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Synthesis of Aza Analogs of the Herbicide Sindone B[a]

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Summary. The synthesis of a series of quinoline and isoquinoline derivatives *via* condensation of 1,3-dicarbonyl compounds with enaminonitrile **1** is described yielding hydrophilic analogs of the herbicide Sindone B.

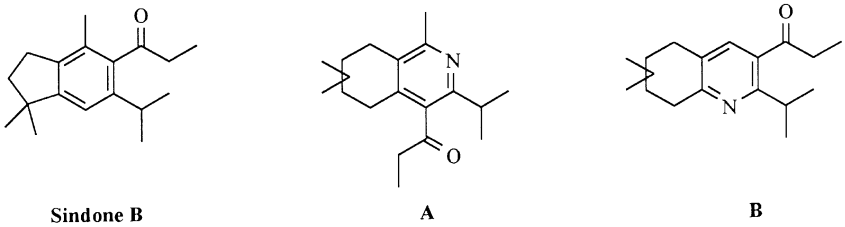
Keywords. Herbicides; Sindones; Quinolines; Isoquinolines.

Synthese von Azaanaloga des Herbizids Sindone B

Zusammenfassung. Die Synthese einer Reihe von Chinolin- und Isochinolinderivaten über Kondensation von 1,3-Dicarbonylverbindungen mit dem Enaminonitril **1** wird beschrieben, wobei hydrophile Analoga des Herbizids Sindone B erhalten wurden.

Introduction

Some time ago, a new type of herbicidal compounds – later called sindones – has been found by chance in the course of routine biological screening of a series of products originally aimed as flavouring compounds and fragrances from the musk type [1a]. The compound showing biologically most interesting results within this class was Sindone B, a product with good selectivity against grass weeds. Unfortunately, adequate herbicidal activity has been reached only at application rates of about 2 kg/ha, too much for a modern herbicide. In 1994 we have



Sindone B A B

Scheme 1

[a] Dedicated to Prof. Dr. *Gottfried Heinisch* on the occasion of his 60th birthday
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published the synthesis of N,N-dimethyl-isobenzofuranamines as isosteric analogs of Sindone B [1b]. In the present paper we report the synthesis of some quinoline and isoquinoline derivatives of the general formulae **A** and **B** designed as even more hydrophilic analogs of Sindone B.

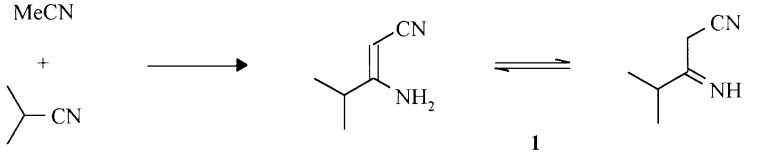
Results and Discussion

Our synthetic strategy towards the target compounds was based on the reaction of enaminonitrile **1** with various 1,3-dicarbonyl compounds **2** derived from cyclopentanone or cyclohexanone. It can be considered as a useful modification of a procedure published previously [2] where various enaminoaldehydes and -ketones were reacted with β-ketoesters and symmetrical 1,3-diketones. There are two synthetic approaches described in the literature that lead to the desired enaminonitrile **1** [3a, 3b]. Using a slightly modified procedure of Ref. [3a], we could achieve an almost quantitative yield by performing this reaction in *THF* instead of diethyl ether with *LDA* as base. NMR data show that in $CDCl_3$ solution **1** exists in an equilibrium with its imine tautomer (see Experimental).

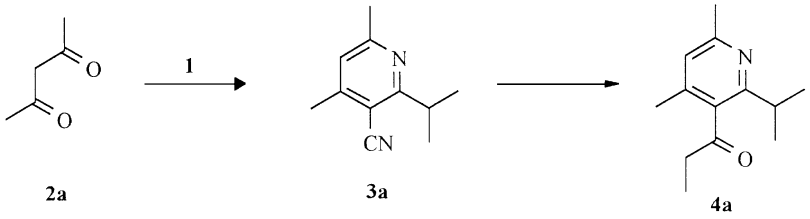
In a model reaction, acetylacetone was chosen to react with **1**. Reaction of the resulting nitrile **3a** with EtMgBr yielded the corresponding imine which subsequently was hydrolyzed to the propanone **4a**.

So far not being commercially available, the 1,3-dicarbonyl compounds required for the construction of the target compounds were synthesized mainly using published procedures [4a–f]. The diketone **2d** was made available by the approach shown in Scheme 4.

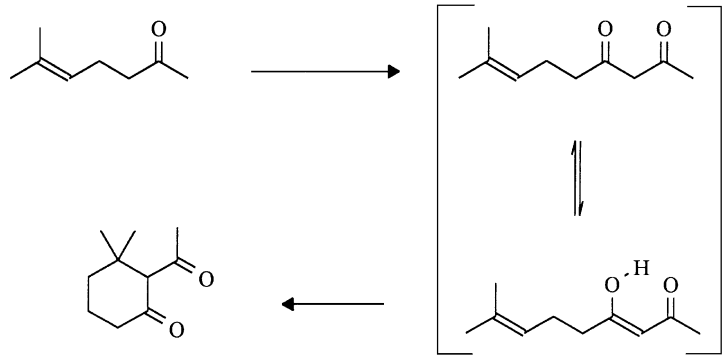
In our first experiments, 2-acetylcyclohexanones **2c–e** were reacted with **1** and a catalytic amount of ammonium acetate, yielding a mixture of the corresponding quinoline and isoquinoline derivatives in each case. As we failed to separate the isomers by chromatographic methods, only the isoquinoline-4-carbonitriles **3c–e** could be isolated in modest yields by recrystallization of the crude mixture. Taking into account the chosen reaction conditions, the mechanism of the reaction should



