Further investigations into the structural requirements for bioactivation of enones

ABSTRACT

This chapter mainly deals with the synthesis of a variety of enones, designed to further study the structure-bioactivation-relationship. Known dopamine (DA) agonists, like N-alkylated DA (6.1) and N-n-propyl-3-(3,4-dihydroxyphenyl)-piperidine (6.3) served as targets for synthesis of their enone equivalents. These enones possess an increased structural flexibility relative to the pharmacologically active enones 2.3a and 5.16a reported so far. In order to elucidate the relation between the position of the ketone, the double bond and bioactivation, the synthesis of a regioisomer of 2.3 is discussed. All enones were prepared in short, concise multi-step syntheses and obtained in good overall yield.
6.1 INTRODUCTION

Some enone prodrugs were found to induce a potent and long lasting pharmacological effect after oral administration in i.a. the Ungerstedt rat model of Parkinson’s disease (Figure 6.1). The bioactivation of enone prodrugs is thought to proceed by \( \alpha’ \)-hydroxylation and subsequent oxidation to give the corresponding catecholamine (Chapter 2 & 3).

![2.3a and 5.16a](image)

Figure 6.1 Structures of the enone prodrugs 2.3a and 5.16a (assumed absolute configuration).

Synthesis and pharmacological evaluation of new potential enone prodrugs of known DA agonists, like N-alkylated DA (6.1) and N-n-propyl-3-(3,4-dihydroxyphenyl)-piperidine (6.3) therefore seems appropriate (Figure 6.2). Enones like 6.2 and 6.4 both are structurally related to 2.3a and 5.16a yet are less rigid. Pharmacological evaluation of these compounds would provide further insight into the universality of the bioactivation of enones to their corresponding catecholamines.

![6.1 6.2 6.3 6.4](image)

Figure 6.2 Structures of some dopaminergic catecholamines (6.1 and 6.3) and their enone analogs (6.2 and 6.4).

Pharmacological activity *in vivo* is not exclusively reserved for enones like 2.3 (Figure 6.3). The synthesis and pharmacological evaluation of two differently substituted enones (6.5
Further investigations into the structural requirements for bioactivation of enones and 6,6) has been reported.\textsuperscript{4} The $\beta,\gamma$-unsaturated enone (6,5) was found to display moderate dopaminergic activity \textit{in vivo} whilst the $\alpha,\beta$-unsaturated enone (6,6) was found inactive \textit{in vivo}.

![Structures of enones with different ketone positions. The $\alpha,\beta$-unsaturated enones (2,3) and (6,6) and the $\beta,\gamma$-unsaturated enone (6,5).](image)

To investigate this further, we designed the synthesis of two enones (6,7 and 6,8) with the ketone moiety at the two positions on the ring not yet investigated (Figure 6.4). Bioactivation of 6,7 or 6,8 to a corresponding catecholamine could give two products. The products of such bioactivation could have a ‘5,6-dihydroxy’ or a ‘6,7-dihydroxy’ substitution patterns on the aromatic ring. This would correspond with the $\alpha$- and $\beta$-rotameric form of DA agonists respectively. Interesting to note is that the absolute configuration of the pharmacologically active enantiomers of $\alpha$- and $\beta$-rotameric forms is opposite. (S)-5,6-di-OH-DPAT and (R)-6,7-di-OH-DPAT are the active enantiomers of both possible products.\textsuperscript{5-7} Pharmacological evaluation of the separate enantiomers of 6,7 and 6,8 may help to prove the identity of the product or products.

![Structures of more enones with different ketone positions. The $\beta,\gamma$-unsaturated enone (6,5) and the $\alpha,\beta$-unsaturated enones (6,8) and (6,9).](image)
Compound 6.9 is structurally derived from 8-OH-DPAT, a known potent 5-HT$_{1a}$ agonist.\textsuperscript{8} Bioactivation of 6.9, to its corresponding catecholamine would yield the known, mixed DA D$_2$/5HT$_{1a}$ agonist, 7,8-di-OH-DPAT.\textsuperscript{9} The potential serotonergic component to the in vivo action of 6.9 could be extremely useful. Observation of both dopaminergic and serotonergic stereotypy in behavioral models would provide further indications of a more general bioactivation of enones to catecholamines.

