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$NaBH_4$ REDUCTION OF CYCLIC IMIDES

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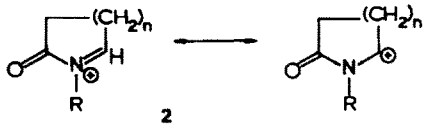
Abstract—One of the carbonyl functions of succinimides and glutarimides is selectively reduced by sodium borohydride in presence of hydrochloric acid yielding ω-carbinol-lactams. Some factors influencing the reduction process are discussed. Depending on the conditions pyrrolidinones, cyclic enamides or dimeric lactams are formed upon treatment of the ω-carbinol-lactams with acid.

The α-amido-alkylation reaction involving the linear acylimmonium species **1** constitutes an important area in organic synthesis.[2]

Although a great number of methods exists for the preparation of this type of reactive intermediate comparatively little is known about its cyclic equivalent in which the reagent possesses the cyclic structure **2**.



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The preparation of **2** could formally be considered as being possible either by the acid catalyzed elimination of HX from –NR–CHX-substituted lactams or via protonation of cyclic enamides. A facile synthetic entry into this category of intermediates would allow the preparation of a variety of heterocyclic compounds and could be of potential value as a general method of synthesis for several alkaloidal systems.[3]

Recently the preparation of pyrrolin-2-ones[4] and 5-alkoxy- and 5-hydroxy-2-pyrrolidinones[5] was reported. The latter compounds may serve as suitable precursors for the desired types of acylimmonium intermediate. Additional methods of preparation include cyclization of γ-amino-vinyl-acetates[6] and photo-oxidation[7] or alkaline H_2O_2-oxidation[4] of pyrrole derivatives. The latter procedures suffer from considerable limitations as only relatively simple heterocyclic systems are accessible, while the experimental procedure is often laborious and yields are low. Therefore a new method of preparing 5-hydroxy- or 5-alkoxy-2-pyrrolidinones via a pH controlled $NaBH_4$ reduction of succinimides allowed a general entrance to this field of heterocyclic synthesis both with regard to the availability of starting materials as well as to the experimental procedure which is extremely mild and simple to perform. In the present communication some aspects of the reduction process as applied to a number of differently substituted imides will be discussed.[8]

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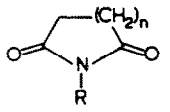

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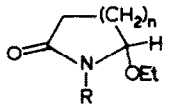

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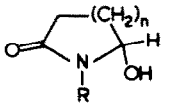

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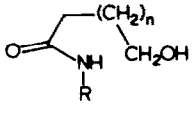

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a R = Me , n=1
b R = Me , n=2
c R = H , n=1
d R = H , n=2
e R = Ph , n=1
f R = PhOMe , n=1
g R = $PhNO_2$, n=1

As was reported earlier[5] $NaBH_4$/HCl reduction of imide **3a** in EtOH/H_2O 9:1 and destroying the excess of $NaBH_4$ with HCl gave 1-methyl-5-ethoxy-2-pyrrolidinone (**4a**) in nearly quantitative yield. On the assumption that the hydroxy compound **5a** was initially formed and converted into the ethoxy compound **4a** under catalytic influence of acid ("*acid work-up*"), the reduction procedure was repeated in 100% ethanol keeping the solution alkaline after completion of the reduction ("*base work-up*"). Direct evaporation of the solvent and $CHCl_3$ extraction of the residue gave an oil, b.p. 120–123°/0·08 mm, PMR ($CDCl_3$) δ 2·84 (s, 3H, CH_3N) 5·15 (1H, –CHOH–), which analyzed correctly for 1-methyl-5-hydroxy-2-pyrrolidinone (**5a**). Proof of this structure was obtained by conversion of **5a** into the ethoxy compound **4a** in nearly quantitative yield by treatment with HCl in ethanol (p_H 3–4) for 30 min at 0–5°. From these results it follows that either the hydroxy or the ethoxy compound can be prepared selectively depending on the work-up procedure.

Next the $NaBH_4/H^{\oplus}$ reduction of succinimides differently substituted at nitrogen was investigated together with the influence of the ring size on the course of the reaction. Within the latter objective 1-Me-glutarimide (**3b**) was converted quantitatively into the oily 1-methyl-6-ethoxy-piperidone-2 (**4b**) following "acid work-up".

In a similar manner N-unsubstituted ω-carbinol-lactams, until now only accessible via cyclization

procedures,[9] could be smoothly prepared via this technique. The crystalline 2-pyrrolidinone **4c**, m.p. 48–53°, PMR δ ($CDCl_3$) 4·96 d (C_5–H) as well as the 2-pyridinone **4d**, m.p. 45° (dec), PMR δ ($CDCl_3$) 4·66 d (C_6–H) were obtained in nearly quantitative yield starting from imides **3c** and **3d** respectively.