Scheme 2

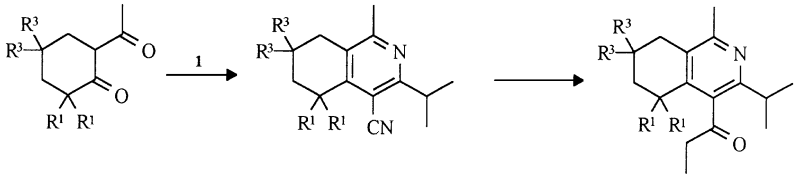


Scheme 3



2d

Scheme 4



	R^1	R^3
2c	H	H
2d	Me	H
2e	H	Me

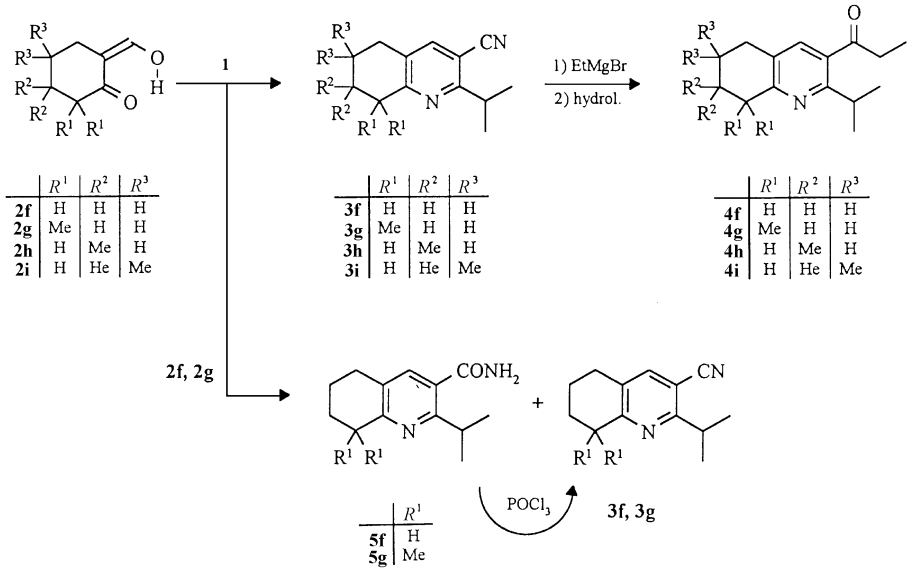
	R^1	R^3
3c	H	H
3d	Me	H
3e	H	Me

	R^1	R^3
4c	H	H
4d	Me	H
4e	H	Me

Scheme 5

consist of an initial *Knoevenagel* condensation of the enamino moiety with one of the carbonyl groups followed by the attack of the amino group at the second carbonyl group, thus leading to cyclization. The formation of the isoquinoline isomer as the main product reflects the higher reactivity of the ring carbonyl group. The nitriles **3c–e** were now easily transformed to the propanones **4c–e** in the reaction mentioned for **4a** (Scheme 5). Attempts to perform an analogous cyclization of **1** with 2-acetylcyclopentanone (**2b**) were very disappointing as only tars were obtained.

Taking into account the results so far, the availability of the corresponding quinoline derivatives as main products became an interesting issue. In order to achieve this, we had to interchange the reactivity of the two carbonyl groups starting with 2-formylcyclohexanones **2f–i** that exist mainly as the 2-hydroxymethylene tautomers. In our first attempt we reacted **1** with 2-hydroxymethylenecyclohexanone (**2f**) under the same reaction conditions and isolated a mixture of the expected carbonitriles **3f** and the corresponding carboxamide **5f** which could be easily isolated by crystallization. As this caboxamide was easily dehydrated to the carbonitrile by $POCl_3$, its isolation was not necessary. Instead, the crude mixtures of **3** and **5** were subsequently reacted with $POCl_3$ leading to the pure carbonitriles **3**. The following transformation was again performed with an excess



	R^1	R^2	R^3
2f	H	H	H
2g	Me	H	H
2h	H	Me	H
2i	H	He	Me

	R^1	R^2	R^3
3f	H	H	H
3g	Me	H	H
3h	H	Me	H
3i	H	He	Me

	R^1	R^2	R^3
4f	H	H	H
4g	Me	H	H
4h	H	Me	H
4i	H	He	Me

	R^1
5f	H
5g	Me

Scheme 6

of EtMgBr and yielded the target compounds **4f–i** upon hydrolysis of the imine intermediates.