The compounds described in this chapter so far have only been preliminary pharmacologically evaluated. Therefore, this chapter deals only with the design and synthesis of miscellaneous enones. The total syntheses are presented and discussed.

6.2 CHEMISTRY

6.2.1 Synthesis of DA derived enones

A number of synthetic methods for enone derivatives of N-alkylated DA have been reported in literature. Commonly they are prepared by a Birch reduction of the corresponding phenol or anisol.\textsuperscript{10-15} We have used a different and more convenient strategy, similar to the strategy used in Chapter 5 for the synthesis of ynenone 5.20.\textsuperscript{16-18} By reacting vinyl magnesium bromide with enol ether 5.19, a dienone (6.10) was obtained in quantitative yield (Scheme 6.1).\textsuperscript{19} Secondary amines readily reacted with 6.10 regiospecifically to give the desired compounds. A (2-phenyl)ethylamine substituent was introduced to improve lipophilicity.

\[
\begin{align*}
5.19 & \xrightarrow{a} 6.10 \\
6.11, R = R' = Et & \quad 6.12, R = R' = n-Pr \\
6.13, R = R' = n-Bu & \quad 6.14, R = n-Pr, R' = 2-Phet
\end{align*}
\]

**Scheme 6.1** Synthesis of N-alkylated DA derived enones. Reagents and conditions: a) CH$_2$=CHMgBr, THF, RT, 2h; b) N,N-diethylamine or N,N-di-n-propylamine or N,N-di-n-butylamine or N-(2-phenyl)ethyl-N-n-propylamine, acetonitrile, Cs$_2$CO$_3$, RT, 3h.
The final products were obtained in good overall yield (≈ 90%). Compounds 6.11 and 6.12 could be purified by distillation under vacuum. The other two products were purified by column chromatography and, at first, proved unstable on the column. To prevent decomposition, the silica used had been saturated with NH₃ gas. Upon investigation it became evident that under strong acidic conditions, 6.12 decomposed readily. When an acidic solution containing decomposed 6.12 was treated with an excess of diethylamine, 6.11 was detected as the only product. This proves the reversibility of the amination (step b, Scheme 6.1) under acidic conditions.

In Chapter 5, reversible amination was described for 5.14, 5.14a, 5.14b, and 5.16.²⁰ For 5.16, this was an advantage since intramolecular re-amination occurred that favored the desired and more stable trans isomer. Here, spontaneous re-amination is unlikely to occur because it would have to occur intermolecularly with equimolar quantities of the reagents. Furthermore, the presence of other nucleophiles in vivo could give different products rendering bioactivation to N-alkylated DA analogs impossible. If de-amination of enones of type 6.2 is occurring in vivo, that would bring forward a potential hazard with regard to the formation of toxic metabolites and covalent binding of 6.10 to proteins.

6.2.2 Synthesis of a 3-piperidinyl enone

Synthesis of an n-propyl-piperidine enone analog was accomplished in 3 steps (Scheme 6.2). The first step to give 5.20 and subsequent addition of a secondary amine were discussed in Chapter 5 and conducted under identical conditions. N-n-(3-chloro)propyl-N-n-propylamine was synthesized from 1-bromo-3-chloropropane using N-n-propylamine.²¹ The secondary amine readily reacts with ynenone 5.20.¹⁶ After heating the initially formed intermediate to reflux for 10h, all starting material was converted to dienaminone 6.16 that was isolated in good yield. The presence of both Cs₂CO₃ and KI is required to make the reaction proceed. Selective reduction of the double bond with NaBH₃CN in the presence of a minimal amount of acetic acid gave 6.4. The reaction proceeds for about 60% without the presence of acetic acid. The enamine in 6.16 proved more reactive towards reduction than the enamine intermediate (2.2) reported in the synthesis of 2.3 in Chapter 2. Selectivity for reduction of the desired double bond in 6.16 was controlled by the reaction temperature and no by-products were detected.
Scheme 6.2 Synthesis of a 3-piperidinyl enone (6.4). Reagents and conditions: a) CH≡CMgBr, THF, RT, 2h; b) N-n-(3-chloro)propyl-N-n-propylamine, Cs₂CO₃, KI, acetonitrile, reflux, 10h; c) NaBH₃CN, THF, AcOH, 0°C, overnight.

