A New Synthesis of 1,2,3,4-Tetrahydro-2-methyl-4-phenylisoquinolines

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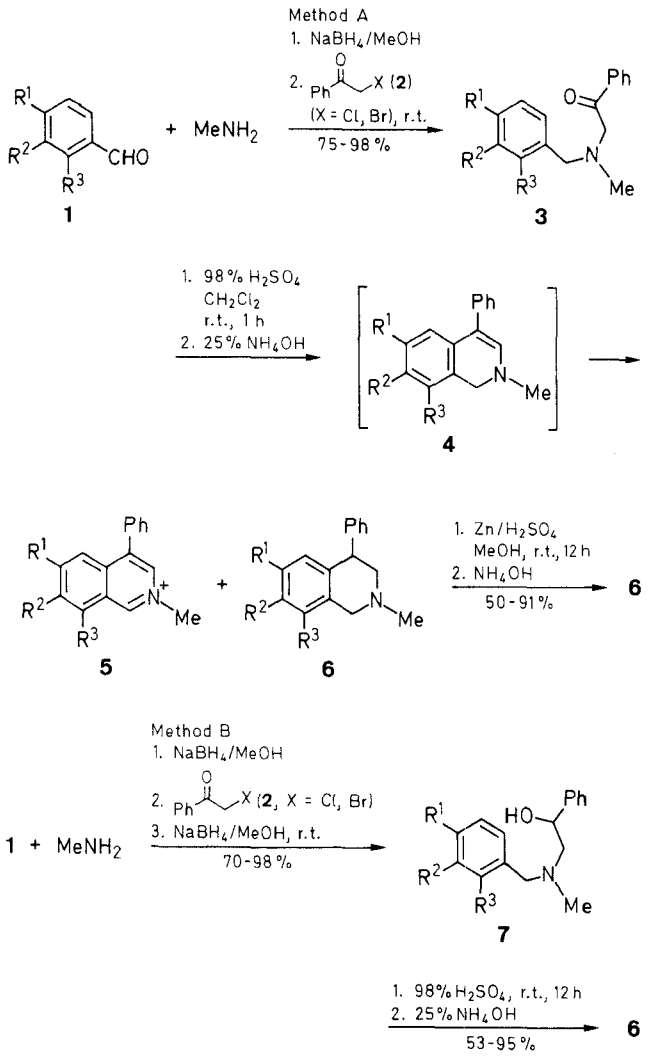
1,2,3,4-Tetrahyro-2-methyl-4-phenylisoquinolines **6** are obtained from aromatic aldehydes **1**, methyl amine and α-haloacetophenones **2** in the presence of sodium borohydride followed by cyclization with sulfuric acid and zinc in methanol.

The synthesis of 1,2,3,4-tetrahydro-4-phenylisoquinolines is of considerable interest due to their biological activity and as naturally occuring alkaloids.[1-3] Some are valuable medicaments, which are distinguished in particular by centrally stimulating, thymoleptic, and antiarrhythmic action.[1,4,5]

1,2,3,4-Tetrahydro-4-phenylisoquinolines have been obtained by reduction[6] of 1,4-dihydro-4-phenyl-3(2*H*)-isoquinolinones.[7,8] 4(2*H*)-Dihydroisoquinolinones have also been transformed to 1,2,3,4-tetrahydro-4-phenylisoquinolines by arylation with phenyllithium followed by dehydration and reduction.[9] However, the most popular synthesis are based on the use of *N*-alkyl-*N*-benzyl-2-amino-1-phenylethanols as key intermediates, which are readily cyclized in sulfuric acid media. Several approaches have been developed for the synthesis of these intermediates:

- alkylation of *N*-alkyl benzylamines with α-haloacetophenones followed by reduction;[1]
- reaction of styrene oxides with *N*-alkyl benzylamines;[10] and
- amination of aromatic aldehydes with α-amino alcohols in the presence of sodium borohydride.[5,11]

Now we report a new synthesis of 1,2,3,4-tetrahydro-2-methyl-4-phenylisoquinolines **6** using *N*-benzyl-*N*-methylaminoacetophenones **3** as key intermediates. The synthesis of these intermediates is a one-pot reaction, starting from aromatic aldehydes **1** methyl amine, and α-haloacetophenones **2**.