As was stated earlier[10] the major problem in a reduction of this type is the ring-cleavage of the initially formed oxy-anion **A** to the amide aldehyde **B** and further reduction to amide alcohol **C** (Scheme 1). Protonation of **A** and **B** will lead to **D** and **E** respectively which might be expected to form a tautomeric equilibrium in which **D** is by far the preferred form. Of relevance to the latter aspect is the fact that the existence of amide-aldehyde **E** never has been proved with any certainty. The recently reported synthesis of isolongistrobine[11] in which a similar intermediate has been prepared via $NaIO_4$–OsO_4 cleavage of an alkene precursor shows PMR spectral data which are characteristic for compounds of type **D**.

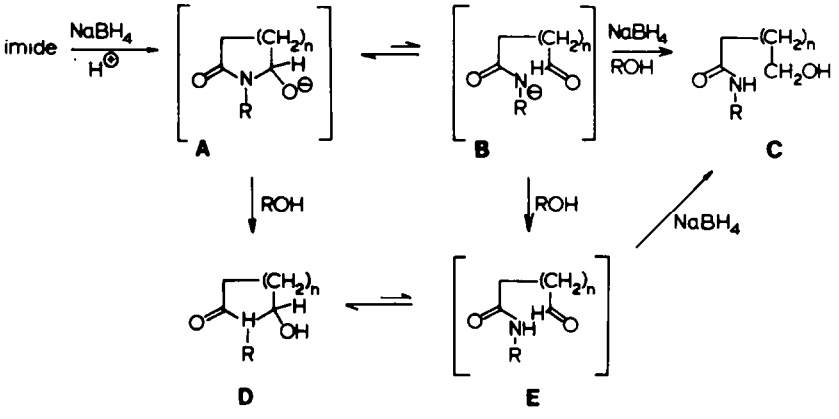
Factors expected to have influence on the reaction sequence **A** → **B** → **C** are the ring size, the nature of R and the presence of ring substituents.†

however, a different solvent combination had to be used (DMF/EtOH 2:1). Therefore the behaviour of **3e**, **3f** and **3g** was also investigated upon carrying out reductions at −20° during 4 hr in the latter solvent combination. The results given in the table confirmed the expected influence of the N-substituent on this type of reduction.

The yield of **5g** could be somewhat improved upon a further lowering of the reaction temperature (−40°, yield 38%).

As with regard to the mechanism of the reduction of the role of $H^{\oplus}$ deserves some comment. In absence of $H^{\oplus}$ the reduction proceeds sluggishly and incomplete while the majority of the product consists of ringopened material. On the other hand the addition of a minor quantity of HCl has no significant influence on the acidity of the solution as was proven by p_H-monitoring. In case of unsymmetrically ringsubstituted imides the presence of $H^{\oplus}$ does also not affect the regio-selectivity of the reduction.[14]

Our first hypothesis in which the role of HCl was tentatively assigned to convert the supposedly less stable OH-lactam into a more stable ethoxy derivative[15] is shown to be incorrect by the results of this work.



SCHEME 1

As mentioned above the reduction of glutarimide derivatives can be carried out in a satisfactory manner although its stability under the usual conditions seemed somewhat less and ring opening **A** → **B** (n = 2) occurred more readily. Therefore in general lower reaction temperatures were required.

As with regard to the second factor—the nature of R—it may be anticipated that a substituent R capable of extending the amide resonance in **B** will also enhance the formation of **C**. In this connection the observation of Horii c.s.[13] is of interest; $NaBH_4$-reduction of 1-phenylsuccinimide (**3e**) gave a mixture of alcohol **6e** and γ-butyrolactone as the sole products. On the contrary $NaBH_4/H^{\oplus}$ reduction of **3e** at −21° and "acid work-up" gave the ethoxy derivative **4e** (52%) together with amide alcohol **6e** (46%). "Base work-up" afforded a similar result (52%, **5e**).

In case R = *p*-MeOAr the ring opening **A** → **B** is expected to be supressed which indeed was found to be the case. Reduction of **3f** at −21° and "acid work-up" gave 88% of **4f** against 12% of **6f**.

In case R = *p*-NO_2Ar ("base work-up") a yield of 13% of **5g** against 87% of **6g** was obtained. In this experiment,

†The results of the amide hydrolysis of various ring substituted lactams[12] clearly show a considerable influence of substituents on the rate of ring opening.

Table 1. $NaBH_4/H^{\oplus}$ reduction in DMF/EtOH (2:1) at −20°

Compound	3[a]	4[a]	6[a]
3a	**3a** (100%)	—	—
3e	**3e** (80%)	**4e** (20%)	—
3f	**3f** (95%)	**4f** (5%)	—
3g	**3g** —	**4g** (13%)	**6g** (87%)

[a]Yields have been determined by PMR after work-up of the reduction product.

