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# ENAMINE CHEMISTRY—XVIII§

## THE FORMATION OF HEXAHYDROCHROMANE-8a-AMINES BY REDUCTIVE CYCLISATION OF ENAMINES

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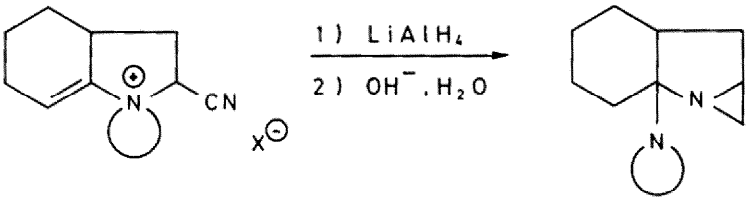
**Abstract**— Enamines (**1**) derived from cyclohexanone or cyclopentanone are reacted with electrophilic olefins (ethyl acrylate, ethyl 2-methylacrylate, ethyl 2-butenoate) to give the new enamines, **2**. When **2** is reacted with $LiAlH_4$, reductive cyclisation takes place giving hexahydrochromane-8a-amines of octahydrocyclopentapyrane-7a-amines, **3**, in quantitative yields. **3** is hydrolyzed with dilute aqueous hydrochloric acid to hexahydrochromane-8a-ols of octahydrocyclopentapyrane-7a-ols (**4**) and reacts also with oxalic acid in refluxing dioxane to form the condensed dihydropyranes, **5**.

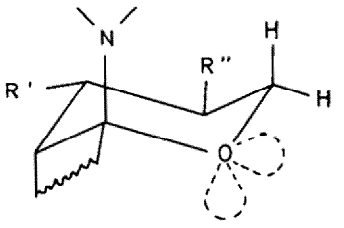
In a recent publication[1] a method for the synthesis of condensed aziridines by reductive cyclisation of 2-cyano-hexahydroindolium salts was described.




Using a mild procedure for hydrolysis of the reaction mixture (the salts were treated with dilute NaOH for 15 min.) it was possible to preserve the amine part (of the original enamine) in the reduction products. As an extension of this work we now wish to report on the synthesis of hexahydrochromane-8a-amines (**3**), by $LiAlH_4$-reduction of **2**. The starting enamines (**2**) are formed by Michael addition[2-4] of electrophilic olefins to the enamines, **1**. The structure of the alkylated enamines (**2**) is determined by spectroscopic data and by comparison with similar known compounds.[3] From the $^1H$ NMR spectra is seen that the integrals of the vinylic proton in **2** varies between 0.2 H and 0.8 H showing that compounds **2** are mixtures of isomers.

