An Expedient Synthesis of Benzo[h]quinazolin-4(3H)-one: Structure of Samoquasine A Revisited

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Received 24 June 2003

SYNTHESIS 2003, No. 15, pp 2292–2294
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Abstract: An expedient four-step synthesis of benzo[h]quinazolin-4(3H)-one (1) starting from 1-tetralone is reported. The claimed identity of samoquasine A with perlolidine (4) has been discussed in the light of the present synthesis.

Keywords: thiourea, condensation, heterocycles, natural products, sulfur, dehydrogenations

Benzo[h]quinazolines, their 5,6-dihydro derivatives and the corresponding quinazolin-4(3H)-ones constitute a small group of heterocycles which are important either from the synthetic viewpoint,1a–e e.g. for the preparation of the triazasteroidal skeleton,1b or as bioactive compounds, e.g. antitumor or antidepressive agents2a,b and inhibitors of platelet aggregation.3 A new cytotoxic alkaloid, designated samoquasine A, was isolated by a Japanese group from the seeds of custard apple (Annona squamosa) and was identified as ‘3,4-dihydrobenzo[h]quinazolin-4-one’ (1) (Figure 1) from detailed spectroscopic analysis.4 Although the 2-methyl (2) and 2-ethyl (3) derivatives of 1 are known synthetically,1d the parent molecule 1 appeared not to have been synthesised until then, which prompted a Taiwanese group to report a new synthesis of 1–3.5 They concluded in this report that samoquasine A was definitely different from 1 and also from perlolidine (4), isolated earlier from rye grass6a,b and this time from A. squamosa.5 They further suggested the benzo[j]phthalazin-4(3H)-one structure (5) for samoquasine A.

In view of this structural controversy and the reported low overall yield (34%) of synthetic 1, we have developed a new and expedient synthesis of 1 in a higher overall yield, which we report herein.

Since the most general pyrimidine ring synthesis involves the reaction of a 1,3-dicarbonyl compound with a suitable N–C–N fragment,7 we planned to condense an appropriate β-keto ester with thiourea and desulphurise the resulting 2-mercapto-4-pyrimidinone. Following Krapcho’s method of β-ethoxycarbonylation of cycloheptanone,8 1-tetralone was converted to its 2-methoxycarbonyl derivative (6) in excellent yield by treatment with sodium hydride and dimethyl carbonate. Compound 6 was found from 1H NMR data to exist as an equimolar mixture of the keto and enol tautomers (see Experimental). Condensation of 6 with thiourea efficiently provided 1,2,5,6-tetrahydro-2-thioxobenzo[h]quinazolin-4(3H)-one (7). Desulphurisation of 7 by Raney nickel (W2) produced the 5,6-dihydro derivative of 1, i.e. 5,6-dihydrobenzo[h]quinazolin-4(3H)-one (8) in very good yield. Subsequent dehydrogenation of 8 by 10% palladised charcoal in refluxing ortho-dichlorobenzene furnished the target molecule (1) in an overall yield of 43.5% starting from 1-tetralone (Scheme 1). The 1H and 13C NMR spectral data of our final product agreed quite well with those reported for 1 by the Taiwanese group.5

Our work reaffirms the non-identity of samoquasine A with 1, in agreement with the Taiwanese observation. Pertinently, the original Japanese workers have published in

![Figure 1](image_url)

Scheme 1  Reagents and conditions: i) NaH, Me3CO3, 115 °C, 5 h; HCl (3 M); ii) NaOMe, MeOH, SC(NH2)2, reflux, 10 h; glacial HOAc; iii) Raney Ni (W2), EtOH, reflux, 4 h; iv) 10% Pd–C, o-C6H4Cl2, reflux, 48 h

SYNTHESIS 2003, No. 15, pp 2292–2294
Advanced online publication: 29.09.2003
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the meantime a brief statement (in ‘Additions and Corrections’ of a journal)\textsuperscript{10} that they identified samoquasine A as perlodilone (4) and, therefore, withdrew this trivial name samoquasine A. This identity remains highly doubtful to us particularly on the following grounds: (a) samoquasine A was reported not to melt up to 300 °C whereas perlodilone had a melting point of 280–282 °C. (b) samoquasine A was freely soluble in chloroform, but the NMR data of perlodilone could not be measured in CDCl\textsubscript{3} and had to be recorded in pyridine-d\textsubscript{6}. and (c) samoquasine A displayed a \textsuperscript{13}C NMR signal at δ = 101.6 but perlodilone did not record any signal in this region.

