

Efficient Preparation of Substituted 5,6,7,8-Tetrahydroquinolines and Octahydroacridine Derivatives

Dirk Sielemann, Ralf Keuper, and Nikolaus Risch*

Paderborn, Universität-GH, FB 13 – Fachbereich Chemie und Chemietechnik

Received April 16th, 1999

Dedicated to Prof. Dr. Karl Drexhage on the Occasion of his 65th Birthday

Keywords: Domino reaction, Mannich bases, Iminium salts, Tetrahydroquinolines, Octahydroacridines

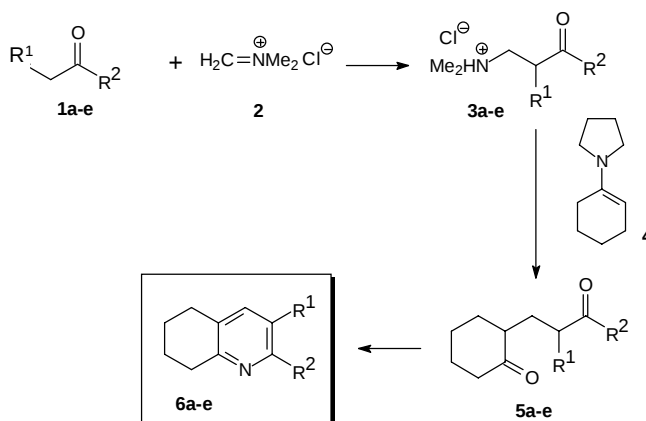
Abstract. The reaction of the enamine **4** with different β -amino ketone hydrochlorides **3a–e** affords the diketones **5a–e** which can be cyclized to the corresponding mono- and

disubstituted tetrahydroquinolines **6a–e**. Furthermore the preparation of the octahydroacridines **8f** and **8g** by using a straightforward multi step sequence is described.

Quinolines and their derivatives, especially the tetrahydroquinolines, occur in numerous natural products [1, 2]. Many tetrahydroquinoline derivatives show interesting physiological activities and have found attractive applications as pharmaceuticals and agrochemicals as well as being general synthetic building blocks [2]. Chiral 5,6,7,8-tetrahydroquinolines [3] are the most convenient starting points for the synthesis of the corresponding optically active 2,2'-bipyridines and 1,10-phenanthrolines [4, 5]. Furthermore tetrahydroquinolines and partially hydrogenated acridine derivatives have been prepared and studied with regard to their possible activity as acetylcholinesterase inhibitors [6] and their effects on the memory improvement of Alzheimer patients. In the last few years interest has been focused on 5,6,7,8-tetrahydroquinolin-8-one derivatives since they play an important role as starting material for the synthesis of oligopyridines. Oligopyridines bearing 2,2'-bipyridine, 2,2':6',2''-terpyridine or 1,10-phenanthroline subunits are extremely versatile building blocks for the construction of metallo-supramolecular systems. Different syntheses have been developed for these heterocycles, but due to their great importance, the development of novel synthetic methods remains an active research area [7]. For this reason we were interested in simple approaches towards 5,6,7,8-tetrahydroquinoline derivatives [8].

Our studies in the field of ternary iminium salts led to the development of one pot reactions yielding a wide range of functionalized pyridines, bipyridines and terpyridines [9]. All these reactions are based on the ability of Mannich bases to form α,β -unsaturated ketones by thermally induced amine elimination. It is known that enamines as well as ketones are easily alkylated by these Michael acceptors to form 1,5-diketones [10] which can be converted to the corresponding pyridine derivatives

by treatment with ammonia. We chose to prepare several substituted 5,6,7,8-tetrahydroquinolines by treating the β -amino ketone hydrochlorides **3a–e** [11] with the pyrrolidine enamine of cyclohexanone **4**. Heating a solution of the hydrochlorides **3a–e** in the presence of enamine **4** afforded the expected 1,5-diketones **5a–e** which can be isolated in good to moderate yields.



