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7-Amino-5,6,7,8-tetrahydroquinolines. Preparation from 5,6-Dihydroquinoline and Nitrogen Nucleophiles

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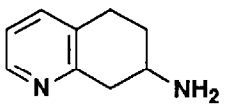
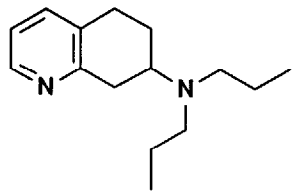
Key Words: 7-Amino-5,6,7,8-tetrahydroquinolines; 5-HT_{1A} receptor ligands; 5,6-dihydroquinoline; *N*-alkylhydroxylamines; *O*-benzylhydroxylamine

Abstract: *The preparation of 7-amino-5,6,7,8-tetrahydroquinolines is described. These agents are 5-HT_{1A} receptor ligands related to 8-OH-DPAT.*

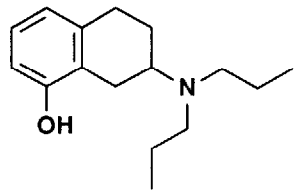
As part of a project whose aim was the design of novel 5-HT_{1A} receptor ligands, we wished to make 7-dipropylamino-5,6,7,8-tetrahydroquinoline (**3g**). This compound was postulated to be an 5-HT_{1A} receptor agonist by analogy with 8-hydroxy-*N,N*-dipropyl-2-aminotetralin (8-OH-DPAT),[1] and would serve as a tool for elucidating some of the structural/electronic requirements for ligand binding to the 5-HT_{1A} receptor. We report herein the preparation of the hitherto unreported **3g** and related compounds.[2] In particular, we summarise the results of our investigations into the reactions of nitrogen nucleophiles with 5,6-dihydroquinoline (**1**) and describe a high yielding preparation of the primary amino compound **3a**.



3a



3g



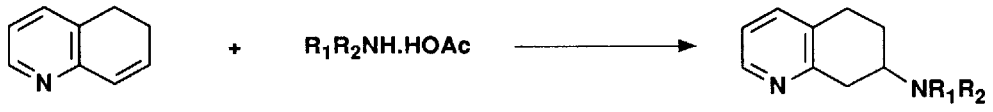
8-OH-DPAT

2-(2-Aminoethyl)pyridines have been prepared from the acid-catalysed reaction of amines with 2-vinylpyridines.[10-12] Accordingly, the initial approach to 7-amino-5,6,7,8-tetrahydroquinolines was an investigation of the acid catalysed addition of amines to 5,6-dihydroquinoline (**1**)[13] using piperidine as the representative amine (Table 1).

In refluxing methanol and using two equivalents of piperidinium acetate, a GLC yield of 32% of the piperidine adduct **3j** was obtained after 21 h. A small increase in yield was observed when a longer reaction time (67 h) was used. At a temperature of 70°, it was found that methanol was the best solvent for the reaction. The need for an acid catalyst was confirmed by the formation of only a trace of the product in the absence of acid catalysis. The yield of the product was substantially reduced when piperidinium chloride was used.

The optimal conditions discovered were subsequently used for the synthesis of a range of 7-amino-5,6,7,8-tetrahydroquinolines **3a-o** (Table 1).

TABLE 1. Reaction of 5,6-Dihydroquinoline (1) with Ammonium Acetates (2a-o)[a]



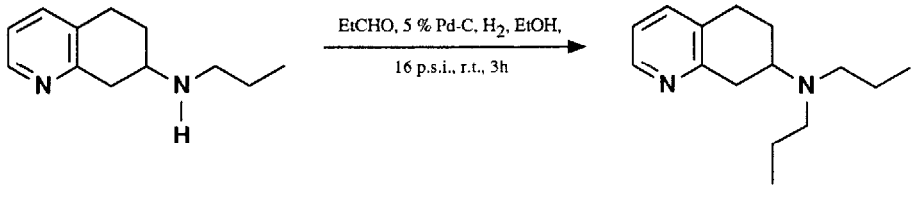
1 2a-o 3a-o

Entry	R_1	R_2	Isolated (GLC) Yield (%)[b]
a	H	H	12 (9)
b	H	Me	82 (81)
c	H	Pr	48 (45)
d	H	$PhCH_2$	66 (30)
e	H	Ph	88 (66)
f	Me	Me	41 (24)
g	Pr	Pr	0 (-[c])
h	$-(CH_2)_3-$		63 (-[c])
i	$-(CH_2)_4-$		66 (41)
j	$-(CH_2)_5-$		43 (32)
k	$-(CH_2)_6-$		4 (-[c])
l	$-(CH_2)_2-O-(CH_2)_2-$[d]		73 (52)
m	$-(CH_2)_2-NH-(CH_2)_2-$[e]		0[f] (-[c])
n	$-(CH_2)_2-N(CH_2Ph)-(CH_2)_2-$[g]		43 (-[c])
o	$-(CH_2)_2-N(2-OMe-C_6H_4)-(CH_2)_2-$[h]		50 (-[c])