To conclude, we have developed a new, expedient and more efficient synthesis of 1, which sheds some light on the existing structural controversy about samoquasine A and can also be utilised for the preparation of 4-amino- or alkylaminobenzo[h]quinazolines and benzo[h]-quinazolin-2,4-diones.

Mps were determined on a Toshniwal apparatus and are uncorrected. IR spectra were recorded on a Nicolet Impact 410 spectrophotometer, LR EI-MS in AEI MS 30 and JEOL JMS-AX505HA, HR FAB-MS (using m-nitrobenzyl alcohol as liquid matrix) in JEOL JMS-700 MS. Spectral analyses. Column chromatography was performed on silica gel (60–120 mesh, Qualigens, India) and TLC was carried out on silica gel G (Merck, India) plates. PE refers to petroleum ether boiling at 60–80 °C.

**Methyl 1-Oxo-1,2,3,4-tetrahydro-naphthalene-2-carboxylate (6)**

Sodium hydride (2.74 g, 60% suspension in mineral oil) was freed by washing with hot EtOAc (2 mL) and HCl (3 M; 100 mL), and extracted with Et\textsubscript{2}O (3 × 10 mL). The resulting cake was heated at 115°C for 5 h. The organic phase was washed successively with sat. aq NaHCO\textsubscript{3} (3 × 10 mL), and H\textsubscript{2}O, dried (Na\textsubscript{2}SO\textsubscript{4}) and crystallised from EtOAc to afford 6. Yield: 0.303 g (85%); white needles; mp 230–234°C. IR (Nujol): 3314, 1652, 1559, 1222, 1149, 751 cm\textsuperscript{–1}.

**5,6-Dihydrobenzo[f]quinazolin-4(3H)-one (8)**

Raney Ni (W2)\textsuperscript{11} (two spatulas) was added to a solution of 1-tetralone (4.38 g, 24 mmol) in dehydrated EtOH (20 mL) and the mixture was refluxed for 10 h. The mixture was filtered hot through a Celite bed and the solvent was distilled off and the residue was dissolved in hot H\textsubscript{2}O, dried (Na\textsubscript{2}SO\textsubscript{4}) and crystallised from EtOAc to give 8. Yield: 0.336 g (85%); white needles; mp 234°C.

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H NMR (CDCl\textsubscript{3}): δ = 12.426 (s, 1 H, NH), 8.144 (s, 1 H, H-2), 8.312 (d, 1 H, J = 7 H, H-10), 7.344 (t, 1 H, J = 6.5 H, H-8), 7.371 (t, 1 H, J = 8 H, H-9), 7.261 (d, 1 H, J = 6.5 H, H-7), 2.825 (t, 2 H, J = 7.5 H, CH\textsubscript{2}-6), 2.646 (t, 2 H, J = 7.5 H, CH\textsubscript{2}-5).
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13 C NMR (DMSO-d\textsubscript{6}): δ = 161.9 (C-4), 154.3 (C-10b), 148.3 (CH-2), 139.0 (C-6a), 133.1 (C-10a), 130.9 (CH-8), 128.8 (CH-7), 127.6 (CH-9), 125.8 (CH-10), 120.8 (CH-8a), 27.1 (CH\textsubscript{2}-6), 19.9 (CH\textsubscript{2}-5).
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MS: m/z (%) = 198 (M\textsuperscript{+}, 71), 197 (100), 169 (15), 129 (24), 115 (16).

HRMS: m/z calculated for C\textsubscript{12}H\textsubscript{10}ON\textsubscript{2}: 198.0793; found: 198.0795 (M\textsuperscript{+}).

**Benzo[h]quinazolin-4(3H)-one (8)**

A solution of 8 (0.198 g, 1 mmol) in hot o-C\textsubscript{6}H\textsubscript{4}Cl\textsubscript{2} (7 mL) containing 10% Pd/C (0.60 g) was added for 48 h when 8 was consumed (TLC). The mixture was filtered hot through a Celite bed and washed with hot EtOAc (2 × 10 mL). The solvent was distilled off from the pooled filtrates under reduced pressure to furnish a white fluffy solid, which was crystallised from EtOAc to give 1. Yield: 0.156 g (80%); pale yellow flakes; mp 304–306°C (lit.\textsuperscript{5} mp 244–245°C).
Acknowledgements

The authors express their sincere thanks to the Director, Bose Institute for providing laboratory facilities, to Mr. B. Majumdar, NMR Facilities, B. I. for recording the spectra and to the C.S.I.R., Govt. of India for providing a Senior Research fellowship (S.S.).

References


