

Regioselective Cycloadditions of 1-Acylamino Dienes.* Synthesis of Hydrogenated Quinolines

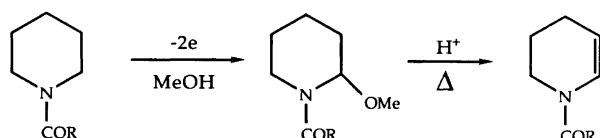
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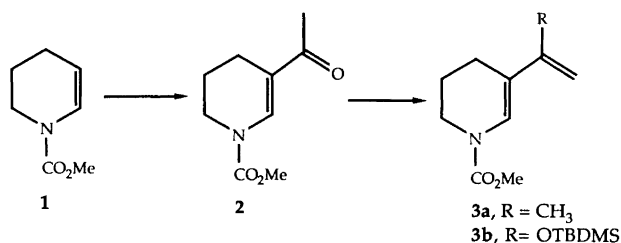
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β -Acetylated enamides derived from *N*-methoxycarbonylpiperidine have been converted into the acylamino dienes **3a** and **3b**. These undergo a regio- and stereo-selective Diels–Alder reaction with dienophiles with preferential formation of the *endo* adduct.

Cyclic enamides and enecarbamates are substances easily accessible *via* electrochemical methoxylation according to the Ross–Ebersson–Nyberg procedure¹ followed by elimination of methanol^{2,3} according to Scheme 1.

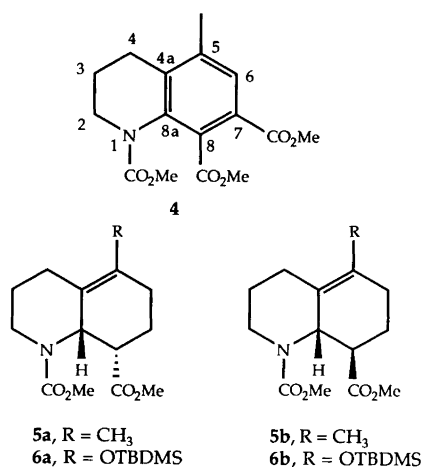


In our continued efforts to apply the above electrochemical reaction to the synthesis of natural products,⁴ we considered the possibility of using enamides and enecarbamates as dienophiles in [2+4]-cycloadditions. This would give access to hydrogenated quinoline and indole derivatives (using the enamide from piperidine and pyrrolidine, respectively) and ultimately to alkaloids containing these ring systems, such as pumiliotoxins, and *Lycopodium* and *Sceletium* alkaloids. However, the relatively high electron density of enamides and enecarbamates suggests a correspondingly low reactivity as dienophiles.⁵ Preliminary experiments⁶ using the electron-poor diene 2-phenylsulfonyl-1,3-butadiene⁷ gave discouraging results. Similar results were obtained from attempts to catalyze the cycloaddition of the enamide and cyclohexadiene with the radical cation of tris-(*p*-bromophenyl)amine.⁸ However, *N*-acylamino *dienes* are known to react with various dienophiles to give substituted cyclohexenes with high regio- and stereo-selectivity.^{9–11} In this report, we present results from our studies on the transformation of the cyclic enecarbamate **1** into hydrogenated quinolines *via* a [2+4]-cycloaddition of an intermediate *N*-acyl-1-amino diene.



Results and discussion

Acetylation³ of the enecarbamate **1** with CH₃COCl/SnCl₄ gave the conjugated enone **2** in 84% yield.[†] Reaction of **2** with MeMgI in THF, followed by immediate elimination of water by treatment with the strongly acidic resin Amberlyst[®] 15 gave the diene **3a** (52% from **2**).



The diene **3a** is fairly reactive towards a number of dienophiles. Thus, reaction with acetylenedicarboxylic acid dimethyl ester (refluxing toluene, 15 h) gave complete con-

* Part 4 in the series: Synthetic Applications of Electrochemically Produced α -Methoxy Amides. For Part 3, see Ref. 4.

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[†] The yield reported by Shono *et al.*³ was improved by a simplified purification procedure: see the Experimental part.

version to the Diels–Alder adduct which was identified after dehydrogenation with DDQ as the tetrahydroquinoline derivative **4** (38% from **3**).