Experimental

^{1}H and ^{13}C NMR spectra were recorded from $CDCl_3$ solutions on a BRUKER AC 200 or a JEOL FX 90 Q NMR spectrometer and related to *TMS* ($\delta = 0$ ppm). Melting points were determined on a Kofler hot stage microscope and are uncorrected. Elemental analyses were performed at the Institute of Physical Chemistry, University of Vienna; the data for C, H, N were within 0.3% of the calculated values. Reactions were monitored by TLC using alumina backed silica 60 F_{254} plates (Merck 5554) and visualized using UV light. Column chromatography was performed using Kieselgel 60 (0.040–0.063 mm, Merck 9385). All solvents were distilled prior to use.

Acetylacetone (**2a**), 2-acetylcyclopentanone (**2b**), and 2-acetylcyclohexanone (**2c**) are commercially available and were used without further purification. The following compounds utilized as starting materials were prepared according to the Refs. cited: 2-acetyl-4,4-dimethyl-cyclohexanone (**2e**) [4d], 2-hydroxymethylenecyclohexanone (**2f**) [4b], 2-hydroxymethylene-6,6-dimethylcyclohexanone (**2g**) [4e], 2-hydroxymethylene-5,5-dimethylcyclohexanone (**2h**) [4b, 4c], and 2-hydroxymethylene-4,4-dimethylcyclohexanone (**2i**) [4b, 4f].

3-Amino-4-methyl-2-pentenenitrile (**1**, $C_6H_{10}N_2$)

A 2.5 *M* *n*-BuLi solution in hexane (61.4 ml, 152.4 mmol) was slowly added to a solution of 15.52 g (152.4 mmol) (*i*-Pr)$_2$NH in 150 ml of dry *THF* under nitrogen at -10°C. After stirring for 30 min at this temperature, the solution was cooled to -80°C and treated with 6.00 g (146.2 mmol) of CH_3CN dissolved in 15 ml of dry *THF*. After 10 min, 10.10 g (146.2 mmol) of isobutyronitrile dissolved in 20 ml of dry *THF* were added dropwise. The suspension was warmed to room temperature, stirred overnight, and poured on ice/water. After evaporation of the organic solvent, the remaining emulsion was extracted twice with 100 ml of diethyl ether. The combined organic layers were dried over

anhydrous sodium sulfate, filtered, and evaporated. The resulting crude product was purified by *Kugelrohr* distillation to give 15.62 g (97%) of a pale yellow, partially crystalline oil.

B.p.: 75–80°C/0.05 mbar (Ref. [3a]: 92–94°C/0.5 mbar); ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 4.60 (bs, enamine-NH_2 and imine-NH), 3.90 and 3.80 (2s, CH_2CN and C=CHCN), 3.20 and 2.38 (2 sept, 1H, imine- and enamine-C*H*$(CH_3)_2$, $J = 9$ Hz), 1.19 and 1.14 (2d, 6H, imine- and enamine-$(CH_3)_2$, $J = 9$ Hz) ppm.

2-Acetyl-6,6-dimethylcyclohexanone (**2d**, $C_{10}H_{16}O_2$)

A solution of 39.70 g (314.6 mmol) 6-methyl-5-hepten-2-one and 83.18 g (943.5 mmol) ethyl acetate in 150 ml of dry diethyl ether was added under nitrogen to a mechanically stirred suspension of 42.46 g (755.4 mmol) sodium ethanolate in 250 ml of dry diethyl ether over a period of 3 h while keeping the temperature between −25 and −20°C. The cooling bath was then removed, and the mixture was stirred for another 20 h. The reaction mixture was hydrolyzed with 400 ml of ice/water and extracted with 200 ml of diethyl ether. The organic layer was extracted with 100 ml of 2 *N* sodium hydroxide, the combined aqueous layers were acidified to $pH = 1$ by addition of conc. hydrochloric acid and extracted twice with 250 ml of diethyl ether. The combined ether layers were dried over anhydrous sodium sulfate, filtered, and evaporated. The product was purified by distillation to give 33.77 g (64%) of 4-hydroxy-8-methyl-3,7-nonadien-2-one (which is in a tautomeric equilibrium with 8-methyl-7-nonen-2,4-dion) as a colorless liquid.

B.p.: 102–103.5°C/13 mbar (Ref. [4c]: 105–107°C/15 mbar); ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 5.49 (s), 5.16–4.92 (m, 1H, H-7), 3.70–3.54 (m), 2.60–2.49 (m), 2.31 (s), 2.30 (s), 2.23 (s), 2.17 (s), 2.11 (s), 2.04 (s), 1.70 and 1.63 (2s, 3H each, C-9 and 8-CH_3) ppm.

To a solution of 30.00 g (178.3 mmol) of 4-hydroxy-8-methyl-3,7-nonadien-2-one in 250 ml of dry dichloromethane, 11.62 g (44.6 mmol) $SnCl_4$ in 50 ml of dry dichloromethane were added under nitrogen at 0°C. After the addition was completed, the resulting solution was stirred for 20 h at room temperature. Then another 11.62 g (44.6 mmol) $SnCl_4$ in 50 ml of dry dichloromethane were added at once. After 1 h of stirring the reaction was hydrolyzed by addition of 200 ml of water. The aqueous layer was extracted with 100 ml of dichloromethane, and the combined organic layers were dried over sodium sulfate, filtered, and evaporated. The product was purified by distillation to give 25.20 g (84%) of 2-acetyl-6,6-dimethyl-cyclohexanone (**2d**) as a colorless liquid.