6.2.3 Isomers of compound 2.3 (1)

The β,γ-unsaturated enone (6.5) was reported to be the only product of a Birch reduction of 7-methoxy-2-(N,N-di-n-propylamino)tetralin (7-MeO-DPAT, 6.17), followed by an acidic hydrolysis (Scheme 6.3). Only after prolonged heating in acid the β,γ-unsaturated enone was converted into the α,β-unsaturated enone 6.6.

Scheme 6.3 Synthesis of 6.5 and 6.6. Reagents and conditions: a) Na/NH₃ (l), THF, EtOH, – 60°C, 3h; b) H⁺/H₂O, RT, 1h; c) H⁺/H₂O, 80°C, 3h.
This rearrangement was accompanied by a substantial de-amination of the N,N-di-n-propylamine moiety (30%). Which of the compounds lost its amine group was not reported. In the cases we reported on, de-amination occurred under strong acidic conditions, in α,β-unsaturated enones to give α,β,γ,δ-unsaturated enones. For 7-keto enones this de-amination is not reversible under acidic conditions. Again because intermolecular re-amination is unlikely to occur because of the aforementioned reasons.

A Birch reduction of 6-methoxy-2-(N,N-di-n-propylamino)tetralin (6-MeO-DPAT, 6.18) was the reaction of choice to obtain an enone product in only two steps (Scheme 6.4). The reaction was carried out with sodium metal in liquid NH₃. After acidic hydrolysis of the reaction mixture 6.8 was isolated as the only product. Surprisingly, even after mild acidic hydrolysis no trace of 6.7 were detected. It is well described in literature on Birch reductions, that 6.19 is the intermediate after reducing this type of substituted aromatic ring.¹⁰ This indicates that the position of the amine facilitates the rearrangement of the double bond. TLC analysis, GC analysis and ¹H-NMR analysis showed the enantiospecific formation of one diastereomer of 6.8.

![Scheme 6.4 Synthesis of 6.8. Reagents and conditions: a) Na/NH₃ (l), THF, EtOH, –60°C, 3h; b) H⁺/H₂O, RT, 3h.](image)

**6.2.4 Isomers of compound 2.3 (2)**

Synthesis of 6.9 was achieved in four steps (Scheme 6.5). Enamine formation followed by catalytic hydrogenation and hydrolytic work-up gave the known compound 6.21 in excellent yield (94%).²²,²³ A Wittig reaction as described in Chapter 5 was used to introduce a C₄ moiety to give 6.22. Subsequent treatment of 6.22 with PPA, gave the desired product 6.9 in good yield.²⁴ It was observed by GC-MS that the initially formed cyclization product was the ethyl enolether (6.23) of 6.9. This intermediate was not isolated since hydrolysis of excess PPA also rapidly liberated the ketone.
In Chapter 4, the orally active oxime derivatives of 2.3 are described. Since this same approach might also work for 6.9, the oxime derivative (6.24) was synthesized (Scheme 6.6). Hydroxylamine hydrochloride was reacted with 6.9 in methanol to give 6.24 quantitative yield. As a hydrochloric salt, compound 6.24 proved hygroscopic, therefore, the maleate salt was prepared.

Scheme 6.5 Synthesis of 6.9. Reagents and conditions: a) Pr₂NH, toluene, TsOH, reflux, 24h; ii) H₂, 10% Pd/C, RT, 16h; b) Br⁻(Ph)₃P⁺(CH₂)₃CO₂Et, t-BuOK, DMF, 0°C, 24h; c) PPA, 100°C, 3h; d) H⁺/H₂O, RT, 3h.

Scheme 6.6 Synthesis of 6.24. Reagent and conditions: a) NH₃OH·HCl, MeOH, RT, 3h.
6.3 CONCLUSIONS

We have succeeded in the preparation of a number of new potential enone prodrugs. Pharmacological evaluation could provide a more complete picture of the structural requirements for bioactivation of enones to their corresponding catecholamines. All enones were prepared in short, concise multistep syntheses and obtained in good overall yield.