From the available evidence the role of HCl is accounted for in the following manner: firstly an activation of the carbonyl group may take place similar to that as has been observed in the reactions of cyanoborohydride.[16] Furthermore the reduction process is favoured by the enhanced exchange of the borate ester,[17] while the ring opening of the initially formed oxy anion (*cf* **B** Scheme 1) is inhibited by addition of acid. The latter undesired process will also be suppressed by lowering of the reaction temperature.

Acid treatment of γ- and δ-oxy-lactams

As was already mentioned the OH-derivative **5a** was converted quantitatively into the OEt-derivative **4a** upon

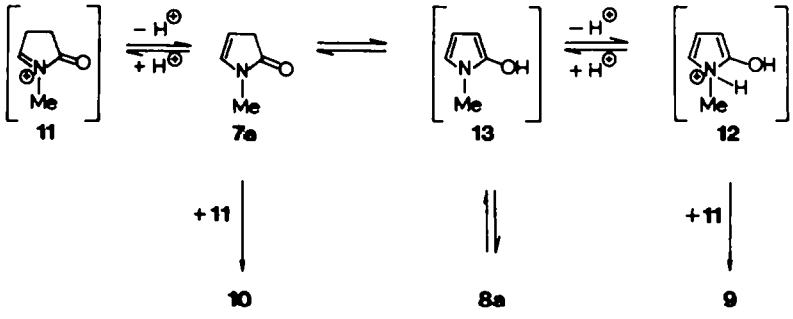
treatment with HCl/EtOH at 0°. In the same manner **5g** afforded **4g**. In return the transformation OEt→OH proved also be possible. Upon treatment at reflux of **4f** in a dioxane/H_2O mixture to which a silica-alumina catalyst[18] was added **5f** was obtained in nearly quantitative yield. These transformations may involve direct S_N2 displacement or reaction via an acylimmonium intermediate.

Upon heating ethoxy-lactam **4d** in toluene at reflux the 3,4-dihydro-2-pyridone **7d** was obtained quantitatively as a colourless oil. The N-Me derivative **4b** remained largely unchanged under these conditions. However, addition of a trace of *p*-TsOH or alternatively a small quantity of **7d** sufficed to complete the conversion **4b**→**7b**, thus proving the elimination to be weakly acid-catalyzed. Quite opposite results were found in the acid treatment of γ-alkoxypyrrolidinones **4** and **5** (n = 1). Upon treatment of **4c** with *p*-TsOH only a limited amount of the pyrrolin-2-one **8c** was obtained, the bulk of the remaining material being polymeric in nature. Refluxing **4a** in C_6H_6 however, without addition of acid afforded the N-Me derivative **8a** in 50% yield after chromatography. Minor amounts of **7a** present in the crude reaction product could not be obtained in pure form. Although after repeated chromatography a certain enrichment of fractions containing **7a** could be reached, a spontaneous conversion of **7a**→**8a** prevented isolation of pure **7a**.

Highly interesting behaviour was noted upon refluxing of **4a** in C_6H_6/*p*-TsOH. The major product obtained after column chromatography in 55% yield possessed an $M^{\oplus}$ peak at $m/e = 194$ in the mass spectrum which indicated the formation of a dimer of **7a** (or **8a**). According to PMR this dimer proved to be the C_3–C_5 coupling product **9**, easily characterized by the position of its C_4-olefinic signal ($\delta = 6{\cdot}80$ ppm). Starting from **8a** the yield of **9** could be raised to 79%.

Rather unexpectedly a second type of dimer was formed upon reaction of **4a** in refluxing C_6H_6/silica-alumina catalyst. Although the latter catalyst is also acidic in nature a completely different dimerization occurred leading to **10**, which was obtained as an unstable solid. Conclusive evidence about its structure was provided by mass and PMR spectral data. Especially the position of the C_3 olefinic proton found at $\delta = 6{\cdot}00$ ppm was indicative, while the rest of the spectrum was similar to a large degree with the spectrum of **9**.

The observed reaction behaviour is tentatively explained as follows (Scheme 2):

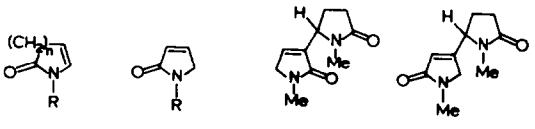


SCHEME 2

Attack of the immonium species **11** on respectively the C = C–N moiety in the enamide **7a** or on the C = C–OH in **12** would lead to the formation of different products.