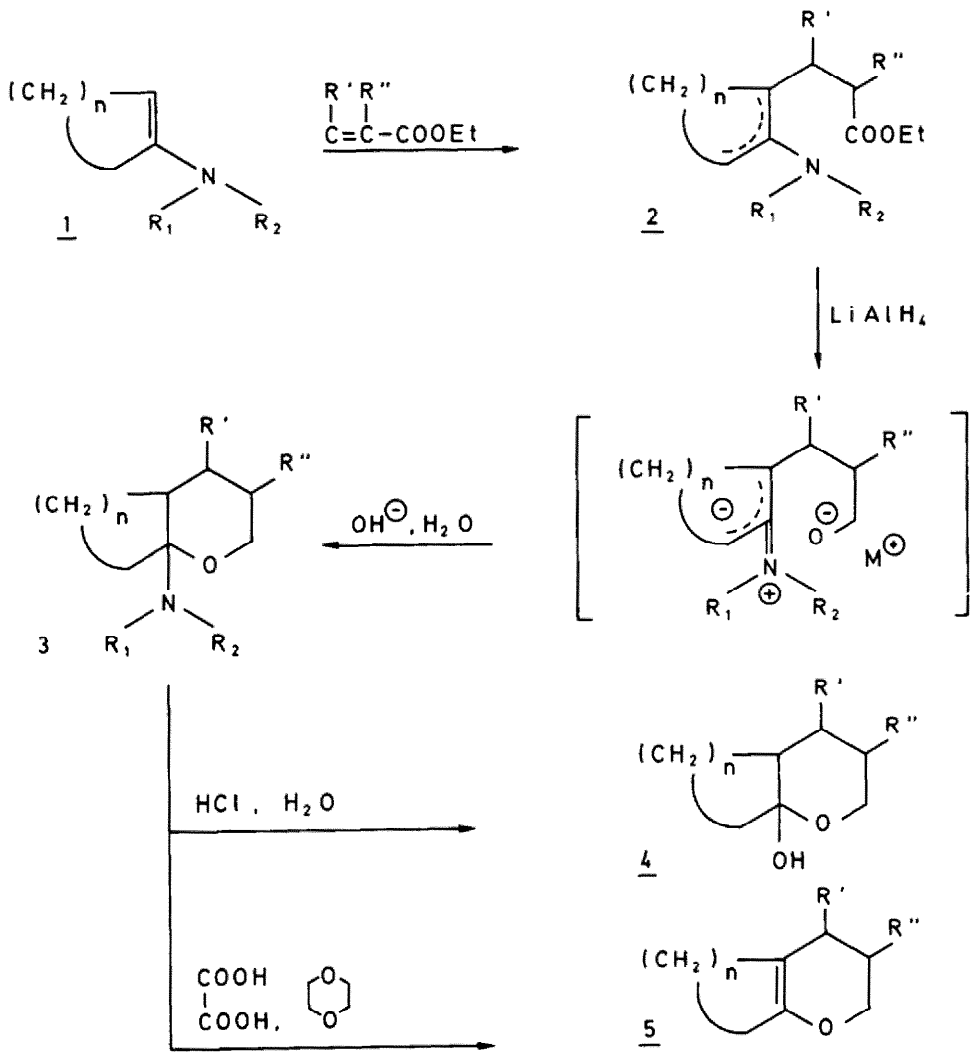
It is well known that $LiAlH_4$ reduces esters to alcohols[5] under mild neutral conditions in almost quantitative yields, and that the enamine function under such conditions remains intact.[6] Formation of the *N,O* acetals (**3**) is therefore a result of an intramolecular nucleo-philic addition of the intermediate alcoholate (or alcohol) to the enamine function. *N,O*-acetals are quite stable towards basis but undergo elimination of the amine when treated with acids. In aqueous media (HCl, $H_2O$) the semiacetals (**4**) are formed, while reaction under nonaqueous conditions (oxalic acid, dioxane) results in formation of vinylic ethers **5**.

The structure of **3** is proved by $^1H$ NMR, $^{13}C$ NMR, IR and mass spectroscopy and by elemental analyses. The $^1H$ NMR spectra of **3** (Table 3) show no olefinic and hydroxyl protons. The methylenic protons at C-2 ($\alpha$ to oxygen) exhibit two separate signals at $\delta$ 3.4–3.5 ppm and $\delta$ 3.9–4.0 ppm respectively, corresponding to different shielding from oxygen:



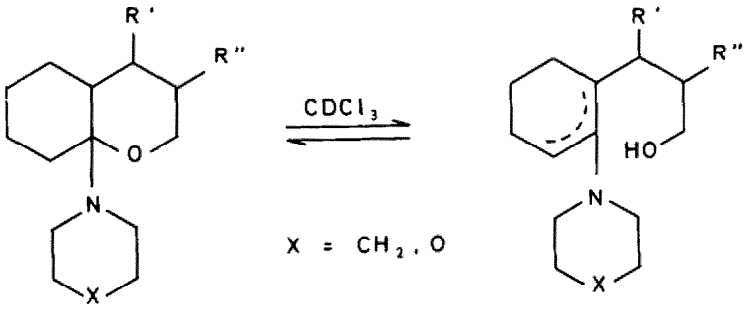

When R'' = Me, the shifts are lowered by 0.2 ppm. As a first approximation an ABX-spin system[9] is considered (AB = $C\underline{H}_2O$ and X = $C\underline{H}_2$-$CH_2$-O or $C\underline{H}$-$CH_2$-O), but in most cases the coupling patterns are too complex to justify a complete analysis, due to the existence of different stereoisomers. From the $^{13}C$ NMR spectra (Table 3) the carbon atoms of **3** are assigned as follows: The quaternary *N,O*-substituted

§Part XVII H. Kolind-Andersen and S.-O. Lawesson, *Bull. Chem. Soc. Belg.* **86**, 543 (1977).