6.4 EXPERIMENTAL SECTION

General remarks. Melting points were determined in open glass capillaries on an Electrothermal digital melting-point apparatus and are uncorrected. $^1$H-NMR and $^{13}$C-NMR spectra were recorded at 200 MHz and 50.3 MHz, respectively, on a Varian Gemini 200 spectrometer. The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Chemical shifts are given in δ units (ppm) and are relative to the solvent. Coupling constants are given in Hertz (Hz). The spectra recorded were consistent with the proposed structures. IR spectra were obtained on a ATI-Mattson spectrometer. Electronic ionization (EI) mass spectra were obtained on a Unicam 610-Automass 150 GC-MS system. Chemical ionization (CI) mass spectra were recorded by the Mass Spectrometry Unit of the University of Groningen. Elemental analyses were performed by the Analytical Chemistry Section at Parke Davis (Ann Arbor, MI) or by the Microanalytical Department of the University of Groningen and were within ± 0.4 % of the theoretical values, except where noted. All chemicals used were commercially available (Aldrich or Acros) and were used without further purification.

3-(N-n-Propyl-piperidin-3-yl)-cyclohexen-2-one (6.4) 3-(N-n-Propyl-1,4,5,6-tetrahydro-pyridin-3-yl)-cyclohexen-2-one (6.16) (5.0 g, 22.8 mmol) was dissolved in THF (100 mL). At 0°C, acetic acid (1.38 mL, 22.8 mmol) was added followed by introduction of NaBH₃CN (1.9 g, 30.0 mmol) in small portions maintaining the temperature. After the addition was complete the mixture was stirred for 1h at this temperature and then at RT overnight. Work-up by addition of water (50 mL) and saturated aqueous NaHCO₃ (50 mL) followed by extraction with dichloromethane (5 x 50 mL). The combined organic layers were dried (MgSO₄) and evaporated. The residue was purified by column chromatography (silica, dichloromethane/ethanol 20:1) to give a colorless oil, which was converted to the hydrochloride.
Recrystallization from di-isopropyl ether gave 4.2 g, 17.5 mmol (77%), mp 184-185°C. IR (KBr) 3396, 2941, 2469, 1667, 1455 cm⁻¹; ¹H-NMR (CDCl₃) δ 5.83 (s, 1H), 3.85 (d, 2H), 2.29-2.56 (m, 7H), 1.23-2.17 (m, 10H), 0.88 (t, 3H) ppm; ¹³C-NMR (CDCl₃) δ 198.4, 165.1, 123.4, 59.0, 55.6, 51.9, 41.6, 36.0, 27.3, 26.9, 22.8, 21.2, 17.6, 10.2 ppm; MS (EI) m/z 221 (M+); Anal. (C₁₄H₂₃NO·HCl) C, H and N.

6-(N,N-di-n-Propylamino)-4,4a,5,6,7,8-hexahydro-3H-naphthalen-2-one (6.8)

To a stirred solution of 6-MeO-DPAT (6.18) (1.03 g, 3.95 mmol) in tetrahydrofuran (12 mL), iso-propanol (12 mL), and liquid ammonia (30 mL), at –60°C, was added sodium metal (1.7 g, 75 mmol) in small pieces. The solution was stirred for 2h at –60°C and then iso-propanol (24 mL) was added carefully. The temperature was allowed to rise to RT overnight, leaving the ammonia to evaporate. The residue was diluted with water (60 mL) and was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried (MgSO₄) and evaporated to give a yellow oil.

The yellow oil was dissolved in diethyl ether (25 mL) and was extracted with 4N HCl (2 x 15 mL). The combined acidic layers were basified to pH = 11 using concentrated ammonia. Extraction with diethyl ether (5 x 50 mL), drying of the organic phase (MgSO₄) gave a yellow oil. TLC analysis showed the presence of two compounds. GC analysis indicated that there was one major product (80%) and some starting material (10%). Purification by column chromatography (silica, ethyl acetate/ethanol (9/1)) gave a colorless oil. Yield 0.53 g, 2.13 mmol (54%). IR (neat) 3201, 2978, 1710, 1536, 1358 cm⁻¹; ¹H-NMR (CDCl₃) 5.79 (s, 1H), 2.68-2.76 (m, 1H), 2.22-2.44 (m, 9H), 1.67-2.16 (m, 3H), 1.66 (dd, 1H), 1.39 (br q, 6H), 0.83 (t, 6H) ppm; ¹³C-NMR (CDCl₃) δ 198.1, 164.6, 122.9, 57.1, 51.2, 35.7, 34.9, 34.8, 33.1, 27.8, 26.9, 20.8, 10.3 ppm; MS (EI) m/z 249 (M+);