The regio- and stereo-selectivity of the cycloaddition reaction was investigated using methyl acrylate as the dienophile. Reaction with **3a** (refluxing toluene, 15 h) gave a mixture of adducts (88:12 by GC analysis, 85% isolated yield) which, after separation by column chromatography, was identified as the *endo* and *exo* adducts **5a** and **5b**. No other regioisomer could be detected. The preferential formation of the *endo* product **5a** is in accordance with the stereochemistry observed in [2+4]-cycloadditions of acyclic 1-acylamino dienes⁹ and also, recently reported, for *N*-dienyl lactams.¹¹

Another entry into the acylamino diene system from **2** is through its enolate. Thus **2** was treated sequentially with LDA (THF, -78°C) and *tert*-butyldimethylsilyl chloride (TBDMSCl) to give the silyl enol ether **3b** in 70% yield. Compound **3b** undergoes a facile Diels–Alder reaction with methyl acrylate (refluxing toluene, 15 h) to give two isomeric products in a ratio of 78:22 in 74% yield. After separation, these were identified as the *endo* and *exo* adducts **6a** and **6b**, respectively. The observed regioselectivity is in accordance with the regioselectivity of 2-silyloxy dienes in [2+4]-cycloadditions which have been studied extensively by Danishefsky.¹² Fortunately, this effect is complementary to the directive effect of the *N*-acylamino substituent in the diene **3b**.

The identification of the cycloadducts is based solely on their 300 MHz ^1H NMR spectra. These were run at 50°C in order to avoid broadening of the signals due to the slow rotation around the amide bond. The coupling pattern was elucidated by performing double irradiation and two-dimensional (COSY) NMR experiments. Thus, the coupling between H-8a and H-8 was 6.3 Hz for both **5a** and **6a**, whereas for the two *exo* isomers this coupling was 9.8 Hz (**5b**) and 9.3 Hz (**6b**). This coupling pattern agrees well with the proposed structures, assuming the same pseudo-chair conformation for the cyclohexene ring in the four compounds. This assumption is supported by the chemical shift of H-8; in the *exo* isomers, this proton appears at 2.5 ppm

as expected for a pseudo-axial position, whereas in the *endo* isomers, it appears at 3.3 ppm indicating a pseudo-equatorial position.

Finally, the silyl enol ethers **6a** and **6b** were desilylated using Bu_4NF in THF. Compound **6a** gave a mixture of two ketones (88% isolated yield) which were identified as the *trans*- and *cis*-fused decahydroquinolines **7a** and **7b** (ratio 66:34) while **6b** gave one single isomer identified as the *cis*-fused compound **7c** (62% isolated yield).

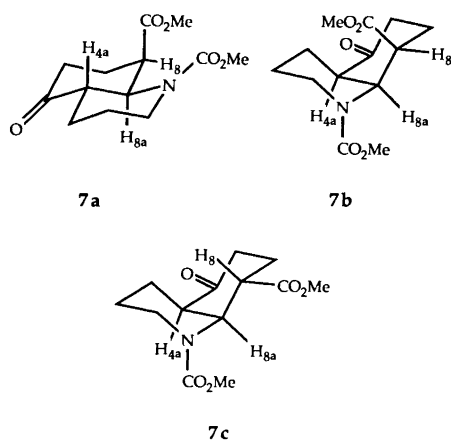
The stereochemistry of the bicyclic ketones **7a**, **7b** and **7c** was unravelled using the respective ^1H – ^1H coupling constants of H-8a, available from the 300 MHz ^1H NMR spectra using the same techniques as above. In the proton NMR spectra of the two *cis*-fused compounds **7b** and **7c**, H-8a occurs at 4.62 and 4.67 ppm, respectively, showing a vicinal coupling constant to H-4a of 6.4 and 5.3 Hz indicating a *cis* ring fusion. In contrast, H-8a in compound **7a** appears at 3.70 ppm as a doublet of doublets ($J = 13$ and 4.5 Hz), the smaller coupling constant being the *cis* coupling between H-8a and H-8 and the larger being the *trans* diaxial coupling between H-8a and H-4a. The observed differences between the chemical shifts of H-8a in the *cis*- and *trans*-fused compounds are in agreement with the ^1H NMR spectra of the related *cis*-¹³ and *trans*-fused¹⁴ decahydroquinoline-5-carboxylic acids reported by Witiak and co-workers.

The formation of *cis*-fused decahydroquinolines in the desilylation reactions was to us at first somewhat surprising. However, for the related *N*-benzoyldecahydroquinolin-4-one, it has been established that the thermodynamically most stable isomer is the *cis*-fused compound.¹⁵ The predominant formation of the *trans*-fused isomer **7a** from the *endo* isomer is probably caused by the steric strain inflicted by the axial ester group in **7b** on the axial proton on C-4, an effect which would shift the equilibrium towards the *trans*-fused decahydroquinoline **7a**.