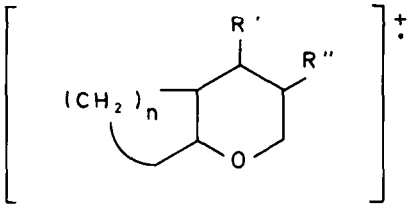



carbon (C-7a or C-8a) at $\delta$ 96–100 for cyclopentane compounds and at $\delta$ 86–89 for cyclohexane compounds, C-2 at $\delta$ 60–63 (R″ = H) and at $\delta$ 67–69 (R″ = Me), carbons $\alpha$ to nitrogen in the amine part at $\delta$ 43–50, the tertiary C-4a at $\delta$ 35–42 and the rest at $\delta$ 20–33. Further, compounds **3e, f, i, j** exhibited weak C=C signals at $\delta$ 144–40 and $\delta$ 127–24 due to ring chain tautomerism (for a review, see Ref. 10).

However compounds **3** exhibit no IR-absorption between 1430 and 2900 $cm^{-1}$ (film), showing that neat **3** does exist as the cyclic tautomers only. Also mass spectra of **3** show the expected fragmentation pattern.



Base peak ($M^{\cdot} - N\langle^{R_1}_{R_2}$) corresponds to the ion:



The structures of the semiketals (**4**) and the condensed dihydropyranes (**5**) are easily determined by comparing the spectroscopic data with those of known compounds.[3,11,12]

As a conclusion it may be stated that by reductive cyclisation of certain enamines (**2**) an alternative route to pyrane derivatives is at hand. This reaction type seems to be of wide scope and a variety of heterocycles may be synthesized in a similar way.

## EXPERIMENTAL

$^1$H NMR spectra were recorded at 60 MHz on a Varian A-60 spectrometer ($CDCl_3$) and the $^{13}$C NMR spectra at 20 MHz on a CFT 20 Varian instrument ($CDCl_3$). TMS was used as internal reference standard. Chemical shifts values are expressed in $\delta$-values. IR-spectra were recorded on a Beckmann IR-18 spectrometer. Mass spectra were recorded on a Micromass 7070 mass spectrometer operating at 70 eV using direct inlet. Silica gel 60 (Merck) was used for column chromatography. M.ps and b.ps are uncorrected. Elementary analyses were carried out by NOVO Micronalytical Laboratory, NOVO Industry A/S, Novo Allé, DK-2880 Bagsværd, supervised by Dr. R. E. Amsler.

*Starting materials.* Compounds **2a-j** were prepared by known methods.[2-4] Alkylation was performed in anhydrous dioxane (**2a-f**) and in absolute ethanol (**2g-j**).

Spectral data of **2g-j**. Ethyl-3-[2-(1-pyrrolidino)-2-cyclohexenyl]-2-methyl-propionate, **2g**. $^1$H NMR ($\delta$-ppm): 4.4 (s, 0.8 H) H C=C, 4.2 (q, $J$ = 7 Hz, 2 H) $CH_2$–O, 2.7–3.2 (m, 4 H) $CH_2$ N, 1.0–2.0 (m, 20 H). MS: 265 ($M^+$), 236, 220, 164 (base peak), 151. IR: 1730 cm$^{-1}$ (s), 1630 cm$^{-1}$ (s). (Found: C, 71.75; H, 10.25; N, 4.79. Calc.: C, 72.45; H, 10.19; N, 5.28%).