7-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2H-naphthalen-1-one (6.9)

To a cooled (0°C) suspension of KOtBu (1.13 g, 10.1 mmol) in dry dimethylformamide (4 mL) flushed with N₂ was added dropwise a solution of (3-ethoxycarbonyl)triphenyl-phosphonium bromide (5.10 g, 11.2 mmol) in dry, N₂ flushed dimethylformamide (11 mL). When the addition is complete, the mixture was stirred at 0°C for 30 min. Then a solution of 4-di-n-propylamino-cyclohexanone (6.21, 2.00 g, 10.2 mmol) in dry, N₂ flushed dimethylformamide (4 mL) was added dropwise at 0°C. After stirring at 0°C for 4 h the temperature was allowed to rise to RT.
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and stirring was continued overnight. Water (25 mL) was added and the mixture was filtered through Celite (2 g). The filtrate was extracted with hexane (5 x 25 mL). The combined organic layers were dried (MgSO₄), filtered and evaporated to give 2.86 g of a light yellow oil. Distillation of the oil in vacuo (108°C, 0.2 mm Hg) afforded 6.22 slightly contaminated with triphenylphosphine oxide.

A solution of the Wittig adduct (1.0 g, 3.4 mmol) in hexane (3 mL) was added to PPA (20 g) at 115°C while stirring. After 4h stirring at that temperature the reaction mixture was allowed to cool to about 80°C when crushed ice (50 g) was introduced. Stirring was continued and the solution was allowed to cool to RT. 5N aqueous NaOH was added until pH = 8 and then the solution was extracted with ethyl acetate (5 x 40 mL). The combined organic layers were dried (MgSO₄), filtered and evaporated. The residue was purified by column chromatography (silica, dichloromethane/ethanol, 20:1) and subsequently converted to the hydrochloric salt. Yield 0.57 g, 2.3 mmol (67%), mp 185-186°C. IR (neat) 2955, 2822, 1666, 1382,1069 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.72-2.77 (m, 1H), 2.21-2.56 (m, 11H), 1.82-2.00 (m, 4H), 1.34-1.54 (m, 5H), 0.83 (t, 3H) ppm; ¹³C-NMR (CDCl₃) δ 197.5, 155.0, 129.7, 129.5, 55.0, 51.1, 36.1, 31.0, 29.3, 24.1, 22.1, 20.8, 20.2, 10.3 ppm; MS (EI) m/z 249 (M⁺); Anal. (C₁₆H₂₇NO·HCl) C, H and N.

3-Vinyl-2-cyclohexen-1-one (6.10)¹⁹ To a solution of 1.0N vinylmagnesium bromide in tetrahydrofuran (50 mL) was added under N₂ and stirring 3-ethoxy-2-cyclohexen-1-one (3.75 g, 26.8 mmol) in tetrahydrofuran (12.5 mL). The mixture was stirred at RT for 20h when it was acidified with 1N HCl (200 mL). After stirring for 15 min the acidic phase was extracted with dichloromethane (5 x 50 mL). The combined organic extracts were washed with water (2 x 50 mL) and dried (MgSO₄). Evaporation of the solvent gave an oil that was purified by column chromatography (silica, ethyl acetate/hexane 1:9) to yield a yellow oil, 2.71 g, 22.6 mmol, 84%). Analyses were in agreement with literature data.