B.p.: 98–100°C/13 mbar (Ref. [4c]: 107–108°C/16 mbar); ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 3.44 (s, 1H, H-2), 2.75–1.25 (m, 6H, H-4, H-5 and H-6), 2.24 (s, 3H, $COCH_3$), 1.07 and 0.98 (2s, 3H each, $(CH_3)_2$, *cis* and *trans*) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 207.0 and 204.2 (2s, 2 CO), 73.9 (d, C-2), 38.7 (t, C-4), 38.6 (s, C-3), 34.8, 32.8, 27.4, 25.1 (q, CO*C*H_3), 21.3 (t, C-5) ppm; the NMR data are given for the main tautomer (diketo form).

Method A: General procedure for the condensation of enaminonitrile **1** *with 1,3-dicarbonyl compounds* **2**

A mixture of 25.0 mmol **1**, 25.0 mmol **2**, and 25.0 mmol ammonium acetate was heated overnight at 110°C. After cooling to room temperature, 100 ml of diethyl ether were added. The resulting mixture was dried over anhydrous sodium sulfate, filtered, and evaporated. The crude products were purified by recrystallization, *Kugelrohr* distillation, or column chromatography as stated below.

4,6-Dimethyl-2-(1-methylethyl)-3-pyridinecarbonitrile (**3a**, $C_{11}H_{14}N_2$)

The product was purified by *Kugelrohr* distillation and by column chromatography (petroleum ether:ethyl acetate = 15:1). Yield: 76%; colorless crystals; m.p.: 49–50.5°C, b.p.: 70–75°C/0.08 mbar; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 6.88 (s, 1H, H-5), 3.49 (m, 1H, C*H*$(CH_3)_2$, $J = 7$ Hz),

2.56 and 2.50 (2s, 3H each, 4-CH_3 and 6-CH_3), 1.32 (d, 6H, $(CH_3)_2$, $J = 7$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 169.1 (s, C-2), 161.2 (s, C-6), 150.7 (s, C-4), 121.4 (d, C-5), 116.2 (s, CN), 105.4 (s, C-3), 34.5 (d, *C*H$(CH_3)_2$), 24.5 (q, 6-CH_3), 21.5 (q, $(CH_3)_2$), 20.0 (q, 4-CH_3) ppm.

5,6,7,8-Tetrahydro-1-methyl-3-(1-methylethyl)-4-isoquinolinecarbonitrile (**3c**, $C_{14}H_{18}N_2$)

The crude product was first purified by *Kugelrohr* distillation and by column chromatography (petroleum ether:ethyl acetate = 15:1) to give 69% of a pale yellow, partially crystalline isomer mixture consisting of approximately 80% **3c** and 20% 5,6,7,8-tetrahydro-4-methyl-2-(1-methylethyl)-3-quinolinecarbonitrile. This mixture was recrystallized from 80% MeOH to give 38% of **3c**. Colorless crystals; m.p.: 44.5–46°C; b.p.: 80–85°C/0.004 mbar; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 3.70–3.25 (m, 1H, C*H*$(CH_3)_2$, $J = 7$ Hz), 3.00–2.80 (m, 2H, H-5), 2.75–2.50 (m, 2H, H-8), 2.47 (s, 3H, 1-CH_3), 2.00–1.75 (m, 4H, H-6 and H-7), 1.30 (d, 6H, $(CH_3)_2$, $J = 7$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 165.4 (s, C-3), 160.0 (s, C-1), 148.4 (s, C-4a), 128.1 (s, C-8a), 116.0 (s, CN), 105.2 (s, C-4), 33.9 (d, CH), 28.0 (t, C-5 and C-8), 25.3 (q, 1-CH_3), 22.4 and 22.0 (2t, C-6 and C-7), 21.3 (q, $(CH_3)_2$) ppm.

5,6,7,8-Tetrahydro-1,5,5-trimethyl-3-(1-methylethyl)-4-isoquinolinecarbonitrile (**3d**, $C_{16}H_{22}N_2$)

The crude product was submitted to a *Kugelrohr* distillation (85–150°C/0.001 mbar). The yellow, milky distillate was then purified chromatographically (petroleum ether:ethyl acetate = 20:1) and finally recrystallized from 80% MeOH. Yield: 36%; colorless crystals; m.p.: 60.5–63.5°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 3.42 (hpt, 1H, C*H*$(CH_3)_2$, $J = 7$ Hz), 3.05–2.80 (m, 2H, H-5), 2.48 (s, 3H, 1-CH_3), 1.95–1.55 (m, 4H, H-6 and H-7), 1.42 (s, 6H, $(CH_3)_2$), 1.31 (d, 6H, CH(C*H*$_3)_2$, $J = 7$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 165.2 (s, C-3), 161.0 (s, C-1), 149.5 (s, C-4a), 136.8 (s, C-8a), 116.8 (s, CN), 105.9 (s, C-4), 42.7 (t, C-7), 34.0 (d, CH), 33.3 (s, C-8), 30.6 (t, C-5), 28.6 (q, $(CH_3)_2$), 27.2 (q, CH_3), 21.6 (q, CH(*C*H$_3)_2$), 18.0 (t, C-6) ppm.