In conclusion, we have shown, that the enecarbamate **1** can easily be converted into decahydroquinoline derivatives *via* a regioselective Diels–Alder reaction. Studies on the applications of this to the synthesis of bicyclic alkaloids are underway and will be the subject of future reports.

Experimental

General. All chemicals used were of highest commercial quality and were used without further purification. Light petroleum (b.p. 60 – 80°C) and ethyl acetate, used for chromatography, were distilled before use. Reaction mixtures were analyzed by capillary GLC using a Varian 3400 gas chromatograph equipped with a Varian 4270 integrator on a $25\text{ m} \times 0.25\text{ mm}$ OV 1701 column and by TLC on commercially available silica gel/aluminium foil plates. Flash chromatography was performed according to Taber.¹⁶ ^1H NMR spectra were recorded on a Varian XL 300 or a JEOL PMX 60 machine in CDCl_3 ; δ in ppm downfield from Me_4Si as an internal standard. Mass spectra were obtained using direct inlet on a Finnigan 4021 mass spectrometer at 70 eV. Elemental analysis was carried out by the Department of Ana-



lytical Chemistry, Chemical Center, Lund, or *Mikro Kemi AB*, Uppsala, Sweden.

5-Acetyl-1-methoxycarbonyl-1,2,3,4-tetrahydropyridine (2). The procedure of Shono *et al.*³ was used. The crude product obtained from acetyl chloride (57 ml, 0.80 mol), stannic chloride (94 ml, 0.8 mol) and **1** (11.3 g, 80 mmol) was purified as follows: after the aqueous work-up, the solution was dried with anhydrous MgSO₄, filtered and evaporated. The reddish oily residue was filtered through a short silica-gel column (5×5 cm) and distilled in a Kugelrohr apparatus at 90–95 °C (0.4 mmHg). Yield: 11.8 g (81 %) of **2** as white crystals. Analytical data were in agreement with those reported by Shono *et al.*³

1-Methoxycarbonyl-5-(2-propenyl)-1,2,3,4-tetrahydropyridine (3a). A solution of methylmagnesium iodide (21 mmol) in diethyl ether (20 ml) was slowly added to a stirred solution of **2** (3.84 g, 21 mmol) in dry THF (20 ml) kept at –70 °C. The mixture was allowed to attain ambient temperature and then quenched with saturated NH₄Cl and ice. The aqueous layer was extracted with CH₂Cl₂, and the combined organic phases were washed with sat. aq. NH₄Cl, dried (MgSO₄), filtered and evaporated. The crude product was then dissolved in CH₂Cl₂ (40 ml) and 0.2 g of the strongly acidic resin Amberlyst® 15 was added. After being stirred for 1 h, the solution was filtered and evaporated. Purification of the residue by column chromatography on silica gel (light petroleum/EtOAc 9:1) gave 1.97 g (52 % from **2**) of **3a** as a colorless oil. ¹H NMR (60 MHz): 7.1 (br s, 1 H), 4.9 (m, 2 H), 3.8 (s, 3 H), 3.4–3.7 (m, 2 H) 1.5–2.4 (m, 7 H). MS (*m/z*, rel. %): 181 (*M*⁺, 100), 166 (30), 140 (12), 122 (14), 41 (49). Anal. C₁₀H₁₅NO₂: C, H, O.

5-[1-(tert-Butyldimethylsilyloxy)vinyl]-1-methoxycarbonyl-1,2,3,4-tetrahydropyridine (3b). To a stirred solution of diisopropylamine (13.1 mmol) in dry THF (40 ml) was added dropwise butyllithium (1.5 M in hexane, 12.2 mmol) at –70 °C under an atmosphere of argon. After the reaction had been stirred for 1 h, a solution of **2** (2.0 g, 10.9 mmol) in dry THF (5 ml) was added dropwise and stirring was continued for an additional hour. A solution of TBDMSCl (4.54 g, 18.5 mmol) in dry THF (10 ml) was added, and the reaction mixture was allowed to reach ambient temperature. After evaporation of the solvent, the residue was extracted twice with light petroleum. The solvent was evaporated and the product was purified by passage through a short (3×3 cm) column of neutral alumina using light petroleum/EtOAc (9:1) as the eluant. Yield: 2.28 g (70 %) of **3b** as a colorless oil. ¹H NMR (60 MHz): 7.3 (br s, 1 H), 4.1 (m, 2 H), 3.7 (s, 3 H), 3.4–3.6 (m, 2 H), 1.8–2.2 (m, 4 H), 0.9 (s, 9 H), 0.1 (s, 6 H).

