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Microbiological Transformations, Part 9[1]. Microbiological Transformations of 1,2,5,6-Tetrahydropyrrolo[3,2,1-i,j]-quinolin-4-one and of Derivatives of 1,2,3,5,6,7-Hexahydropyrido[3,2,1-i,j]quinoline with the Fungus Cunninghamella elegans

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Abstract. Incubation of 1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-3(5H)-one with C. elegans resulted in oxidation at the C-7 benzylic position, whereas 1-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-5(3H)-one gave products resulting from oxidation at both benzylic positions. cis- and trans-1-Hydroxy-3-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-5(3H)-ones were produced on incubation of 5-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-3(5H)-one with C. elegans, in addition to trans-1-hydroxy-5-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-3(5H)-one. Incubation of 1,2,5,6-tetrahydropyrrolo[3,2,1-i,j]quinolin-4-one with C. elegans resulted in dehydrogenation to 1,2-dihydropyrrolo[3,2,1-i,j]quinolin-4-one. Incubation of 2,3,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-1(5H)-one with C. elegans resulted in benzylic attack at C-7.

The majority of simple reduced N-heterocyclic systems undergoing successful microbiological transformations have been shown to possess an amide grouping[2] which is usually a N-benzoyl or N-acetyl function. If, as has been suggested[3], the amide function acts as a means of binding the molecule to the enzyme surface, then the stereochemistry about this function may have some influence on the direction of microbiological oxygenation. Accordingly, 1,2,5,6-tetrahydropyrrolo[3,2,1-i,j]quinolin-4-one (1), substituted 1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-3(5H)-ones (2) in which the amide functions are fixed, and 2,3,6,7-tetrahydropyrido [3,2,1-i,j]quinolin-1(5H)-one (3) which lacks the amide function, were synthesised by standard routes[4,5,6] and incubated with the fungus Cunninghamella elegans. The transformations are summarised in Scheme 1. The structures of the transformed products were based on ^{1}H n.m.r. data (see Experimental Section).

In the incubation of the 1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-3(5H)-ones (2), (7) and (11) with C. elegans, the products result from attack at the benzylic position (C-1 or C-7). This is comparable to the results[9] of incubation of derivatives of 1,2,3,4-tetrahydroquinoline with C. elegans, (summarised in Scheme 2) where benzylic attack was also favoured.

Both cis- and trans-isomers of 1-hydroxy-3-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-5(3H)-one, (12) and (13), are produced from incubation of 5-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-3(5H)-one

(11) with C. elegans. The cis-isomer was found to be optically active as was trans-2-methyl-1(p-toluoyl)-1,2,3,4-tetrahydroquinolin-4-ol (27) produced by incubation of 2-methyl-1,2,3,4-tetrahydroquinoline with C. elegans[9]. 4-Methyl-1-(p-toluoyl)-1,2,3,4-tetrahydroquinoline (23)[9] and 1-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-5(3H)-one (7) gave similar products on incubation with C. elegans, resulting from benzylic hydroxylation at the methyl substituted carbon atoms. It is most likely that the dehydro-derivative (8) is produced by dehydration of the other benzylically hydroxylated compound (10).

Comparison of the incubation of N-acetylindoline (29)[9] and 1,2,5,6-tetrahydropyrrolo[3,2,1-i,j]quinolin-4-one (1) with C. elegans shows hydroxylation in the 3-position of N-acetylindoline compared with dehydrogenation of (1) to give (4). It is most likely, however, that C-6 hydroxylation of (1) occurs first followed by dehydration to (4).

Benzylic attack of 2,3,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-1(5H)-one (3) occurred at C-7, despite the absence of the amide group, but the carbonyl group is an electron rich site suitable for binding to the enzyme.

EXPERIMENTAL

General experimental details, incubation procedures and method of extraction of broth are as given previously[10].

1,2,5,6-Tetrahydropyrrolo[3,2,1-i,j]quinolin-4-one. - β-Chloropropionyl chloride (20 g) was added dropwise to a mixture of indoline (17.9 g) and dry acetone (80 ml). The mixture was boiled for 1 hour and on cooling the solution was poured into stirred dilute hydrochloric acid (200 ml). A crude product formed which was recrystallised from aqueous ethanol in the presence of charcoal to give N-(β-chloropropionyl)indoline. This (14.0 g) was mixed intimately with aluminium chloride (20 g) and heated for fifteen min. On cooling, excess aluminium chloride was decomposed by the addition of a chilled mixture of concentrated hydrochloric acid (20 ml) and water (500 ml). Extraction with ether, followed by removal of the solvent gave a solid which sublimed at 135° (bath) at 2 mmHg to give 1,2,5,6-tetrahydropyrrolo[3,2,1-i,j]quinolin-4-one as needles, m.p. 108-110° (lit.,[4] 112-113°).