[a]All products gave satisfactory spectral and analytical data. [b]GLC yields were consistently lower than isolated yields owing perhaps to a retro reaction on the glc column. [c]Not measured. [d]4-Morpholinyl. [e]1-Piperazinyl. [f]A 10% yield of 1,4-bis(5,6,7,8-tetrahydroquinolin-7-yl)-piperazine was obtained. [g]4-Benzyl-1-piperazinyl. [h]4-(2-Methoxyphenyl)-1-piperazinyl.

General experimental procedure: 5,6-dihydroquinoline (**1**) (1.31 g, 10 mmol), aniline (1.86 g, 20 mmol), and glacial acetic acid (1.2 ml, 20 mmol) in methanol (4 ml) is heated under reflux for 21 h. The solution is diluted with water, basified with 5*N*-NaOH, and extracted with ether. The extracts are dried (Na_2SO_4) and evaporated *in vacuo* to furnish the crude product which is purified by chromatography [alumina; ethyl acetate - toluene (1:5)] to give **3e** (1.84 g, 88 %), m.p. 102-103°C (from di-isopropyl ether) (Found: C, 80.4; H, 7.2; N, 12.5. $C_{15}H_{16}N_2$ requires C, 80.3; H, 7.2; N, 12.5 %).

The *N,N*-dipropylamino compound **3g** could not be obtained by the reaction of dipropylammonium acetate with 5,6-dihydroquinoline but was simply prepared from the *N*-propylamino compound **3c** by reductive acylation with propanal (Scheme 1).

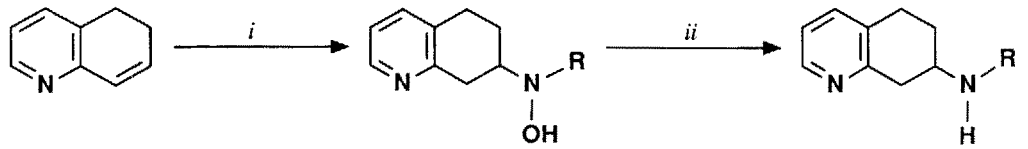


3c 3g, 44%

Scheme 1

Compound **3a** was identified as an intermediate for the preparation of a number of substituted 7-amino-5,6,7,8-tetrahydroquinolines but it was formed in low yield under the conditions of Table 1. An investigation of the reaction of other nitrogen nucleophiles[14] with 5,6-dihydroquinoline (**1**) led to the identification of two further routes for the preparation of **3a**.[17]

The reaction of hydroxylamine with 5,6-dihydroquinoline (**1**) gave multi-component mixtures resulting from 1:1 and 2:1 adducts of 5,6-dihydroquinoline with hydroxylamine.[18] The reaction of *N*-alkylhydroxylamines,[19] however, produced *N,N*-dialkylhydroxylamines **4a-c** in good yields (Scheme 2) which were reduced either catalytically in the case of **4a** or with aqueous titanium (III) chloride[20] in the case of **4b** and **4c** to give **3a-c**.

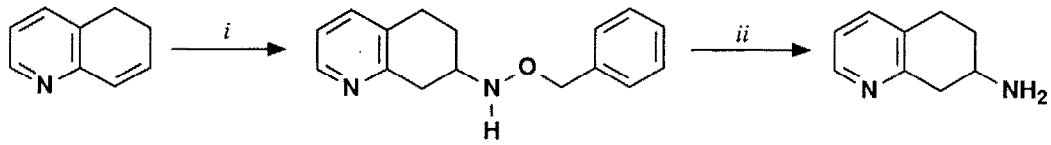


1 — **4a**, R = PhCHMe, 56 %; **4b**, R = Me, 65 %; **4c**, R = Pr, 49 % — **3a**, R = H, 30 %; **3b**, R = Me, 11 %; **3c**, R = Pr, 80 %

Scheme 2

Reagents: *i*, RNHOH.HCl, MeOH, r.t., 1h; *ii*, H_2, $Pd(OH)_2$, H_2SO_4-HOAc, 50 p.s.i. (R = PhCHMe) or 20 % aq. $TiCl_3$, MeOH, r.t., 1h (R = Me, Pr).