In the latter reaction the intermediacy of the elusive 2-OH-pyrrole[20] **13** has to be invoked which in relatively strong acid medium will be preferentially protonated at the nitrogen thereby blocking the enamide reactivity. The dimerization then proceeds by C_3–C_5 coupling. On the other hand, in less acidic medium the enamide character is dominating which leads to C_4–C_5 coupling. Although the formation of **7a** by protonation and subsequent hydride transfer from **8a** has been postulated[19] the latter process seems unlikely in view of the reaction circumstances used and the results described in the foregoing.

Finally, additional support for the suggested pathway came from dimerization experiments with dihydropyridone **7b** or 6-OEt-pyridone-2 (**4b**) under influence of both *p*-TsOH and silica-alumina catalyst. In all experiments the sole product obtained was the dimer **14** which in view of the virtual non-existence of a resonance stabilized enolic amide form, is the only product expected to form.



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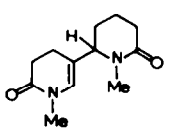
b R = Me, n = 2
c R = H, n = 1
d R = H, n = 2



EXPERIMENTAL

Preparation of imides. The imides were generally prepared[21] by heating an appropriate primary amine with a dicarbocylic acid or its anhydride during 1–2 hr at 200–250°. In the preparation of the N–H and N-methyl imides a large excess of a 25% ammonia soln or 35% methylamine soln in water was used; heating at 200–250° was continued till no more amine was liberated. The dark brown coloured products wer purified by recrystallization or distillation. The N-aryl imides were prepared by heating the anhydride with one equivalent of the corresponding aniline-derivative at 200°.

Imide		yield	b.p.	m.p.
1-Methylsuccinimide	**3a**	86%		67–69° (EtOH)
1-Methylglutarimide	**3b**	84	240–246°	
Glutarimide	**3d**			144–146° (acetone)
1-Phenylsuccinimide	**3e**	90		153–155° (EtOH)
1-*p*-Methoxyphenyl-succinimide	**3f**	80		160–162° (EtOH)
1-*p*-Nitrophenyl-succinimide	**3g**	34		209–211° ($CHCl_3$)

General procedure for the $NaBH_4/H^+$ *reduction.* The $NaBH_4/H^+$ reductions were carried out with a stirred soln of the imide in 90% or abs EtOH at temps of −20 to +5° with an excess of $NaBH_4$. At regular intervals (mostly 15 min) 2–3 drops of acid were added: 2 N HCl if 90% EtOH and 2 N HCl in EtOH if 100% EtOH was used. The reaction time was 4–5 hr. Four work-up methods were followed in which the methods B and D were used when products were water soluble.

Method A (acidic). The excess of $NaBH_4$ was destroyed in 15–30 min at the temp of reaction by adding acid till pH = 3. The mixture was stirred for an additional 45–60 min at +5° and poured into water. Extraction with $CHCl_3$ and work-up of the extract afforded the reaction product.

Method B (acidic). As method A, but after stirring at pH = 3 the mixture was neutralized with a 1% KOH aq in EtOH. The mixture was evaporated to dryness. Extraction of the residue with $CHCl_3$ and evaporation of the extract afforded the reaction product.

Method C (basic). After reduction the cooled soln was poured into water. Extraction with $CHCl_3$ and work-up of the extract afforded the reaction product.

Method D (basic). After the reduction of EtOH was removed under reduced pressure while the mixture was kept at 5–10°. The residue was cooled and extracted with CH_2Cl_2. Evaporation of the extract afforded the reaction product.

1-*Methyl-5-ethoxy-2-pyrrolidinone* **4a**. **3a** (2·000 g; 17·70 mmole) was reduced in EtOH (200 ml) with 2·50 g of $NaBH_4$ at 0° during 5 hr. Work-up (method B) afforded **4a** as an oil (2·161 g). Vacuum distillation provided 2·014 g (14·08 mmole) of **4a** (62–66°/0·1 mm, bath temp 140–160°), yield: 80%. IR ($CHCl_3$): 1680 (vs) (lactam-CO). PMR: δ ($CDCl_3$) 1·18 (t, 3H, $-OCH_2-CH_3$) 1·78–2·46 (4H, –4H, $-CH_2-CH_2-$) 2·83 (s, 3H, $-N-CH_3$) 3·53 (q, 2H, $-OCH_2-CH_3$) 4·92 (m, 1H, N–CH–OEt). MS: *m/e* = 27 (38%) 31 (54) 39 (30) 41 (33) 42 (100) 68 (64) 97 (68) 98 (64) 143 (2) M^+.