1,2,6,7-Tetrahydropyrido[3,2,1-i,j]quinolin-3(5H)-one. - 1,2,3,4-Tetrahydroquinoline (20 g) in anhydrous acetone (80 ml) was refluxed for 2 h with 1-β-chloropropionyl chloride (20 g). The mixture was poured into dilute hydrochloric acid giving an oily product, which was dissolved in chloroform, dried over sodium sulphate and the solvent removed under reduced pressure. The crude product was heated over a small flame with powdered aluminium chloride (40 g) until no more hydrogen chloride was evolved. A dark solid resulted and this was treated with chilled dilute hydrochloric acid. The product was extracted with ether, dried over sodium sulphate and distilled. The distillate crystallised to give 1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-3(5H)-one as a white solid, m.p. 55° (lit.,[5] 55°).

1-Methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-5(3H)-one. - 4-Methylquinoline (50 g) in glacial acetic acid was reduced by hydrogen in the presence of Adams platinum oxide catalyst (1 g). Removal of the catalyst by filtration was followed by basification of the filtrate with 30% sodium hydroxide solution. The solution was extracted with ether, dried (Na_2SO_4) and the solvent removed by distillation to give 4-methyl-1,2,3,4-tetrahydroquinoline as an oil, b.p. 80° at 0.5 mmHg. β-Chloropropionyl chloride (20 g) was added dropwise, with stirring, to 4-methyl-1,2,3,4-tetrahydroquinoline (20 g) in anhydrous acetone (80 ml). The mixture was heated under reflux and, on cooling, was poured into dilute hydrochloric acid. The solution was extracted with chloroform, dried (Na_2SO_4) and the solvent removed under reduced pressure giving 1-(β-chloropropionyl)-4-methyl-1,2,3,4-tetrahydroquinoline (25.5 g, 70%). 1-(β-Chloropropionyl)-4-methyl-1,2,3,4-tetrahydroquinoline (10 g) was heated with powdered aluminium chloride (20 g) until the evolution of hydrogen chloride had ceased. The resulting oil was treated with chilled dilute hydrochloric acid. The product was extracted with chloroform, dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification of the brown viscous product was carried out by applying it in a minimum amount of solvent (chloroform) to the surface of a column of Woelm neutral alumina (900 g, activity IV). Elution with 10% ether in light

petroleum gave 1-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-5(3H)-one as a colourless oil. (Found: C, 77.4; H, 7.7; N, 6.9. $C_{13}H_{15}NO$ requires C, 77.6; H, 7.5; N, 7.0%).

5-Methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-3(5H)-one. - Quinaldine (50 g) in glacial acetic acid (150 ml) was reduced by Adams platinum oxide catalyst (1 g) under hydrogen. The catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent. The remaining solution was basified with 30% sodium hydroxide solution, extracted with chloroform and dried (Na_2SO_4). Evaporation of the solvent gave 2-methyl-1,2,3,4-tetrahydroquinoline as an oil, b.p. 100° at 0.2 mmHg. 2-Methyl-1,2,3,4-tetrahydroquinoline (25 g) in anhydrous acetone (100 ml) was refluxed for 2 h with β-chloropropionyl chloride (25 g). The mixture was poured into dilute hydrochloric acid forming an oily product, which was extracted with chloroform, dried (Na_2SO_4) and the solvent evaporated. Powdered aluminium chloride (50 g) was added to the oily product and the mixture gently heated until the evolution of hydrogen chloride had ceased. Chilled dilute hydrochloric acid was then added to decompose the excess aluminium chloride. The product was extracted with ether, dried (Na_2SO_4) and the solvent removed by distillation. The residue (25 g) was dissolved in a minimum amount of chloroform and applied to a column of Woelm neutral alumina (900 g, activity IV). Elution with 10% ether in light petroleum gave 5-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]-quinolin-3(5H)-one as a colourless oil. (Found: C, 77.8; H, 7.5; N, 6.9. $C_{13}H_{15}NO$ requires C, 77.6; H, 7.5; N, 7.0%).