Entry	R ¹	R ²	Yield 5	Yield 6
a	H	C ₆ H ₅	39	42 ^{a)}
b	H	4-BrC ₆ H ₄	62	45
c	H	<i>t</i> -C ₄ H ₉	77	76
d	Me	C ₆ H ₅	46	33
e	C ₆ H ₅	C ₆ H ₅	67	54

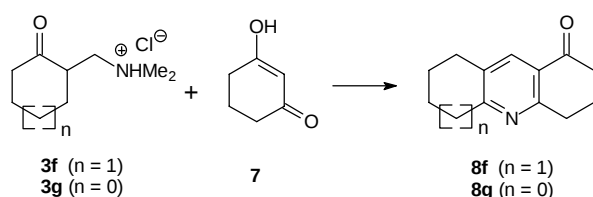
^{a)} The overall yield can be increased to 40% if the diketone **5a** is not purified

Scheme 1 Preparation of diketones **5a–e** and tetrahydroquinolines **6a–e**

The final cyclization is achieved by refluxing the dicarbonyl compound **5** in the presence of an ammonia source (e.g. hydroxylammonium hydrochloride). The

isolation of the intermediate 1,5-diketone **5** is not necessary, and the cyclization of **5** can be carried out without further purification of the crude product. This procedure provides higher yields of the tetrahydroquinoline **6**.

These results prompted us to develop a similar reaction sequence for the preparation of acridine derivatives. Instead of employing the enamine **4** we used the very reactive 1,3-cyclohexanedione **7** (see scheme 2). The reaction between Mannich base **3f** and **3g**, respectively, and **7** was carried out in the presence of ammonium acetate so that the 1,5-diketone is cyclized *in situ* to the 1,4-dihydropyridine and octahydroacridine derivative, respectively. After workup small amounts of 1,4-dihydropyridine are present which can be converted to the corresponding octahydroacridine derivative by stirring a solution of the crude product with SiO₂ under an oxygen atmosphere. This simple procedure allows us to prepare the octahydroacridine **8f** in 76% and **8g** in 42% yield.



Scheme 2 Preparation of octahydroacridine derivatives **8f** and **8g**

Our method is distinguished by its simplicity and high yields in comparison with known literature procedures [12]. It is noteworthy that the acridine derivative **8** is quite similar to known pharmacologically interesting acridine compounds [6]. Considerable attention has been focused on these heterocycles, because of their bactericidal, central stimulating [13], coronary dilating [14], antifibrillatory, spasmolytic and antihypertensive activity [15].

We thank the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft for the financial support of this work.

Experimental

All reactions were conducted under argon atmosphere unless otherwise indicated. Anhydrous solvents were distilled as follows: CHCl₃, CH₃CN were distilled from P₄O₁₀; EtOH was distilled from Na. Melting points are uncorrected. ¹H and ¹³C NMR spectra were recorded on a Bruker ARX 200 spectrometer, using TMS as internal standard. Infrared frequencies are reported in units of cm⁻¹. MS data were obtained from a VG Fisons MD 800.

Preparation of the β-amino ketone hydrochlorides (**3a–g**)

The Mannich bases are synthesized according to the method described by Tietze/Kinast [11].

3-Dimethylamino-1-phenyl-propane-1-one hydrochloride (**3a**)

Prepared from 4.32 g (22.0 mmol) of acetophenone (**1a**) and 2.0 g (22.0 mmol) of *N,N*-dimethylmethyle ammonium chloride (**2**). Yield 4.54 g of colourless crystals (73%), *m.p.* 152 °C [16]. – ¹H NMR (200 MHz, CDCl₃) δ/ppm = 12.43 (bs, 1H), 7.96 (m, 2H), 7.62–7.41 (m, 3H), 3.74 (m, 2H), 3.60 (m, 2H), 2.86 (s, 6H). – ¹³C NMR (50 MHz, CDCl₃) δ/ppm = 196.2 (s), 135.8 (s), 134.52 (d), 129.30 (d), 128.7 (d), 53.1 (t), 43.7 (q), 34.2 (t). – IR (KBr) ν/cm⁻¹ = 2541, 2433, 1688, 1470, 1445, 1336, 1217, 959, 757, 700.

1-(4-Bromo-phenyl)-3-dimethylamino-propan-1-one hydrochloride (**3b**)

Prepared from 10.4 g (52.0 mmol) 4-bromoacetophenone (**1b**) and 4.65 g (52.0 mmol) of *N,N*-dimethylmethyle ammonium chloride (**2**). Yield 11.5g of colourless crystals (76%), *m.p.* 193 °C [17]. – ¹H NMR (200 MHz, CDCl₃) δ/ppm = 12.6 (bs, 1H), 7.91 (d, ³J = 8.6 Hz, 2H), 7.68 (d, ³J = 8.6 Hz, 2H), 3.78 (t, ³J = 7.1 Hz, 2H), 3.54 (t, ³J = 7.1 Hz, 2H), 2.89 (s, 3H). – IR (KBr) ν/cm⁻¹ = 2993, 2547, 2433, 1688, 1579, 1398, 1222, 1067, 964.

