FREE-RADICAL CYCLIZATION OF 2-(*o*-BROMOBENZOYL)-1-(2-PROPENYL)-1,2,3,4-TETRAHYDROISOQUINOLINE: SYNTHESIS OF 7-METHYL-6,7,8,9-TETRAHYDRO-5*H*-BENZOCYCLOHEPTEN-5,8-IMINE

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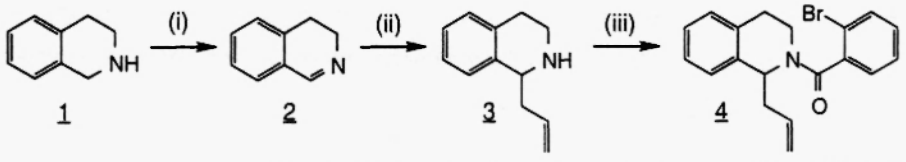
Abstract: Free-radical cyclization of 2-(*o*-bromobenzoyl)-1-(2-propenyl)-1,2,3,4-tetrahydroisoquinoline, mediated with tributyltin hydride, proceeded to give *N*-benzoyl-7-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5,8-imine. One diastereomer was separated and the amide hydrolysed with aqueous hydrochloric acid to give 7-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5,8-imine.

Whilst working with the readily available model system, 1-(2-propenyl)-1,2,3,4-tetrahydroisoquinoline 3, we have investigated a series of reactions including a free-radical cyclization to the benz-fused tropane system 5. Reporting of our results in this area has been prompted by the recent publication of related work by Ikeda *et al* (1).

2-(*o*-Bromobenzoyl)-1-(2-propenyl)-1,2,3,4-tetrahydroisoquinoline 4 was prepared from commercially available 1,2,3,4-tetrahydroisoquinoline 1 in a 3-step sequence (scheme 1) and with a total yield of 49%. Compound 4 can also be made in a one-pot reaction from 2 (80% yield) by direct *N*-acylation of the intermediate zinc precursor of 3.

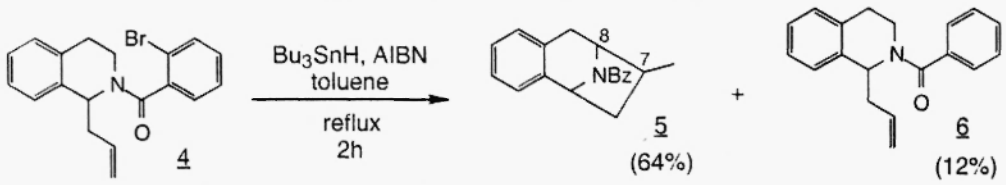
Scheme 1: Preparation of the cyclization precursor 4.



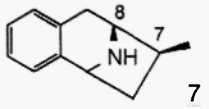
Reagents and Conditions: (i) NBS, CH_2Cl_2, r.t., 1.2h (2) (ii) allyl bromide, Zn, THF, 0°C to r.t., 2d (iii) *o*-bromobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, r.t., 4.5h.

A solution of tributyltin hydride, and AIBN free-radical initiator, in toluene was slowly added to a refluxing solution of 2-(*o*-bromobenzoyl)-1-(2-propenyl)-1,2,3,4-tetrahydroisoquinoline 4 in toluene. After further heating, work-up and column chromatography, a 64% yield of the desired product, *N*-benzoyl-7-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5,8-imine 5. was obtained together with debrominated *N*-benzoyl-1-(2-propenyl)-1,2,3,4-tetrahydroisoquinoline 6 (12%) (scheme 2).

Scheme 2: Free-radical cyclization of 4.



Although cyclization gave exclusively the 5-*exo-trig* product, a mixture of diastereomers (ratio 2:1) was obtained. These results are consistent with those from the analogous piperidine system reported by Ikeda *et al.* (3). Preference for H-transfer from the 3-position to the aryl radical initially generated from 4 can be explained in terms of the likely preferred amide rotamer being as shown in 4. The major diastereomer was isolated by multi-sweep preparative thin layer chromatography. The *exo* cyclised structure was clearly evidenced in the ^1H NMR of this diastereomer by the methyl doublets at 1.02ppm and 1.19ppm for the minor and major rotamers respectively. Debenzoylation of this diastereomer with aqueous hydrochloric acid gave the free amine, 7-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5,8-imine 7. 2D NMR experiments (HSQC and HMBC) were used to assign the ^1H and ^{13}C resonances of this compound. The relative stereochemistry across the C7-C8 bond has been assigned as *cis* due to the H-8 resonance at 3.39ppm being a doublet ($J_{8,9}$=4.9Hz), and the H-7 proton a doublet of quartets ($J_{7,6}=J_{7,Me}$=6.8Hz) at 2.10ppm. High resolution mass spectrometry (chemical ionisation) confirmed the molecular formula of $C_{12}H_{15}N$ for 7 (calculated for $(M+H)^+$ 174.1283, measured 174.1280).



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A short, convenient and potentially flexible synthesis has thus been developed to the pharmacologically interesting (4) reduced 5*H*-benzocyclohepten-5,8-imine system.

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References:

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