2,3,6,7-Tetrahydropyrido[3,2,1-i,j]quinolin-1(5H)-one. - A solution of 1,2,3,4-tetrahydroquinoline (266 g) and acetic acid (200 g) was heated and acrylonitrile (200 g) was dropped in over a period of 6 h. The mixture was then heated under reflux overnight. Neutralisation of the reaction mixture with potassium carbonate solution, followed by extraction with chloroform (600 ml) gave N-(β-cyanoethyl)-1,2,3,4-tetrahydroquinoline (297 g, 79.8%) as an oil, b.p. 144° at 0.18 mmHg. A solution of potassium hydroxide (175 g) in water (1.25 l) and the cyano-derivative (123.5 g) was boiled under reflux until a clear solution resulted. Concentrated hydrochloric acid was added to the cooled solution until 1-(β-carboxyethyl)-1,2,3,4-tetrahydroquinoline separated as an oil. The oil was induced to crystallise by the addition of a small amount of ethanol.

Recrystallisation from cyclohexane gave colourless crystals, m.p. 70° (lit.,[6] m.p. 69-71°). This acid (62 g) and dry xylene (450 ml) were added to a mixture of phosphorus pentoxide (45 g) and kieselguhr (22.5 g) and the mixture was boiled under reflux, with stirring for 1 h. The xylene was decanted and the crude product extracted with further portions (2 x 100 ml) of xylene. The combined extracts were evaporated under reduced pressure and distilled. The distillate crystallised to give 2,3,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-1(5H)-one as yellow needles, m.p. 62.5° (lit.[6], 62.5 - 63.5°).

Incubation of 1,2,5,6-tetrahydropyrrolo[3,2,1-i,j]quinolin-4-one (1) with Cunninghamella elegans. - 1,2,5,6-Tetrahydropyrrolo[3,2,1-i,j]quinolin-4-one (2.2 g) in acetone (35 ml) was added to Cunninghamella elegans in the nutrient medium (7 l, 35 flasks). Incubation was continued for 4 d. The extracted material was chromatographed over Woelm neutral alumina (100 g, activity IV). Elution with ether gave 1,2-dihydropyrrolo[3,2,1-i,j]quinolin-4-one (4) (10 mg) as colourless needles, m.p. 150°. (Found: C, 77.0; H, 5.5; N, 8.0. $C_{11}H_9NO$ requires C, 77.2; H, 5.3; N, 8.2%); νmax 1642 cm^{-1}; δ 7.69 (1H, d J=9Hz, 5-H), 7.26 (3H, m, aromatic), 6.67 (1H, d J=9Hz), , 6-H), 4.46 (2H, t, 2-H) and 3.42 (2H, t, 1-H), m/e 171 (M^+).

Incubation of 1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-3(5H)-one (2) with Cunninghamella elegans. - A solution of 1,2,6,7-tetrahydropyrido[3,2,1-i,j]-quinolin-3(5H)-one (3.0 g) in acetone (75 ml) was added to Cunninghamella elegans in the nutrient medium (15 l, 75 flasks). After incubation for 3 d, the material was extracted and chromatographed over alumina (400 g, activity IV).

Elution with 50% ether in light petroleum gave 2,3,6,7-tetrahydropyrido-[3,2,1-i,j]quinolin-1,5-dione (5) (56 mg), m.p. (ethanol) 119°. (Found: C, 71.7; H, 5.5; N, 6.9. $C_{12}H_{11}NO_2$ requires C, 71.6; H, 5.5; N, 7.0%); νmax 1665 and 1685 cm^{-1}; δ 7.83 (1H, d, 10-H), 7.13 (2H, m, aromatic), 4.30 (2H, t, 3-H) and 2.76 (6H, m, 2-H, 6-H, 7-H), m/e 201 (M^+).

Elution with ether gave 1-hydroxy-1,2,6,7-tetrahydro[3,2,1-i,j]quinolin-5(3H)-one (6) (92 mg), m.p. 123°. (Found: C, 70.9; H, 6.5; N, 6.8. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9%); νmax 3560, 3410-3370 cm^{-1}; δ (270 MHz) 7.03 (3H, m, aromatic), 4.78 (1H, s, ArCHOH), 4.10 (1H, ($J_{3eq,2ax}$ 5 Hz, $J_{3eq,2eq}$ 5 Hz, $J_{3eq,3ax}$ -15 Hz, 3_{eq}-H), 3.65 (1H, m, 3_{ax}-H), 3.37 (1H, s, ArCHOH), 2.80 (2H, m, 6-H), 2.55 (2H, m, 7-H), 2.00 (2H, m, 2-H), m/e 203 (M^+).