Ethyl-3-[2-(1-pyrrolidino)-2-cyclohexenyl]-3-methyl-propionate, **2h**. $^1$H NMR: 4.65 (t, $J$ = 4 Hz, 0.6 H), 4.15 (q, $J$ = 7 Hz, 2 H), 0.8–3.0 (m, 24 H). MS: 265, 250, 236, 220, 178, 164, 151 (base peak). IR: 1730 cm$^{-1}$ (s), 1630 cm$^{-1}$ (s). Found: C, 71.77; H, 10.34; N, 4.51. Calc.: C, 72.45; H, 10.19; N, 5.28%).

Ethyl-3-[2-(1-piperidino)-2-cyclohexenyl]-2 methyl propionate, **2i**. $^1$H NMR: 4.75 (s (broad), 0.25 H), 4.12 (q, $J$ = 7 Hz, 2 H), 1.0–2.9 (m, 26 H). MS: 279 ($M^+$), 234, 178 (base peak), 165. IR: 1730 cm$^{-1}$ (s), 1625 cm$^{-1}$ (s). (Found: C, 72.20; H, 9.96; N 4.87. Calc.: C, 73.12; H, 10.39; N, 5.02%).

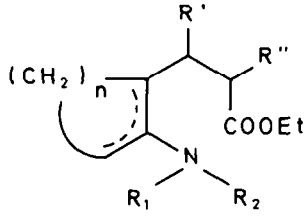
Ethyl-3-[2-(1-piperidino)-2-cyclohexenyl]-3-methyl-propionate, **2j**. $^1$H NMR: 4.9 (t, $J$ = 4 Hz, 0.7 H), 4.17 (dq, $J$ = 6.5 Hz, 2 H), 1.28 (t, $J$ = 6.5 Hz, 3 H), 1.0 (d, $J$ = 6 Hz) and 0.8 (d, $J$ = 6 Hz) together 3 H. MS: 279, 284, 270, 234, 192 (base peak), 165, 164. IR: 1725 cm$^{-1}$ (s), 1625 cm$^{-1}$ (s). (Found: C, 73.14; H, 10.58; N, 4.95. Calc.: C, 73.12; H, 10.39; N, 5.02%).

*General procedure for the reductions* **2** → **3**. To an ice-cooled soln of $LiAlH_4$ (0.05 mole) in anhydrous ether (50 ml, stirring, $N_2$) **2** (0.05 mole) is added dropwise (5–10 min). Stirring is then continued at room temp. for 3 hrs. Work-up procedure: At 0° 1.9 g $H_2O$ are added dropwise (5 min) followed by 1.43 g 30% NaOH + 14.3 g $H_2O$. The icebath is removed and stirring is continued for 15 min. The mixture is then filtered and extracted twice with ether. The combined ether-extracts are dried ($MgSO_4$), concentrated, and distilled under reduced pressure.

Typical mass spectrum: **3d**: 209 ($M^+$), 180, 166, 164, 156, 139 (base peak), 113, 70. Typical IR spectrum: **3d**: 2900 cm$^{-1}$ (s), 1420 cm$^{-1}$ (m), 1360, 1330.

*Acid hydrolysis* (**3** → **4**). Compound **3** (0.005 mole) is refluxed with 0.1 N HCl (0.0055 mole) for 6 hr. The semiacetal **4** is extracted with $CHCl_3$ and purified on column (silica gel, ether/p. ether: 50/50). **4**, n = 2, R′ = R″ = H. Yield 61%. $^1$H NMR: 3.4–3.9 (m, 2 H) $CH_2$–O, 3.15 (s, 1 H) OH, 1.2–2.2 (m, 11 H). MS: 142 ($M^+$), 125 (base peak), 113. **4**, n = 3, R′ = R″ = H. Yield 82%. M.p. 74° (petroleum ether). $^1$H NMR: 3.5–4.0 (m), 2.68 (s), 1.2–2.0 (m, 13 H). MS: 156 ($M^+$), 139, 113 (base peak). $^{13}$C NMR: 100.29, 64.61, 47.66, 42.62, 33.54, 30.39, 29.82, 28.85, 27.14. **4**, n = 3, R′ = H, R″ = Me. Yield 100%. M.p. 64° (not recrystallized). $^1$H NMR: 3.4–3.9 (m),