1, 3–7	R^1	R^2	R^3	1, 3–7	R^1	R^2	R^3
a	OMe	OMe	H	**e**	$-OCH_2O-$		H
b	OH	OMe	H	**f**	OMe	H	H
c	H	OMe	OMe	**g**	H	H	H
d	H	OMe	H	**h**	H	H	NH_2

The procedure (Method A) includes a reductive amination of an aromatic aldehyde **1** with methylamine in the presence of sodium borohydride. The *N*-methyl benzylamine formed is not isolated but directly alkylated with α-haloacetophenone **2** to afford the amino ketone **3**.

The amino ketones **3** obtained as intermediates in this reaction can be isolated and characterized (Table 1). Treatment of **3** with concentrated sulfuric acid or polyphosphoric acid affords an unstable 1,2-dihydroisoquinoline **4** (observed by TLC and IR spectrum), which is spontaneously converted to two products: the major product **6** and the second product which was identified (^{1}H-NMR and mass spectra) as isoquinolinium salt **5**. In the presence of methanol and zinc, the product is only 1,2,3,4-tetrahydro-2-methyl-4-phenylisoquinoline **6**. The reaction from **3** to **6** proceeds only with aldehydes having at least one methoxy group or methylenedioxy group.
If, following the above procedure for the preparation of amino ketone **3**, a further quantity of sodium borohydride was added after the final step, the product of the reaction is the amino alcohol **7**. This procedure (Method B) improves the known method for the synthesis of *N*-benzyl-*N*-alkyl-2-amino-1-phenylethanols **7**, which are key intermediates in the synthesis of **6**. The reaction of **1** to **7**, via Method B can be performed as a one pot reaction. Direct treatment of **7** with concentrated sulfuric acid lead to product **6**. The yields and spectral data of amino alcohols **7** are given in Table 1 and the yield of **6** are given in Table 2 (Method B). The product **6f** was obtained by cyclization of **7f** with polyphosphoric acid at 80 °C for 5 hours. Nomifensine (1,2,3,4-tetrahydro-2-methyl-4-phenyl-8-isoquinolinamine, **6h**) was obtained by this method in an overall yield of 95% (Table 2).

Table 1. Yield and ^{1}H-NMR Characterization of Intermediates **3** and **7**

Entry	Yields (%)[a]		^{1}H-NMR ($CDCl_3$/TMS), δ, J(Hz)	
	3	**7**	**3**	**7**
a	92	90	2.35 (s, 3H), 3.55 (s, 2H), 3.70 (s, 2H), 3.75 (s, 6H), 6.70 (s, 3H), 7.25–7.40 (m, 3H), 7.80–7.90 (m, 2H)	2.28 (s, 3H), 2.42 (s, 2H), 3.40–3.60 (m, 2H), 3.80 (s, 6H), 4.45–4.75 (m, 1H), 6.75 (s, 3H), 7.25 (s, 5H)
b	80	79	2.40 (s, 3H), 3.60 (s, 2H), 3.65 (s, 2H), 3.80 (s, 3H), 6.75 (s, 2H), 6.80 (s, 1H), 7.20–7.40 (m, 3H), 7.80 (d, 1H, J = 5), 7.90 (d, 1H, J = 5)	2.30 (s, 3H), 2.45 (s, 2H), 2.55 (d, 2H, J = 5), 3.50 (d, 2H, J = 7), 3.80 (s, 3H), 4.70 (t, 1H, J = 10), 6.70 (s, 3H), 7.25 (s, 5H)
c	80	80	2.42 (s, 3H), 3.75 (s, 2H), 3.80 (s, 2H), 3.85 (s, 6H), 6.70–7.00 (m, 3H), 7.25–7.45 (m, 3H), 7.80 (d, 1H, J = 5), 7.90 (d, 1H, J = 5)	2.22 (s, 3H), 2.38 (s, 2H), 3.60 (d, 2H, J = 5), 3.75 (s, 6H), 4.50–4.75 (m, 1H), 6.80 (s, 3H), 7.20 (s, 5H)
d	90	90	2.50 (s, 3H), 3.65 (s, 2H), 3.70 (s, 2H), 3.75 (s, 3H), 6.70–7.00 (m, 2H), 7.25–7.50 (m, 5H), 7.75–8.00 (m, 2H)	2.30 (s, 3H), 2.48 (s, 2H), 2.50 (d, 2H, J = 5), 3.55 (d, 2H, J = 5), 3.50–3.70 (m, 2H), 3.72 (s, 3H), 4.45–4.70 (m, 1H), 6.80 (s, 2H), 7.30 (s, 6H)
e	86	75	2.35 (s, 3H), 3.55 (s, 2H), 3.75 (s, 2H), 5.90 (s, 2H), 6.70 (s, 2H), 6.80 (s, 1H), 7.20–7.45 (m, 3H), 7.80 (d, 1H, J = 5), 7.95 (d, 1H, J = 4)	2.30 (s, 3H), 2.45 (s, 2H), 2.55 (d, 2H, J = 6), 3.50 (d, 2H, J = 7), 4.55–4.70 (m, 1H), 5.90 (s, 2H), 6.70 (s, 2H), 6.75 (s, 1H), 7.30 (s, 5H)
f	75	70	2.35 (s, 3H), 3.60 (s, 2H), 3.70 (s, 2H), 3.75 (s, 3H), 6.70 (s, 1H), 6.80 (s, 2H), 7.10–7.40 (m, 4H), 7.75 (d, 1H, J = 5), 7.90 (d, 1H, J = 5)	2.25 (s, 3H), 2.32 (s, 2H), 2.42 (d, 2H, J = 5), 3.55 (d, 2H, J = 6), 3.72 (s, 3H), 4.50–4.78 (m, 1H), 6.65 (s, 1H), 6.80 (s, 2H), 7.02 (s, 1H), 7.22 (s, 5H)
g	95	93	2.40 (s, 3H), 3.72 (s, 2H), 3.82 (s, 2H), 7.30 (s, 5H), 7.40 (s, 2H), 7.75–8.05 (m, 2H)	2.25 (s, 3H), 2.45 (s, 2H), 2.55 (d, 2H, J = 5), 3.55 (d, 2H, J = 7), 4.58–4.80 (m, 1H), 5.60 (s, 2H), 7.20 (s, 6H)
h	98	98	2.80 (s, 3H), 3.70 (s, 2H), 4.35 (s, 2H), 7.20 (s, 5H), 7.30–7.50 (m, 2H), 7.80–8.10 (m, 2H)	2.40 (s, 3H), 2.75 (s, 2H), 3.85 (d, 2H, J = 6), 5.56–5.80 (m, 1H), 7.20 (s, 5H), 7.45 (s, 2H), 7.48 (s, 2H), 7.80 (s, 1H)