1-Dimethylamino-4,4-dimethyl-pentan-3-one hydrochloride (**3c**)

Prepared from 19.8 g (0.20 mol) of 3,3-dimethyl-2-butanone (**1c**) and 18.0 g (0.19 mol) of *N,N*-dimethylmethyle ammonium chloride (**2**). Yield 27.1 g of colourless crystals (76%), *m.p.* 175 °C [18]. – ¹H NMR (200 MHz, CDCl₃) δ/ppm = 12.65 (bs, 1H), 3.25 (m, 4H), 2.81 (s, 3H), 2.78 (s, 3H), 1.14 (s, 9H). – ¹³C NMR (50 MHz, CDCl₃) δ/ppm = 212.5 (s), 53.2 (t), 43.6 (q), 32.3 (t), 26.74 (q). – IR (KBr) ν/cm⁻¹ = 2977, 2577, 2474, 1703, 1465, 1383, 1093, 964.

3-Dimethylamino-2-methyl-1-phenyl-propane-1-one hydrochloride (**3d**)

Prepared from 2.7 g (20.0 mmol) propiophenone (**1d**) and 4.65 g (22.0 mmol) of *N,N*-dimethylmethyle ammonium chloride (**2**). Yield 3.7 g of colourless crystals (74%), *m.p.* 165 °C [19]. – ¹H NMR (200 MHz, CDCl₃) δ/ppm = 12.43 (bs, 1H), 8.09 (m, 2H), 7.49 (m, 3H), 4.50 (m, 1H), 3.83 (m, 1H), 3.17 (m, 1H), 2.88 (s, 3H), 2.60 (s, 3H), 1.32 (d, ³J = 7.3 Hz, 3H). – ¹³C NMR (50 MHz, CDCl₃) δ/ppm = 201.3 (s), 134.7 (s), 134.7 (d), 129.6 (d), 129.3 (d), 59.2 (t), 45.6 (q), 42.5 (q), 38.0 (d), 18.9 (q). – IR (KBr) ν/cm⁻¹ = 2929, 2686, 2619, 1688, 1465, 1222, 979, 700.

3-Dimethylamino-1,2-diphenyl-propan-1-one hydrochloride (**3e**)

Prepared from 4.32 g (22.0 mmol) of benzylphenylketone (**1e**) and 2.0 g (22.0 mmol) of *N,N*-dimethylmethyle ammonium chloride (**2**). Yield 4.54 g of a white solid (72%), *m.p.* 168 °C [9a]. – ¹H NMR (200 MHz, CDCl₃) δ/ppm = 12.75 (bs, 1H), 8.05 (d, ³J = 7.4 Hz, 2H), 7.53–7.25 (m, 8H), 5.89 (dd, ³J = 7.8 Hz, ⁴J = 3.5 Hz, 1H), 4.12 (dd, ²J = 12.7 Hz, ³J = 7.8 Hz, 1H), 3.34 (dd, ²J = 12.7 Hz, ³J = 3.5 Hz, 1H), 2.73 (s, 6H). – ¹³C NMR (50 MHz, CDCl₃) δ/ppm = 197.4

(s), 136.1 (s), 135.2 (s), 134.4 (d), 130.1 (d), 129.7 (d), 129.3 (d), 129.1 (d), 128.8 (d), 128.7 (d), 60.1 (t), 49.7 (d), 43.7 (q). – IR (KBr) ν/cm^{-1} = 2950, 2660, 1678, 1460, 1383, 1238, 1145, 938, 767, 694.

2-Dimethylaminomethyl-cyclohexanone hydrochloride (3f)

Prepared from 2.0 g (20.0 mmol) cyclohexanone and 1.86 g (20.0 mmol) of *N,N*-dimethylmethyle ammonium chloride (2). Yield 3.0 g of colourless crystals (83%), *m.p.* 159 °C [20]. – ^1H NMR (200 MHz, CDCl_3) δ/ppm = 3.69 (m_c , 1H), 3.15 (m_c , 2H), 2.93 (s, 3H), 2.86 (s, 3H), 2.34 (m_c , 2H), 2.06 (m_c , 2H), 1.92–1.70 (m, 2H). – ^{13}C NMR (50 MHz, CDCl_3) δ/ppm = 210.2 (s), 57.4 (t), 47.3 (q), 45.6 (q), 42.7 (d), 42.4 (t), 34.5 (t), 28.3 (t), 25.3 (t).

