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# SYNTHESES AND STEREOCHEMISTRY OF 4-HYDROXY TETRAHYDROISOQUINOLINES IN THE 1-BENZYL AND 1-PHENETHYL SERIES. EFFICIENT ROUTES TO ISOPAVINES AND HOMOISOPAVINES

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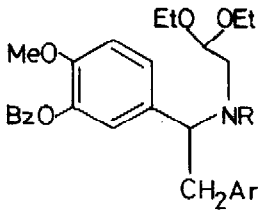
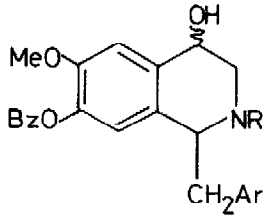
*Summary:* The title compounds have been prepared in high yield via cyclisation of urethane acetals.

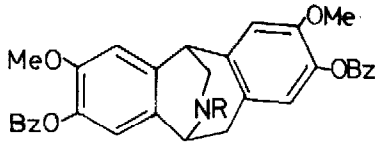
1-Benzylisoquinoline alkaloids oxygenated at C-4 occur naturally in the protoberberine[1], Erythrina[2] and aporphine[3] series, and may be biosynthetic intermediates en route to the isopavine and aromatic isoquinoline alkaloids[4]. Also hydroxylation at C-4 of a 1-phenethylisoquinoline alkaloid may be a key step in the biosynthesis of colchicine. 4-Hydroxy-1-benzyltetrahydroisoquinolines (THIQ's) have been obtained by hydroboration of a dihydroisoquinoline[6] (not readily accessible) and, very recently, by 1-alkylation of a 4-hydroxy-N-nitroso THIQ.[7] We now report a synthesis of diastereomeric 4-hydroxy THIQ's[8] which we believe to have considerable potential for studies of alkaloid synthesis and biosynthesis, and the first assignment of relative stereochemistry in the 1-benzyl and 1-phenethyl series.[9]




(1) R = Me
(5) R = $CO_2Et$




(3) R = Me
(7) R = $CO_2Et$

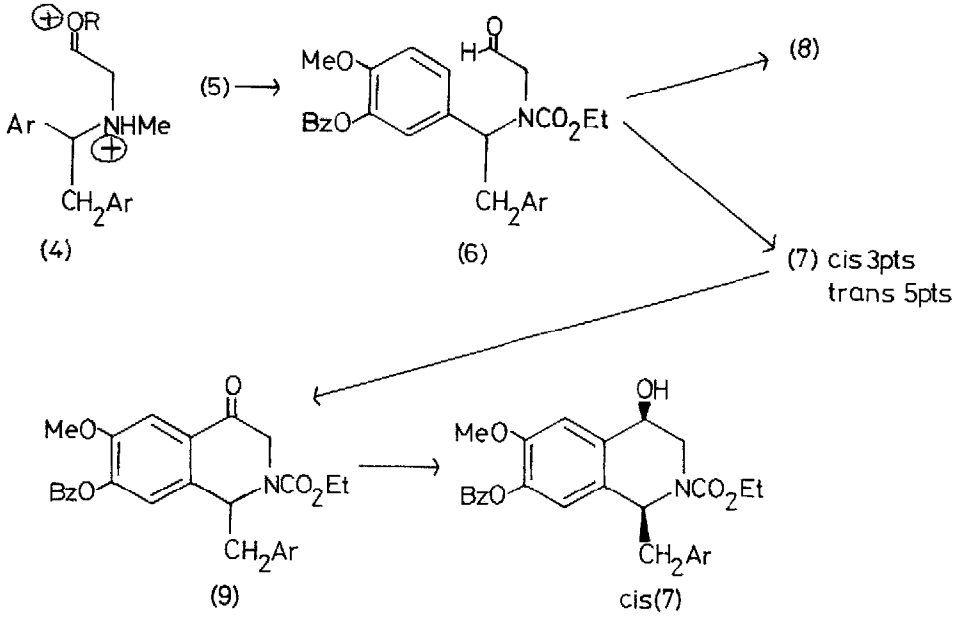



(2) R = Me
(8) R = $CO_2Et$

Ar = 3-benzyloxy-4-methoxyphenyl

Acid-catalysed cyclisation of amino-acetals such as (1) is a standard procedure[10] for the synthesis of isopavines, e.g. (2). The 4-hydroxy THIQ (3) is surely an intermediate in this transformation but its isolation has been reported on only a single occasion when a nitro group in Ar inhibited the second cyclisation.[11] In the hope of obtaining the acid-sensitive intermediate (3), the amino-acetal (1) was treated under a wide range of conditions and a mixture of cis and trans (3) was indeed obtained in 40% yield by using acetone/conc. HCl (5:2) at room temperature. The isopavine (2) was also formed and its yield increased under more vigorous conditions at the expense of (3); however the acetal (1) was virtually inert under milder conditions and the product ratio could not be further improved.