[a] Yields of isolated products **3** and **7** based on **1**.

Table 2. 1,2,3,4-Tetrahydro-2-methyl-4-phenylisoquinolines **6** Prepared

Product	Yield (%)[a]		mp (°C) (solvent)	Molecular Formula[b] or Lit. mp (°C)	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS (70 eV) M^+, m/z
	Method A	Method B				
6a	81	85	94 (Et_2O/EtOH)	$C_{18}H_{21}NO_2$ (283.3)	2.35 (s, 3H), 2.78–3.05 (m, 2H), 3.58 (s, 5H), 3.80 (s, 3H), 4.0–4.22 (m, 1H), 6.25 (s, 1H), 6.45 (s, 1H), 7.12 (s, 5H)	283
6b	50	70	178–180 (Et_2O/MeOH)	$C_{17}H_{19}NO_2$ (269.7)	2.32 (s, 3H), 2.80–3.00 (m, 2H), 3.52 (s, 2H), 3.74 (s, 3H), 3.95–4.25 (m, 1H), 6.15 (s, 1H), 6.30 (s, 1H), 7.02 (s, 5H)	269
6c	68	72	185–187[c] (EtOH)	$C_{18}H_{21}NO_2$ (283.3)	2.40 (s, 3H), 2.70–3.00 (m, 2H), 3.55 (s, 2H), 3.74 (s, 3H), 3.80 (s, 3H), 4.00–4.20 (m, 1H), 7.10 (s, 5H), 7.22 (s, 1H), 7.28 (s, 1H)	283
6d	67	81	225–227[c] (EtOH)	$C_{17}H_{19}NO$ (253.7)	2.40 (s, 3H), 2.80–3.00 (m, 2H), 3.62 (s, 2H), 4.00–4.25 (m, 1H), 6.50–6.60 (m, 3H), 7.15 (s, 5H)	253
6e	72	70	212–214[c] (Et_2O/EtOH)	$C_{17}H_{17}NO_2$ (267.3)	2.40 (s, 3H), 2.72–2.95 (m, 2H), 3.48 (s, 2H), 3.85–4.15 (m, 1H), 5.70 (s, 2H), 6.25 (s, 1H), 6.58 (s, 1H), 7.10 (s, 5H)	267
6f	–	53	194–197[c] (Et_2O/EtOH)	$C_{17}H_{19}NO$ (253.7)	2.32 (s, 3H), 2.75–3.05 (m, 2H), 3.55 (s, 3H), 3.68 (s, 2H), 4.05–4.28 (m, 1H), 6.37 (s, 1H), 6.68 (s, 1H), 6.80 (s, 1H), 7.10 (s, 5H)	253
6g	–	85	169–174[c] (Et_2O/EtOH)	$C_{16}H_{17}N$ (223.3)	2.38 (s, 3H), 2.90–3.05 (m, 2H), 3.62 (s, 2H), 4.20 (t, 1H, J = 11), 6.95 (s, 2H), 7.00 (s, 2H), 7.15 (s, 5H)	223
6h	–	95	199–201[d] (Et_2O/EtOH)	199–201[1]	2.42 (s, 3H), 2.62–2.82 (m, 2H), 3.50 (s, 2H), 4.00–4.30 (m, 1H), 6.20 (s, 1H), 6.45 (s, 1H), 6.71 (s, 1H), 7.15 (s, 5H)	239

