Synthesis of Pyrano[3,2-*c*]quinolin-5-one Alkaloids: Veprisine, 7-Dimethylallyloxy-*N*-methylflindersine and *cis*-3,4-Dihydroxy-7-methoxy-2,2,6-trimethyl-3,4,5,6-tetrahydro-2*H*-pyrano[3,2-*c*]quinolin-5-one

J. Chem. Research (S), 1997, 184–185
J. Chem. Research (M), 1997, 1201–1215

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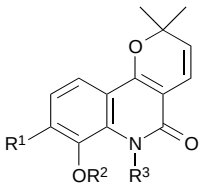
Condensation of the appropriate 4-hydroxyquinolin-2-ones with 3-methylbut-2-enal gave pyrano[3,2-*c*]quinolin-5-ones which were further elaborated to the three alkaloids named in the title.

Veprisine (**1a**), 7-dimethylallyloxy-*N*-methylflindersine (**1b**), 7-hydroxy-*N*-acetyloxymethylflindersine (**1c**) and the *cis*-diol of 7-methoxyflindersine (**3**) are examples of pyrano[3,2-*c*]quinolin-5-ones which have been isolated in recent years from plant species of the Rutaceae family.[1–4] Most of the viable syntheses of these alkaloids involve the cyclisation of the corresponding 3-prenyl-4-hydroxyquinolin-2-ones.



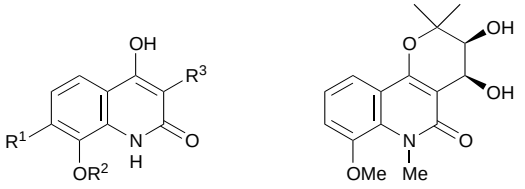
1

a R^1 = OMe, R^2 = Me, R^3 = Me
b R^1 = H, R^2 = $CH_2CH{=}CMe_2$, R^3 = Me
c R^1 = H, R^2 = H, R^3 = CH_2OAc
d R^1 = H, R^2 = H, R^3 = Me
e R^1 = H, R^2 = CH_2Ph, R^3 = H
f R^1 = H, R^2 = H, R^3 = H
g R^1 = OMe, R^2 = Me, R^3 = H
h R^1 = H, R^2 = Me, R^3 = H
i R^1 = H, R^2 = Me, R^3 = Me
j R^1 = H, R^2 = $SiMe_2Bu^t$, R^3 = H
k R^1 = H, R^2 = CH_2Ph, R^3 = Me
l R^1 = H, R^2 = $CH_2CH{=}CMe_2$, R^3 = H
m R^1 = H, R^2 = THP, R^3 = H
n R^1 = H, R^2 = THP, R^3 = Me
o R^1 = H, R^2 = THP, R^3 = CH_2OAc

Fig. 1

We now report the successful synthesis of the pyrano[3,2-*c*]quinolin-5-one alkaloids named in the title from the 4-hydroxyquinolin-2-ones **2** and 3-methylbut-2-enal by utilisation of the method of De Groot and Jansen[7] for the formation of 2*H*-pyrans by one-step condensation of an α,β-unsaturated aldehyde with 1,3-diketones.

The two starting 8-methoxy- and 7,8-dimethoxy-4-hydroxyquinolin-2-ones (**2b** and **2a** respectively) were prepared by the condensation of the corresponding aromatic amines and malonic acid in the presence of phosphorus oxychloride.[8] The 8-benzyloxy-4-hydroxyquinolin-2-one (**2c**) could not be prepared this way since the acidic reaction conditions would result in the removal of the benzyl group. The alternative method to prepare 8-benzyloxy-4-hydroxyquinolin-2-one by the condensation of 2-benzyloxyaniline with diethyl malonate was unsuccessful.