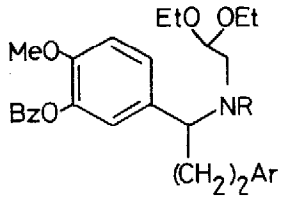
Because of the basic nitrogen in (1), the acetal hydrolysis step must proceed via the doubly-charged ion (4). Masking the basic nitrogen permits hydrolysis at lower acidity and isopavine formation can be avoided. Thus hydrolysis of the urethane-acetal (5) using $HCO_2H$/acetone (1:3) gave the aldehyde (6). Cyclisation of (6) (6 N $H_2SO_4$/acetone (3:5) then gave a 3:5 mixture of cis and trans alcohols[12] (7) in 89% yield. Under more acidic conditions ($HCO_2H$, neat, 1h.) the reaction proceeded further to generate the isopavine (8) in quantitative yield. Isopavine (8) is also formed in quantitative yield from the acetal precursor (5) ($HCO_2H$, neat, 1hr.).




Ar = 3-benzyloxy-4-methoxyphenyl

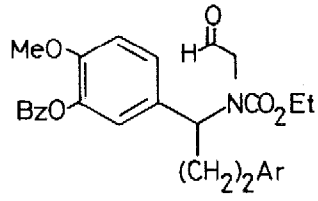
The identity of alcohols (7) was proved by acetylation ($Ac_2O$/py) and by oxidation (pyridinium chlorochromate/$CH_2Cl_2$) to the ketone (9). Borohydride reduction of (9) gave only the high Rf isomer (t.l.c. $SiO_2/Et_2O$) of (7) and this product is assigned the cis configuration on mechanistic grounds, an assignment which is consistent with the $^1$H-n.m.r. spectra of the entire set of 4-hydroxy THIQ's described herein.

In the 1-phenethyl series treatment of the N-methyl acetal (10) with 6N HCl had given a mixture of 4-hydroxy THIQ isomers and homoisopavine isomers.[13,14] By using urethane acetals (11a,b) as substrates the intermediate aldehydes (12a,b) could again be isolated by mild acidic hydrolysis. Cyclisation of (12a,b) then gave a high yield of either a mixture of cis and trans alcohols[15] (13a,b) or the homoisopavines (14a,b) according to the choice of reaction conditions. The homoisopavines (14a,b) could again be prepared in high yield by direct cyclisation of (11a,b), (see above) and the cis/trans mixtures of alcohols (13a,b) could be converted into pure cis (13a,b) (high Rf isomer in each case) by borohydride reduction of the corresponding ketone.

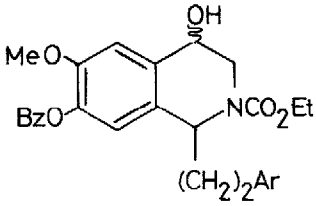



(10) R=Me, Ar=3,4-dimethoxy-5-benzyloxyphenyl

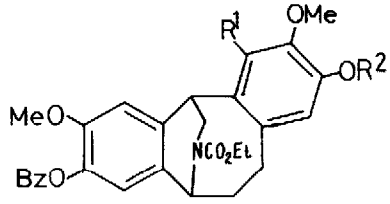
(11a)
(11b) R=$CO_2Et$




(12a)
(12b)




(13a)
(13b)




(14a) $R^1$=H, $R^2$=Bz

(14b) $R^1$=OMe, $R^2$=Me

Series a Ar=3-benzyloxy-4-methoxyphenyl
Series b Ar=3,4,5-trimethoxyphenyl

Urethanes (7) and (13a,b) have been reduced to the corresponding N-methyl derivatives ($LiAlH_4$/THF) and this correlation allows a stereochemical assignment

for the isomers of this series. Also each 4-hydroxy THIQ has been debenzylated by catalytic hydrogenolysis ($H_2$/Pd/THF). Further studies on the reactions of these interesting isoquinolines are in progress.

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14. cf. S.F. Dyke and P. Warren, Tetrahedron, 1979, 35, 1857.
15. Cis alcohols: H-5, $\delta$ 7.05 - 7.09: trans alcohols: $\delta$ 6.81 - 6.84.


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