Incubation of 1-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-5(3H)-one (7) with Cunninghamella elegans. - 1-Methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]-quinolin-5(3H)-one (2.5 g) in ethanol (63 ml) was added to Cunninghamella elegans in the nutrient medium (12.5 l, 63 flasks). After incubation for 3-4 d, the material was extracted and chromatographed over alumina (500 g, activity IV).

Elution with 20% ether in light petroleum gave 1-methyl-1,2-dihydropyrido-[3,2,1-i,j]quinolin-5(3H)-one (8) (97 mg) as an oil. (Found: C, 78.4; H, 6.3; N, 7.0. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.6; N, 7.0%); νmax 1648 cm^{-1}; δ 7.71 (1H, J=9Hz, 6-H), 7.33 (3H, m, aromatic), 6.73 (1H, J=9Hz, 7-H) 4.25 (2H, m, 3-H), 3.00 (1H, m, 1-H), 2.15 (2H, m, 2-H) and 1.42 (3H, d, CH_3).

Elution with 50% ether in light petroleum gave 1-hydroxy-1-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-5(3H)-one (9) (84 mg) an an oil. (Found: C, 72.0; H, 7.0; N, 6.3. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.45%); νmax 3590, 3550 and 1657 cm^{-1}; δ 7.60-6.97 (3H, m, aromatic), 3.98 (2H, m, 3-H), 2.77 (4H, m, 6-H, 7-H), 2.50 (1H, broad s, OH), 2.03 (2H, m, 2-H) and 1.62 (3H, s, CH_3).

Elution with ether gave trans-1-hydroxy-7-methyl-1,2,6,7-tetrahydropyrido-[3,2,1-i,j]quinolin-3(5H)-one (10) (32 mg) as an oil. (Found: C, 71.7; H, 7.3; N, 6.3. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.45%). νmax 3602, 3300-3405 and 1659 cm^{-1}; δ (270 MHz) 7.32-6.87 (3H, m, aromatic), 4.70 (1H, t, ArCHOH), 3.90 (1H, m, 5_{eq}-H, 3.60 (1H, m, 5_{ax}-H), 2.57 (2H,) ($J_{2ax,2eq}$ -10 Hz, $J_{2ax,1'eq}$ 5 Hz 2-H), 2.97 (3H, m, 6-H, 7-H) and 1.28 (3H, d, CH_3).

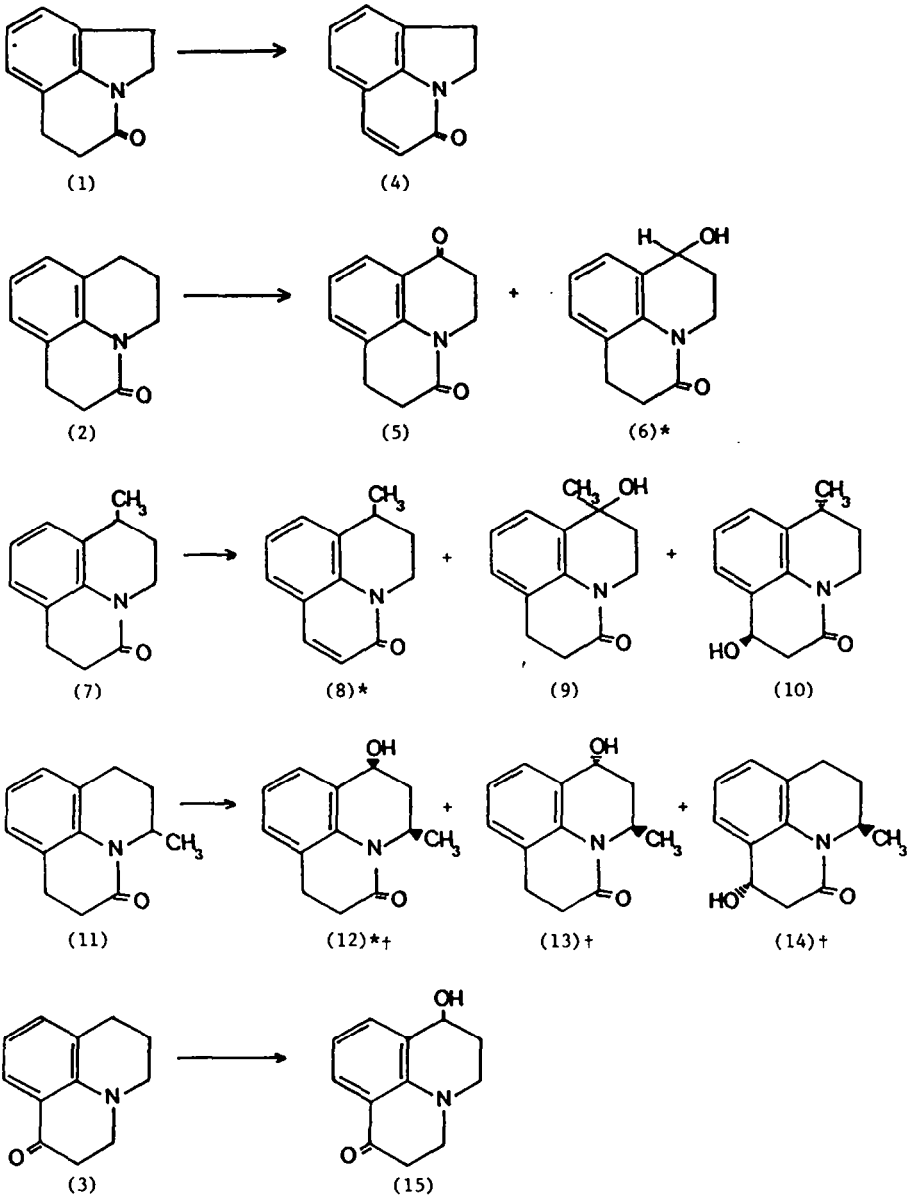
Incubation of 5-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-3(5H)-one (11) with Cunninghamella elegans. - 5-Methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]-quinolin-3(5H)-one (3 g) in ethanol (75 ml) was added to Cunninghamella elegans in the nutrient medium (15 l, 75 flasks). Incubation was continued for 3 d. The combined extracted material (4 g) was chromatographed over neutral alumina (400 g, activity IV).