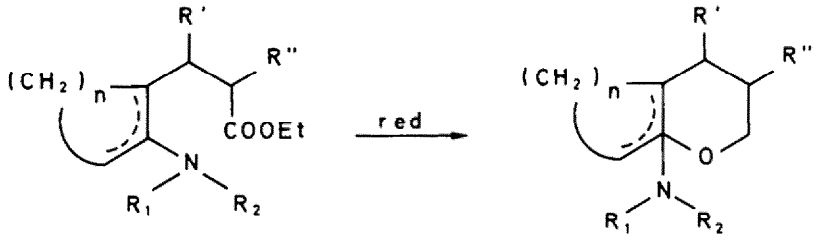
Table 1. Starting material



**2**

| 2 | n | $R_1R_2$ | R′ | R″ | Reaction time hrs. | Yield % | Bp. (°C/torr) |
|---|---|---|---|---|---|---|---|
| **a** | 2 | $(CH_2)_4$ | H | H | 8 | 76 | 110–15/0.25 |
| **b** | 2 | $(CH_2)_5$ | H | H | 8 | 70 | 118–25/0.3 |
| **c** | 2 | $CH_2CH_2OCH_2CH_2$ | H | H | 8 | 53 | 120–25/0.35 |
| **d** | 3 | $(CH_2)_4$ | H | H | 8 | 70 | 120–30/0.2 |
| **e** | 3 | $(CH_2)_5$ | H | H | 8 | 78 | 120–23/0.4 |
| **f** | 3 | $CH_2CH_2OCH_2CH_2$ | H | H | 8 | 51 | 125–35/0.25 |
| **g** | 3 | $(CH_2)_4$ | H | Me | 16 | 70 | 120/0.2 |
| **h** | 3 | $(CH_2)_4$ | Me | H | 16 | 64 | 144/0.7 |
| **i** | 3 | $(CH_2)_5$ | H | Me | 64 | 59 | 120/0.5 |
| **j** | 3 | $(CH_2)_5$ | Me | H | 64 | 33 | 126/0.4 |

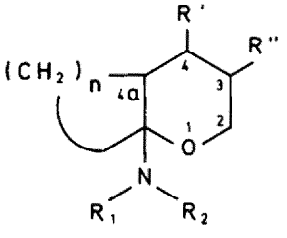
Table 2.




2 3

| 2 | Yield of 3 (%) | Bp. (°C/torr) | Analyses (%) Found C | H | N | Calc. C | H | N |
|---|---|---|---|---|---|---|---|---|
| a | 100 | 66/0.15 | 72.75 | 10.73 | 6.21 | 73.85 | 10.77 | 7.18 |
| b | 100 | 77-79/0.25 | 73.72 | 10.86 | 6.25 | 74.64 | 11.00 | 6.70 |
| c | 100 | 110/0.25 | 68.08 | 10.10 | 5.83 | 68.25 | 9.95 | 6.64 |
| d | 98 | 80/0.2 | 73.99 | 11.01 | 6.20 | 74.64 | 11.00 | 6.70 |
| e | 96 | 102/0.25 | 75.27 | 11.23 | 6.10 | 75.34 | 11.21 | 6.28 |
| f | 100 | 92/0.15 | 68.80 | 10.26 | 6.81 | 69.33 | 10.22 | 6.72 |
| g | 100 | 96/0.4 | 74.81 | 11.41 | 5.85 | 75.34 | 11.21 | 6.28 |
| h | 100 | 110/0.5 | 74.99 | 11.20 | 5.99 | 75.34 | 11.21 | 6.28 |
| i | 100 | 120/0.2 | 75.56 | 11.46 | 5.77 | 75.95 | 11.39 | 5.91 |
| j | 100 | 116/0.3 | 75.58 | 11.27 | 5.92 | 75.95 | 11.39 | 5.91 |