1-*Methyl-6-ethoxy-2-piperidone* **4b**. **3b** (1·142 g, 8·99 mmole) was reduced in EtOH (100 ml) with 1·30 g $NaBH_4$ at −10° during 4·5 hr. Work-up (method B) afforded **4b** as an oil (1·350 g, 8·60 mmole), yield: 95%. IR ($CHCl_3$): 1635 (vs) (lactam-CO); PMR: δ ($CDCl_3$) 1·20 (t, 3H, $-OCH_2-CH_3$) 1·4–2·5 (6H, $-CH_2-CH_2-CH_2-$) 2·94 (s, 3H, $N-CH_3$) 3·53 (q, 2H, $-OCH_2-CH_3$) 4·55 (m, 1H, N–CH–OEt).

5-*Ethoxy-2-pyrrolidinone* **4c**. **3c** (3·578 g, 36·14 mmole) was reduced in EtOH (150 ml) with 2·00 g $NaBH_4$ at 0° during 4 hr. Work-up (method B) afforded **4c** as an oil, which crystallized from ether to give 4·108 g (31·84 mmole) of **4c**. An analytical sample was distilled under reduced pressure (b.p. 81–90°/0·01 mm, bath temp 150–170°), yield: 88%, m.p. 48–53° (ether). IR ($CHCl_3$): 3430, 3200 (m) (NH) 1690 (vs) (lactam-CO); PMR: δ ($CDCl_3$) 1·17 (t, 3H, $-OCH_2-CH_3$) 3·1–3·9 (m, 2H, $-OCH_2-CH_3$) 5·00 (m, 1H, N–CH–OEt) 8·3–8·8 (1H, N–H). MS: *m/e* = 27 (30%) 28 (70) 29 (27) 31 (29) 41 (33) 46 (40) 56 (28) 84 (100) 114 (24) 129 (9) M^+ (*Anal.* $C_6H_{11}NO_2$ M = 129·16. Calc. C 55·79; H, 8·58; N, 10·85%. Found: 55·8, 8·7, 10·9).

6-*Ethoxy-2-piperidone* **4d**. **3d** (4·735 g, 41·90 mmole) was reduced in EtOH (250 ml) with 3·63 g $NaBH_4$ at 5° during 4 hr. Work-up (method B) afforded **4d**, which was crystallized from ether to give 5·122 g (35·61 mmole) of **4d**, yield: 85%, m.p. 45° dec. (ether). IR: 3480, 3190 (NH) 1670 (s) (lactam-CO). PMR: δ ($CDCl_3$) 1·21 (t, 3H, $-OCH_2-CH_3$) 3·23–3·85 (m, 2H, $-OCH_2-CH_3$) 4·67 (m, 1H, N–CH–OEt) 7·7–8·1 (1H, N–H). MS: *m/e* = 55 (38%) 98 (100) 143 (5) M^+ (Anal. $C_7H_{13}NO_2$ M = 143·18. Calc.: C, 58·72; H, 9·15; N, 9·78%. Found: 58·8 9·2 9·9).

1-*Phenyl-5-ethoxy-2-pyrrolidinone* **4e**. **3e** (0·497 g, 2·84 mmole) was reduced in EtOH (250 ml) with 0·94 g $NaBH_4$ at −21° during 5 hr. Work-up (method A) afforded a pale yellow oil (0·550 g), which showed 2 spots on TLC (silicagel, $CHCl_3$/acetone 4/1) with R_f 0·11 and 0·50. Column chromatography on silicagel with $CHCl_3$/acetone 5/1 as an eluent afforded the fraction corresponding with R_f 0·50 as a pale yellow oil (0·305 g), yield: 52%. IR (liquid film): 1700 (vs) (lactam-CO); PMR: δ ($CDCl_3$) 1·16 (t, 3H, $O-CH_2-CH_3$) 2·05–2·97 (4H, $-CH_2-CH_2-$) 3·45 (q, 2H, $O-CH_2-CH_3$) 5·37 (m, 1H, N–CH–OEt) 7·10–7·60 (5H, aromatic H).

1-p-*Methoxyphenyl-5-ethoxy-pyrrolidinone* **4f**. **3f** (0·592 g, 2·84 mmole) was reduced in EtOH (250 ml) with 0·94 g $NaBH_4$ at −21° during 5 hr. Work-up (method A) afforded a pale yellow oil (0·660 g), which showed 2 spots on TLC (silicagel, $CHCl_3$/acetone 4/1) with R_f 0·09 and 0·45. Column chromatogreaphy on silicagel with $CHCl_3$/acetone 5/1 as an eluent afforded the fraction corresponding with R_f 0·45 as an oil (0·585 g), which crystallized after cooling, yield: 88%, m.p. 46–48° (di-isopropylether). IR (KBr): 1685 (vs) (lactam-CO); PMR: δ ($CDCl_3$) 1·11 (t, 3H, $O-CH_2-CH_3$) 1·96–3·00 (4H, $-CH_2-CH_2-$) 3·44 (q, 2H, $O-CH_2-CH_3$) 3·78 (s, 3H, $-O-CH_3$) 5·30 (m, 1H, N–CH–OEt) 6·8–7·6 (4H, aromatic H). MS: *m/e* = 190 (100%) 235 (98) M^+ (Anal. $C_{13}H_{17}NO_3$ M = 235·27. Calc. C, 66·36; H, 7·28; N, 5·95%. Found: 66·3 7·4 5·9.)