Elution with 50% ether in light petroleum gave cis-1-hydroxy-3-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-5(3H)-one (12) (251 mg), m.p. (ethanol) 102-103°. (Found: C, 71.8; H, 6.7; N, 6.2. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.45%). νmax 3608, 3200-3100 and 1658 cm^{-1}; δ (270 MHz) 7.23 (3H, m, aromatic), 4.99 (1H, m, 3-H), 4.72 (1H, t, CHOH) 2.80-2.55 (4H, m, 6-H, 7-H), 2.37 (1H, s, ArCHOH), 2.10 (2H, m, 2-H) and 1.57 (3H, d, CH_3), m/e 217 (M^+). $[\alpha]_D^{25}$ = +62.7°.

Elution with 75% ether in light petroleum gave trans-1-hydroxy-3-methyl-1,2,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-5(3H)-one (13) (30 mg) as an oil. (Found: C, 71.6; H, 7.0; N, 6.55. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.45%); νmax 3590, 3420-3390 and 1660 cm^{-1}; δ (270 MHz) 7.25 (3H, m, aromatic), 5.0 (1H, m, 3-H), 4.88 (1H, $J_{1'ax',2ax}$ 11 Hz, $J_{1'ax',2eq}$ 5.5 Hz, CHOH), 2.67 (4H, m, 6-H, 7-H) 2.34 (1H, s, ArCHOH), 2.20 (1H, $J_{2eq,2ax}$ -11 Hz, $J_{2eq,1'ax'}$ 5.5 Hz, $J_{2eq,3eq}$ 3.0 Hz, 2_{eq}-H), 1.82 (1H, $J_{2ax,1'ax'}$ 11 Hz, $J_{2ax,2eq}$ -11 Hz, $J_{2ax,3eq}$ 4.5 Hz, 2_{ax}-H), 1.22 (3H, d, CH_3), m/e 217 (M^+).

Elution with ether gave trans-1-hydroxy-5-methyl-1,2,6,7-tetrahydropyrido-[3,2,1-i,j]quinolin-3(5H)-one (14) (26 mg) as an oil. (Found: C, 72.0; H, 6.75; N, 6.2. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.45%). νmax 3600, 3400-3360 and 1658 cm^{-1}; δ 7.24 (3H, m, aromatic), 4.95 (1H, q, 5-H), 4.80 (1H, $J_{1'ax',2ax}$ 10 Hz, $J_{1'ax',2eq}$ 5 Hz, 1_{ax}-H), 2.78 (2H, m, 7-H), 2.51 (2H, m, 2-H). 2.33 (1H, s, ArCHOH), 2.33 (1H, s, ArCHOH), 1.80 (2H, m, 6-H), 1.12 (3H, d, CH_3).