2 **3**

a R^1 = OMe, R^2 = Me, R^3 = H
b R^1 = H, R^2 = Me, R^3 = H
c R^1 = H, R^2 = CH_2Ph, R^3 = H
d R^1 = H, R^2 = H, R^3 = H
e R^1 = H, R^2 = Me, R^3 = CH_2Ph

Fig. 2

The modified scheme involved the synthesis of 7-hydroxyflindersine (**1f**) which could be prepared by the condensation of 3-methylbut-2-enal with 4,8-dihydroxyquinolin-2-one (**2d**). Demethylation of 8-methoxy-4-hydroxyquinolin-2-one (**2b**) to **2d** was unsuccessful. Synthesis of **2d** was finally achieved by the aluminium chloride demethylation and debenzylation of 8-methoxy-3-benzyl-4-hydroxyquinolin-2-one (**2e**).[9]

Condensation of quinolin-2-ones **2a**, **2b** and **2d** with 3-methylbut-2-enal in refluxing pyridine in the presence of anhydrous magnesium sulfate gave the desired pyrano[3,2-*c*]quinolin-5-ones **1g**, **1h** and **1f** in yields ranging from 44 to 69%.

N-Methylation of 7,8-dimethoxyflindersine (**1g**) using NaH–MeI gave veprisine (**1a**) in 90% yield. This synthesis is the most efficient to date with an overall yield of 51% for the three-step synthesis. The spectral data obtained for **1a** corresponded to literature values.[1]

The *cis*-diol **3** was synthesised by the osmium tetroxide oxidation of 7-methoxy-*N*-methylflindersine (**1i**), formed by the methylation of 7-methoxyflindersine (**1h**). The spectral data obtained corresponded to the structure **3** for the oxidation product. No literature data are available in order to make a comparison.

Since the synthesis of 7-dimethylallyloxy-*N*-methylflindersine (**1b**) from 7-hydroxyflindersine (**1f**) would involve *O*-alkylation and *N*-methylation and methylation by most conditions would result in a dimethylated product, protection of the hydroxy group is necessary prior to *N*-methylation. The first-choice protecting group was the *tert*-butyldimethylsilyl group and under normal silylating conditions **1f** gave 7-*tert*-butyldimethylsilyloxyflindersine (**1j**) in 42% yield. *N*-Methylation with LDA and MeI was unsuccessful and methylation under more basic conditions resulted in desilylation giving **1f** as the major product.

The benzyl group was the second-choice protecting group and 7-benzyloxyflindersine (**1e**) was prepared in a modest 20% yield with NaOEt–$PhCH_2Cl$. *N*-Methylation of **1e** with NaH–MeI yielded 7-benzyloxy-*N*-methyflindersine (**1k**) but

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deprotection by triphenylmethyl fluoroborate could not be achieved.

At this stage it was decided that direct dimethylallylation might yield a reasonable amount of the *O*-allylated derivative which could then be *N*-methylated to give **1b**. Treatment of **1f** with 1-bromo-3-methylbut-2-ene in the presence of sodium methoxide gave 7-dimethylallyloxyflindersine (**1l**) in very low yield which was *N*-methylated to **1b**. Spectral data confirmed the formation of **1l** and **1b**.

Since the overall yield for the synthesis of **1b** by the above method was very poor, it was decided to look for another protecting group for the hydroxy function and the tetrahydropyranyl group was an obvious choice. Tetrahydropyranylation of **1f** with dihydropyran and toluene-*p*-sulfonic acid was achieved in 59% yield. 7-Tetrahydropyranyloxyflindersine (**1m**) was *N*-methylated nearly quantitatively to 7-tetrahydropyranyloxy-*N*-methylflindersine (**1n**). Deprotection of **1n** was achieved by stirring in a 5% solution of methanolic hydrochloric acid to yield 7-hydroxy-*N*-methylflindersine (**1d**). **1b** was finally prepared by reaction of **1d** with 1-bromo-3-methylbut-2-ene and anhydrous K_2CO_3 in dry acetone. All the structures for the intermediates and the final product were established by mass spectroscopy and ^{1}H NMR. The spectral data were in complete agreement with literature values reported for the natural product.[2]

Synthesis of 7-hydroxy-*N*-acetyloxymethylflindersine (**1c**) could not be achieved since *N*-alkylation of **1m** with chloromethyl acetate under a number of different conditions was unsuccessful.

Techniques used: ^{1}H NMR, IR, MS

References: 10

Figures: 2

Received, 2nd December 1996; Accepted, 19th February 1997
Paper E/6/08110J

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