1-*p-Nitrophenyl-5-ethoxy-2-pyrrolidinone* **4g**. 0·077 g of **5g** (0·34 mmole) in EtOH (25 ml) was stirred at 5° during 2 hr at pH = 3 and then poured into dil $NaHCO_3$ aq. Extraction with $CHCl_3$ and work-up of the extract afforded **4g** as a solid (0·083 g, 0·33 mmole), yield: 95%, m.p. 89–91° (ether). IR (KBr): 1720 (s) (lactam-CO) PMR: δ (CD_3COCD_3): 1·15 (t, 3H, $O-CH_2-CH_3$), 2·05–3·95 (4H, $-CH_2-CH_2-$) 3·59 (q, 2H, $O-CH_2-CH_3$), 5·68 (m, 1H, N–CH–OEt) 7·8–8·4 (4H, aromatic H). MS: *m/e* = 205 (100%) 250 (38·5) M^+ (Anal. $C_{12}H_{14}N_2O_4$ M = 250·25. Calc. C, 57·59; H, 5·64; N, 11·20%. Found: 57·6 5·7 11·1).

1-*Methyl-5-hydroxy-2-pyrrolidinone* **5a**. **3a** (3·763 g, 33·30 mmole) was reduced in EtOH (200 ml) with 3·50 g $NaBH_4$ at 0° during 4 hr. Work-up (method D) afforded **5a** as a pale pink oil (2·153 g, 18·72 mmole). An analytical sample was distilled under reduced pressure (b.p. 120–123°/0·08 mm, bath temp 185–205°), yield: 56%. IR ($CHCl_3$): 3310 (m) (OH) 1670 (vs) (lactam-CO); PMR: δ ($CDCl_3$) 1·75–2·5 (4H, $-CH_2-CH_2-$) 2·84 (s, 3H, $N-CH_3$) 5·15 (m, 1H, N–CH–OH) 5·5–6·2 (1H, –OH). MS: *m/e* = 42 (83%) 68 (47) 97 (100). (Anal. $C_5H_9NO_2$ M = 115·13. Calc. C, 52·16; H, 7·88; N, 12·17%. Found: 52·2 8·0 12·1).

1-*Phenyl-5-hydroxy-2-pyrrolidinone* **5e**. **3e** (0·200 g, 1·14 mmole) was reduced in EtOH (25 ml) with 0·30 g $NaBH_4$ at −21° during 5 hr. Work-up (method C) afforded a pale yellow oil (0·201 g), which showed 2 spots on TLC (silicagel, $CHCl_3$/acetone 4/1) with R_f 0·11 and 0·25. Column chromatography on silicagel with $CHCl_3$/acetone 10/1 as an eluent afforded 0·115 g of **5e** (R_f 0·25), yield: 52%, m.p. 116–119° (C_6H_6/p.a. 60/80). IR (KBr): 3220 (s) (OH) 1660 (vs) (lactam-CO); PMR: δ ($CDCl_3$) 1·70–2·80 (4H, $-CH_2-CH_2-$) 4·73 (d, 1H, –OH)) 5·48 (m, 1H, N–CH–OH) 7·04–7·54 (5H, aromatic H). MS: *m/e* = 160 (20%) 177 (100) M^+ (Anal. $C_{10}H_{11}NO_2$ M = 177·21. Calc. C, 67·78; H, 6·26%. Found: 67·8 6·3).

1-p-*Methoxyphenyl-5-hydroxy-2-pyrrolidinone* **5f**. A soln of **4e** (0·122 g, 0·52 mmole) in a mixture of dioxane/H_2O 5/2 (7 ml) with 0·061 g of a silica-alumina catalyst was refluxed 4 hr and then poured into water (25 ml). Extraction with $CHCl_3$ and work-up of the extract afforded **5f** as a solid (0·098 g, 0·42 mmole), yield: 91%, m.p. 132–135° (EtOH). IR (KBr): 3220 (s) (OH) 1720 (vs) (lactam-CO); PMR: δ ($CDCl_3$) 1·70–2·50 (4H, $-CH_2-CH_2-$) 3·74 (s, 3H, $-OCH_3$) 5·53 (m, 1H, N–CH–OH) 6·22 (d, 1H, –OH) 6·86–7·64 (4H, aromatic H). MS: *m/e* = 190 (16%) 207 (100) M^+ (Anal. $C_{11}H_{13}NO_3$ M = 207·22. Calc.: C, 63·75; H, 6·32; N, 6·76%. Found: 63·7 6·4 6·7).