5,6,7,8-Tetrahydro-1,7,7-trimethyl-3-(1-methylethyl)-4-isoquinolinecarbonitrile (**3e**, $C_{16}H_{22}N_2$)

The product was purified by column chromatography (petroleum ether:diethyl ether = 2:1) and by recrystallization from ethanol. Yield: 41%; yellow powder; m.p.: 85–87°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 3.43 (hpt, 1H, C*H*$(CH_3)_2$, $J = 7$ Hz), 2.90 (t, 2H, H-5), 2.45 (s, 3H, CH_3), 2.33 (s, 2H, H-8), 1.58 (t, 2H, H-6), 1.28 (d, 6H, CH(C*H*$_3)_2$), 1.00 (s, 6H, $(CH_3)_2$) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 165.7 (s, C-3), 160.7 (s, C-1), 147.7 (s, C-4a), 127.9 (s, C-8a), 116.5 (s, CN), 105.1 (s, C-4), 39.4 (t, C-8), 34.1, 33.9, 29.0 (s, C-7), 28.0 (q, $(CH_3)_2$), 25.6 (q, CH_3), 22.9 (q, C-5), 21.6 (q, CH(*C*H$_3)_2$) ppm.

Method B: General procedure for the synthesis of **3f–i**

The crude products derived from method *A* or the isolated intermediates **5f**, **g** were treated with 30 ml of $POCl_3$ and the resulting mixture was heated under reflux for 1 h. Then, the excess reagent was distilled off and the residue was hydrolyzed with ice/water. After adjusting to $pH = 9$ with 2 *N* NaOH, the resulting mixture was extracted twice with 100 ml of diethyl ether. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated. The crude products were purified by column chromatography and/or *Kugelrohr* distillation as mentioned below.

5,6,7,8-Tetrahydro-2-(1-methylethyl)-3-quinolinecarbonitrile (**3f**, $C_{13}H_{16}N_2$)

The partially crystalline crude product was recrystallized from ethyl acetate yielding pure 5,6,7,8-tetrahydro-2-(1-methylethyl)-3-quinolinecarboxamide (**5f**): Yield: 34%; colorless crystals; m.p.:

185–186.5°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 7.34 (s, 1H, H-4), 5.90 (bs, 2H, $CONH_2$), 3.47 (hpt, 1H, C*H*$(CH_3)_2$, $J = 6.8$ Hz), 3.00–2.60 (m, 4H, H-5 and H-8), 2.00–1.70 (m, 4H, H-6 and H-7), 1.30 (d, 6H, $(CH_3)_2$, $J = 6.8$ Hz) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 170.5 (s, CO), 160.0 (s, C-2), 156.5 (s, C-8a), 135.1 (d, C-4), 128.8 and 128.1 (2s, C-3 and C-4a), 32.2 (t, C-8), 31.2 (d, CH), 27.5 (t, C-5), 22.6 and 22.4 (2t, C-6 and C-7), 22.4 (q, $(CH_3)_2$) ppm.

The mother liquor from the recrystallization was evaporated and the residue submitted to column chromatography (petroleum ether:ethyl acetate = 15:1) and then purified by *Kugelrohr* distillation. Yield: 31% **3f**; colorless crystals; m.p.: 39–40.5°C, b.p: 80–85°C/0.007 mbar; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 7.51 (s, 1H, H-4), 3.44 (hpt, 1H, C*H*$(CH_3)_2$, $J = 6.8$ Hz), 3.05–2.70 (m, 4H, H-5 and H-8), 2.00–1.70 (m, 4H, H-6 and H-7), 1.33 (d, 6H, $(CH_3)_2$, $J = 6.8$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 165.6 (s, C-2), 161.1 (s, C-8a), 139.8 (d, C-4), 129.3 (s, C-4a), 116.9 (s, CN), 104.2 (s, C-3), 33.8 (d, CH), 32.8 (t, C-8), 27.6 (t, C-5), 22.2 and 21.9 (2t, C-6 and C-7), 21.2 (q, $(CH_3)_2$) ppm.

5,6,7,8-Tetrahydro-8,8-dimethyl-2-(1-methylethyl)-3-quinolinecarbonitrile (**3g**, $C_{15}H_{20}N_2$)

The partially crystalline crude product was recrystallized from diisopropyl ether to give pure 5,6,7,8-Tetrahydro-8,8-dimethyl-2-(1-methylethyl)-3-quinolinecarboxamide (**5g**). Yield: 26%; colorless crystals; m.p.: 159–160°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 7.32 (s, 1H, H-4), 6.05 and 5.75 (2 bs, $CONH_2$), 3.46 (hpt, 1H, C*H*$(CH_3)_2$, $J = 6.8$ Hz), 2.78–2.67 (m, 2H, H-5), 1.90–1.70 (m, 4H, H-6 and H-7), 1.31 (s, 6H, $(CH_3)_2$), 1.28 (d, 6H, CH(C*H*$_3)_2$, $J = 6.8$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 170.7 (s, $CONH_2$), 162.9 (s, C-8a), 159.6 (s, C-2), 134.3 (d, C-4), 127.3 and 126.2 (2s, C-3 and C-4a), 37.8 (t, C-7), 35.9 (s, C-8), 30.9 (d, CH), 29.3 (q, $(CH_3)_2$), 28.5 (t, C-5), 21.9 (q, CH(*C*H$_3)_2$), 18.4 (t, C-6) ppm.