[a] Yield of isolated product **6** based on **1**.
[b] Satisfactory microanalyses obtained: C ±0.34, H ±0.22, N +0.27.
[c] Mp of the HCl salts.
[d] Mp of the maleate salt.

1,2,3,4-Tetrahydro-2-methyl-4-phenylisoquinolines 6; General Procedure:

Method A for **6a–e**: A solution of aldehyde **1** (10 mmol) and 40% aq. $MeNH_2$ solution (0.4 g, 1 mL, 13 mmol) in MeOH (10 mL) is stirred for 10 min at r.t. Solid $NaBH_4$ (0.19 g, 5 mmol) is added portionwise, and the mixture is stirred for 1 h. α-Bromoacetophenone (**2**, X = Br; 1.99 g, 10 mmol) is added at once, and stirring is continued at r.t. for 45–50 min. Then water (50 mL) is added and the mixture is extracted with CH_2Cl_2 (3 × 10 mL) and the combined extracts are dried (Na_2SO_4). Removal of solvent at this stage affords compounds **3**, which are isolated separately and characterized spectroscopically (Table 1).

For the preparation of **6**, the CH_2Cl_2 solution is treated with 98% H_2SO_4 (5 mL), then stirred for 1 h at r.t. The solvent is evaporated at reduced pressure, and the residue is dissolved in MeOH (50 mL). To the stirred solution is added Zn powder (1.36 g, 20 mmol) portionwise, and the mixture is left for 12 h at r.t. Then water (50 mL) is added, and the suspension is basified with 25% NH_4OH. The resulting suspension is extracted with CH_2Cl_2, the organic layer is dried (Na_2SO_4), and the solvent is removed by distillation in vacuum. The crude **6a,b** are purified by recrystallization. The HCl salts of **6c–e** are obtained with 36% aq. HCl in EtOH at 0°C, and recrystallized from EtOH.

1,2-Dihydro-2-methyl-4-phenyl-6,7-dimethoxyisoquinoline (5a):

A solution of the isolated amino ketone **3a** (2.73 g, 9 mmol) in CH_2Cl_2 is stirred with 98% H_2SO_4 (6 mL) for 1 h at r.t. The mixture is poured into crushed ice and basified with 25% NH_4OH, and stirred for 1 h at r.t. The resulting emulsion is extracted with CH_2Cl_2 (3 × 10 mL), the combined extracts are dried (Na_2SO_4), and the solvent evaporated. The residue is dissolved in Et_2O (10 mL) and cooled. The crystals obtained after chilling, are filtered; yield: 0.8 g (25%); mp 215–216°C.

MS: m/z = 260 (M^+).

^{1}H-NMR (DMSO/TMS): δ = 3.90 (s, 3H), 4.02 (s, 3H), 4.40 (s, 3H), 7.25 (s, 1H), 7.60 (s, 5H), 7.80 (s, 1H), 8.48 (s, 1H), 9.46 (s, 1H).