1-*p-Nitrophenyl-5-hydroxy-2-pyrrolidinone* **5g**. **3g** (0·440 g, 2·00 mmole) was reduced in a mixture of DMF/EtOH 2/1 (75 ml) with 0·75 g $NaBH_4$ at −40° during 4·5 hr. Work-up (method C) afforded a mixture, which showed 3 spots on TLC (silicagel $CHCl_3$/acetone 4/1) with R_f 0·10, 0·30 and 0·42. Column chromatography on silicagel with $CHCl_3$/acetone 10/1 as an eluent afforded the fraction with R_f 0·30 as a solid (0·169 g) which was pure **5g** according to PMR (0·76 mmole), yield: 38%, m.p. 163–165° (EtOH). IR (KBr): 3280 (s) (OH) 1665 (vs) (lactam-CO); PMR: δ ($CDCl_3$) 1·90–2·90 (4H, $-CH_2-CH_2-$) 5·56 (d, 1H, –OH) 5·88 (m, 1H, N–CH–OH) 7·95–8·30 (4H, aromatic H). MS: *m/e* = 205 (15%) 222 (100) M^+ (Anal. $C_{10}H_{10}N_2O_4$ M = 222·20. Calc. C, 54·05; H, 4·54; N, 12·61%. Found: 53·9 4·4 12·6).

1-*Methyl-3,4-dihydro-2-pyridone* **7b**. A soln of **4b** (corresponding with 52·12 mmole of 1-methyl-glutarimide **3b**) in C_6H_6 (250 ml) was refluxed during 1 hr with 0·104 g *p*-TsOH, using a Dean-Stark apparatus, filled with molecular sieves 4A. Work-up as described for **9** afforded a greenish oil (5·845 g). Distillation under reduced pressure afforded 4·540 g (40·90 mmole) of **7b** (62–66°/6 mm, bath

temp 88–94°), yield: 79%. IR ($CHCl_3$): 1660 (vs) (lactam-CO). PMR: δ ($CDCl_3$) 2·15–2·6 (m, 4H, $-CH_2-CH_2-$) 3·02 (s, 3H, N–CH_3) 5·02–5·22 (m, 1H, N–CH=CH–) 5·96–6·12 (m, 1H, N–CH=CH–). MS: *m/e* = 42 (79%) 68 (100) 70 (20) 82 (21) 111 (95) M^+ (Anal. C_6H_9NO M = 111·14. Calc. C, 64·84; H, 8·16; N, 12·60%. Found: 64·7 8·1 12·5).

3,4-Dihydro-2-pyridone **7d**. A soln of **4d** (2·950 g, 20·63 mmole) in toluene (150 ml) was refluxed during 1 hr using a Dean-Stark apparatus, filled with molecular sieves 4A. The solvent was evaporated and the residue was distilled under reduced pressure. The compound **7d** distilled at 55–70°/$5\cdot10^{-5}$ mm (bath temp 130°) and 1·525 g (15·72 mmole) or **7d** was obtained as an oil, yield: 76%. IR ($CHCl_3$) 1675 (vs) 1650 (vs). PMR: δ ($CDCl_3$) 4·98–5·19 (m, 1H, –CH=CH–N) 6·0–6·2 (m, 1H, –CH=CH–N) 8·1–8·8 (1H, N–H). MS: *m/e* = 43 (29%) 54 (32) 56 (22) 68 (24) 69 (26) 97 (100) M^+ (Anal. C_5H_7NO M = 97·11. Calc. C, 61·84; H, 7·27; 14·42%. Found: 61·9 7·4 14·4).

1-Methyl-3-pyrrolin-2-one **8a**. A soln of **4a** (corresponding with 22·09 mmole of 1-methyl-succinimide **3a**) in C_6H_6 (300 ml) was refluxed during 3 days, using a Dean-Stark apparatus, filled with molecular sieves 4A. Evaporation of the solvent afforded a yellow oil (1·917 g), which showed 2 spots on TLC (silicagel, benzene/acetone 1/2) with R_f 0·29 and 0·44. Column chromatography on silicagel with C_6H_6/acetone 1/1 as an eluent afforded the fraction with R_f 0·29 as an oil (1·069 g), which was pure **8a** according to PMR (11·02 mmole). The oil solidified as temps below 5°, yield: 50%. IR ($CHCl_3$): 1700 (s) 1675 (vs). PMR: δ ($CDCl_3$) 3·15 (s, 3H, N–CH_3) 4·2 (s, 2H, N–CH_2–C=C) 6·15–6·38 (m, 1H, CO–CH=CH–) 7·2–7·43 (m, 1H, CO–CH=CH–).