3-(2-N,N-Diethylamino)ethyl-cyclohexen-2-one (6.11) 3-Vinyl-cyclohex-2-enone (6.10) (0.75 g, 6.1 mmol) was dissolved in acetonitrile (1 mL) and N,N-diethylamine (1.3 g, 16 mmol) was added followed by Cs₂CO₃ (50 mg). After stirring the mixture at rt for 3 h it was diluted with diethyl ether (100 mL), filtered and evaporated to dryness. The residue was distilled in vacuo (120°C, 0.01 mm Hg) to give a slightly yellow oil, which was converted to the hydrochloride salt. Recrystallization from isopropyl ether/isopropyl alcohol yielded: 1.3 g, 5.6
mmol (91%), mp 148-149 °C. IR (KBr) 2948, 2851, 1661; $^1$H-NMR (CDCl$_3$) $\delta$ 5.86 (d, 1H), 2.48-2.67 (m, 6H), 2.27-2.39 (m, 6H), 1.96 (m, 2H), 1.02 (t, 6H) ppm; $^{13}$C-NMR (CDCl$_3$) $\delta$ 198.3, 163.5, 124.8, 48.9, 45.2, 35.7, 33.7, 28.4, 21.2, 10.1 ppm; MS (EI) $m/z$ 195 (M$^+$); Anal. (C$_{12}$H$_{21}$NO·HCl) C, H and N.

3-(2-N,N-di-n-Propylamino)ethyl-cyclohexen-2-one (6.12) The same procedure was used as for 6.11 but using N,N-di-n-propylamine. Distillation at 175°C (0.01 mm Hg) afforded a colorless oil that was converted to the hydrochloride salt. Recrystallization from isopropyl ether/isopropyl alcohol yielded: 1.2 g, 4.6 mmol (75%), mp 95-97°C. IR (KBr) 2962, 2613, 1667; $^1$H-NMR (CDCl$_3$) $\delta$ 5.84 (d, 1H), 2.65 (m, 2H), 2.27-2.60 (m, 9H), 1.99 (m, 2H), 1.39-1.51 (m, 5H), 0.86 (t, 6H) ppm; $^{13}$C-NMR (CDCl$_3$) $\delta$ 198.2, 163.5, 124.9, 54.2, 50.1, 35.7, 33.7, 28.4, 21.2, 18.5, 10.4 ppm; MS (EI) $m/z$ 223 (M$^+$); Anal. (C$_{14}$H$_{25}$NO·HCl) C, H and N.

3-(2-N,N-di-n-Butylamino)ethyl-cyclohexen-2-one (6.13) The same procedure was used as for 6.11 but using N,N-di-n-butylamine. Purification by column chromatography (silica, ethyl acetate) yielded a colorless oil that was converted to the hydrochloride salt. Recrystallization from isopropyl ether/isopropyl alcohol gave 1.3 g, 5.6 mmol (91%), mp 115-117°C. IR (KBr) 2959, 2494, 1661; $^1$H-NMR (CDCl$_3$) $\delta$ 5.84 (d, 1H), 2.60 (q, 2H), 2.26-2.44 (m, 8H), 1.96 (m, 3H), 1.21-1.46 (m, 8H), 0.87 (t, 6H) ppm; $^{13}$C-NMR (CDCl$_3$) $\delta$ 198.2, 163.6, 124.9, 52.0, 50.2, 35.7, 33.8, 28.4, 27.5, 21.2, 19.1, 12.5 ppm; MS (CI) $m/z$ 252 (M+1); Anal. (C$_{16}$H$_{28}$NO·HCl) C, H and N.

3-(N-(2-Phenyl)ethyl-N-n-propylamino)ethyl-cyclohexen-2-one (6.14) The same procedure was used as for 6.11 but using N-(2-phenyl)ethyl-N-n-propylamine. Purification by column chromatography (silica, ethyl acetate) yielded a colorless oil that was converted to the hydrochloride salt. Recrystallization from ether/ethanol gave 1.8 g, 5.6 mmol (91%), mp 110-112°C. IR (KBr) 2937, 2538, 2442, 1667; $^1$H-NMR (CDCl$_3$) $\delta$ 7.15-7.83 (m, 5H), 5.95 (s, 1H), 3.07 (t, 2H), 2.83, (q, 2H), 2.27-2.50 (m, 6H), 2.04 (p, 4H), 1.47-1.64 (m, 4H), 0.86 (t, 3H) ppm; MS (CI) $m/z$ 286 (M+1); Anal. (C$_{19}$H$_{27}$NO·HCl) C, H and N.