Method B, *for* **6a–g**: A mixture of aldehyde **1** (10 mmol) and 40% aq. $MeNH_2$ (0.4 g, 1 mL, 13 mmol) is stirred for 10–15 min at r.t. Solid $NaBH_4$ (0.19 g, 5 mmol) is added portionwise, and the mixture is stirred for 1 h. α-Bromoacetophenone (**2** (X = Br); 1.99 g, 10 mmol) is added at once, and the mixture is stirred for 45–50 min at r.t. Solid $NaBH_4$ (0.57 g, 15 mmol) is added again in portions, and the stirring is continued at r.t. for 3 h. Then water (30 mL) is added, and the mixture is extracted with CH_2Cl_2 (3 × 10 mL) and the combined extracts are dried (Na_2SO_4). Removal of solvent at this stage affords compounds **7**, which are isolated and characterized spectroscopically (Table 1). For the preparation of **6**, the CH_2Cl_2 solution is treated with 98% H_2SO_4 (15 mL).

The mixture is stirred for 12 h at r.t., then crushed ice (50 g) is added. The solution is basified with 25% NH_4OH, extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers are dried (Na_2SO_4). The solvent is evaporated by distillation, and the crude product is purified by recrystallization as free base or salt.

1,2,3,4-Tetrahydro-2-methyl-4-phenyl-8-isoquinolinamine (Nomiensine) (6h):

A mixture of 2-Nitrobenzaldehyde (7.55 g, 50 mmol) and 40% aq. $MeNH_2$ (2 g, 5 mL, 65 mmol) are stirred 10 min at r.t. in MeOH (50 mL). Solid $NaBH_4$ (0.95 g, 25 mmol) is added in several portions, and the stirring is continued for 1 h. A solution of α-bromoacetophenone (**2** (X = Br); 9.95 g, 50 mmol) in MeOH (20 mL) is then added dropwise over 15–20 min, and stirring is continued for 30 min. Solid $NaBH_4$ (2.85 g, 75 mmol) is added again in portions, and the mixture is stirred at r.t. for 3 h. Water (50 mL) is added, and the solution is extracted with CH_2Cl_2 (3 × 50 mL). The extract is dried (Na_2SO_4), and the solvent is evaporated at reduced pressure. The residue is dissolved in EtOH (50 mL) and zinc (9.8 g, 150 mmol, powder) is added. Conc. HCl (50 mL) is added dropwise over 2 h to the stirred and cooled suspension (0–5°C). Water (50 mL) is added, then 20% aq. NaOH is added to make the media alkaline, and the mixture is extracted with CH_2Cl_2 (3 × 50 mL). The extract is dried (Na_2SO_4) and the solution is evaporated to a volume of 70 mL. 98% H_2SO_4 (75 mL) is added to the solution, and the mixture is stirred at r.t. for 10–12 h. Crushed ice (50 g) is added, and the mixture is extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers are dried (Na_2SO_4), and the solution is evaporated at reduced pressure to afford **6h**; yield: 11.3 g (95%).

The yellow oil is dissolved in EtOH (50 mL) and an equimolar amount of a maleic acid (5.68 g) is added to the solution. The resulting suspension is chilled and filtered to give the maleate salt of **6h** as white crystals; mp 199–210°C.

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(1) *British Patent* 1164192 (1969), Hoechst AG; *C.A.* **1970**, *72*, 21621.
(2) Shamma, M., in: *The Isoquinoline Alkaloids, Chemistry and Pharmacology*, Academic Press, New York, 1972, p. 497.
(3) Shamma, M.; Moniot, J.L.; in: *The Isoquinoline Alkaloid Research*, 1972–1977, Plenum Press, New York, 1978, p. 389.
(4) Trepanier, D.L.; Sunder, S. *J. Med. Chem.* **1973**, *16*, 342.
(5) Bobowski, G.; Jeffrey, G. *J. Heterocycl. Chem.* **1982**, *19*, 21.
(6) Ehrhart, G.; Schmitt, K.; Hoffmann, I.; Ott, H. *German Patent* 1670848 (1979), Hoechst AG; *C.A.* **1980**, *93*, 46442.
(7) Gardent, J.; Hamon, M. *Bull. Soc. Chim. Fr.* **1966**, 556.
(8) Petrov, O.; Ognyanov, V.; Mollov, N. *Synthesis* **1987**, 637.
(9) Jung, E.; Schirdewahn, J.; Schmitt-Nilson, G. *German Patent* 2635276 (1977); *C.A.* **1977**, *87*, 5827.
(10) Hara, H.; Shirai, R.; Hoshino, Os. *Heterocycles* **1984**, *21*, 696.
(11) Schwan, T.S.; Loug Heed, G.S.; Burrous, S.E. *J. Heterocycl. Chem.* **1974**, *11*, 807.