The mother liquor from the recrystallization was evaporated and subsequently submitted to *Kugelrohr* distillation (75–110°C/0.001 mbar) and column chromatography (petroleum ether:ethyl acetate = 25:1). Yield: 21% **3g**; colorless crystals; m.p.: 47–49°C; b.p.: 80–85°C/0.003 mbar; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 7.49 (s, 1H, H-4), 3.41 (hpt, 1H, C*H*$(CH_3)_2$, $J = 6.8$ Hz), 2.76–2.67 (m, 2H, H-5), 1.88–1.70 (m, 4H, H-6 and H-7), 1.32 (s, 6H, $(CH_3)_2$), 1.30 (d, 6H, CH(C*H*$_3)_2$, $J = 6.8$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 168.1 (s, C-8a), 166.1 (s, C-2), 140.3 (d, C-4), 128.5 (s, C-4a), 117.6 (s, CN), 104.2 (s, C-3), 38.2 (t, C-7), 37.4 (s, C-8), 34.3 (d, CH), 29.9 (q, $(CH_3)_2$), 29.3 (t, C-5), 21.9 (q, CH(*C*H$_3)_2$), 19.0 (t, C-6) ppm.

5,6,7,8-Tetrahydro-7,7-dimethyl-2-(1-methylethyl)-3-quinolinecarbonitrile (**3h**, $C_{15}H_{20}N_2$)

The product was purified by *Kugelrohr* distillation. Yield: 32%; yellow oil; b.p.: 85–90°C/0.02 mbar; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 7.55 (s, 1H, H-4), 3.41 (hpt, 1H, C*H*$(CH_3)_2$, $J = 6.8$ Hz), 2.78 (t, 2H, H-5), 2.70 (s, 2H, H-8), 1.58 (t, 2H, H-6), 1.29 (d, 6H, CH(C*H*$_3)_2$, $J = 6.8$ Hz), 1.00 (s, 6H, $(CH_3)_2$) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 166.4 (s, C-2), 161.1 (s, C-8a), 140.1 (d, C-4), 128.1 (s, C-4a), 117.4 (s, CN), 104.5 (s, C-3), 46.7 (t, C-8), 34.8 (t, C-6), 34.2 (d, CH), 29.8 (s, C-7), 27.9 (q, $(CH_3)_2$), 24.8 (t, C-5), 21.6 (q, CH(*C*H$_3)_2$) ppm.

5,6,7,8-Tetrahydro-6,6-dimethyl-2-(1-methylethyl)-3-quinolinecarbonitrile (**3i**, $C_{15}H_{20}N_2$)

The product was purified by *Kugelrohr* distillation. Yield: 81%; yellow oil; b.p.: 75–80°C/0.02 mbar; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 7.49 (s, 1H, H-4), 3.43 (hpt, 1H, C*H*$(CH_3)_2$, $J = 6.8$ Hz), 2.93 (t, 2H, H-8), 2.50 (s, 2H, H-5), 1.66 (t, 2H, H-7), 1.29 (d, 6H, CH(C*H*$_3)_2$), 1.00 (s, 6H, $(CH_3)_2$) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 166.0 (s, C-2), 160.5 (s, C-8a), 140.6 (d, C-4), 128.7 (s, C-4a), 117.2 (s, CN), 104.5 (s, C-3), 41.7 (t, C-5), 35.1 (t, C-7), 34.0 (d, CH), 29.9 (t, C-8), 29.0 (s, C-6), 27.5 (q, $(CH_3)_2$), 21.6 (q, CH(*C*H$_3)_2$) ppm.

Method C: General procedure for the synthesis of 1-pyridinyl-1-propanones **4**

To a solution of 100 mmol EtMgBr in 70 ml of diethyl ether (prepared from magnesium turnings and EtBr in the usual manner), a solution of 20 mmol carbonitrile **3** in 30 ml of dry diethyl ether was added at ambient temperature. Then the resulting mixture was heated under reflux (35 h for **4a**, **4c–e**, 3 h for **4f–i**). After evaporating the solvent, 10 ml of water and 150 ml of 2 *N* HCl were added. After heating to reflux (20 h for **4a**, **4c–e**, 2 h for **4f–i**) the mixture was cooled to room temperature, and the *pH* was adjusted to 9 by addition of 2 *N* NaOH. The resulting mixture was extracted twice with 100 ml of diethyl ether. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated. The resulting crude products were purified by *Kugelrohr* distillation, column chromatography, or recrystallization (see below).

1-(4,6-Dimethyl-2-(1-methylethyl)-3-pyridinyl)-1-propanone (**4a**, $C_{13}H_{19}NO$)

The product was purified by *Kugelrohr* distillation. Pale yellow oil; b.p.: 75–80°C/1.3 mbar; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 6.73 (s, 1H, H-5), 2.85–2.55 (m, 3H, C*H*$(CH_3)_2$ and C*H*$_2$CH$_3$), 2.48 (s, 3H, 6-CH_3), 2.14 (s, 3H, 4-CH_3), 1.25 (d, 6H, $(CH_3)_2$, $J = 7$ Hz), 1.19 (t, 3H, CH_2CH_3, $J = 7.3$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 209.2 (s, CO), 160.2 and 157.6 (2s, C-2 and C-6), 141.7 (s, C-4), 133.6 (s, C-3), 121.6 (d, C-5), 38.3 (t, *C*H$_2$CH$_3$), 33.4 (d, *C*H$(CH_3)_2$), 23.9 (q, 6-CH_3), 22.2 (q, $(CH_3)_2$), 18.3 (q, 4-CH_3), 7.4 (q, CH$_2$*C*H$_3$) ppm.