The preparation of **3a** outlined in Scheme 2 required the prior synthesis of *N*-(α-methylbenzyl)hydroxylamine.[21] A more straightforward and higher yielding preparation of **3a** involved the use of the commercially available *O*-benzylhydroxylamine[22] (Scheme 3). The reaction of 5,6-dihydroquinoline with *O*-benzylhydroxylamine gave the 1:1 adduct[23] **5** which was reduced catalytically. The product was purified *via* the *tert*-butoxycarbonyl (Boc) derivative to give **3a** in high overall yield.



1 — **5**, 57 % — **3a**, 64 %

Scheme 3

Reagents: *i*, $NH_2OCH_2Ph.HCl$, MeOH, r.t., 18 h; *ii*, H_2, Raney Ni, EtOH, 50 p.s.i., r.t., Boc_2O, CH_2Cl_2; TFA

In conclusion we have described the first preparations of 7-amino-5,6,7,8-tetrahydroquinolines.[24] The pharmacological properties of these compounds will be the subject of further publications.

References and Notes

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2. 5,6,7,8-Tetrahydroquinolines with amino substituents at the 5-,[3,4] 6-,[5] and 8-[6-9] positions have been described but 7-amino-5,6,7,8-tetrahydroquinoline and 5,8-dihydroquinolin-7(6*H*)-one are unknown.
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14. Hydrazoic acid,[15] pyrrolyl anion,[16] lithium diisopropylamide, phthalimide/tritonB, dipropylamine/mercuric acetate, and ammonia under high pressure conditions gave little or no reaction with 5,6-dihydroquinoline.
15. For the reaction of hydrazoic acid with 2-vinylpyridine see Boyer, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 5248-5252.
16. For the reaction of 1-sodiopyrrole with 2-vinylpyridine, see reference 10.
17. The catalytic hydrogenation of **3d** produced **3a** contaminated with compounds derived from reduction of the pyridine ring.
18. The reaction of hydroxylamine hydrochloride with 2-vinylpyridine gives the 2:1 adduct *N,N*-bis(2-pyridinylethyl)hydroxylamine. See Bauer, L.; Shoeb, A.; Agwada, V. C. *J. Org. Chem.* **1962**, *27*, 3153-3155.
19. For the addition of *N*-alkylhydroxylamines to 2-vinylpyridine, see Sayigh, A. A. R.; Ulrich, H.; Green, M. *J. Org. Chem.* **1964**, *29*, 2042-2043. For the addition of *N,N*-dialkylhydroxylamines to 2-vinylpyridine to give 2-[2-(*N,N*-dialkylamino)ethyl]pyridine *via* an unusual deoxygenation reaction, see Paquette, L. A. *J. Org. Chem.* **1962**, *27*, 2870-2873. The addition of *N,N*-diethylhydroxylamine to 5,6-dihydroquinoline under a number of reaction conditions gave an unidentified product which was not *N,N*-diethyl-7-amino-5,6,7,8-tetrahydroquinoline.
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21. *N*-Methylhydroxylamine was obtained from the Aldrich Chemical Co. Ltd.. *N*-Propylhydroxylamine was prepared from propanal oxime by borane-dimethyl sulphide reduction in 94% yield. *N*-(α-methylbenzyl)hydroxylamine was prepared from acetophenone oxime and sodium cyanoborohydride/acetic acid in 67% yield. *N*-Benzylhydroxylamine was an obvious candidate for addition to 5,6-dihydroquinoline but this compound was difficult to isolate. For a discussion of the properties of *N*-benzylhydroxylamine see Feuer, H.; Vincent, B. F.; Bartlett, R. S. *J. Org. Chem.* **1965**, *30*, 2877-2880.
22. *O*-Benzylhydroxylamine was obtained from the Aldrich Chemical Co. Ltd..
23. This result contrasts with the reaction of *O*-benzylhydroxylamine with the less sterically hindered 2-vinylpyridine which gives a 1:2 adduct. See reference 18.
24. 5,6,7,8-Tetrahydro-7-methoxyquinoline was successfully isolated from the reaction of sodium methoxide with 5,6-dihydroquinoline in hot methanol.

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