3-(N-n-Propyl-1,4,5,6-tetrahydro-pyridin-3-yl)-cyclohexen-2-one (6.16) 3-Ethynyl-cyclohex-2-enone (5.20) (3.20 g, 26.8 mmol) and N-n-(3-chloro)propyl-N-n-propylamine
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(4.50 g, 33.2 mmol)\(^{21}\) were mixed in acetonitrile (50 mL). Cs\(_2\)CO\(_3\) (100 mg) and KI (200 mg) were added and the mixture was refluxed under N\(_2\) for 10h. After cooling the mixture was diluted with water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine, dried (MgSO\(_4\)) and evaporated. The resulting dark oil was purified by column chromatography (silica, ethyl acetate) to give a yellow red oil. Yield 5.1 g, 23.3 mmol (87%). IR (neat) 2932, 2871, 1589, 1538, 1157 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 6.84 (s, 1H), 5.69 (s, 1H), 3.04-3.12 (m, 4H), 2.44 (t, 2H), 2.33 (t, 2H), 2.18 (t, 2H), 1.83-2.03 (m, 4H), 1.49-1.64 (m, 2H), 0.87 (t, 3H) ppm; \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 197.0, 158.5, 140.1, 112.1, 102.4, 56.6, 44.3, 35.6, 23.6, 21.4, 20.2, 20.1, 19.7, 9.6 ppm; MS (CI) \(m/z\) 220 (M+1); Anal. (C\(_{14}\)H\(_{21}\)NO) C, H and N.

4-(N,N-di-n-Propylamino)-cyclohexan-1-one (6.21) A mixture of N,N-di-n-propylamine (20 mL, 277 mmol), 1,4-cyclohexadione monoethyleneacetal (6.20, 10.0 g, 64 mmol) in 1,2-dichloroethane (25 mL), and p-toluenesulphonic acid (50 mg) in toluene was refluxed under Dean-Stark conditions for 24h. After cooling to room temperature the solvent was evaporated and the residue was dissolved in ethanol (250 mL). After addition of 10% Pd/C (100 mg) the enamine was reduced at 3 atm, at RT, overnight. Work-up by filtration over Celite\textsuperscript{®}, and evaporation of the solvent. The residue was redissolved in tetrahydrofuran and stirred with 4N HCl (400 mL) for 3h to hydrolyze the protecting group. After adjusting the pH to about 10 (Na\(_2\)CO\(_3\)), the aqueous layer was saturated with solid NaCl. The alkaline solution was then extracted with ethyl acetate (5 x 100 mL). The combined extracts were dried (Na\(_2\)SO\(_4\)), and evaporated. Distillation of the residue at 81-85°C (0.05 mm Hg) afforded 6.21 as a colorless oil (lit. 90-95°C, 0.1 mm Hg).\(^{22}\) Yield 11.8 g (60 mmol, 94%). MS (EI) \(m/z\) 197 (M+).

7-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2\(^{\text{H}}\)-naphthalen-1-one oxime (6.24) Free base of 6.9 (0.20 g, 0.80 mmol) and hydroxylamine hydrochloride (0.15 g, 2.2 mmol) were mixed in methanol (10 mL) and stirred at RT for 18 hours. The solvent was removed under vacuum, excess aqueous Na\(_2\)CO\(_3\) was added which was extracted with ether (3 x 20 mL). The combined ethereal layers were dried (MgSO\(_4\)), filtered and evaporated to give a colorless oil which was converted to the maleate salt. The salt was recrystallized from iso-propanol to give a white powder. Yield: 0.30 g, 0.78 mmol (98%), mp 121-123°C. IR (KBr) 3201, 2978, 1710, 1536, 1358 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 2.72-2.89 (m, 2H), 2.00-2.63 (m, 12H), 1.25-1.90 (m,
7H), 0.86 (t, 6H) ppm; $^{13}$C-NMR (CDCl$_3$) $\delta$ 154.5, 138.7, 123.9, 55.4, 51.2, 30.6, 28.7, 24.7, 23.1, 20.7, 19.7, 19.4, 10.4 ppm; MS (EI) $m/z$ 264 (M$^+$); Anal. (C$_{16}$H$_{28}$N$_2$O·Maleate) C, H and N.

### 6.5 REFERENCES


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