General procedure for cycloaddition. The diene (5 mmol) was dissolved in toluene (25 ml) and the solution was deaerated with argon for 5 min. The dienophile (8 mmol) and a trace amount of hydroquinone were added, and the

solution was refluxed until the starting diene had been consumed, as indicated by GLC or TLC. After evaporation of the solvent, the residue was purified as described below.

5-Methyl-1,2,3,4-tetrahydroquinoline-1,7,8-tricarboxylic acid trimethyl ester (4). The crude cycloadduct (from 1.22 mmol **3a**) was dissolved in benzene (10 ml) and a solution of DDO (0.28 g, 1.22 mmol) in benzene (15 ml) was added. After the reaction had been refluxed for 2 h, the hydroquinone was filtered off and the solvent was evaporated. Purification by column chromatography on silica gel (CH₂Cl₂/Et₂O 8:2) gave **4** as white crystals in 57 % yield from **3a**. M.p. 91–92 °C. ¹H NMR (300 MHz, 50 °C): 7.41 (s, 1 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 3.78–3.85 (br m, 2 H), 3.65 (s, 3 H), 2.68 (br t, 2 H), 2.30 (s, 3 H), 1.99 (br m, 2 H). MS (*m/z*, rel. %): 321 (*M*⁺, 43), 290 (25), 262 (100), 230 (30). Anal. Found: C 59.8; H 5.96; N 4.36. Calc. for C₁₆H₁₉NO₆: C 59.0; H 5.84; N 4.34.

5-Methyl-1,2,3,4,6,7,8,8a-octahydroquinoline-1,8-dicarboxylic acid dimethyl ester (5a and 5b). The crude product (a mixture of isomers in the ratio 88:12 according to GLC) was subjected to column chromatography on silica gel using light petroleum/EtOAc (7:3) as the eluant. Some mixed fractions were isolated which were purified by one additional chromatographic separation. Total yield of **5a** and **5b**: 88 %.

5a: ¹H NMR (300 MHz, 50 °C): 4.54 (br d, H-8a), 3.79 (dd, *J* 6.9, 13.4 Hz, H-2_{eq}), 3.65 (s, CO₂Me), 3.55 (s, CO₂Me), 3.30 (ddd, *J* 6.3, 4.0, 4.0 Hz, H-8), 2.92 (left half of an AB system with two additional couplings: *J*_{AB} 6.3 Hz, *J*_d 13.5, 10.6 Hz, H-2_{ax}), 2.60 (m, 1 H), 2.38 (m, 1 H), 1.70–2.00 (m, 5 H), 1.65 (s, CH₃), 1.6 (m, 1 H). MS (*m/z*, rel. %): 267 (*M*⁺, 3), 208 (37), 181 (100), 166 (22), 148 (16). Anal. C₁₄H₂₁NO₄: C, H, O.

5b: ¹H NMR (300 MHz, 50 °C): 4.67 (d, *J* 9.8 Hz, H-8a), 3.90 (dd, *J* 13.6, 8.1 Hz, H-2_{eq}), 3.66 (s, CO₂Me), 3.64 (s, CO₂Me), 2.73 (ddd, *J* 13.9, 11.3, 7.0 Hz, H-2_{ax}), 2.5 (m, 2 H), 1.8–2.1 (m, 5 H), 1.61 (s, CH₃), 1.5 (m, 2 H). MS (*m/z*, rel. %): 267 (*M*⁺, 3), 208 (56), 181 (100), 166 (21), 148 (18). Anal. C₁₄H₂₁NO₄: C, H, O.

5-tert-Butyldimethylsilyloxy-1,2,3,4,6,7,8,8a-octahydroquinoline-1,8-dicarboxylic acid dimethyl ester (6a and 6b). The crude product (a mixture of isomers in the ratio 78:22 according to GLC) was purified by column chromatography on a neutral alumina column, using light petroleum/EtOAc (9:1) as the eluant, to give pure **6a** and **6b** in a total yield of 74 %.

6a: ¹H NMR (300 MHz, 50 °C): 4.61 (br d, H-8a), 3.79 (dd, *J* 13.0, 7.3 Hz, H-2_{eq}), 3.71 (s, CO₂Me), 3.60 (s, CO₂Me), 3.28 (ddd, *J* 6.3, 3.3, 3.3 Hz, H-8), 2.9 (m, 2 H), 2.48–2.62 (m, 2 H), 1.55–2.04 (m, 5 H), 0.91 (s, *t*-Bu), 0.16 (s, MeSi), 0.15 (s, MeSi). MS (*m/z*, rel. %): 270 (*M*+1, 10), 238 (12), 194 (51), 135 (72), 44 (100).