2-Dimethylaminomethyl-cyclopentanone hydrochloride (3g)

Prepared from 1.49 g (20.0 mmol) cyclopentanone and 1.87 g (20.0 mmol) of *N,N*-dimethylmethyle ammonium chloride (2). Yield 2.84 g of colourless crystals (89%), *m.p.* 150 °C [9b]. – ^1H NMR (200 MHz, CDCl_3) δ/ppm = 3.41 (m_c , 1H), 3.02 (m_c , 1H), 2.86 (t, 3J = 4.43 Hz, 6H), 2.76 (m_c , 2H), 2.38 (m_c , 1H), 2.10 (m_c , 2H), 1.83 (m_c , 2H). – IR (KBr) ν/cm^{-1} = 3015, 2963, 2853, 2672, 2595, 2479, 1732, 1474, 1408, 1159, 1115, 1009, 964, 926, 824.

Preparation of the 1,5-Diketones (5a–e) (General Procedure)

The reactions were carried out by refluxing 0.1 mol of the pyrrolidine enamine 4 [21] with 0.1 mole of the Mannich base in 100 mL of dioxane for 16 h. After addition of 30 mL of water, the reaction mixture was refluxed for 1 h. The solution was cooled to room temperature, and additional 100 mL of water were added. The reaction mixture was extracted with CH_2Cl_2 (4 × 40 mL). The organic layer was washed with 20 mL of dilute HCl, 20 mL of water and dried over Na_2SO_4 . Rotary evaporation yielded brown oils which were purified either by Kugelrohr distillation or chromatography.

2-(3-Oxo-3-phenyl-propyl)-cyclohexanone (5a)

Prepared from 3.4 g (16.0 mmol) of Mannich base 3a and 2.4 g (16.0 mmol) of enamine 4. Yield 1.43 g (39%) of an oil after chromatography on SiO_2 , petroleum ether/EtOAc, 9:1. – ^1H NMR (200 MHz, CDCl_3) δ/ppm = 7.96 (dd, 3J = 7.0 Hz, 4J = 1.3 Hz, 2H), 7.48 (m_c , 3H), 3.03 (m_c , 2H), 2.34 (m_c , 3H), 2.08 (m_c , 2H), 1.85 (m_c , 2H), 1.66 (m_c , 2H), 1.39 (m_c , 2H). – ^{13}C NMR (50 MHz, CDCl_3) δ/ppm = 213.6 (s), 200.6 (s), 137.2 (s), 133.4 (d), 128.9 (d), 128.5 (d), 50.3 (d), 48.1 (t), 36.7 (t), 35.0 (t), 28.5 (t), 25.5 (t), 24.9 (t). – IR (KBr) ν/cm^{-1} = 2935, 2852, 1698, 1678, 1595, 1585, 1445, 1367, 1316, 1274, 1222, 741, 685.

2-(3-Oxo-3-(4-brom-phenyl)-propyl)-cyclohexanone (5b)

Prepared from 2.6 g (8.9 mmol) of Mannich base 3b and 1.34 g (8.9 mmol) of enamine 4. Yield 1.7 g (62%) of an oil after flash chromatography on SiO_2 , petroleum ether/EtOAc, 3:1. – ^1H NMR (200 MHz, CDCl_3) δ/ppm = 7.86 (d, 3J = 8.2 Hz, 2H), 7.60 (d, 3J = 8.2 Hz, 2H), 3.02 (m_c , 2H), 2.40 (m_c , 2H), 2.10 (m_c , 3H), 1.83 (m_c , 2H), 1.65 (m_c , 2H), 1.47 (m_c , 2H). – ^{13}C NMR (50 MHz, CDCl_3) δ/ppm = 212.6 (s), 199.6 (s), 135.9 (s), 132.2 (d), 130.2 (d), 128.5 (s), 50.34 (8d), 42.7 (t), 36.8 (t), 35.1 (t), 28.5 (t), 25.5 (t), 24.9 (t). – IR (KBr)

ν/cm^{-1} = 2924, 2551, 1703, 1683, 1590, 1460, 1398, 1072, 1005, 824.