1-(5,6,7,8-Tetrahydro-1-methyl-3-(1-methylethyl)-4-isoquinolinyl)-1-propanone (**4c**, $C_{16}H_{23}NO$)

The product was first purified by column chromatography (petroleum ether:ethyl acetate = 15:1) and then by *Kugelrohr* distillation. Colorless crystals, m.p.: 71–72°C; b.p.: 80–85°C/0.02 mbar; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 2.90–2.40 (m, 7H, C*H*$(CH_3)_2$, C*H*$_2$CH$_3$, H-5 and H-7), 2.44 (s, 3H, 1-CH_3), 1.90–1.65 (m, 4H, H-6 and H-7), 1.24 (d, 6H, $(CH_3)_2$, $J = 6.8$ Hz), 1.20 (t, 3H, CH_2CH_3, $J = 7.2$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 209.6 (s, CO), 156.4 and 155.9 (2s, C-1 and C-3), 140.0 (s, C-4a), 133.4 (s, C-4), 127.4 (s, C-8a), 38.2 (t, *C*H$_2$CH$_3$), 32.9 (d, CH), 26.3* (t, C-5), 25.7* (t, C-8), 22.3, 22.2, (q, $(CH_3)_2$), 22.1, 21.6, 7.3 (q, CH$_2$*C*H$_3$) ppm.

1-(5,6,7,8-Tetrahydro-1,5,5-trimethyl-3-(1-methylethyl)-4-isoquinolinyl)-1-propanone (**4d**, $C_{17}H_{25}NO$)

The crude product was first purified by *Kugelrohr* distillation and then submitted to column chromatography (petroleum ether:ethyl acetate = 35:1). Pale yellow crystals; m.p.: 68.5–69.5°C; b.p.: 90–100°C/0.005 mbar; ^{1}H NMR($CDCl_3$, δ, 90 MHz): 2.77–2.43 (m, 5H, C*H*$(CH_3)_2$, C*H*$_2$CH$_3$ and H-5), 2.68 (s, 3H, 1-CH_3), 1.80–1.60 (m, 4H, H-6 and H-7), 1.38 (s, 6H, $(CH_3)_2$), 1.24 (d, 6H, CH(C*H*$_3$)$_2$, $J = 7.0$ Hz), 1.20 (t, 3H, CH$_2$C*H*$_3$, $J = 7.2$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 210.7 (s, CO), 157.1 and 155.5 (2s, C-1 and C-3), 140.6 (s, C-4a), 136.0 (s, C-8a), 133.7 (s, C-4), 42.5 (t, C-7), 38.3 (t, *C*H$_2$CH$_3$), 33.2 (s, C-8), 32.9 (d, CH), 28.8 (q, $(CH_3)_2$), 28.3 (t, C-5), 26.7 (q, 1-CH_3), 22.3 (q, CH(*C*H$_3$)$_2$), 18.3 (t, C-6), 7.4 (q, CH$_2$*C*H$_3$) ppm.

1-(5,6,7,8-Tetrahydro-1,7,7-trimethyl-3-(1-methylethyl)-4-isoquinolinyl)-1-propanone (**4e**, $C_{17}H_{25}NO$)

The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 35:1). Pale yellow crystals; m.p.: 66–68°C; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 2.87–2.42 (m, 5H, C*H*$(CH_3)_2$, C*H*$_2$CH$_3$ and H-8), 2.95 (s, 2H, H-5), 2.48 (s, 3H, 1-CH_3), 1.80–1.72 (m, 2H, H-7), 1.28 (s, 6H, $(CH_3)_2$), 1.22 (d, 6H, CH(C*H*$_3$)$_2$, $J = 7.0$ Hz), 1.20 (t, 3H, CH$_2$C*H*$_3$, $J = 7.2$ Hz) ppm; ^{13}C NMR

($CDCl_3$, δ, 50 MHz): 210.4 (s, CO), 156.7 and 154.5 (2s, C-1 and C-3), 140.5 (s, C-4a), 141.2 (s, C-8a), 133.7 (s, C-4), 42.4 (s, C-7), 38.3 (t, CH_2CH_3), 33.2 (s, C-6), 32.9 (d, CH), 28.8 (q, $(CH_3)_2$), 28.3 (t, C-5), 26.7 (q, 1-CH_3), 23.3 (t, C-8), 22.4 (q, $CH(CH_3)_2$), 7.4 (q, CH_2CH_3) ppm.