6b: ¹H NMR (300 MHz, 50 °C): 4.80 (d, *J* 8.9 Hz, H-8a), 3.89 (dd, *J* 13.5, 7.8 Hz, H-2_{eq}) 3.63 (s, CO₂Me), 3.62 (s,

CO₂Me), 272–2.84 (m, 2 H), 2.50 (ddd, *J* 11.4, 9.2, 3.8 Hz, H-8), 2.1–2.25 (m, 2 H), 1.85–2.08 (m, 3 H), 1.5–1.7 (m, 3 H), 0.92 (s, *t*-Bu), 0.14 (s, MeSi), 0.13 (s, MeSi). MS (*m/z*, rel. %): 270 (*M*+1, 9), 269 (11), 238 (12), 183 (53), 168 (40), 141 (100).

Perhydro-5-oxoquinoline-1,8-dicarboxylic acid dimethyl ester (7a, 7b, 7c). The TBDMS enol ether (**6a** or **6b**) was dissolved in dry THF and the solution was cooled to –70°C. A solution of Bu₄NF in THF (1.1 equiv.) was added and the reaction mixture was allowed to attain ambient temperature. The reaction mixture was quenched with saturated aq. NH₄Cl and extracted three times with CH₂Cl₂. The combined organic phases were dried (MgSO₄) and evaporated, and the product(s) were purified by column chromatography on silica gel. Yield from **6a**: 88% of **7a** and **7b** in the ratio 66:34, separated using light petroleum/EtOAc (1:3) as the eluant. Yield from **6b**: 62% of **7c**, purified using light petroleum/EtOAc (1:2) as the eluant.

7a: M.p. 51–55°C. ¹H NMR (300 MHz): 3.90 (ddd, *J* 14.1, 7.5, 1.5 Hz, H-2_{eq}), 3.73 (s, CO₂Me), 3.71 (s, CO₂Me), 3.70 (dd, *J* 13, 4.5 Hz, H-8a), 3.49 (ddd, *J* 4.9, 4.9, 2.8 Hz, H-8), 3.30 (dt, *J*_t 13.1, *J*_d 3.2 Hz, H-4a), 3.08 (ddd, *J* 14.1, 12.1, 5.8 Hz, H-2_{ax}), 2.69 (dt, *J*_d 6.5, *J*_t 14.5 Hz, 1 H), 2.20–2.37 (m, 2 H), 2.10 (dddd, *J* 13.5, 10.5, 3.0, 2.2 Hz, 1 H), 1.74–1.96 (m, 2 H), 1.29 (dddd, *J* 14.1, 12.7, 10.4, 8.2 Hz, 1 H). MS (*m/z*, rel. %): 270 (*M*+1, 10), 194 (49), 135 (72), 44 (100). Anal. C₁₃H₁₉NO₅: C, H, O.

7b: M.p. 71–73°C. ¹H NMR (300 MHz): 4.62 (t, *J* 6.4 Hz, H-8a), 4.02 (dd, *J* 13.6, 5.0 Hz, H-2_{eq}), 3.73 (s, CO₂Me), 3.71 (s, CO₂Me), 3.13 (apparent q, *J* 5.3 Hz, H-8), 3.07 (ddd, *J* 16.1, 11.1, 5.6 Hz, 1 H), 2.52–2.71 (m, H-2_{ax}, H-4a), 2.13–2.37 (m, 2 H), 1.81–2.11 (m, 2 H), 1.40–1.75 (m, 3 H). MS (*m/z*, rel. %): 270 (*M*+1, 7), 269 (10), 210 (37), 183 (52), 168 (41), 141 (100). Anal. C₁₃H₁₉NO₅: C, H, O.

7c: M.p. 96–100°C. ¹H NMR (300 MHz, 50°C): 4.67 (dd, *J* 11.8, 5.3 Hz, H-8a), 4.10 (dd, *J* 14.5, 3.8 Hz, H-2_{eq}), 3.70 (s, CO₂Me), 3.68 (s, CO₂Me), 3.20 (dt, *J*_d 3.7, *J*_t 11.8 Hz, H-8), 2.97 (dt, *J*_d 2.6, *J*_t 13.5 Hz, H-2_{ax}), 2.59 (dt, *J*_d

12.0, *J* 5.0 Hz, H-4a), 2.31–2.50 (m, 2 H), 2.09–2.20 (m, 1 H), 1.88–2.03 (m, 1 H), 1.65–1.82 (m, 4 H). MS (*m/z*, rel. %): 269 (*M*⁺, 4), 210 (69), 183 (42), 168 (67), 141 (73), 55 (100). Anal. C₁₃H₁₉NO₅: C, H, O.

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