2-(3-Oxo-3-(tert-butyl)-propyl)-cyclohexanone (5c)

Prepared from 25.2 g (0.14 mol) of Mannich base 3c and 21.0 g (0.14 mol) of enamine 4. Yield 21.3 g (77%) of an oil after distillation, *b.p.* 175 °C/0.9 mbar. – ^1H NMR (200 MHz, CDCl_3) δ/ppm = 2.52 (m_c , 2H), 2.41–2.19 (m, 3H), 2.19–1.97 (m, 2H), 1.97–1.71 (m, 2H), 1.71–1.48 (m, 2H), 1.48–1.24 (m, 2H), 1.10 (s, 9H). – ^{13}C NMR (50 MHz, CDCl_3) δ/ppm = 216.5 (s), 213.7 (s), 50.7 (d), 44.5 (s), 42.6 (t), 35.0 (d), 34.5 (t), 28.5 (d), 26.8 (q), 25.9 (t), 24.6 (t). – IR (KBr) ν/cm^{-1} = 2935, 2862, 1713, 1481, 1445, 1367, 1305, 1129, 1062, 985.

2-(2-Methyl-3-oxo-3-phenyl-propyl)-cyclohexanone (5d)

Prepared from 2.4 g (10.6 mmol) of Mannich base 3d and 1.51 g (10 mmol) of enamine 4. Yield 1.1 g (46%) of an oil after distillation, *b.p.* 190 °C/0.8 mbar.

2-(3-Oxo-2,3-diphenyl-propyl)-cyclohexanone (5e)

Prepared from 2.14 g (7.4 mmol) of Mannich base 3e and 1.12 g (7.4 mmol) of enamine 4. Yield 1.5 g (67%) of an oil which slowly crystallizes after distillation, *b.p.* 200 °C/0.8 mbar. – ^1H NMR (200 MHz, CDCl_3) δ/ppm = 8.03 (m_c , 2H), 7.63–7.20 (m, 8H), 4.94 (m_c , 1H), 2.54–1.31 (m, 9H). – ^{13}C NMR (50 MHz, CDCl_3) δ/ppm = 214.1 (s), 213.9 (s), 200.4 (s), 198.1 (s), 140.6 (s), 138.5 (s), 136.6 (s), 137.0 (s), 135.0 (s), 133.6 (d), 133.4 (d), 133.3 (s), 129.9 (d), 129.4 (d), 129.3 (d), 129.2 (d), 129.1 (d), 129.1 (d), 129.0 (d), 128.4 (d), 127.6 (d), 127.4 (d), 127.3 (d), 51.6 (d), 51.0 (d), 49.3 (d), 48.1 (d), 45.8 (t), 42.8 (t), 35.8 (t), 35.3 (t), 34.4 (t), 35.6 (t), 28.7 (t), 28.6 (t), 25.5 (t).

Preparation of the 5,6,7,8-Tetrahydroquinolines (6a–e) (General Procedure)

The diketone (10.0 mol) and hydroxylammonium hydrochloride (10.0 mol) were refluxed in 10 mL of ethanol for 3 h. The reaction mixture was neutralized with Na_2CO_3 . After addition of 50 mL of water the solution was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were dried over Na_2SO_4 . Rotary evaporation yielded the crude products which were purified either by Kugelrohr distillation or chromatography.

2-Phenyl-5,6,7,8-tetrahydroquinoline (6a)

Prepared from 1.43 g (6.3 mmol) of diketone 5a and 0.44 g (6.3 mmol) of hydroxyl-ammonium hydrochloride. Yield 0.55 g (42%) of an oil after distillation, *b.p.* 150–160 °C/0.3 mbar [10a]. – ^1H NMR (200 MHz, CDCl_3) δ/ppm = 7.95 (mc, 2H), 7.38 (m_c , 5H), 3.00 (t, 3J = 6.2 Hz, 2H), 2.77 (t, 3J = 6.2 Hz, 2H), 1.88 (m_c , 4H). – ^{13}C NMR (50 MHz, CDCl_3) δ/ppm = 157.7 (s), 155.1 (s), 140.4 (s), 137.9 (d), 131.2 (s), 129.1 (d), 127.8 (d), 127.3 (d), 118.4 (d), 33.3 (t), 29.0 (t), 23.7 (t), 23.3 (t). – IR (KBr) ν/cm^{-1} = 2929, 2862, 1594, 1564, 1455, 1253, 1253, 1129, 1031, 772, 736, 695. – MS (EI/70 eV) *m/z* (%) = 208 (100) [M^+], 195 (11), 181 (30), 154 (3), 141 (6), 115 (10), 77 (9).

