7.4%); $\nu_{max.}$ 1 690 and 1 660 cm^{-1}; δ 7.97 (1 H, d, 5-H), 7.60—7.21 (3 H, m, ArH), 4.23 (2 H, t, CH_2), 2.80 (2 H, t, CH_2), and 2.30 (3 H, s, Me).

Incubation of 4-*Methyl*-1-(p-*toluoyl*)-1,2,3,4-*tetrahydroquinoline* (**19**) *with* C. elegans.—4-Methyl-1-(*p*-toluoyl)-1,2,3,4-tetrahydroquinoline (3.7 g) in ethanol (75 ml) was added to *C. elegans* in the nutrient medium (15 l, 75 flasks). Incubation was continued for 3—4 days. The extracts were chromatographed over Woelm neutral alumina (400 g, activity IV) and elution with 50% ether in light petroleum gave 4-*methyl*-1-(p-*toluoyl*)-1,2,3,4-*tetrahydroquinolin*-4-*ol* (**20**) (75 mg) as an oil (Found: C, 76.9; H, 7.2; N, 5.2. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%); $\nu_{max.}$ 3 600, 3 410—3 450, and 1 640 cm^{-1}; δ 7.57 (1 H, m, ArH), 7.05 (7 H, m, ArH), 3.76 (2 H, m, 2-H), 3.47 (1 H, s, CHO*H*), 2.37 (3 H, s, Ar*Me*), 2.13 (2 H, t, 3-H), and 1.67 (3 H, s, Ar*Me*). Elution with ether gave 1-(p-*hydroxymethylbenzoyl*)-4-*methyl*-1,2,3,4-*tetrahydroquinoline* (**21**) (70 mg) m.p. 92—93 °C (Found: C, 76.8; H, 7.2; N, 4.7. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%); $\nu_{max.}$ 3 608, 3 420, and 1 650 cm^{-1}; δ 6.94 (8 H, m, ArH), 4.58 (2 H, s, $ArCH_2OH$), 3.88 (2 H, m, 2-H), 3.41 (1 H, m, $ArCH_2OH$), 2.98 (1 H, q, 4-H), 2.02 (2 H, m, 3-H), and 1.42 (3 H, d, ArMe).

Incubation of 2-*Methyl*-1-(p-*toluoyl*)-1,2,3,4-*tetrahydroquinoline* (**22**) *with* C. elegans.—2-Methyl-1-(*p*-toluoyl)-1,2,3,4-tetrahydroquinoline (3.5 g), dissolved in ethanol, was incubated with *C. elegans*, grown in the nutrient medium (15 l, 75 flasks) for 3 days at 25 °C. The extracted material was chromatographed over Woelm neutral alumina (400 g, activity IV). Elution with 50% ether in light petroleum gave *trans*-2-methyl-1-(*p*-toluoyl)-1,2,3,4-tetrahydroquinolin-4-ol (**23**) (105 mg), m.p. 135 °C (Found: C, 76.9; H, 6.7; N, 4.5. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%), $\nu_{max.}$ 3 630, 3 400—3 420, and 1 630 cm^{-1}; δ 7.58 (1 H, d, ArH), 7.06 (6 H, m, ArH), 6.55 (1 H, d, ArH), 4.80 (2 H, m, ArC*H*OH, 2-H), 3.28 (1 H, s, ArCHO*H*) 2.69 (1 H, m, 3_{eq}-H) ($J_{3eq,2eq}$ 5 Hz and $J_{3eq,4'ax'}$ 7.5 Hz), 2.31 (3 H, s, Ar*Me*), 1.45 (1 H, m, 3_{ax}-H) (1 H, m, 3_{ax}-H) ($J_{3ax,3eq}$ −12.5 Hz, $J_{3ax,4'ax'}$ 10 Hz and $J_{3ax.2eq}$ 7.5 Hz), and 1.25 (3 H, d, Ar*Me*); $[\alpha]_D^{25°}$ = +42.5°. Elution with ether gave 1-(p-*hydroxymethylbenzoyl*)-2-*methyl*-1,2,3,4-*tetrahydroquinoline* (**24**) (65 mg), m.p. 103—104 °C (Found: C, 76.8; H, 6.9; N, 5.1. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%). $\nu_{max.}$ 3 626, 3 400—3 430, and 1 630 cm^{-1}; δ 7.76 (8 H, m, ArH), 4.97 (1 H, q, 2-H), 4.65 (2 H, s, $ArCH_2OH$), 2.79 (2 H, m, 4-H), 2.38 (2 H, m, 3-H), 2.08 (1 H, s, $ArCH_2OH$), and 1.23 (3 H, d, Me).