1-Methyl-3-[5'-(1'-methyl-2'-pyrrolidinonyl)]-3-pyrrolin-2-one **9**

(a) *From ethoxylactam* **4a**. A soln of **4a** (corresponding with 10·05 mmole of 1-methyl-succinimide **3a**) in C_6H_6 (100 ml) was refluxed with 0·025 g *p*-TsOH during 2·25 hr, using a Dean-Stark apparatus, filled with molecular sieves 4A. The soln was washed with sat $NaHCO_3$ aq (10 ml) and sat NaCl aq (10 ml). The water layers were washed with $CHCl_3$ (6 × 50 ml). The organic layers were combined, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded 0·885 g of yellow crystals. This product showed on TLC (silicagel, MeOH/EtOH 1/1) one spot (R_f 0·41) and weak spots of some by-products. Column chromatography on silicagel with R_f 0·41 as yellowish crystals. The crystals were collected with ether (0·533 g, 2·75 mmole of **9**, 55% yield).

(b) *From 1-methyl-3-pyrrolin-2-one* **8a**. A soln of **8a** (0·596 g, 6·14 mmole) in C_6H_6 (60 ml) was refluxed with 0·015 g *p*-TsOH during 2 hr. Work-up as described above afforded pure **9** (0·471 g, 2·43 mmole) in 79% yield; m.p. 81–92° dec. IR ($CHCl_3$): 1680 (vs) (lactam-CO). PMR: δ ($CDCl_3$) 1·80–3·20 (m, 4H, $-CH_2-CH_2-$) 2·75 (s, 3H, N–CH_3) 3·04 (s, 3H, N–CH_3) 4·02 (s, 2H, N–CH_2–C=C–) 4·32–4·65 (m, 1H, N–CH–C=C) 6·84 (m, 1H, –CH=C–CO). MS: *m/e* = 42 (38%) 95 (31) 98 (33) 123 (25) 151 (35) 166 (29) 179 (22) 194 (100) M^+.

1-Methyl-4-[5'-(1'-methyl-2'-pyrrolidonyl-]-3-pyrrolin-2-one **10**

A soln of **4a** (corresponding with 12·97 mmole of 1-methyl-succinimide **5**) in C_6H_6 (150 ml) was refluxed during 17 hr with 4·0 g of silica-alumina catalyst, using a Dean-Stark apparatus, filled with molecular sieves 4A. The catalyst was removed by filtration. Work-up of the filtrate as described for **9** afforded 0·743 g of a yellow oil. The main component showed on TLC (silicagel, MeOH/EtOH 1/1) a spot with R_f 0·39. Column chromatography on silicagel with MeOH/EtOH 1/1 as an eluent afforded the fraction with R_f 0·39 as a solid, which was collected with ether: 0·310 g (1·60 mmole) of **14**, yield: 24%, m.p. 40–95° dec. IR ($CHCl_3$): 1680 (vs) (lactam-CO). PMR: δ ($CDCl_3$) 1·75–3·1 (m, 4H, $-CH_2-CH_2-$) 2·76 (s, 3H, N–CH_3) 3·00 (s, 3H, N–CH_3) 3·98 (s, 2H, N–CH_2–C=C–) 4·32–4·63 (m, 1H, N–CH–C=C) 5·98 (m, 1H, –C=CH–CO). MS: *m/e* = 42 (36%) 79 (20) 98 (65) 136 (62) 193 (20) 194 (100) M^+.

1-Methyl-5-[6'-(1'-methyl-2'-piperidonyl)]-3,4-dihydro-2-pyridone **14**

A soln of **4b** (0·540 g, 3·44 mmole) in C_6H_6 (150 ml) was refluxed during 20 hr with 1·08 g of silica-alumina catalyst, using a Dean-Stark apparatus, filled with molecular sieves 4A. The catalyst was removed by filtration. Work-up of the filtrate as described for **9** afforded 0·267 g of **14**, yield: 70%, m.p. 102–107° (ether). IR (KBr): 1640 (s) (lactam-CO). PMR: δ ($CDCl_3$) 1·60–2·70 (10H, CO–CH_2–CH_2–CH_2–, CO–CH_2–CH_2–C=C) 2·90 (s, 3H, N–CH_3) 3·07 (s, 3H, N–CH_3) 3·84–4·02 (m, 1H, –N–CH–C) 5·91 (s, 1H, N–CH=C). MS: *m/e* = 137 (46%) 151 (72) 222 (100) M^+ (Anal. $C_{12}H_{18}N_2O_2$ M = 222·28. Calc. C, 64·84; H, 8·16; N, 12·60%. Found: 64·7 8·1 12·6).

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