2-(4-Brom-phenyl)-5,6,7,8-tetrahydroquinoline (6b)

Prepared from 1.66 g (5.4 mmol) of diketone 5b and 0.38 g (5.4 mmol) of hydroxylammonium hydrochloride. Yield

0.70 g (45%) of a white solid after chromatography on SiO₂, petroleum ether/Et₂O, 5:1, *m.p.* 109 °C. – ¹H NMR (200 MHz, CDCl₃) δ/ppm = 7.87 (m_c, 2H), 7.59 (m_c, 2H), 7.45 (s, 2H), 3.02 (t, ³J = 6.2 Hz, 2H), 2.83 (t, ³J = 6.2 Hz, 2H), 1.92 (m_c, 4H, CH₂). – ¹³C NMR (50 MHz, CDCl₃) δ/ppm = 157.9 (s), 153.0 (s), 139.2 (s), 137.9 (d), 132.1 (d), 131.6 (s), 128.8 (d), 123.1 (s), 118.0 (d), 32.2 (t), 29.0 (t), 23.6 (t), 23.2 (t). – IR (KBr) ν/cm⁻¹ = 2940, 1579, 1455, 1072, 1005, 813.

2-(tert-Butyl)-5,6,7,8-tetrahydroquinoline (6c)

Prepared from 21.3 g (0.11 mol) of diketone **5c** and 7.3 g (0.11 mol) of hydroxylammonium hydrochloride. Yield 15.0 g (76%) of a liquid after distillation, *b.p.* 97 °C 1 mbar [22]. – ¹H NMR (200 MHz, CDCl₃) δ/ppm = 7.31 (d, ³J = 8.0 Hz, 1H), 7.11 (d, ³J = 8.0 Hz, 1H), 2.95 (t, ³J = 6.3 Hz, 2H), 2.77 (t, ³J = 6.3 Hz, 2H), 1.89 (m_c, 4H), 1.39 (s, 9H). – ¹³C NMR (50 MHz, CDCl₃) δ/ppm = 166.5 (s), 156.2 (s), 137.2 (d), 129.1 (s), 116.5 (d), 37.4 (s), 33.3 (t), 30.8 (q), 28.9 (t), 23.8 (t), 23.3 (t). – IR (KBr) ν/cm⁻¹ = 2952, 2852, 1595, 1568, 1488, 1468, 1350, 1132, 823.

2-Phenyl-3-methyl-5,6,7,8-tetrahydroquinoline (6d)

Prepared from 1.0 g (4.6 mmol) of diketone **5d** and 0.88 g (4.6 mmol) of hydroxylammonium hydrochloride. Yield 0.34 g (33%) of an oil after chromatography on SiO₂, petroleum ether/Et₂O, 2:1. – ¹H NMR (200 MHz, CDCl₃) δ/ppm = 7.39 (m_c, 5H), 7.23 (s, 1H), 2.94 (t, ³J = 6.2 Hz, 2H), 2.76 (t, ³J = 6.2 Hz, 2H), 2.24 (s, 3H). – ¹³C NMR (50 MHz, CDCl₃) δ/ppm = 156.2 (s), 154.8 (s), 14.1 (s), 139.6 (d), 131 (s), 129.4 (d), 128.6 (d), 128.1 (s), 127.0 (d), 32.7 (t), 28.8 (t), 23.8 (d), 23.3 (d), 19.9 (q). – IR (KBr) ν/cm⁻¹ = 2929, 2852, 1564, 1435, 1429, 1248, 1021, 783, 741, 705.

2,3-Diphenyl-5,6,7,8-tetrahydroquinoline (6e)

Prepared from 1.5 g (5.0 mmol) of diketone **5e** and 0.36 g (5.0 mmol) of hydroxylammonium hydrochloride. Yield 0.5 g (54%) of white crystals after chromatography on SiO₂, petroleum ether/Et₂O, 10:1, *m.p.* 105 °C [23]. – ¹H NMR (200 MHz, CDCl₃) δ/ppm = 7.38 (s, 1H), 7.33 (m_c, 2H), 7.20 (m_c, 8H), 3.03 (t, ³J = 6.3 Hz, 2H), 2.83 (t, ³J = 6.3 Hz, 2H), 1.80 (m_c, 4H). – ¹³C NMR (50 MHz, CDCl₃) δ/ppm = 156.6 (s), 154.7 (s), 140.9 (s), 140.6 (s), 139.6 (d), 133.8 (s), 131.2 (s), 130.4 (d), 130.0 (d), 128.6 (d), 128.3 (d), 127.8 (d), 127.3 (d), 33.0 (t), 28.9 (t), 23.7 (t), 23.3 (t). – IR (KBr) ν/cm⁻¹ = 2924, 2857, 1543, 1445, 1424, 1248, 1070, 990, 767, 700. – MS (EI/70 eV) *m/z* (%) = 285 (100) [M⁺], 256 (13), 215 (5), 165 (3), 133 (6), 127 (10), 114 (6), 77 (4).