Incubation of N-*Benzoyl*-1,2,3,4-*tetrahydroisoquinoline with* C. elegans.—*N*-Benzoyl-1,2,3,4-tetrahydroisoquinoline (3 g) in ethanol (75 ml) was added to *C. elegans* in the nutrient medium (15 l, 75 flasks). Incubation was continued for 3—4 days. The extracts were chromatographed over Woelm neutral alumina (400 g, activity IV). Elution with ether gave N-*benzoyl*-1,2,3,4-*tetrahydroisoquinolin*-4-*ol* (**27**) (149 mg) as an oil (Found: C, 75.9; H, 5.7; N, 5.8. $C_{16}H_{15}NO_2$ requires C, 75.9; H, 6.0; N, 5.5%), $\nu_{max.}$ 3 590, 3 420—3 345, and 1 640 cm^{-1}; δ 7.47 (1 H, s,

ArH), 7.38—6.98 (8 H, m, ArH), 4.88 (1 H, m, ArC*H*OH), 4.90 (2 H, s, 1-H), 3.80 (1 H, m, 3-H), 3.76 (1 H, m, 3-H), and 2.78 (1 H, ArC*H*OH); $[\alpha]_D^{25°} = +3.53°$.

Incubation of N-(p-*Toluoyl*)-1,2,3,4-*tetrahydroisoquinoline* (**28**) *with* C. elegans.—*N*-(*p*-Toluoyl)-1,2,3,4-tetrahydroisoquinoline (1.7 g) was dissolved in acetone (25 ml) and added to *C. elegans* in the nutrient medium (5 l, 25 flasks). Incubation was continued for 3 days. The extracted material was chromatographed over alumina (100 g, activity IV) and elution with ether gave N-(p-*hydroxymethylbenzoyl*)-1,2,3,4-*tetrahydroisoquinoline* (**30**) (110 mg), m.p. 98—99 °C (Found: C, 76.2; H, 6.6; N, 5.0. $C_{17}H_{17}NO_2$ requires C, 76.4; H, 6.4; N, 5.2%), $\nu_{max.}$ 3 596, 3 390, and 1 630 cm^{-1}; δ 7.66 (4 H, s, ArH), 7.46 (4 H, s, ArH), 4.92 (4 H, s, 1-H_2 and ArCH_2OH), 3.88 (2 H, m, CH_2), and 3.00 (3 H, t, 4-H and ArCH_2O*H*).

Incubation of N-(p-*Ethylbenzoyl*)-1,2,3,4-*tetrahydroisoquinoline* (**29**) with C. elegans.—A solution of *N*-(*p*-ethylbenzoyl)-1,2,3,4-tetrahydroisoquinoline (3 g) in acetone (75 ml) was added to the fungus in the nutrient medium (15 l, 75 flasks). After 3 days incubation, extraction was followed by chromatography over neutral alumina (400 g, activity IV). Elution with ether gave N-[p-*hydroxyethyl*)*benzoyl*]-1,2,3,4-*tetrahydroisoquinoline* (**31**) (81 mg), m.p. 110 °C (Found: C, 76.7; H, 6.8; N, 5.0. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%); $\nu_{max.}$ 3 407, 3 604, and 1 625 cm^{-1}; δ 7.37 (4 H, s, ArH), 7.12 (4 H, s, ArH), 4.87 (1 H, s, ArC*H*OH), 4.73 (2 H, s, 1-H), 3.90 (2 H, m, 3-H), 2.91 (2 H, m, 4-H), 2.50 (1 H, m, ArCHO*H*), and 1.50 (3 H, d, Me); *m/z* 281 (M^+).

Incubation of N-(p-*Tolylacetyl*)-1,2,3,4-*tetrahydroisoquinoline* (**32**) *with* C. elegans.—A solution of *N*-(*p*-tolylacetyl)-1,2,3,4-tetrahydroisoquinoline (3 g) in acetone (75 ml) was added to *C. elegans* in the nutrient medium (15 l, 75 flasks). Incubation was continued for 3 days. The extracted material was chromatographed over neutral alumina (400 g, activity IV).

Elution with ether gave N-(p-*hydroxymethylphenylacetyl*)-1,2,3,4-*tetrahydroisoquinoline* (**33**) (35 mg) as an oil (Found: C, 76.8; H, 6.75; N, 5.0. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%); $\nu_{max.}$ 3 597, 3 387—3 420, and 1 668 cm^{-1}; δ 7.28 (4 H, s, ArH), 7.17 (4 H, s, ArH), 4.78 (2 H, s, 1-H), 4.68 (2 H, s, ArCH_2OH, 3.83 (2 H, s, COCH_2), 3.66 (2 H, m, 4-H), 2.81 (2 H, m, 3-H), and 2.38 (1 H, m, ArCH_2O*H*).

Incubation of N-(p-*Toluoyl*)-2,3,4,5-*tetrahydro*-1H-1-*benzazepine* (**34**) *with* C. elegans.—*N*-(*p*-Toluoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (4.0 g) dissolved in ethanol, was incubated with *C. elegans* grown in the nutrient medium (20 l, 100 flasks) for 3 days at 25 °C. The extracted material was chromatographed over Woelm neutral alumina (400 g, activity IV). Elution with ether gave 5-*hydroxy*-N-(p-*toluoyl*)-2,3,4,5-*tetrahydro*-1H-1-*benzazepine* (**35**) (30 mg), m.p. 144 °C (Found: C, 76.8; H, 6.7; N, 4.9. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%); $\nu_{max.}$ 3 604, 3 320—3 242, and 1 625 cm^{-1}; δ 6.77 (8 H, m, ArH), 4.57 (1 H, m, Ar C*H*OH), 3.13 (3 H, m), 2.23 (3 H, s, Me), and 1.97 (4 H, m, 3-H, 4-H); *m/z* 281 (M^+).

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