1-(5,6,7,8-Tetrahydro-2-(1-methylethyl)-3-quinolinyl)-1-propanone (**4f**, $C_{15}H_{21}NO$)

The product was purified by *Kugelrohr* distillation. Colorless crystals; m.p.: 55–58°C; b.p.: 75–80°C/0.015 mbar; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 7.37 (s, 1H, H-4), 3.36 (hpt, 1H, $CH(CH_3)_2$, $J = 6.8$ Hz), 3.00–2.65 (m, 6H, CH_2CH_3, H-5 and H-8), 2.00–1.70 (m, 4H, H-6 and H-7), 1.25 (d, 6H, $(CH_3)_2$, $J = 6.8$ Hz), 1.18 (t, 3H, CH_2CH_3, $J = 7.2$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 204.5 (s, CO), 161.4 (s, C-2), 158.6 (s, C-8a), 135.1 (d, C-4), 130.8* (s, C-3), 128.1* (s, C-4a), 35.2 (t, CH_2CH_3), 32.3 (d, CH), 31.6 (t, C-8), 28.0 (t, C-5), 22.6 and 22.4 (2t, C-6 and C-7), 22.2 (q, $(CH_3)_2$), 8.0 (q, CH_2CH_3) ppm.

1-(5,6,7,8-Tetrahydro-8,8-dimethyl-2-(1-methylethyl)-3-quinolinyl)-1-propanone (**4g**, $C_{17}H_{25}NO$)

The product was purified by *Kugelrohr* distillation and subsequent recrystallization from MeOH. Colorless crystals; m.p.: 69–70.5°C; b.p.: 80–85°C/0.003 mbar; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 7.37 (s, 1H, H-4), 3.39 (hpt, 1H, $CH(CH_3)_2$, $J = 6.8$ Hz), 2.86 (q, 2H, CH_2CH_3, $J = 7.2$ Hz), 2.78–2.70 (m, 2H, H-5), 1.85–1.75 (m, 4H, H-6 and H-7), 1.33 (s, 6H, $(CH_3)_2$), 1.25 (d, 6H, $CH(CH_3)_2$, $J = 6.8$ Hz), 1.18 (t, 3H, CH_2CH_3, $J = 7.2$ Hz) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 205.3 (s, CO), 165.5 (s, C-8a), 161.8 (s, C-2), 135.6 (d, C-4), 130.5* (s, C-3), 127.2* (s, C-4a), 38.6 (t, C-7), 37.0 (t, C-8), 35.4 (t, CH_2CH_3), 32.2 (d, CH), 30.0 (q, $(CH_3)_2$), 29.6 (t, C-5), 22.6 (q, $CH(CH_3)_2$), 19.4 (t, C-6), 8.4 (q, CH_2CH_3) ppm.

1-(5,6,7,8-Tetrahydro-7,7-dimethyl-2-(1-methylethyl)-3-quinolinyl)-1-propanone (**4h**, $C_{17}H_{25}NO$)

The product was purified by *Kugelrohr* distillation and subsequent column chromatography (petroleum ether:ethyl acetate = 5:1). Pale yellow oil; b.p.: 80–85°C/0.01 mbar; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 7.38 (s, 1H, H-4), 3.34 (hpt, 1H, $CH(CH_3)_2$, $J = 6.8$ Hz), 2.83 (q, 2H, CH_2CH_3, $J = 7.2$ Hz), 2.73 (t, 2H, H-5), 2.67 (s, 2H, H-8), 1.56 (t, 2H, H-6), 1.22 (d, 6H, $CH(CH_3)_2$, $J = 6.8$ Hz), 1.18 (t, 3H, CH_2CH_3, $J = 7.2$ Hz), 1.00 (s, 6H, $(CH_3)_2$) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 205.2 (s, CO), 161.8 (s, C-2), 158.4 (s, C-8a), 135.1 (d, C-4), 131.0 (s, C-3), 126.8 (s, C-4a), 46.4 (t, C-8), 35.4 (t, CH_2CH_3), 35.1 (d, CH), 31.8 (t, C-6), 29.8 (s, C-7), 28.0 (q, $(CH_3)_2$), 25.1 (t, C-5), 22.4 (q, $CH(CH_3)_2$), 8.2 (q, CH_2CH_3) ppm.

1-(5,6,7,8-Tetrahydro-6,6-dimethyl-2-(1-methylethyl)-3-quinolinyl)-1-propanone (**4i**, $C_{17}H_{25}NO$)

The product was purified by *Kugelrohr* distillation. Pale Yellow oil; b.p.: 86–90°C/0.02 mbar; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 7.34 (s, 1H, H-4), 3.34 (hpt, 1H, $CH(CH_3)_2$, $J = 6.8$ Hz), 2.90 (t, 2H, H-8), 2.85 (q, 2H, CH_2CH_3, $J = 7.2$ Hz), 2.50 (s, 2H, H-5), 1.65 (t, 2H, H-7), 1.25 (d, 6H, $CH(CH_3)_2$, $J = 6.8$ Hz), 1.17 (t, 3H, CH_2CH_3, $J = 7.2$ Hz), 0.99 (s, 6H, $(CH_3)_2$) ppm; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 205.2 (s, CO), 161.7 (s, C-2), 157.9 (s, C-8a), 135.8 (d, C-4), 131.1 (s, C-3), 127.5 (s, C-4a), 42.2 (t, C-5), 35.5 (t, CH_2CH_3), 35.4 (d, CH), 31.8 (t, C-7), 29.6 (t, C-8), 29.2 (s, C-6), 27.7 (q, $(CH_3)_2$), 22.4 (q, $CH(CH_3)_2$), 8.2 (q, CH_2CH_3) ppm.

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