Preparation of the Hexahydroacridinones (8f–g) (General Procedure)

A suspension of 5 mmol of the appropriate carbonyl compound, 5 mmol of the β-amino ketone hydrochloride and 15 mmol of ammonium acetate (anhydrous) in 25–30 mL of absolute ethanol were refluxed for 3–4 h under argon. After cooling to room temperature, the ethanol was removed *in vacuo*. The crude product was dissolved in a mixture of 35–40 mL CH₂Cl₂, 15–20 mL of H₂O and 5 mL of 25% ammonia solution. The organic layer was separated, and the residual aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were washed with H₂O and dried with Na₂SO₄. After removal of the solvent, the residue was dis-

solved in 25 ml of CH₂Cl₂, and circa 2 g of SiO₂ are added. The mixture was stirred under an oxygen atmosphere over night and then filtered. The filter cake was washed thoroughly with CH₂Cl₂/MeOH, 10:1. The solvent was removed in vacuo, and the residue was purified by flash chromatography on Al₂O₃, CH₂Cl₂.

3,4,5,6,7,8-Hexahydro-2H-acridin-1-one (8f)

Prepared from 5.0 g (21.6 mmol) of Mannich base **3f**, 2.42 g (21.6 mmol) of 1,3-cyclohexandione (**7**) and 4.99 g (64.8 mmol) of NH₄OAc. Yield 3.56 g (76%) of a yellow solid after flash chromatography on Al₂O₃, CH₂Cl₂, *m.p.* 96 °C [12a]. – ¹H NMR (200 MHz, CDCl₃) δ/ppm = 7.98 (s, 1H), 3.10 (t, ³J = 6.1 Hz, 2H), 2.97 (t, ³J = 6.1 Hz, 2H), 2.83 (t, ³J = 6.1 Hz, 2H), 2.68 (m_c, 2H), 2.19 (m_c, 2H), 1.91 (m_c, 4H). – ¹³C NMR (50 MHz, CDCl₃) δ/ppm = 198.7 (s), 162.9 (s), 160.9 (s), 135.6 (d), 131.5 (s), 126.3 (s), 39.0 (t), 33.5 (t), 32.6 (t), 28.7 (t), 23.2 (t), 22.9 (t), 22.5 (t). – IR (KBr) ν/cm⁻¹ = 3021, 2999, 2941, 2876, 2557, 1998, 1693, 1635, 1556, 1425, 1363, 1332, 1284, 801.

1,2,3,5,6,7-Hexahydro-cyclopenta[b]quinolin-8-one (8g)

Prepared from 680 mg (3.84 mmol) of Mannich base **3g**, 430 mg (3.84 mmol) of 1,3-cyclohexandione (**6**) and 887 mg (11.52 mmol) of NH₄OAc. Yield 304 mg (42%) of a white solid after flash chromatography on Al₂O₃, CH₂Cl₂, *m.p.* 59 °C [12a]. – ¹H NMR (200 MHz, CDCl₃) δ/ppm = 8.63 (s, 1H), 2.88 (m_c, 6H), 2.51 (t, ³J = 6.1 Hz, 2H), 2.02 (m_c, 4H). – ¹³C NMR (50 MHz, CDCl₃) δ/ppm = 198.4 (s), 171.1 (s), 162.4 (s), 136.1 (s), 130.6 (d), 126.4 (s), 38.9 (t), 35.0 (t), 32.8 (t), 30.5 (t), 23.3 (t), 22.4 (t). – IR (KBr) ν/cm⁻¹ = 2939, 1690, 1602, 1408, 1360, 1210, 924.