Table 3. Spectral data of 3




3

| 3 | $^1$H NMR $CH_2O$ | $^{13}$C NMR N-C-O | $CH_2$-O | $CH_2$-N | C-4a |
|---|---|---|---|---|---|
| a | 3.5-4.0 (m) | 99.98 | 63.84 | 50.04 | 42.74 |
| b | 4.0 (m)<br>3.5 (t, J 5 Hz) | 100.65 | 63.39<br>63.29 | 50.29 | 40.31<br>40.17 |
| c | 4.0 (m)<br>3.5 (t, J 5 Hz) | 96.25 | 59.51 | 46.50<br>46.02 | 35.82 |
| d | 3.45-3.9(m) | 87.94 | 61.46 | 43.86 | 37.47 |
| e | 3.9 (t, J 5 Hz)<br>3.4 (t, J 5 Hz) | 87.41 | 59.98<br>59.63 | 45.17 | 34.41 |
| f | 3.95(t, J 6 Hz)<br>3.45(t, J 6 Hz) | 86.92 | 60.44<br>59.76 | 44.68 | 33.79 |
| g | 3.3-3.8 (m) | 89.03<br>86.54 | 69.21<br>66.70 | 44.15<br>43.39 | 37.97<br>36.60 |
| h | 3.5-3.9 (m) | 89.12<br>87.17 | 61.85<br>60.43 | 44.26<br>43.34 | 35.58 |
| i | 3.2-3.7 (m) | 89.89<br>86.96 | 69.98<br>65.42 | 45.15<br>44.84 | 34.86<br>34.48<br>33.44 |
| j | 3.4-3.9 (m) | 89.62 | 60.58 | 44.99<br>42.37 | 36.87<br>33.66 |

2.55 (s), 1.1–1.9 (m, 12 H), 0.90 (d, $J$ = 6 Hz, 3 H). **4**, n = 3, R′ = Me, R″ = H. Yield 100%. M.p. 94° (petroleum ether). $^1$H NMR: 3.5–4.0 (m), 2.20 (s), 1.0–1.9 (m, 12 H), 0.85 (d, $J$ = 6 Hz, 3 H). MS: 170, 155, 153, 137, 127 (base peak).

*Elimination with oxalic acid* (**3** → **5**). Compound **3** (0.02 mole) and oxalic acid (0.02 mole) dissolved in 40 ml anhydrous dioxane are refluxed for 6 hr. After standing overnight the oxalate is filtered off. The soln. is concentrated under vacuum, dissolved in ether, washed with water and dried ($MgSO_4$). **5** is purified either by distillation or by column chromatography ($SiO_2$, ether/p. ether: 10/90). **5**, n = 2, R′ = R″ = H. Yield 48% from **3a**. $^1$H NMR: 3.98 (t, $J$ = 5.5 Hz, 2 H) $CH_2O$, 1.4–2.4 (m, 1 H). IR: 1695 cm$^{-1}$ (s). MS: 124 ($M^+$, base peak), 96. **5**, n = 3, R′ = R″ = H. Yield 83% from **3d**. $^1$H NMR: 3.90 (t, $J$ = 5 Hz), 1.4–2.1 (m, 12 H). $^{13}$C NMR: 147.08, 104.14, 65.59, 29.15, 27.46, 25.45, 23.48, 23.37, 23.25. IR: 1690 cm$^{-1}$ (s). MS: 138 ($M^+$, base peak), 110. **5**, n = 3, R′ = H, R″ = Me. Yield 68% from **3g**. $^1$H NMR: 3.90 (m, 1 H) and 3.50 (m, 1 H), 1.4–2.2 (m, 11 H), 0.95 (d, $J$ = 6 Hz, 3 H). IR: 1700 cm$^{-1}$ (s). MS: 152 ($M^+$, base peak), 137, 124. (Found: C, 78.57; H, 10.48. Calc.: C, 78.95; H, 10.53%). **5**, n = 3, R′ = Me, R″ = H. Yield 93% from **3h**. $^1$H NMR: 3.90 (t, $J$ = 4.5 Hz), 1.4–2.3 (m, 11 H), 1.0 (d, $J$ = 6 Hz, 3 H). (Found: C, 78.24; H, 10.62. Calc. C, 78.95; H, 10.53%).

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