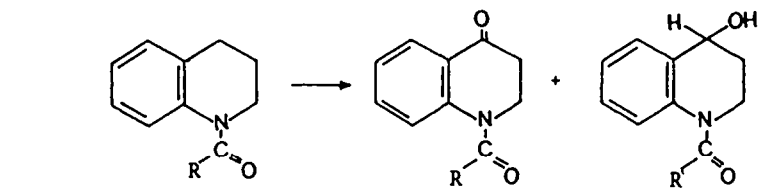
Incubation of 2,3,6,7-tetrahydropyrido[3,2,1-i,j]quinolin-1(5H)-one (3) with Cunninghamella elegans. - A solution of 2,3,6,7-tetrahydropyrido[3,2,1-i,j]-quinolin-1(5H)-one (1.5 g) in acetone (25 ml) was added to Cunninghamella elegans in the nutrient medium (5 l, 25 flasks). Incubation was continued for 3 d. Extraction followed by chromatography over Woelm alumina (100 g, activity IV) gave, on elution with ether 7-hydroxy-2,3,6,7-tetrahydropyrido[3,2,1-i,j]-quinolin-1(5H)-one (15) (160 mg) as yellow crystals, m.p. 109°. (Found: C, 70.7; H, 6.65; N, 6.8. $C_{12}H_{13}NO$ requires C, 70.9; H, 6.4; N, 6.9%). νmax 3580, 3400 and 1664 cm^{-1}; δ 7.77 (1H, d, aromatic), 7.38 (1H, d, aromatic), 6.68 (1H, t, aromatic), 4.75 (1H, t, CHOH), 3.33 (4H, m, 3-H, 5-H), 2.71 (2H, m, 2-H), 2.40 (1H, s, CHOH) and 2.02 (2H, m, 6-H).



Scheme 1 - Products from the incubations of 1,2,5,6-tetrahydropyrrolo [3,2,1-i,j]quinolin-4-one and of 1,2,3,5,6,7-hexahydropyrido [3,2,1-i,j]quiniline

* Denotes major product.

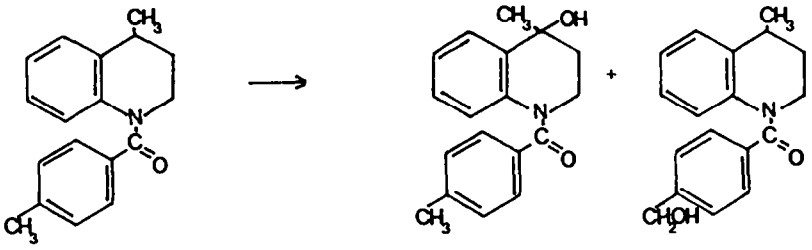
† In compounds (12)-(14) the expectation[7] is for the methyl group to adopt the axial orientation. This was confirmed by the low field ^1H n.m.r. absorption of 3-H (deshielded by amide carboxyl[8]) and the narrow width of the 3-H signals.



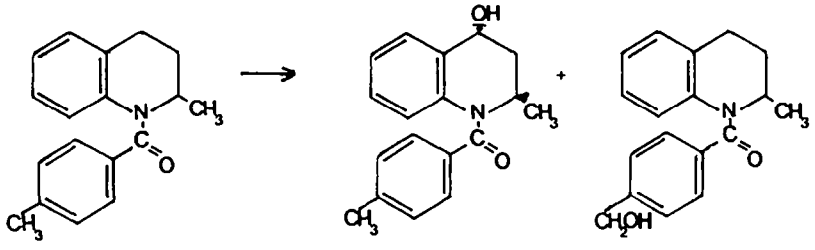
(16) R = Ph
(19) R = p-tolyl
(21) R = Me

(17) R = Ph
(20) R = p-tolyl
(22) R = Me

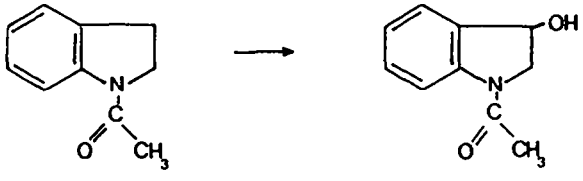
(18) R = Ph



(23) (24) (25)



(26) (27) (28)



(29) (30)

Scheme 2 - Product from the incubation of 1,2,3,4,-tetrahydroquinolines and of N-acetyl-indoline with C. elegans

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