References

- [1] J. P. Michael, *Nat. Prod. Rep.* **1997**, *14*, 605
- [2] M. Balasubramanian, J. G. Keay in: *Comprehensive Heterocyclic Chemistry II*, A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Eds., Pergamon Press, Oxford 1996, Vol. 5, Chapter 5.06, 245
- [3] G. Chelucci, S. Cossu, G. Scano, F. Soccolini, *Heterocycles*, **1990** *31*, 1397
- [4] C. Botteghi, A. Schionato, G. Chelucci, H. Brunner, A. K. Kurzingen, U. Obermann, *J. Organomet. Chem.* **1989**, *370*, 17
- [5] C. Rosini, C. Bertucci, D. Pini, P. Salvadori, F. Soccolini, G. Delogu, *J. Chem. Soc., Chem. Commun.* **1983**, 287
- [6] F. Gatta, M. R. Del Giudice, M. Pomponi, M. Marta, *Heterocycles* **1992**, *34*, 991; HP-029 (9-amino-1,2,3,4-tetrahydroacridin-1-ol) and HP-128 [(9-benzylamino-1,2,3,4-tetrahydroacridin-1-ol) Hoechst-Roussel.
- [7] (a) T. W. Bell, P. J. Cragg, A. Firestone, A. D.-I. Kwok, J. Liu, R. Ludwig, A. Sodoma, *J. Org. Chem.* **1998**, *63*, 2231; (b) V. Grosshenny, F. M. Romero, R. Ziessel, *J. Org. Chem.* **1997**, *62*, 1491
- [8] R. P. Thummel, *Synlett* **1992**, *1*; A. P. Marchand, *Aldrichimica Acta* **1995**, *28*, 95
- [9] (a) R. Keuper, N. Risch, U. Flörke, H.-J. Haupt, *Liebigs Ann.* **1996**, 705; (b) R. Keuper, N. Risch, *Liebigs Ann.* **1996**, 717; (c) R. Keuper, N. Risch, *Eur. J. Org. Chem.* **1998**, 2609
- [10] (a) N. S. Gill, K. B. James, F. Lions, K. T. Potts, *J. Am. Chem. Soc.* **1952**, *74*, 4923; (b) M. v. Strandtmann, M. P. Cohen, J. Shavel, *J. Am. Chem. Soc.* **1965**, *30*, 3241; (c) H.

- J. Roth, R. Troschütz, Arch. Pharm. **1977**, 310, 48; (d) R. Troschütz, H. J. Roth, Arch. Pharm. **1978**, 311, 400; (e) H. J. Roth, E. Schumann, Arch. Pharm., **1970**, 303, 268.
- [11] G. Kinast, L. F. Tietze, Angew. Chem. **1976**, 88, 261
- [12] (a) C. Ruangsriyanand, H. J. Rimek, F. Zymalkowski, Chem. Ber. **1970**, 103, 2403; (b) T. W. Bell, Y.-M. Cho, A. Firestone, K. Healy, J. Liu, R. Ludwig, S. D. Rothenberger, Organic Synth. Coll. Vol. VIII **1990**, 69, 226
- [13] T. Nagakome, Ger. Offen. 2. 103, 805; ref. in Chem. Abstr. **1971**, 75, 98464
- [14] Adalat® [Bayer AG]
- [15] F. Bossert, Ger. Offen. 2. 003. 148; ref. in Chem. Abstr. **1971**, 75, 98464
- [16] A. B. Daruwala, J. E. Gearien, W. J. Dunn, S. P. Benoit, L. Bauer, J. Med. Chem. **1974**, 8, 819
- [17] A. F. Casy, J. L. Myers, J. Chem. Soc. **1965**, 4092
- [18] A. F. Casy, R. R. Ison, Tetrahedron **1969**, 25, 641
- [19] U. Westerwelle, A. Esser, N. Risch, Chem. Ber. **1991**, 124, 571
- [20] F. F. Blicke, F.J. Mc Carty, J. Org. Chem. **1959**, 24, 1069
- [21] G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovicz, R. Terrell, J. Am. Chem. Soc. **1963**, 85, 207
- [21] G. Chelucci, S. Cossu, F. Soccolini, J. Heterocycl. Chem. **1986**, 23, 1283
- [23] E. C. Taylor, J. E. Macor, L. G. French, G. Larry, J. Org. Chem. **1991**, 56, 1807

Address for correspondence:
Prof. Dr. N. Risch
Fachbereich Chemie und Chemietechnik
der Universität-GH Paderborn
Warburger Str. 100
D-33098 Paderborn
Fax: Internat. code (0) 5251-60-3245
e-Mail: nr@chemie.uni-paderborn.de